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STUDIES DIRECTED TOWARD THE SYNTHESIS OF THE B-RING OF 
LASONOLIDE A

DISSERTATION

Presented in Partial Fulfillment of the Requirements for 
the Degree Doctor of Philosophy in the 
Graduate School of The Ohio State University

By

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2002

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ABSTRACT

Efforts to synthesize natural products are largely driven by the ever growing need for effective chemotherapeutic agents. Lasonolide A is a marine natural product that has been shown to poses high levels of cytotoxicity toward certain cell lines, and thus has medicinal potential. The structure of the natural product is comprised of a 13-membered sidechain appended to a 20-membered macrocyclic ring. The macrocycle itself contains two highly functionalized tetrahydropyran rings (A and B), and five double bonds where both the \( E \) and \( Z \) configurations are represented. At the time this research was initiated, the absolute stereochemistry of the natural product was not known, and determining the stereochemistry was seen as an additional motivation for undertaking the synthesis of lasonolide A.

This dissertation details our efforts to synthesize the B-ring tetrahydropyran of lasonolide A in an enantioselective manner. The foundation of our strategy was based upon the utilization of pyran-forming methodology previously developed in the Hart research group. This method called for the electrophile initiated cyclization of 4-penten-1,3-diol derivatives, which were subject to certain structural constraints in order to meet our synthetic requirements. The need to satisfy these structural requirements while still maintaining an acceptable level of efficiency in the synthesis guided much of the research presented.

Ultimately, two methods were developed for the synthesis of cyclization precursors. The first method used an asymmetric crotylation/Wittig reaction sequence, and the second used an asymmetric aldol/stereoselective reduction sequence. Although each route was found to poses certain limitations, the chemistry developed during these studies eventually led to the synthesis of a pyran ring which is know to be a viable progenitor to the B-ring of lasonolide A.
To Professor David J. Hart
ACKNOWLEDGEMENTS

First and foremost, I would like to thank Professor Hart for his patience, guidance, and endless support. I think I could not have found a better guide for my journey through graduate school. You have inspired me as a chemist, but more importantly you have inspired me as a human being.

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Finally, I would like to thank the staff here at The Ohio State University. None of this would have been possible without the help of: Martha Mcdowell, Dr. Karl Vermillion (and his trusty side-kick Doug Krien), Tim Henthorne, Dr. Judith Gallucci, Ken Petri, and countless others too numerous to name.
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<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>MsCl</td>
<td>methanesulfonyl chloride</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoroborate</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl(dimethyl)silyl</td>
</tr>
<tr>
<td>TBSCl</td>
<td>tert-butyl(dimethyl)silyl chloride</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TESCi</td>
<td>triethylsilyl chloride</td>
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CHAPTER 1
STRUCTURE, BIOLOGICAL ACTIVITY, AND SYNTHETIC APPROACHES
TOWARD LASONOLIDE A

I. INTRODUCTION

Synthetic efforts directed toward biologically active molecules is becoming the standard in the field of target-oriented synthetic organic chemistry. For example, because of the widespread occurrence of various cancers, medicinal chemists are eager to identify new cytotoxic substances with the hope that such compounds will eventually lead to development of a viable chemotherapeutic agent. From the author's perspective, however, the total synthesis of complex natural products is rarely undertaken in an attempt to produce a significant quantity of the compound to be used for medicinal purposes. More often, the goal of a total synthesis is to confirm a proposed structure, to provide a template for evaluation of synthetic methodology, or sometimes, to provide small quantities of the compound to test for biological activity or structure-activity relationships. Based on this perspective, lasonolide A (1) appeared to be a worthy target for total synthesis. This marine natural product is a potent cytotoxin.
(vide infra) and thus offers some promise as a lead compound for the development of antitumor agents.

Furthermore, at the time our studies began, the relative stereochemistry at C$_{28}$ and the absolute stereochemistry, had yet to be determined. We hoped to address these issues with our efforts.

![Figure 1. Lasonolide A](image)

Finally, we saw in lasonolide A the opportunity to demonstrate the utility of pyran-forming synthetic methodology that was developed some time ago in our research group. Perhaps more important than any of these factors, is the tremendous opportunity in the endeavor, to learn more about the field of organic synthesis.

Thus, this thesis will describe research directed toward the synthesis of a portion of lasonolide A, specifically the B-ring. To place this research in
perspective, however, an overview of structural, biological, and synthetic studies conducted elsewhere will first be presented.
II. Structure and Biological Activity of Lasonolide A

Lasonolide A (1) was isolated by McConnell et al in 1992 from the red-orange colored marine sponge *Forcepia sp.*, collected from the waters of the British Virgin Islands. A total of 2.3 mg of the substance was obtained from 100 g of a frozen sample by a combination of extensive solvent partitioning and chromatographic techniques. The natural product is a pale orange oil ([α]_D = +24.4°, c 0.045, CDCl₃) whose molecular formula was shown to be C₄₅H₇₀O₉, as determined by high-resolution FAB-mass spectrometry [(M+H)^+ m/z 697.4243]. Extensive NMR analysis, using 1-D and 2-D techniques, suggested the presence of substructures A-E (Figure 2).

![Figure 2. Substructures of Lasonolide A Proposed by McConnell](image-url)
Based on these data, McConnell and coworkers published structure 2 for lasonolide A (Figure 3). These structural studies did not define the stereochemistry at C28.

Although this was the status of structural studies when the research described in this dissertation was initiated, a recent synthesis of 2 by Lee and coworkers indicated that the NMR spectrum of this compound did not match that of the natural product.3 The reader may have already noticed that structure 2 differs from structure 1 in terms of stereochemistry at the C17–C18 and C25–C26 double bonds.

Figure 3. McConnell's Proposed Structure of Lasonolide A

After some experimentation, the Lee group did prepare a compound with an NMR spectrum matching that of lasonolide A, that shown in Figure 1. Although this is now a moot point, it is not clear from reported data, why the olefin geometry was mistakenly assigned by McConnell.
As already mentioned, lasonolide A is a potent cytotoxin. It was shown to have IC$_{50}$ values against the A-549 human lung carcinoma and murine leukemia cell lines of 40 ng/mL and 2 ng/mL respectively.\textsuperscript{4} Furthermore, the compound was shown to induce inhibition of cell adhesion when it was used in a screen that correlates a lack of adhesion with signal transduction interference.

III. Previous Synthetic Efforts

The first total synthesis of the enantiomer of lasonolide A was reported by Lee and coworkers earlier this year.\textsuperscript{3} The approach to the natural product involved the convergent strategy depicted in Scheme 1. From a retrosynthetic viewpoint, the natural product was to be completed by elaboration of the C$_{23}$ sidechain by formation of the C$_{25}$-C$_{26}$ double bond. The macrocycle itself (see structure 3) was to be synthesized from tetrahydropyrans 4 and 5, with the bond constructions occurring at C$_3$-C$_4$ and C$_{14}$-C$_{15}$ on either side of the macrocycle (Scheme 1). The strategies for preparation of 4 and 5 were similar, both using a stereoselective intramolecular radical cyclization as a key step.
Scheme 1. Lee's Retrosynthesis of the Enantiomer of Lasonolide A
The synthesis of tetrahydropyran 12, whose relationship to 4 is clear, is shown in Scheme 2. Diethyl malate (8), was converted to the Weinreb amide 9 by regioselective reduction of the α-hydroxy ester, selective protection of the primary hydroxyl group as a benzyl ether, and reaction of the remaining ester with the standard aluminum amide. Treatment of the hydroxamic acid with isopropenylmagnesium bromide gave 10, which underwent stereoselective reduction of the ketone, using triethylborane and sodium borohydride, to give the corresponding diol. The two secondary hydroxyl groups were then differentiated by forming the p-methoxybenzylidene acetal and performing a regioselective reduction to give alcohol 11. Alcohol 11 was converted to free radical cyclization precursor 12 upon sequential conjugate addition to ethyl propiolate, deprotection of the PMB-ether, and derivatization with the appropriate chlorosilane. The pyran ring was then formed in a diastereoselective manner using a tandem radical addition reaction initiated by tri-n-butyltin hydride and AIBN. The resulting ester was then converted to 13 via reduction to the alcohol followed by protection as its pivalate derivative. To install the requisite C22 hydroxymethyl group, a Tamao oxidation was employed to convert the silane to the corresponding diol. Protection of the resulting hydroxyl groups, followed by selective deprotection of the primary alcohol, gave compound 14. Conversion of the alcohol to a selenide, followed by oxidation and elimination, gave an olefin that was oxidatively cleaved using catalytic osmium tetroxide and sodium periodate to provide aldehyde 15.
Scheme 2. Lee’s synthesis of the A-Ring

(i) 1.03 equiv BH$_3$·SMe$_2$, 0.05 equiv NaBH$_4$, THF, rt, 1 h; (ii) 1.0 equiv Bu$_3$SnO, benzene, reflux, 16 h; 2.0 equiv BnBr, 1.0 equiv TBAI, reflux, 4 h; (iii) 3.0 equiv Me$_2$NH(OMe)$_2$·HCl, 3.0 equiv Me$_3$Al, THF, 0 °C to rt, 5 h; (iv) 3.0 equiv H$_2$C=C(Me)MgBr, THF, rt, 5 h; (v) 1.1 equiv Et$_3$B, 1.1 equiv NaBH$_4$, THF-MeOH (4:1), -78 °C, 4 h; (vi) 2.5 equiv (p-MeO)PhCH(OMe)$_2$, 0.05 equiv CSA, DCM, rt, 1 h; (vii) 2.5 equiv DIBAL-H, DCM, rt, 5 h; (viii) 1.5 equiv H$_2$C=CCO$_2$Et, 0.2 equiv NMM, MeCN, rt, 2 d; (ix) 1.1 equiv DDQ, DCM-H$_2$O, rt, 1 h; (x) 1.2 equiv BrCH$_2$SiMe$_3$Cl, 1.4 equiv TEA, 0.05 equiv DMAP, benzene, rt, 30 min; (xi) 1.5 equiv Bu$_3$SnH, 0.2 equiv AIBN, benzene (0.02 M), reflux (syringe pump, 4 h); (xii) 1.0 equiv LiBH$_4$, ether, rt, 6 h; (xiii) 1.5 equiv PivCl, 0.05 equiv DMAP, 2.0 equiv pyridine, DCM, rt, 8 h; (xiv) xs 30% H$_2$O$_2$, 3.0 equiv KF, 4.0 equiv KHCO$_3$, THF-MeOH (1:1), rt, 36 h; (xv) 3.0 equiv TBSOTf, 5.0 equiv 2,6-lutidine, DCM, rt, 8 h; (xvi) 0.2 equiv CSA, MeOH, 0 °C, 90 min; (xvii) 1.3 equiv (o-NO$_2$)PhSeCN, 1.3 equiv Bu$_3$P, THF, rt, 2 h; xs 30% H$_2$O$_2$, rt, 5 h; (xviii) 0.05 equiv OsO$_4$, 3.0 equiv NMO, acetone-H$_2$O (3:1), rt, 2 d; 3.0 equiv NaI0$_4$, rt, 5 h; (xix) 2.0 equiv NaBH$_4$, EtOH, 0 °C, 10 min; (xx) conc HCl, MeOH, rt, 5 h; (xxi) 1.5 equiv Me$_2$C(OMe)$_2$, 0.05 equiv PPTS, acetone, rt, 2 h; (xxii) H$_2$, Pd/C, MeOH, rt, 2 h; (xxiii) 5.0 equiv SO$_3$·Pyridine, 10 equiv TEA, DMSO-DCM (1:1), 0 °C 1 h.

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Reduction of the aldehyde to an alcohol and deprotection of the TBS-ether, gave a diol that was protected as acetonide 16. Deprotection of the benzyl ether and oxidation of the alcohol using sulfur trioxide-pyridine complex gave aldehyde 17, a compound that would later be used to form the C\textsubscript{17}-C\textsubscript{19} double bond.

The synthesis of the B-ring (Scheme 3) has several aspects in common with that of the A-ring. Whereas the A-ring began by building on a stereocenter established in a commercially available starting material, the three contiguous stereocenters of the B-ring were set by employing asymmetric reactions. Thus, alkylation of the boron enolate of Evans' chiral imide with benzyloxyacetaldehyde gave β-hydroxy imide 18 with two of the three requisite stereocenters set. The chiral auxiliary was converted to the Weinreb amide under standard conditions, and this compound, like its predecessor for the A-ring, cleanly underwent nucleophilic acyl substitution to provide the α,β-unsaturated ketone 19 (69% for three steps). This compound was subjected to stereoselective reduction using the same type of triethylborane-sodium borohydride reduction as before, and likewise, the resulting syn-1,3-diol was protected as a benzylidene acetal. Regioselective reduction of the acetal gave 20, with the required differentiation between alcohols. Oxidative cleavage of the terminal olefin, followed by reduction and selective protection of the primary alcohol as its TBS-ether, gave 21. This molecule served as the conjugate addition partner for ethyl propiolate, and the TBS-protected alcohol of the resulting β-alkoxy acrylate was converted to the corresponding bromide to give the cyclization precursor 22.
Scheme 3. Lee's Synthesis of the B-Ring

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Bromide 22 was then cyclized via an intermediate free radical, and a series of manipulations eventually afforded aldehyde 23. Application of the Takai protocol to aldehyde 23 gave vinyl iodide 24 with trans:cis selectivity of about 3:1. Synthesis of the trisubstituted olefin at C12 began with selective deprotection of the primary TBS-ether and oxidation of the alcohol to the aldehyde. This compound was subjected to the Still-Gennari protocol to produce 25 with the desired Z-geometry (Z:E = 15:1). Further elaboration of 25 to 26, an appropriate coupling partner for the A-ring pyran, was achieved by sequential reduction of 25 to the allylic alcohol followed by oxidation to the α,β-unsaturated aldehyde.

Formation of macrocycle 132 is shown in Scheme 4. Aldehyde 17 was reacted with sulfone 27 in a Julia-Kocienski reaction to give the corresponding trans olefin with a 12:1 preference over the cis isomer. Deprotection of the TBS-ether followed by reaction with 2-mercaptobenzothiazole in a Mitsunobu-type reaction, provided a sulfide that was oxidized to sulfone 28. This compound underwent a second Julia reaction with 26, the B-ring pyran, to give trans-olefin 29. Removal of the acetonide in the A-ring of 29, followed by selective formation of the primary TBS-ether, allowed for the coupling of the remaining secondary alcohol with acid 30 to provide stannane 31. This compound underwent smooth intramolecular Stille coupling to the desired macrocycle, which was then converted to aldehyde 32 by deprotection of the pivaloate ester and oxidation of the resulting alcohol.
i) 1.8 equiv 27, 1.8 equiv LHMDS, THF-HMPA (5:1), -78 °C; 1.0 equiv 17-78 °C to rt, 12 h; (ii) 1.5 equiv TBAF, THF, rt, 3 h; (iii) 1.5 equiv PPh₃, 1.5 equiv DIAD, 1.5 equiv mercaptobenzenethiazole, THF, 0 °C, 1 h; (iv) 2.0 equiv (NH₄)₆Mo₇O₂₄, 30 equiv H₂O₂, EtOH, 0 °C, 2h; (v) 1.2 equiv LDA, THF, -78 °C; 1.3 equiv 28, THF, -78 °C to rt, 10 h; (vi) 0.005 M CSA, MeOH, 50 equiv (HOCH₂)₂, rt, 8 h; (vii) 3.0 equiv TBSCl, 5.0 equiv imidazole, DCM, rt, 2 h; (viii) 3.0 equiv 30, 4.0 equiv DIC, 2.5 equiv DMAP, DCM, rt, 20 h; (ix) 0.1 equiv Pd₂dba₃, 10 equiv DIPEA, NMP (0.004M), rt, 16 h; (x) 5.0 equiv LiEt₃BH, THF, -78 °C, 1 h; (xi) 5 equiv SO₃·pyridine, 10 equiv TEA, DMSO-DCM (1:1), 0 °C, 2h.

Scheme 4. Formation of the Macrocycle

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The side chain present at C\textsubscript{22} of the natural product was assembled prior to connection to the macrocycle (Scheme 5). Thus, beginning with D-malic acid (33), selective ketal formation, followed by borane reduction and TBS protection gave 34. Transesterification of 34 with alcohol 35, followed by TBS-protection of the resulting secondary alcohol and selective deprotection of the primary alcohol, eventually led to 36.

(i) 1.0 equiv cyclohexanone, 1.5 equiv BF\textsubscript{3}·OEt\textsubscript{2}, ether, 0 °C to rt, 20 h; (ii) 3.0 equiv BH\textsubscript{3}·DMS, 3.0 equiv B(OMe)\textsubscript{3}, THF, 0 °C to rt, 8 h; (iii) 1.2 equiv TBSCI, 1.5 equiv imidazole, DCM, rt, 1 h; (iv) 3.0 equiv 35, 1.0 equiv NaH, THF, rt, 1 h; (v) 1.3 equiv TBSCI, 1.5 equiv imidazole, 0.05 equiv DMAP, DCM, rt, 12 h; HF·pyridine, pyridine, THF, rt, 1 h; (vi) 1.5 equiv PPh\textsubscript{3}, 1.5 equiv I\textsubscript{2}, 3.0 equiv imidazole, THF, rt, 1 h; (vii) 2.0 equiv Ph\textsubscript{3}P, MeCN, reflux, 16 h; (viii) KHMDS, THF, -78 °C.

Scheme 5. Lee's Synthesis of the C\textsubscript{22} Sidechain

The phosphonium salt precursor to 37 was then prepared by conversion of the alcohol to the iodide, followed by displacement with triphenylphosphine.
Completion of the synthesis of lasonolide A was achieved by Wittig reaction between phosphorane 37 and aldehyde 32 (Scheme 4) followed by removal of the remaining TBS groups (60% yield).

As already mentioned, Lee synthesized 1 only after synthesizing 2 and determining that it did not correlate with the NMR of the natural product. The synthesis of 2 required installation of a trans olefin at C17 and a cis olefin at C25. Lee's strategy was nicely adaptable to accommodate this modification, and he was able to synthesize both 1 and 2 using the same chemistry, in a slightly different manner. Specifically, for the synthesis of 1 he used a Julia olefination to install the trans C17 double bond and a Wittig reaction to install the cis C25 double bond. In the synthesis of 2 he used the Wittig reaction for the former double bond and the Julia olefination for the latter.

Although Lee's group is currently the only one to complete a total synthesis of lasonolide A (actually the enantiomer of lasonolide A), there are two other research groups, in addition to our own, who have published results on their progress toward this end. In 1996, Gurjar and coworkers reported a method for the use of 2,2'-spirocyclopropane derivatives to form tertiary chiral centers. Their method was demonstrated in the synthesis of O-glycoside analogs of both the A-ring and the B-ring of lasonolide A.7,8

Their basic strategy was to modify a known hexose backbone so that it was amenable to a stereoselective Simmons-Smith cyclopropanation reaction. Once the cyclopropane had been formed, the ring was opened to give the new
tertiary chiral center. One drawback of this method was the need to subsequently excise portions of the original sugar that were not a desired feature of the target.

Some details of the Gurjar synthesis of an A-ring precursor are shown in Scheme 6. Ketone 38, the oxidation product of methyl 3-O-benzyl-4,6-O-isopropylidene-α-D-glucopyranoside, underwent a Wittig reaction to provide α,β-unsaturated ester 39. Reduction to the allylic alcohol, followed by Simmons-Smith cyclopropanation generated the desired isomer 40, but with only a 2:1 facial selectivity. To effect ring opening, the hydroxyl group was oxidized to the aldehyde 41, and hydrogenolysis of the cyclopropane ring to give 42 was achieved upon exposure of 41 to 10% palladium on carbon in the presence of hydrogen gas and a catalytic amount of triethylamine. Degradation of the aldehyde to the necessary hydroxymethyl group began by conversion of the aldehyde to its tosylhydrazone followed by base induced elimination of nitrogen to give olefin 43. With the quaternary center set, and the vinyl group acting as a latent hydroxymethyl group, the rest of the chemistry depicted in Scheme 6 was employed to install the axial hydroxyl group at C₃ and deoxygenate C₄.
Scheme 6. Gurjar's Synthesis of the A-Ring

These two tasks were nicely done in concomitant fashion by deprotecting the equatorial C₃ benzyl ether of 43 and activating it as the mesylate. The two-step process of removing the acetal and selectively protecting the primary hydroxyl as...
the silyl-ether, allowed for the formation of epoxide 44 upon treatment with KH in THF/HMPA. Subsequent regioselective reduction of the epoxide with LAH gave 45 which has all of the pyran substituents set with the same relative stereochemistry as the target A-ring. The remaining conversion of 45 to 46 was accomplished in a straightforward manner using oxidative cleavage, followed by reduction and protection of the alcohol as the acetate.

Utilization of the same methodology to prepare the B-ring of lasonolide A was not as efficient. As Scheme 7 shows, the method was employed to install the axial methyl group at C₃ of 55. The synthesis begins by formation of the pyranyl pyran 47 in 5 steps from glucose. Once again, reduction of the unsaturated aldehyde to the allylic alcohol gave the key cyclopropanation substrate 48. Although the diastereoselectivity of the Simmons-Smith reaction in the A-ring was not great (2:1), the reaction with 48 completely lacked selectivity and a 1:1 mixture of cyclopropane products were formed in a combined yield of 74%. All attempts to increase the selectivity provided an increase in the wrong diastereomer.
Scheme 7. Gurjar’s Synthesis of the B-Ring

(i) NaBH₄, IR 120(H⁺) resin, MeOH, 0 °C, 5 min; (ii) CH₂=CH₂, Et₂Zn, DCM, -20 °C, 10 h; (iii) Ph₃P, CBr₄, imidazole, DCM, rt, 1 h; (iv) Bu₃SnH, AIBN, toluene, reflux 30 min; (v) 9-BBN, THF, 4 h; 1M NaOAc, H₂O₂, 0 °C, 3 h; (vi) TBDPSCI, imidazole, DMAP, DCM, rt, 4 h; (vii) NaOMe, MeOH, rt, 10 min; (viii) MeOCP₄CH₂(OMe)₂, PPTS, DCM, rt, 30 min; (ix) DIBAL, DCM, -78 °C, 15 min; (x) PhOC(S)COCl, Py-DMAP, DCM, rt, 6 h; (xi) Bu₃SnH, AIBN, toluene, reflux 2 h; (xii) Bu₄NF, THF, rt, 1 h; (xiii) (COCl)₂, DMSO, Et₃N, -78 °C, 30 min; (xiv) (MeO)₂P(O)CH(Me)CO₂Et, NaH, -78 °C, 3 h; (xv) DIBAL, DCM, -78 °C, 15 min; (xvi) (COCl)₂, DMSO, Et₃N, -78 °C, 30 min; (xvii) Ph₃P=CHCO₂Et, benzene, rt, 5 h.
Nonetheless, the cyclopropanes were separable, so the desired isomer 49 was converted to the bromide 50 in preparation for radical induced cleavage of the cyclopropyl group. Although one can imagine three pathways for ring opening, only two of the three possible products (51 and 52) were detected upon treatment of 50 with tri-n-butyltin hydride. Unfortunately, the required product 52 was formed with only a modest preference over 51, and to complicate matters, the 3:2 mixture of compounds were not readily separable. Ultimately the mixture was subjected to hydroboration-oxidation, followed by TBDPS-protection (52→53), and these compounds could be separated.

To achieve deoxygenation at C₂, the acetates of 53 were cleaved and the resulting vicinal diol was protected as a benzylidene acetal. The benzylidene acetal was regioselectively reduced to give 54. The free alcohol was converted to the corresponding xanthate followed by deoxygenation using the Barton-McCombie protocol to give 55. The side chain of the pyran was then elaborated to match functionality found in lasonolide A. Deprotection of the silyl ether followed by oxidation gave the expected aldehyde. This compound underwent cis-selective Homer-Emmons olefination in 80% yield to give the α,β-unsaturated ester 56, which was subsequently homologated using a reduction-oxidation-Wittig reaction sequence to give 57.

Although both of Gurjar’s syntheses arrive at a tetrahydropyran that has all of the requisite stereocenters of the pyrans found in lasonolide A, there are some
problems with the strategy. The lack of good diastereoselectivity in the cyclopropanation steps, coupled with lack of regioselectivity in the opening of the cyclopropane of the B-ring, show the limitations of this methodology as applied to lasonolide A.

Another series of publications that address the synthesis of pyrans directly analogous to those in lasonolide A, has been published by Hoffmann and coworkers from the University of Hannover.9,10 Their work highlights the versatility of 8-oxabicyclo[3.2.1]octanes in the synthesis of enantiopure tetrahydropyran[s. This chemistry, as applied to the A-ring of lasonolide A, is shown in Scheme 8. Hoffmann's synthesis begins with 8-oxabicyclo[3.2.1]oct-6-en-3-one (58), which was desymmetrized by asymmetric deprotonation using (-)-bis[(S)-1-phenylethyl]amidolithium (59), to give rise to a chiral lithium enolate, that when exposed to Mander's reagent, gave exclusively the C-acylation product 60. This β-ketoester underwent alkylation with benzyloxymethyl chloride to give 61 as the only isomer. This material had greater than 95% ee, as determined by the NMR of 61 in the presence of the chiral shift reagent (+)-Eu(hfc)3. The next step was to reduce the ketone. This was accomplished with sodium borohydride in the presence of CeCl3, albeit with low selectivity of 53:47 with 62 as the predominant isomer. The resulting alcohol was converted to the TBS-ether, and the olefin of the oxabicycle was ozonized and immediately reduced to give the corresponding diol 63. To complete Hoffmann's synthesis of the A-ring, the two primary hydroxyls were then chemodifferentiated by formation of lactone 64.
Scheme 8. Hoffmann's Synthesis of the A-Ring

This method has the obvious advantage of rapid, and highly enantioselective access to the required substituted pyran. However, a notable weakness is that carbon electrophiles that undergo alkylation of the enolate of 58 in good yield, appear to be limited to those that have \( sp^2 \) hybridization at the electrophilic carbon. This necessarily leaves one with an awkward circumstance of oxidation state in 64, because the lactone carbonyl will eventually need to be reduced to the methyl group found in the natural product. Furthermore, the
authors report this work as being done in both a racemic and asymmetric fashion. Although no rationale is given as to why, there seems to be a substantial decrease in yield of some reactions (e.g. $60 \rightarrow 61 = 53\%$ racemic; $33\%$ asymmetric) when the operations are done in the asymmetric series of compounds.

Application of the same basic concept to the synthesis of the B-ring pyran required the use of the $\alpha$-methylloxabicyclo[3.2.1]octane rac-65 (Scheme 9), which was produced from the 4+3 cycloaddition of 1,1,3,3-tetrabromo-2-butanone to furan. Samarium iodide reduction of the ketone in 65 and protection of the resulting alcohol proceeded in 56% overall yield to provide rac-66. This compound underwent asymmetric hydroboration, followed by PCC oxidation, to give a good yield of regioisomeric ketones 67 and 68 that were separable by chromatography. Although only 68 is useful in the synthesis being discussed here, it is noteworthy that 67 is an intermediate in Hoffmann's synthesis of ratjadone. Progress from 68 to something that looks very similar to the desired B-ring was quite rapid. First, the ketone was converted to the corresponding silyl ether to provide 69. Then, in a one-pot procedure, 69 was oxidatively cleaved with ozone, and the crude reaction mixture was methylated with diazomethane, and reduced with sodium borohydride. This gave hydroxy ester 70 in 75% yield, with all of the requisite stereocenters set.

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Scheme 9. Hoffmann's Synthesis of the B-Ring

\[ \text{Scheme 9. Hoffmann's Synthesis of the B-Ring} \]
The process of elaboration to a more highly functionalized pyran used, in part, chemistry already shown in both the Lee and Gurjar syntheses. Specifically, after protection of the primary alcohol in 70 as a silyl-ether, the ester was converted to an aldehyde (reduction-oxidation), which was then subjected to the olefination process developed by Still and Gennari to install the trisubstituted double bond (Z:E = 33:1). The side chain ester was again homologated to give 71 using standard protocols. Removal of the TBDMS-group in 71 and activation of the alcohol as its triflate allowed for substitution with cyanide to provide the necessary one carbon homologation to nitrile 72. Further elaboration of 72 to the target of this synthesis was achieved by reduction of the nitrile to the corresponding aldehyde, and a subsequent vinylogous Horner-Emmons olefination to provide the highly elaborated pyran 73.

In summary, three unique approaches to the natural product lasonolide A, or portions thereof, have been presented. The diversity in this work is most clearly evident in the methods used to construct the stereo-defined pyran rings. The Gurjar synthesis relied on the modification of readily available carbohydrates, the Hoffmann method rapidly assembled the pyran framework by employing cycloaddition chemistry, and Lee's synthesis of the pyrans stems from an elegant use of radical cyclizations. Although the methodology presented in the next two chapters is arguably most related to Lee's, in that the pyran is formed through a cyclization reaction, the similarities quickly dissipate as one explores the details. Specifically, the following chapters will describe two
strategies for the synthesis of 4-penten-1,3-diol derivatives that undergo electrophile initiated cyclization reactions to form analogs of the B-ring of lasonolide A. Furthermore, some work will be presented concerning the elaboration of these derivatives to compounds potentially useful in the synthesis of the macrocycle.
CHAPTER 2
SYNTHESIS OF CYCLIZATION PRECURSORS OF THE B-RING VIA AN ASYMMETRIC CROTYLATION ROUTE

I. INTRODUCTION

The work contained in this dissertation constitutes our efforts toward the application of a new method for the stereoselective formation of 2,6-disubstituted-4-hydroxytetrahydropyrans, to a synthesis of the B-ring of lasonolide A (1) (Figure 1). To provide the reader with the background needed to understand and scrutinize this work, a brief overview of this methodology is presented next.

The Hart group has been interested in the synthesis of C-aryl glycosides for some time. During synthetic studies directed toward a natural product called chrysomycin, Merriman found that unsaturated alcohol 7 4 underwent stereospecific addition of an electrophile and the internal nucleophile across the double bond to give exclusively pyran 76 in good yield.11
It was reasoned that formation of the 6-membered ring heterocycle, in preference to a 5-membered tetrahydrofuran, was due to greater stabilization of positive charge on the carbon adjacent to the aromatic ring in the cyclization transition state. The stereochemistry of the product was rationalized based on the assumption that cyclization of the substrate would occur via a chair-like transition state with the maximum number of substituents in equatorial sites (75).

The successful result shown in equation 1 fueled interest in the possibility of using other, more versatile, functional groups to achieve the same stabilization effect. Presumably, this would broaden the scope of this pyran-forming reaction. This issue, along with those concerning the diastereoselectivity of the reaction, later became the focus of studies by Zakarian and Patterson.

It has been shown that cobalt-alkyne complexes such as 77 have the ability to stabilize adjacent cationic character (equation 2).\textsuperscript{12}
In an extension of this concept, Zakarian attempted to cyclize compounds of the type shown in equation 3. Unfortunately, he found that the double bond in 79 was unreactive. In an attempt to determine if the allylic siloxy group was deactivating the olefin, he synthesized a corresponding aryl derivative 80, and found that it did indeed cyclize to the desired pyran.

In fact, it did so with a surprising stereochemical result, in that diastereomer 82, with the greater number of axial substituents, was formed in preference to 81. Although these experiments did not explain why the cobalt-alkyne complex was unreactive, they did show that the olefin was still a viable electrophile in the presence of an allylic oxygen substituent. In other words, the electrophile-initiated cyclization provided access to tetrahydropyran-4-ols.

Formation of the unexpected diastereomer was interesting enough to study in its own right, and Patterson attempted to determine its origin. She synthesized a variety of 4-penten-1,3-diol derivatives and subjected them to the
electrophile initiated cyclization conditions established by Zakarian and others. 

The cyclization precursors were designed to address the issue of steric control versus electronic control in the conformation of the transition state. Thus, cyclization precursors containing a variety of structural features were synthesized. The salient variables were: (1) the presence or absence of gem-dimethyl groups at C2 (2) an increase in bulk of the hydroxyl protecting group at C3 (3) the electron donating ability of the aryl group at C5, and (4) replacement of the C3 oxygen by an alkyl group. As can be seen in the data presented in equations 4-6, an increase in steric effects (gauche interactions) brought about the presence of the gem-dimethyl groups at C2 (see equation 4, 87:88 versus 87:85), or the bulkier oxygen protecting group (see equation 5, 93:94 versus 96:97), did not significantly change the diastereomeric ratio. Only replacement of the C3 oxygen by an alkyl group (see equation 6, 99:100 versus 102:103) showed a profound change in the diastereoselectivity. This implies that an electronic effect influences the conformation of the cyclization precursor in the transition state. While this work does not address the origin of the proposed electronic effect, it does demonstrate a scope for the diastereoselectivity that goes beyond an isolated example. A final point to be taken from these data is that the scope of the aryl group was expanded to include vinylogs of the benzene ring (equation 4). Aryl dienes will play a significant role in the research that follows (vide infra).
With the aforementioned results in mind, and not yet knowing of the erroneous structure of lasonolide A, we envisioned a retrosynthesis of 2 that is depicted in Scheme 10. The research presented here pertains only with strategies relevant to construction of the macrocycle. Thus, starting with 104, we had envisioned closing the macrocycle by a vinylogous Horner-Emmons reaction. To the best of our knowledge, this strategy has not yet been applied to macrocycle formation. Although the specific choice of method for the initial coupling of 105 and 106 was delayed until we had fully explored the scope of the pyran forming reaction, we had identified the C_{18}-C_{17} or C_{17}-C_{18} bonds as potential candidates.
Scheme 10. Retrosynthetic Analysis for Compound 2

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With regard to the synthesis of pyran 106, or an analog thereof, Gurjar and Hoffmann established that elaboration of a compound such as 107 to 106 was feasible, and we felt that this was a low risk element of the strategy. Therefore the objective was reduced in scope to the synthesis of substrates such as 108, and their use in the electrophile initiated cyclization reactions to provide 107. It should be pointed out that the stereochemical course of the cyclization (108→107) was an open question, as substrates of this type (e.g. 83 where R = H and R' = Me) had not been previously investigated.

As the structure 108 is generalized in Scheme 10, it is necessary to comment briefly on the requirements for the group depicted as R. For cyclization of 108 to occur in a 6-endo mode rather than a 5-exo mode, R must be some cation stabilizing species (vide supra). However, it was also necessary for R to be amenable to efficient functionalization after cyclization had been achieved. The effort to find the proper balance between these two requirements has guided much of this work (vide infra). Finally, we had envisioned structures such as 108 coming from Wittig olefination of the lactol 109, the synthesis of which, is the focus of the next section.
II. RESULTS AND DISCUSSION

Our experimental work began with a synthesis of lactol 109 and evaluation of its behavior in Wittig reactions to give cyclization substrates of type 108 (see Scheme 10). The synthesis of lactol 109 required the formation of three contiguous chiral centers. Our plan was to achieve this using an asymmetric crotylation reaction (Scheme 11). Thus, cis-dibenzylxyloxy-2-butene (110) was ozonized to give benzylxoyacetaldehyde (111) in 46% yield. Using methodology developed by Roush and coworkers, crotylboronate 112 was synthesized and reacted with 111, to give homoallylic alcohol 113 in 55% yield. Although the crotylation reaction gave acceptable yields, it was found that the benzylxoyacetaldehyde was unstable during isolation and purification. Through considerable experimentation, a protocol was developed that allowed for use of crude aldehyde in the crotylation reaction, which increased the overall yield of 113 from 110 to 55%. Alcohol 113 was protected as its TBS-ether 114 (90%), and standard hydroboration-oxidation gave the expected primary alcohol 115 in 72% yield.
Scheme 11. Synthesis of Chiral Butyrolactol

Alcohol 115 was oxidized to acid 116, and without purification, the TBS-ether was removed under acidic conditions to give γ-lactone 117 in 68% yield.

Unfortunately, attempts to obtain the desired α-hydroxylactone 118 using Davis'
were frustrated by a difficult separation of the product from
benzenesulfonamide byproduct.

The prospect of having a difficult purification at this early stage of the
synthesis led us to reconsider our route to 109. The new plan involved oxidation
of the alcohol 115 to the aldehyde 119 with the Dess-Martin periodinane,20 which
led to lactol 120 in 95% yield after acidic removal of the silyl ether. Conversion
of 120 to the corresponding mesylate, followed by elimination with triethylamine,
delivered dihydrofuran 121.21 The variable yield of this reaction (40-60%) was
primarily due to facile dimerization of 120 to acetal 122, although the dimer could
be converted back to monomeric lactol 120 by treatment with acid under dilute
conditions (equation 7).

Finally, dihydroxylation of 121 with catalytic osmium tetroxide22 gave a mixture of
diastereomeric diols 109 in 91% yield with an α:β isomer ratio of 2:1 by NMR.

To confirm the relative stereochemistry of the substituents on the lactol
ring, 109 was converted to acetonide 123 in 72% yield by reaction with 2-
methoxypropene in the presence of catalytic p-toluenesulfonic acid (equation 8).
Acetal 123 was then subjected to the nOe studies shown in (Figure 4).
Figure 4. A Nuclear Overhauser Study of Acetonide 123
From these data, one can see that the enhancements observed are consistent with a compound having the expected relative stereochemistry proposed for 123 (Figure 4). Specifically, structure C shows that upon irradiation of H₄ there is enhancement of signals corresponding to H₅ (1.2%) and the C₃-methyl group (2.0%). These observations are consistent with the proposed cis ring juncture, the cis-relationship of the C₃-methyl group to H₄, as well as the trans relationship of H₂ to H₄. Further support for this stereochemical assignment is seen in structure A, where irradiation of H₂ gives an enhancement to H₃ (1.2%) suggesting a cis-relationship, when compared to the enhancement to the C₃-methyl group (0.2%), which is on the opposite face of the ring. The presence of the small enhancement to H₂ (0.3%) from the irradiation of H₄ (figure A) raises some question as to the validity of our proposal. Although we were aware that the interpretation of nOe data obtained from small ring compounds such as these must be done with caution, it will be shown elsewhere that our assessment of the stereochemistry is indeed correct.

With the relative stereochemistry of 109 set in the proper manner, we proceeded with the syntheses of cyclization precursors (see 108 in Scheme 10) using Wittig reactions as outlined in Table 1. Each Wittig reagent was selected with two general purposes in mind: (1) to deliver an olefin that would bias a subsequent cyclization in the required 6-endo mode, and (2) to deliver a sidechain that could be converted into the required C₄ sidechain in compounds of type 106 (see scheme 10). The bromide precursors of the phosphonium salts
124-130 were either prepared by literature procedures (125, 126, 127, 128, 129) or obtained from commercial sources (124, 128, 129).

Their conversion to the phosphonium salts resulted from the displacement of the bromide with triphenylphosphine. Thus, in all cases, a solution of the alkyl bromide in benzene was treated with a slight excess (1.1 equivalents) of triphenylphosphine. The resulting salt was used in subsequent reactions after being collected and dried under vacuum. The yields of 124-130 synthesized in this manner varied somewhat, but could be grouped in the following way: (124-125, 75%); (126-127, 19-25%); (128-130, 42-50%). The purity of the salts also varied slightly, however, no attempt was made to purify them further. Finally, it should also be noted that of the phosphonium salts containing double bonds, only 127 appeared to be a mixture of geometric isomers, and in that case the ratio was 3:1 in favor of the cis isomer.

A typical procedure for carrying out the Wittig reactions using 124-130 involved deprotonation of 2.5 equivalents of the phosphonium salt using an equal amount of potassium tert-butoxide, and the resulting phosphorane was reacted with 109 to give the olefin products shown in Table 1.
The olefinic products (131-134) were formed with varying degrees of selectivity for the desired trans isomer, and these are listed for each entry in Table 1. In all cases, these ratios were determined by the integration of signals corresponding to the olefinic protons in the $^1$H NMR spectra of 131-134. For example, in the

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<td>125</td>
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Table 1. Results of Wittig Olefinations

The olefinic products (131-134) were formed with varying degrees of selectivity for the desired trans isomer, and these are listed for each entry in Table 1. In all cases, these ratios were determined by the integration of signals corresponding to the olefinic protons in the $^1$H NMR spectra of 131-134. For example, in the
case of 131, Hₐ for the *trans* isomer was found to have a chemical shift of δ 6.55 (d, J = 15.9 Hz) whereas Hₐ for the *cis* appeared at δ 6.49 (d, J = 11.8 Hz) (see Figure 5).

![Figure 5. ¹H NMR spectrum of 131 from δ 6.8-5.6](image)

Samples of pure *trans* isomer could be obtained by careful selection of fractions from the column, and this was done for analytical purposes. However, the mixtures of geometric isomers indicated in Table 1 were used in subsequent reactions. Although greater than half of the phosphonium salts prepared underwent the Wittig reaction, the failure of 130 (entry 7) to produce the desired product was particularly disappointing. In our estimation, the vinyl sulfide moiety would have been ideal for facile conversion via hydrolysis to the desired aldehyde at C₅ of 106 (Scheme 10). This would have circumvented the need for a multi-step conversion of the cation stabilizing group, as would be required for 135-138 (vide infra).

With cyclization precursors 131-134 in hand, we proceeded to assess the stereochemical course of their electrophile-initiated cyclizations. Using
conditions established previously in our group, these compounds were found to undergo cyclization to give pyrans 135-138 in moderate yields (Table 2). In a typical reaction, a -78 °C solution of the olefin in dichloromethane was treated with one equivalent of phenylselenenyl chloride. Usual reaction times were 3-5 hours, followed by the addition of an aqueous solution of sodium bicarbonate. The reaction mixture was allowed to warm to room temperature and worked up in the normal manner. The pyran products were then purified using silica gel chromatography. The yields reported in Table 2 are of the purified diastereomer.

The stereochemistry of the pyrans was established by ¹H NMR spectroscopy. For example, in the spectrum of 135 the signal corresponding to H₄ was seen as a doublet (J = 11.2 Hz) indicating its trans-diaxial relationship to H₅. The signal due to H₄ is observed as a broadened singlet, which is indicative of the small couplings one would expect from its gauche relationship to the adjacent trans H₅ and H₃. Unfortunately, the signal corresponding to H₅ was obscured by other resonances and was of little use in this analysis. Pyrans 136-138 also had coupling constants that correlated well with the proposed structure using this analysis.
<table>
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<td>135</td>
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</tr>
<tr>
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<tr>
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Table 2. Results of Electrophile-Initiated Cyclizations

Isomers other than those shown in Table 2 were isolated in two instances, entries 3 and 4. The product mixture resulting from the cyclization of 132 (entry 3) provided a 65% yield of pure diastereomer 137 along with a 10% yield of an equal mixture of 137, and a compound suspected of being a diastereomer which has all substituents equatorial except for the C₂ benzyloxymethyl group. This isomer could result from cyclization via the chair-like transition state opposite of that which produced 137. Although, the numerous signals present in the 'H NMR
of the mixture made definitive identification impossible, two pieces of data supported our assignment. First, the possibility for the minor isomer being the cis isomer of the remaining double bond is ruled out by the fact that the coupling constant for the olefin protons is 15.8 Hz ($\delta$ 6.15). Furthermore, the spectrum shows a signal at $\delta$ 2.70 (t, $J = 10.6$ Hz, 1H), which is consistent with H$_4$ being axial, giving rise to two large couplings to H$_3$ and H$_5$. Also, this pattern is analogous to ones reported by Patterson for diastereomers of the proposed configuration. In the case of entry 4, the product 138 was isolated as a 9:2 mixture of trans:cis olefins, which was clearly seen in the $^1$H NMR of the compound [cis: $\delta$ 6.34 (d, $J = 11.7$ Hz, 1H), trans: $\delta$ 6.44 (d, $J = 15.3$ Hz, 1H)]. It should be noted that we can not say that other isomers are not formed from these reactions. Although no attempt was made to identify all of the products produced, it is clear from the NMR spectra taken of crude reaction products that other isomers are formed to some small degree.

The aforementioned studies established a route to tetrahydropyrans that looked promising for the synthesis of the B-ring of lasonolide A. Thus, at this point it was important to determine the enantioselectivity of the Roush crotylation reaction. We planned to do this in two ways: (1) chiral GC analysis and (2) NMR analysis of Mosher esters$^{27}$ derived from homoallylic alcohol 113. To help with this analysis, a racemic mixture of the diastereomers of 113, namely rac-139, were prepared as shown in equation 9.
With 109 (unknown mixture of enantiomers) and rac-139 in hand, we initially attempted to use chiral GC to analyze their acetate derivatives. The acetates were synthesized by acylation using acetic anhydride under standard conditions. Analysis using a chiral capillary GC column (Chirasil L-Val on WCOT fused silica, 25 m x 0.12 μm film thickness) under a variety of temperature gradients failed to resolve the isomers. We then moved to NMR analysis of the corresponding Mosher esters. Thus, compounds 113 and rac-139 were acylated under standard conditions to give 140-143 as shown in equations 10 and 11. Although the diagnostic signals in the $^1$H NMR of these compounds were not resolved well enough to obtain accurate integrations, the $^{19}$F spectra were useful for this purpose. It was found that the $^{19}$F signals from 142 ($\delta$ -70.7 ) and 143 ($\delta$ -70.3) were resolved from those of 140 and 141 ($\delta$ -70.1 and -70.5).
Thus we were confident that our analysis of 113 was not affected by the presence of rac-139. The ratio of 142 to 143, however, was only 4:1, indicating that the Roush crotylation reaction produced homoallylic alcohol 113 with only a 60% ee.

At this point in the project, results from efforts directed toward the A-ring indicated a need for switching the absolute stereochemistry of our target to ent-113. This coincided with our need to explore another crotylation method in order to synthesize the necessary homoallylic alcohol with high enantioselectivity. Thus, we turned to crotylation methodology developed by Brown and coworkers. Treatment of aldehyde 111 with crotylborane 144, gave ent-113 in 28% yield after oxidative work up and column chromatography (equation 13). Once again, the enantiomeric excess of the product was determined using the
Mosher ester derivative, and in this case the ratio of 142 to 143 was found to be about 25:1, corresponding to an approximate ee of 92%.

Although some attempts were made to increase the yield of the crotylation reaction, no significant success was achieved. We felt it was likely that in this case, the use of the crude aldehyde in the reaction was causing the lower yields. Rather than trying to increase the yield of the crotylation reaction, it was decided to pursue another route to the cyclization precursors.

Although the crotylation route allowed us to synthesize the compounds in Table 1 and confirm the stereochemical course of their cyclization reactions, it had a few notable drawbacks. The most obvious drawback, was the lack of a crotylation method that would give both acceptable yields and enantioselectivities in our hands. However, there were also difficulties associated with the Wittig reaction. Aside from producing mixtures of olefin geometrical isomers, the Wittig reaction appeared to be limited in the scope of phosphonium salts that could be used. As an alternative strategy, we decided to explore the possibility of using an aldol reaction to gain access to the necessary ene-diols. Specifically, we hoped to synthesize cyclization precursors containing the aforementioned vinyl
sulfide moiety that was not accessible using the Wittig chemistry (see entry 7, Table 1). The development of this strategy and its application toward the synthesis of viable B-ring progenitors will be presented in the next chapter.
CHAPTER 3
SYNTHESIS OF CYCLIZATION PRECURSORS OF THE B-RING VIA AN ALDOL ROUTE

I. INTRODUCTION

As stated at the end of the last chapter, there were several problems associated with our approach to the enantioselective syntheses of cyclization precursors (108 in Scheme 10) utilizing crotylation methodology. We felt that the primary limitation to the strategy was the narrow scope that the Wittig reaction offered with respect to installing useful functionality appended to the initial double bond. In an attempt to expand our access to cyclization precursors not available through the previous method, we decided to develop a new route that used an aldol reaction as the key step. Any synthesis of compounds such as 108 must contend with the need for introducing asymmetry into the molecule, and we recognized the opportunity to use one of the several asymmetric versions of the aldol reaction to accomplish this task. Specifically, our immediate goal was to synthesize a cyclization precursor containing a vinyl sulfide group and to study its electrophile initiated cyclization.
As cation stabilizing groups of this type had not yet been shown to provide the required 6-endo mode of cyclization (vide supra), the formation of the pyran in preference to the furan, as well as the diastereoselectivity of the reaction, were open questions.

To quickly obtain information regarding the feasibility of our new strategy, we decided to synthesize a model system first. This would not only facilitate rapid access to systems for exploring the cyclization, but also offer the opportunity to simplify the stereochemical analysis of the diastereomeric products obtained. The following section will elaborate on the synthesis of a model system containing the vinyl sulfide moiety and describe the results obtained regarding its use in subsequent pyran-forming reactions. In addition, details will be given on the development of the aldol strategy to provide pyrans that have been shown to be viable progenitors of the B-ring of lasonolide A.

II. RESULTS AND DISCUSSION

The model system chosen for exploring the aldol route was one used by Patterson in the methodology studies depicted in equation 4 (vide supra). Systems of this type provide an obvious simplification with regard to structure determination and stereochemical analysis. The synthesis of the model system began with the preparation of the known compound 3-phenylthiopenta-2,4-dienal 152 (Scheme 12). Thus, propargyl alcohol (149) was oxidized to the
corresponding aldehyde 150 by the slow addition of chromic acid at reduced pressure. The propargaldehyde was distilled from the reaction mixture as it was formed, producing 150 in 25% yield. Although the reaction yield was low, the reaction could be easily scaled up to provide significant quantities of material for use in subsequent reactions.

Scheme 12. Synthesis of Dienal 152

Aldehyde 150 underwent conjugate addition of thiophenol to provide β-phenylthioacrolein (151) as an inseparable mixture of geometric isomers in 65% yield. The ratio of trans to cis was on the order of 6:1, as determined from the 1H NMR by integration of signals from the olefin protons. Treatment of 151 with N-2,2-bis(trimethylsilyl)ethylidine-tet-butylamine in the presence of zinc bromide (10 mol%), followed by hydrolysis of the intermediate iminodiene using aqueous zinc chloride, provided dienal 152. Although this reaction set the geometry of the α,β-double bond with a high degree of trans-selectivity, the products were still a mixture of isomers at the γ,δ-position. However, the desired (E,E)-isomer was

(i) CrO₃, aq H₂SO₄, 0 °C to rt at 30 torr; (ii) PhSH, Et₂O, reflux; (iii) (TMS)₂CHCH=N-t-Bu, ZnBr₂ (10 mol%), THF, rt, 1 h, then ZnCl₂, H₂O, 1 h.
separable by chromatography and a 55% yield of 152 was obtained after purification.

The synthesis of the cyclization substrate 155 began with condensation of the lithium enolate of ethyl isobutyrate (153) with aldehyde 152 to give β-hydroxyester 154 in 68% yield (Scheme 13). Reduction of crude ester 154 with DIBAL in toluene at -0 °C gave the desired diol 155 in 51% yield after column chromatography. The geometry of the olefins was not established in 155 due to overlapping signals for the vinyl protons in the 1H NMR spectrum, but it was reasonable to assume that the E,E-geometry was retained. We proceeded with the electrophile-initiated cyclization of 155 using the standard conditions. Thus, when exposed to phenylselenenyl chloride at -78 °C, 155 reacted to give several products. After careful purification using column chromatography, compounds 156-159 were isolated in varying degrees of purity. A small amount (ca 5% of total mass of products) of an inseparable mixture of compounds whose 1H NMR spectrum indicated a structural resemblance to 156-158 was also isolated.
Scheme 13. Cyclization of Vinyl Sulfide 155

Although definitive structures could not be assigned to these minor products, it was suspected that they were furan isomers resulting from a 5-exo-cyclization of 155.

The structure and relative stereochemistry of compounds 156-158 was determined primarily by interpretation of their $^1$H NMR spectra. As shown in Figure 6, the splitting pattern for $H'_3$ in 157 was a triplet ($\delta$ 2.75, $J = 11.0$ Hz), which is consistent with its trans-diaxial relationship to $H'_4$ and $H'_2$. The pattern for $H_3$ in the major product (156) was a doublet of doublets ($\delta$ 3.40, $J = 11.0, 2.4$ Hz).
Hz), indicative of its gauche relationship to H₄ and trans relationship to H₂. The assignment was further supported by the differences seen in the coupling patterns of H₄ and H'₄. The latter showed a large coupling to H'₃ (δ 3.09, J = 11.0 Hz) while only a small coupling was seen for H₄ (δ 3.37). The proposed structure of 156 was further supported by ¹³C NMR and mass spectral data. Although the yield of 156 (48%) was acceptable, it should be pointed out that the compound was still contaminated with small amounts of impurities after chromatography. Furthermore, the presence of byproduct 159, possibly arising from O-selenenylation followed by sequential sigmatropic rearrangements and hydrolysis, indicated the significant potential for side reactions of 155.

![Figure 6. Comparison of ¹H NMR Spectra of Isomers 156 and 157](image)

The poor results for the cyclization of 155 were disappointing. Because of the aforementioned and other (vide infra) problems, we abandoned the idea of

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using a vinyl sulfide as the C7 side chain of the B-ring. A publication by Rousseau addressing the mild oxidation of alcohols using hypervalent bromine-collidine complexes, however, provided the impetus for our next series of studies. Rosseau and coworkers noted that attempts to oxidize 4-methoxybenzyl alcohols gave products resulting in the conversion of the benzylic alcohol to the corresponding aldehyde (equation 13).³²

This result suggested a facile conversion of a styryl group to the aldehyde needed for later elaboration. The general strategy we envisioned for a model system to test the feasibility of this idea is shown in equation 14.

The conversion of 90 to 163 would involve halohydrin formation across the double bond, followed by reductive removal of the bromine and selenium atoms. The reader may note that the order of these two operations, could in theory, be
switched. It should be pointed out, however, that compound 90 was previously synthesized by Patterson, and we therefore knew something about this chemistry. For example, we knew that attempts to remove the phenylselenenyl group of 90 via radical reduction led to migration of the \( \beta \)-methoxystyryl group to C3 of the tetrahydropyran (90). This process presumably occurs by cyclization of a C3 radical to a cyclopropyl carbinyl radical, followed by fragmentation of the intermediate radical to give a C2 radical, followed by reduction to give the migration product. Also a factor in this plan, was the potential for removing both the bromine and selenium from the molecule in one step. This would not be possible if the order of operations were switched. Finally, the plan called for the single step conversion of 163 to 164 using the collidine reagent 161.

In preparation for the synthesis of 90, dienal 165 was prepared by a known procedure in a 40% yield from pyridine•sulfur trioxide complex (Scheme 14).\(^{33,34}\) Aldehyde 165 was reacted with the lithium enolate of ethyl isobutyrate (153) at -78 °C, and the resulting \( \beta \)-hydroxy ester was protected \textit{in situ} as a triethylsilyl ether to give 166. Treatment of crude 166 with DIBAL at -78 °C provided diol 167 in 74% yield (from 153) after chromatography. Treatment of a dichloromethane solution of 167 with phenyl selenenyl chloride\(^{35}\) at -78 °C gave the expected pyran 90. It is notable that the silyl group was cleaved during the reaction and the 4-hydroxypyran was obtained as a single diastereomer in 57% yield after purification by column chromatography. Previous experience with this molecule indicated that re-protecting the hindered alcohol would be difficult, so
we proceeded without doing so. Installation of the benzylic alcohol was accomplished by reaction with NBS in an acetone-water mixture to give bromohydrin 168 in 75% yield. Although 168 was probably produced as a mixture of diastereomers, as indicated by the presence of a second product spot by thin-layer chromatography, only the major diastereomer (of unknown configuration) was isolated and characterized at this stage.

\begin{align*}
\text{AcOEt} \quad &\xrightarrow{i} \quad \begin{array}{c}
\text{R} \\
\text{OTES}
\end{array} \\
\text{153} \\
\end{align*}

\begin{align*}
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{90} \\
\end{align*}

\begin{align*}
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{166} \quad &\xrightarrow{\text{R} = \text{CO}_2\text{Et}} \quad \begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{167} \quad &\xrightarrow{\text{R} = \text{CH}_2\text{OH}} \quad \begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{74\% from 153} \\
\end{align*}

\begin{align*}
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{165} \\
\text{CHO} \\
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{166} \\
\end{align*}

\begin{align*}
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{168} \\
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{169} \\
\end{align*}

\begin{align*}
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{170} \\
\begin{array}{c}
PMP \\
\text{Se}
\end{array} \\
\text{169} \\
\end{align*}

(i) LDA, THF, -78 °C; 165, THF; TESCl warm to rt; (ii) DIBAL, toluene, -78 °C; (iii) PhSeCl, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C; (iv) NBS, acetone-H\textsubscript{2}O (2:1); (v) n-Bu\textsubscript{3}SnH, AIBN, benzene, reflux; (vi) 161, CH\textsubscript{2}Cl\textsubscript{2}, rt

Scheme 14. Synthesis of a Model System for Testing 161 as an Oxidant
Diol 168 was then exposed to standard radical reduction conditions using tri-n-butyltin hydride and AIBN in refluxing benzene. This effected reduction of both the bromine atom and the selenide to give 169 in 85% yield. Although we were not sure about the selectivity of the oxidizing agent in the next reaction, we decided to try the cleavage on 169 without attempting to first selectively protect the pyran hydroxyl group. When a solution of the diol in dichloromethane was treated with 1.5 equivalents of bis(sym-collidine)bromine(I) hexafluorophosphate (161) at room temperature, a single product spot appeared immediately by TLC. However, the reaction did not go to completion even after several hours. Concentration of the reaction mixture and chromatography of the residue gave a 52% yield of the desired product 170 along with 30% recovered diol 169. The $^1$H NMR of 170 was consistent with the proposed structure [δ 1.89 (br s, 1H, OH), 9.76 (dd, $J = 2.8, 1.8$ Hz, 1H, CHO)], as were the $^{13}$C NMR, IR, and mass spectral data. Encouraged by these results, we were eager to proceed with the development of an asymmetric route to substrates that could lead to the B-ring of lasonolide A.

Our initial studies involved reactions between 90 and pseudoephedrine amides, as well as Evans' oxazolidiones. The aldol products we prepared by these reactions are shown in Figure 7 (171 and 172). In the case of the pseudoephedrine amides, we found that analysis of product mixtures by $^1$H NMR were complicated by the presence of the signals originating from the chiral
auxiliary (possibly amide geometrical isomers). The bottom line is that we were not able to conveniently determine the stereoselectivity of the reaction.

Figure 7. Pseudoephedrine and Oxazolidinone Products of Aldol Reaction

A switch to Evans' auxiliary solved this analytical problem, and the diastereoselectivity of the reaction was high (95:5 by integrations of the diastereomeric signals in the $^1$H NMR). We found it difficult, however, to achieve selective removal of the auxiliary when such manipulations were required. Although it was not unequivocally confirmed, we suspected that reactions of 172 with nucleophiles occurred at both the endo-cyclic and exo-cyclic carbonyl groups. Eventually, we determined that the thiazolidinethione auxiliary developed by Nagao and coworkers was a viable alternative.39

The chiral auxiliary used in the Nagao protocol was synthesized in 20-gram quantities starting from commercially available D-valine as described in the literature.40 The amino acid was reduced to the amino alcohol via a procedure developed by the Meyers group (NaBH₄, I₂).41 The amino alcohol was then converted to the thiazolidinethione by reaction with carbon disulfide in the

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presence of aqueous potassium hydroxide. Using this method, the thiazolidinethione was prepared in 50% overall yield from the amino acid. Synthesis of the required S,O-imide (173) was achieved in 95% yield by acylation of the auxiliary with propionyl chloride in the presence of pyridine. Condensation of the tin enolate of 173 with dienal 165 proceeded smoothly to give a 79% yield of a mixture of diastereomeric β-hydroxy imides 174 in a 95:5 ratio, based on integration of the 1H NMR signals of the methyl doublets (major: δ 1.15, minor: δ 1.16) (equation 15).

\[
\begin{align*}
&\text{173} & \xrightarrow{(i) \text{Sn(OTf)}_2, \text{ethyl piperidine, CH}_2\text{Cl}_2, -70 ^\circ\text{C}; 165, \text{CH}_2\text{Cl}_2, -70 ^\circ\text{C}} & \text{174} & \xrightarrow{(ii) \text{Me}_2\text{AlN(OCH}_3\text{)(CH}_3\text{), CH}_2\text{Cl}_2, -10 ^\circ\text{C}} & \text{175} \\
\end{align*}
\]

(i) Sn(OTf)$_2$, ethyl piperidine, CH$_2$Cl$_2$, -70 °C; 165, CH$_2$Cl$_2$, -70 °C (ii) Me$_2$AlN(OCH$_3$)(CH$_3$), CH$_2$Cl$_2$, -10 °C.

The S,O-imide 174 was converted to Weinreb amide 175 by the dropwise addition of a solution of 174 in dichloromethane to a -10 °C solution of 3 equivalents of the corresponding aluminum amide derived from N,O-dimethylhydroxylamine and Me$_2$Al. The reaction was allowed to stir for 3 h at -5 °C and was then subjected to aqueous acidic workup. Chromatographic purification of the products gave greater than 90% yields of the Weinreb amide 175 and 80% yields of the recovered chiral auxiliary.
With two of the three required stereogenic centers set in the aldol reaction, we next concerned ourselves with installation of the third stereogenic center. Our specific target was diol 179, with both a hydroxyl group and a benzyloxymethyl group at the stereogenic center at C2. To arrive at 179 from the hydroxamic acid derivative 175, we considered two options (Scheme 15). In one option (path A), reduction of 175 to aldehyde 177 would allow for the C2 stereochemistry to be set by addition of a carbon nucleophile. The other option (path B) called for reaction of 175 with a nucleophile to give a ketone (178), followed by a stereoselective reduction to set the stereochemistry at C2.

Scheme 15. Two Options for Establishing the C2 Stereocenter

It is notable that the facial approach of the nucleophile to the carbonyl of 177 and 178 would have to be different in order to arrive at the proper configuration at C2. A brief analysis is depicted below. Figure 8 shows the analysis of 180, (a mimic
for 177 or 178) according to the Felkin-Ahn model. One would expect 180 to react from conformation of 180b (R vs. H) which should be lower in energy than 180a (R vs. Me). Reaction from conformation 180b also involves attack of a nucleophile from the face of the carbonyl that minimizes steric effects [attack from the side of the smallest substituent (H)].

![Figure 8. Conformational Analysis for 180 Using the Felkin-Ahn Model](image)

Figure 8 shows the analysis according to the chelation model. One can see that coordination of the hydroxyl and carbonyl groups to a Lewis acid gives conformation 180c. In this case the nucleophile will still approach from the least hindered face of the carbonyl group, however, this will be opposite to that seen in the Felkin-Ahn model. The bottom line is that if 177 was an intermediate en route from 175 to 179 (Scheme 15), Felkin-Ahn addition would be required. If 178 was the chosen intermediate, a chelation-controlled addition would be needed.

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Figure 9. Conformational Analysis for 180 Using chelation Model

We decided to first explore the addition of carbon nucleophiles to an aldehyde of type 177. The alcohol of Weinreb amide 175 was protected as TBS-ether 184 in 94% yield using TBSCI and imidazole in dry DMF. Reduction of 184 with DIBAL in THF at -10 °C gave aldehyde 185 in 80% yield (Scheme 16). We hoped to directly install the benzyloxyethylmethyl group with benzyloxethylmethyl lithium to be generated from stannane 182. Stannane 182 is a known compound, and was synthesized in 63% yield using a literature procedure that called for reacting tri-n-butyltin hydride with LDA, followed by quenching with chloromethylbenzyl ether. Transmetalation of 182 (0.9 equivalents) with n-butyllithium at -78 °C in THF, followed by addition of the resulting anion to a solution of aldehyde 185 (1.0 equivalent) gave primarily recovered 185 (60%), along with approximately 10% of 186, the product resulting from β-elimination of the silyl ether [185: δ 1.78 (s, 3H, Me), 3.72 (s, 3H, OCH₃), 6.60-7.31 (two m's, 9H, vinyl and ArH's), 9.35 (s, 1H, CHO)]. Also detected by ¹H NMR were trace amounts of aldehyde 165, indicating that some material had undergone a retro-aldol reaction. The reaction was repeated in the presence of CeCl₃ with no improvement of the results.
Scheme 16. Attempt at Nucleophile Addition to Aldehyde 185

As an alternative nucleophile, we reacted propynylmagnesium bromide with aldehyde 185 in THF at -78 °C and obtained a 42% yield of a 2:1 mixture of diastereomeric alcohols (equation 16).
The ratio of diastereomers was determined by integration of the C₃ methyl doublets. It was not possible, however, to determine the configuration of the major diastereomer from the coupling constants of the spectrum. An attempt was made to elaborate 187 further by reducing the triple bond of the propargylic alcohol to the corresponding vinyl iodide using LiAlH₄ and sodium methoxide followed by the addition of iodine, but this led only to unidentifiable products. The difficulty in adding organolithium reagents to aldehyde 185, coupled with the low selectivity in the addition of the Grignard reagent, led us to pursue our other option (path B in Scheme 15).

Thus, Weinreb amide 184 was treated at -78 °C in THF with the benzyloxymethylthallium (183), generated by the addition of 1.1 equivalents of tert-butyllithium to an equal amount of the stannane 182 (Scheme 17). The expected ketone 188 was obtained in 45% yield along with an 18% yield of recovered starting material. The absence of signals from isomeric compounds in the ¹H NMR of 188 indicated that there were no contaminating products resulting from the epimerization at C₂.
Scheme 17. Conversion of Weinreb Amide 189 to Ketone 190

Compounds 189 and 190 were two interesting byproducts of this reaction. The structures of 189 and 190 were based on analysis of their $^1$H NMR spectra. For example, 189 has signals corresponding to the N-methylamido group [δ 2.78 (d, $J = 4.7$ Hz, 3H, NCH$_3$), 6.18-6.23 (m, 1H, O=CNH)], and 190 has signals consistent with the presence of an α-(N-methoxy)amino ketone [see Figure 10: δ 3.30 (s, 3H, NOCH$_3$), 4.54 (dd, $J = 10.4$, 6.4 Hz, 1H, CH$_2$NH), 4.61 (dd, $J = 10.2$, 7.2 Hz, 1H, CH$_2$NH), 7.01 (t, $J = 7.2$ Hz, 1H, NH)].

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From a mechanistic standpoint, one can envision the formation of 190 via the mechanism shown in Figure 11. Thus, deprotonation of the methyl group on nitrogen in 184 could give an anion which would attack the adjacent carbonyl giving the alkoxyaziridine structure 191. Subsequent breakdown of the tetrahedral intermediate with expulsion of the nitrogen anion, followed by quenching with a proton source, would give 190.
Similarly, one can rationalize the formation of 189 as well as shown in Figure 12. Deprotonation of the \( \text{N-methoxymethyl} \) group, followed by a \( \beta \)-elimination to give formaldehyde and a resonance stabilized amide anion would lead to 193. Protonation of 193 would afford 189.

![Figure 11. A Possible Mechanism for the Formation of 190](image1)

![Figure 12. A Possible Mechanism for the Formation of 189](image2)
Although the yield of 188 was not as high as we would have liked (48%), we proceeded with attempts to reduce the ketone to give the alcohol with the necessary stereochemistry. As the analyses in Figures 8 and 9 show, this required a chelation-controlled reduction, which in turn required deprotection of the TBS-ether of 188. Unfortunately, all attempts to remove the protecting group led to either no reaction or to products resulting from the β-elimination of the silyl ether to give the highly conjugated triene 194 (equation 17).

It was imagined that a more labile silyl group would solve this problem. Thus, Weinreb amide 175 was protected as a TES-ether. The protection proceeded in 94% yield to give 195 when alcohol 175 was treated with TESCl and imidazole in dry DMF. Treatment of 195 with benzylxymethyllithium (183), gave once again a low yield of the ketone (42%), along with recovered starting material (28%) and the TES analogs of the two byproducts 189 and 190 (not quantified in this experiment). Due to the consistent recovery of starting material from these reactions, experiments were done to see if the reaction could be modified to achieve higher conversion to products.
Initially it was believed that unreacted \textit{tert}-butyllithium might be responsible for the rearrangement byproducts. However, these compounds were still identified by TLC when \textit{n}-butyllithium was used as the transmetalating agent. In fact, with \textit{n}-butyllithium as the base we also isolated approximately 11\% of the ketone 197 arising from the addition of \textit{n}-butyllithium to 195 (equation 18).

\begin{equation}
\begin{array}{c}
\text{PMP} \quad \text{OCH}_3 \\
\text{Me} \quad \text{Me} \quad \text{Me}
\end{array}
\begin{array}{c}
in 1.1 \text{ equiv. 182} \\
1.1 \text{ equiv. } \text{n-BuLi}
\end{array}
\begin{array}{c}
\text{THF, -78 °C}
\end{array}
\begin{array}{c}
\text{OTES} \quad \text{OTES} \quad \text{OTES}
\end{array}
\begin{array}{c}
\text{195} \\
\rightarrow
\text{196: 42\%} \\
\text{197: 11\%}
\end{array}
\end{equation}

To minimize this competing reaction, the stoichiometry was modified such that organostannane 182 was used in excess (2 equivalents) relative to the \textit{n}-butyllithium (1.5 equivalents), which in turn was used in excess to the amide 195 (1 equivalent). Despite this modification, the reaction still proceeded with only partial consumption of the starting material. A detailed account of all reaction products formed showed that there was good correlation between the number of millimoles of stannane 182 going into the reaction and the quantity of the \textit{tetrabutyltin} produced during the transmetalation step. That is to say, that recovered 182 and \textit{tetrabutyltin} accounted for 90\% of the starting 182. There was also reasonable mass balance between the amide starting material (195) and the ketone being produced (88\%). The only species not accounted for was the
intermediate benzyloxymethyl lithium (183), which should have been present as the corresponding benzyloxymethylmethyl ether after quenching the reaction. All attempts to detect this "missing" reagent gave no resolution to this problem.

Ultimately, we decided to maximize the yield of ketone 196 to the best of our ability, and proceed with the synthesis. It was found that the highest yield of 196 was obtained when the reaction was run using 5 equivalents of 182, 3 equivalents of n-butyllithium, and 1 equivalent of 195. In this way, excess 182 was recovered, and the ketone was produced in yields ranging from 55-65%.

We next turned to the deprotection of TES ether 196. This was accomplished by addition of 1 equivalent of trifluoroacetic acid to a room temperature solution of 196 in THF and water (5:1) (Scheme 18). After addition of 1 equivalent of solid sodium bicarbonate and a thorough aqueous work up, the crude hydroxy ketone 198 was isolated. This compound was extremely sensitive to both acid and base. Elimination to the undesired triene 194 and retro-aldol reaction were constant problems. To minimize these problems, it became standard procedure to immediately carry out the necessary chelation-controlled reduction of crude 198 at -78 °C in toluene by addition of ethereal zinc borohydride.
Using this protocol, the desired diol 179 could be obtained as a diastereomeric mixture (ca 4:1), as determined by integration of the signals for the C3 methyl groups (minor isomer δ 0.87, major isomer δ 0.93). It should be noted, however, that isomer not seen. 

Scheme 18. Synthesis of Acetate-Protected B-Ring Pyran
that on larger scale reactions (> 500 mg), 179 was often contaminated with triene 194, which was not readily separable by either chromatography or crystallization. Nonetheless, diol 179 did cyclize using the standard protocol employing phenylselenenyl chloride to give pyran 199 in acceptable yields (55-65%). It is interesting to note that throughout this work, epimers of 199 expected to result from the cyclization of the minor diastereomer of 179 were not detected. Of course, this is not to imply that they were not formed, as indeed they should have been. Perhaps, however, their relatively low concentration in the product mixture coupled with the possibility for significantly different mobility on silica gel compared to 199, made the detection of stereoisomers difficult. The structure of 199 was assigned using the same analysis of 1H NMR spectra described earlier in the thesis for related pyrans (e.g. 135, Table 2). We next moved to the tasks of removing the C5 phenylselenenyl group and modifying the C6 sidechain. This called for initial protection of the C4 alcohol. We decided to utilize a silyl group for this purpose. Thus, 199 was reacted with 1.1 equivalents of TBSCI and imidazole in dry DMF. The reaction did not proceed, however, even when two equivalents of the silyl chloride was used. We felt it was likely that the steric environment of the axial hydroxyl group was too crowded to accommodate the bulky silyl ether, and thus, decided to move to an acetate protecting group. Treatment of 199 with excess acetic anhydride (30 equivalents) and stoichiometric pyridine at room temperature gave an 86% yield of acetate 200 after purification by chromatography.
Acetate 200 was then reacted with NBS in a solution of acetone and water (2:1) at 0 °C to provide and this provided a 69% yield of a 63:37 mixture of diastereomeric bromohydrins 201 that were separable by chromatography. The stereochemical identity of the isomers was not discernable from their respective \(^1\)H NMR spectra, and it was decided to take these compounds independently through the following chemistry. We hoped this would have the effect of confirming the regiochemistry of the addition for each isomer, as well as offering the opportunity to determine stereochemistry along the way. Pursuant to this plan, both compounds were separately added to a solution of tri-\(n\)-butyltin hydride in benzene at room temperature, followed by the addition of 1 equivalent of a 1 M solution of triethylborane in hexanes. This accomplished reductive removal of the bromine and selenium heteroatoms within 30 min at room temperature. The crude products resulting from concentration of the reaction mixture were chromatographed to give 85% and 74% yields of 202 (from 201-major) and 203 (from 201-minor) respectively. The \(^1\)H NMR spectra of these compounds were simplified relative to those of 201, and we were able to propose stereochemistry for each based on the coupling patterns observed for the benzylic hydrogens. For example, \(H_b\) in 202 appeared at \(\delta 5.04\) as a broad doublet \((J = 7.5 \text{ Hz})\). On the other hand, \(H_b\) in 203 appeared at \(\delta 4.95\) as a doublet of doublets \((J = 9.6, 3.1 \text{ Hz})\). These vicinal coupling patterns are consistent with the H-bonded structures shown for 202 and 203 in Figure 13.
Figure 13. Comparison of $^1$H NMR Spectra of Isomers 202 and 203

A series of nOe experiments provided further support of the structure assignments, and the data is shown in Figures 14 and 15. The data for 202 (Figure 14) indicate an enhancement of the $H_2$ signal (4.8%) upon irradiation of the proton labeled $H_6$ (see structure A). This supports our proposal that $C_2$ and $C_6$ pyran substituents have a cis relationship. The proposed stereochemistry around the pyran ring was further supported by a 3.3 % enhancement of $H_3$ upon irradiation of $H_2$ (see structure B). This would only be expected if these hydrogens were located on the same face of the ring. Finally, irradiation of $H_4$ gave 2.7% and 2.4% enhancements at $H_3$ and the methyl group, respectively (see structure D).
Figure 14. Difference nOe Study: Major Isomer 202

This supports the proposed gauche relationship of H₄ to these groups. One would not expect to see an enhancement at both H₃ and the methyl if H₄ were axially disposed.

The issue of stereochemistry at C₈ (benzylic alcohol stereochemistry) is nicely addressed by comparing the data shown in figures 14 and 15. For example, irradiation of H₅ in 202 gave only a small enhancement at H₆ (0.77%) (structure A in figure 14). However, irradiation of H₅ in 203 shows a much larger
enhancement at H₈ (2.7%) (structure A in figure 15), consistent with our proposal for an intramolecular hydrogen bond.

![Diagram](image)

**Figure 15. A nOe Study of Minor Isomer 203.**

The isomeric relationship of alcohols 202 and 203 was confirmed when they were independently subjected to oxidation with collidine reagent 161. Both were indeed converted to aldehyde 204, as was confirmed by comprehensive NMR, IR and mass spectral data for each product. The yields in both cases were disappointing however (37% and 42% for 202 and 203, respectively). We had noted that protection of the C₄ hydroxyl would help to increase the efficiency of the collidine reaction, but this did not turn out to be the case.

It was at this stage in my research, that Lee's synthesis of lasonolide A was published. To bring our studies to a conclusion, we felt it was good idea to convert one of our intermediates into one of Lee's intermediates. Thus, we
decided to intersect Lee's synthesis at the point of compound 211 (Scheme 19),
the enantiomer of the radical cyclization product in Lee's synthesis (see structure
22 in Scheme 3).

![Chemical structures and reactions](image)

(i) 1.1 equiv. PhSeCl, CH₂Cl₂, -78 °C; (ii) BnBr, 50% (w/w) NaOH, 10 mol% 
Bu₄Ni, benzene, 60 °C, sonicate; (iii) NBS, acetone-H₂O (2:1), 0 °C to rt; (iv) 
5 equiv. Bu₃SnH, 1 equiv. Et₃B, benzene, rt; (v) 161, CH₂Cl₂, rt; (vi) 
NaHSO₃, EtOH, rt; Ac₂O, DMSO; NaOEt, EtOH.

Scheme 19. Synthesis of a Pyran to Correlate With the Lee Synthesis

The synthesis of 211 is shown in Scheme 19. We had already synthesized
acetate-protected aldehyde 204 (Scheme 18). The new target for synthesis
(211) required installation of a benzyl protecting group on the C₄ hydroxyl instead
of acetate, and conversion of the aldehyde to an ethyl ester. We started by

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reexamining the electrophile-initiated cyclization of 179. This provided 199 in 66% yield along with previously unseen bis-selenide 206 in 26% yield. We will return to this new product later. We next turned to the task of converting 199 to benzyl ether 207. Two of the more standard methods for benzylating sterically hindered alcohols, namely: (1) the use of sodium hydride and tetrabutylammonium iodide in DMF followed by benzyl bromide, and (2) benzyl 2,2,2-trichloroacetimidate and catalytic triflic acid in dichloromethane, failed to give good yields of product (vide infra). It was ultimately found that the hydroxyl group of 199 could be benzylated by treatment with three equivalents of benzyl bromide and catalytic tetrabutylammonium iodide in 50% (w/w) aqueous sodium hydroxide, followed by sonication at 60 °C. This procedure gave a 64% yield of the desired benzyl ether 207 after purification by chromatography over silica gel. The alkene of 207 was reacted with NBS provide the expected mixture of diastereomeric products 208. Without purification, the mixture of bromohydrins was subjected to reduction using the tri-n-butyltin hydride-triethylborane system. This gave a 78% yield (for two steps) of benzylic alcohols 209 after column chromatography. Oxidation of 209 with the collidine reagent 161 gave a disappointing 23% yield of aldehyde 210. Attempts to recover starting material provided compounds unrecognizable by their 'H NMR spectrum. With a small amount (10 mg) of the aldehyde 210 in hand, it was decided to proceed with the conversion to the ethyl ester using a procedure developed by Wuts and coworkers. This process called for conversion of the aldehyde to its bisulfite
derivative, followed by oxidation and solvolysis using sodium ethoxide. Thus a solution of the aldehyde 210 in absolute ethanol was treated with solid sodium bisulfite at room temperature. The crude bisulfite adduct was then treated with a mixture of DMSO and acetic anhydride to achieve oxidation of the adduct. Addition of a solution of sodium ethoxide in absolute ethanol gave the ethyl ester 211 in an undetermined yield after purification by chromatography. Enough of the ester 211 was obtained to achieve characterization by NMR (\(^1\)H and \(^{13}\)C) and mass spectral analysis. We are currently awaiting spectral data requested for the purpose of comparison. Nonetheless, we are quite certain of our structure assignment. This research therefore constitutes the synthesis of a pyran ring known to be a progenitor of the B-ring of lasonolide A.

I will now return to the formation of \(\text{bis-selenide 206}\) in the cyclization of 179 shown in Scheme 19. When the scale of the cyclization reactions was increased to 500 mg or more, this compound, in addition to 199, was isolated in 15-25% yield as a single diastereomer. Compound 206 is presumably formed by a second addition of phenylselenide to the remaining double bond of 199. It is possible that the hydroxyl group arises from hydrolysis of a benzylic bromide during workup, as opposed to trapping with adventitious water in the reaction mixture. In an attempt to further elaborate diol 206 it was reduced using the tri-\(n\)-butyltin hydride-\(\text{Et}_3B\) system, and diol 212 was obtained in 89% yield (Scheme 20).

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Scheme 20. Elaboration of Diol 206

The product diol is a crystalline solid and provided us with material suitable for crystallographic analysis. An ORTEP of 212 is seen in Figure 16. This provides unequivocal support for our assignments of structure and stereochemistry of pyran products of this type.
This material could be potentially useful if one were to develop a method for the differentiation of the two alcohols. The only work we did in this area involved an attempt to subject 212 to collidine oxidation and trap the crude aldehyde as acetal 213. Although some of the desired product was obtained (36%), the crude product mixture was complex and no further attempt was made in this area. Finally, acetal 213 was protected at the benzyl ether 214 in 22% yield by reaction of the corresponding sodium alkoxide with benzyl bromide in the presence of tetrabutyl ammonium iodide. The poor yield of this reaction was eluded to above,
and provided the impetus for the use of the phase-transfer method shown in Scheme 19 (199→207).

The exercise of synthesizing ester 211 in such a poor overall yield clearly implicates the oxidation of benzylic alcohol 209 using the collidine reagent 161 as a weakness in our synthesis. An alternative method for arriving at ester 211 from alcohol 209 is shown in equation 19.

Oxidation of 209 with the Dess-Martin periodinane provided ketone 215 in 89% crude yield. We imagine that 215 will be an excellent substrate for Bayer-Villager oxidation. Given the high migratory aptitude of aryl groups relative to primary allyl groups in such reactions, we imagine that it will be possible to convert 215 to 216. Transesterification would then produce the ethyl ester 211 if so desired. This work is being done concurrent to the preparation of this dissertation, and it is hoped that it will be completed in time for incorporation in the final draft.
This dissertation has outlined in detail two different routes for the synthesis of tetrahydropyran precursors of the B-ring of lasonolide A. The first method relied upon established crotylation methodologies to set the crucial first two stereogenic centers. Further elaboration using the internal stereochemistry established the third stereocenter in the cyclization precursors. This initial strategy used a Wittig reaction to achieve the synthesis of a variety of analogous cyclization precursors, which in turn were used to validate our method for the diastereoselective formation of highly substituted tetrahydropyrans. However, limitations the crotylation methodology, and the failure of key phosphonium salts to participate in the Wittig reaction led us to develop another route to cyclization precursors.

In the second route, an asymmetric aldol reaction was used to introduce chirality and set two stereogenic centers. Installation of the third stereocenter via a chelation controlled reduction developed into a problem that we never were able to resolve with any satisfaction. Although this strategy allowed us to probe a potentially valuable cyclization substrate not available from the first route (vinyl sulfide 155) the cyclization turned out to lack the efficiency we required. This result left us to work primarily with cyclization precursors that could be (and in
fact were) synthesized via either route. With the noted limitations of each route, the former route appears to be the one of choice due to the inherent lability of the advanced intermediate β-hydroxy ketone 198 in the latter route. Regardless of the method used to arrive at cyclization precursors, another problem with our strategy has been the development of an efficient way to elaborate the pyran ring once formed. We had hoped to optimize the use of the hypervalent bromine oxidant 161 to achieve rapid access to the aldehyde oxidation state at C5 (see structure 106 in Scheme 10). However, it now seems that the route outlined at the end of chapter 3 will lead to a more efficient conversion to the desired compounds. Finally, to place the current work in perspective, the synthesis of aldehyde 204 requires 11 steps from aldehyde 165 and thiazolidinethione 173 (2.3% overall yield), as does the synthesis of ketone 215 (5.7% overall yield).
EXPERIMENTS

I. GENERAL EXPERIMENTAL

All melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected as are all boiling points. $^1$H NMR spectra are reported as follows: chemical shifts [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, o = octet), coupling constants in hertz, integration, interpretation]. $^{13}$C NMR data were obtained with Bruker DPX-250, DPX-400, or DRX-500 spectrometers. Infrared spectra were taken with Perkin-Elmer 457 instrument. Mass spectra were obtained in one of the following ways: Electrospray ionization (ESI) mass spectrometry analyses were performed with a 3-Tesla Finnigan-2000 Fourier Transform mass spectrometer. Samples were sprayed from a commercial Analytica electrospray ionization source, and then focused into the FTMS cell using a home-built set of ion optics. For ESI analysis, most compounds were sprayed from a micromolar concentration of the analyte in various solvents mixtures, such as THF/MeOH, with added NaCl. This process generated the sodiated molecular ion (usually as the singly-charged species), denoted as (M+Na)$^+$. But in some cases, acetic acid or trifluoroacetic acid was used to generate the protonated molecular ion (M+H)$^+$ instead.

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Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, diethyl ether, benzene, and toluene were distilled from sodium metal; dichloromethane and ethyl acetate were distilled from calcium hydride. Reactions requiring an inert atmosphere were run under nitrogen. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Standard column chromatography was performed using EM-Science 70-230 mesh silica gel unless otherwise noted.
II. EXPERIMENTAL PROCEDURES

![Chemical Structure](image)

(Z)-1,4-Dibenzylxyloxy-2-butene (110). To a 0°C suspension of 7.8 g (295 mmol) of oil free sodium hydride [11.8 g of a 60% dispersion in mineral oil, washed 3 times with 20 mL of pentane] in 245 mL of dry DMF, was added 12.7 g (144 mmol) of neat 2-butene-1,4-diol in a dropwise manner, at a rate such that the internal temperature remained below 5 °C. Once the addition was complete, 0.5 g (1.5 mmol) of tetra-n-butylammonium iodide was added, followed by dropwise addition of 50.1 g (292.9 mmol) of neat benzyl bromide, keeping the internal temperature below 40 °C. The reaction mixture was stirred at room temperature for 17 h, quenched with the careful addition of 200 mL ice water, and extracted with three 500-mL portions of diethyl ether-hexanes (1:1). The combined extracts were dried (MgSO₄) and concentrated in vacuo. The resulting oil was distilled to give 28.5 g (73%) of olefin 110 as a colorless oil: bp 140-145 °C at 0.2 mm Hg (lit. 170-195 °C/3.6 torr); ¹H NMR (CDCl₃, 250 MHz) δ 3.97 (d, J = 4 Hz, 4H, =CH₂O⁻), 4.4 (s, 4H, OCH₂Ph), 5.71 (t, J = 4 Hz, 2H, =CH), 7.24
(br s, 10H, ArH); $^{13}$C NMR (CDCl$_3$, 62.9 MHz) $\delta$ 66.2 (t), 72.7 (t), 128.1 (d), 128.2 (d), 128.9 (d), 130.0 (d), 138.5 (s).

BnO$\text{CHO}$

2-Benzylxoyacetaldehyde (111). A 1000 mL 3-neck flask equipped with magnetic stir bar, gas inlet adapter, and a gas outlet adapter leading to a solution of saturated aqueous potassium iodide, was charged with 15.0 g (56.0 mmol) of 110 and 500 mL of dry dichloromethane. The solution was cooled in a dry-ice/acetone bath for 20 min under an atmosphere of O$_2$, and ozone was bubbled through the reaction mixture until a pale blue color was seen (approximately 50 min). The reaction mixture was purged of excess ozone by bubbling argon through the solution, and 34 mL (463 mmol) of dimethyl sulfide was added dropwise via addition funnel over 15 min. The solution was stirred at the cold bath temperature for 1.5 h, the cold bath was removed, and stirring continued for an additional 14 h at ambient temperature. The reaction mixture was washed with two 200-mL portions of saturated aqueous NaHCO$_3$, and 100 mL of brine solution. The organic phase was dried (MgSO$_4$) and concentrated to give an oil.
that was chromatographed over 185 g of silica gel (eluted with ethyl acetate-hexane, 1:4) to give 7.1 g (42%) of aldehyde 111 as a pale yellow oil: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 4.10 (s, 2H), 4.63 (s, 2H), 7.34-7.38 (br s, 5H, ArH), 9.71 (s, 1H, CHO).

![Diagram of compound 112]

(R,R)-Diisopropyl-(Z)-crotylboronate (112). A dry 1000 mL 3-neck flask fitted with internal thermometer, magnetic stir bar, under an argon atmosphere was charged with 30.8 g (274.2 mmol) of potassium tert-butoxide (previously dried at 75 °C/0.5 mm Hg for 18 h) and 227 mL of dry THF. The suspension was cooled to $-75$ °C (acetone/CO$_2$) and 27 mL (288.9 mmol) of condensed cis-2-butene was added via cannula, followed by the dropwise addition of 110 mL (275 mmol) of a 2.5 M solution of n-butyllithium in hexanes, at such a rate that the internal temperature remained below $-65$ °C (approximately 2 h). The reaction mixture was warmed to $-25$ °C (ethylene glycol/CO$_2$) for 40 min, cooled back to $-78$ °C, and 63 mL (273.0 mmol) of triisopropyl borate was added via cannula, keeping the internal temperature below $-65$ °C. The reaction mixture was stirred for 10 min and poured into a separatory funnel containing 519 mL of 1N HCl saturated with NaCl. After mixing, the layers were partitioned and
The pH of the aqueous layer was adjusted to approximately 1 with the addition of 115 mL of 1.2 M HCl. The phases were recombined, a solution of 58 mL (275.8 mmol) of diisopropyl tartarate in 97 mL of ether was added, and the contents of the separatory funnel were mixed for five min. The layers were partitioned and the aqueous phase was extracted with four 130-mL portions of ether. The combined organic phases were stirred in the presence of MgSO₄ for 2.5 h, filtered, concentrated, and vigorously stirred under vacuum (0.5 mm/ambient temperature) for 24 h. This gave 78.2 g (96%) of crotylboronate 112, which was dissolved in 262 mL of dry toluene to give an approximately 1M solution: 

\[ \text{PhCH}_2 \text{O} \begin{array}{c} \text{OH} \\ \end{array} \begin{array}{c} \text{CH}_3 \\ \end{array} \]

\[ \text{113} \]

\( (2S, 3R)-3\text{-Methyl-1-phenylmethoxy-4-penten-2-ol (113)} \). A 1000 mL 3-neck flask equipped with magnetic stir bar, gas inlet adapter, and a gas outlet adapter leading to a solution of saturated aqueous potassium iodide, was charged with 21.4 g (79.7 mmol) of 110 and 200 mL of dry dichloromethane. The solution was cooled in a dry-ice/acetone bath for 15 min under an atmosphere of \( \text{O}_2 \) and ozone was bubbled through the reaction mixture until a pale blue color was seen (approximately 80 min). The reaction mixture was purged of excess
ozone by bubbling argon through the solution, and 45 mL (612.7 mmol) of
dimethyl sulfide was added dropwise via addition funnel over 20 min. The
solution was stirred at the cold bath temperature for 1.5 h, the cold bath was
removed, and stirring continued for an additional 18 h at ambient temperature.
The reaction mixture was washed with two 100-mL portions of saturated aqueous
NaHCO₃, and two 100-mL portions of water. The organic phase was dried
(MgSO₄) for two hours and diluted with 150 mL of dry toluene. The resulting
solution was concentrated in vacuo to a volume of approximately 150 mL
(keeping the bath temperature below 30 °C), and the dilution-concentration
process was repeated twice more to achieve a solution of the crude aldehyde
111 in approximately 150 mL of dry toluene. A separate dry 1000 mL 3-neck
flask equipped with a magnetic stir bar, rubber septum, and addition funnel was
charged with 214 mL (approximately 214 mmol) of stock solution of crotyl
boronate (112), and this was diluted with 460 mL of dry toluene and cooled to
-78 °C. The addition funnel was charged with the solution containing the
aldehyde, and this was added to the reaction mixture dropwise over 20 min. The
reaction mixture was stirred at -78 °C for 3.5 h and quenched with the addition of
147 mL of 2N NaOH. The resulting slurry was warmed to 0 °C, stirred for 40 min,
filtered through a bed of celite, and the filter cake was rinsed with three 40-mL
portions of ether. The filtrate was partitioned, and the aqueous layer was
extracted with three 200-mL portions of ether. The combined organic extracts
were dried (K₂CO₃) and concentrated in vacuo, and the resulting oil was
chromatographed over 400 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 15.0 g (46%) of alcohol 113 as a colorless oil: $[\alpha]^20_\text{D} +14.2, \text{c} 1.0, \text{CH}_2\text{Cl}_2$ (lit.$^{49} [\alpha]^20_\text{D} +21.6, \text{c} 0.7, \text{CHCl}_3$); $^1\text{H NMR} \ (\text{CDCl}_3, \ 400 \text{ MHz}) \ \delta \ 1.09 \ (\text{d}, J = 6.7 \text{ Hz}, 3\text{H}, \text{CH}_3), \ 2.25-2.53 \ (\text{br m}, 2\text{H}, \text{CHCH}_3 \text{ and OH}), \ 3.39 \ (\text{dd}, J = 9.5, 7.6 \text{ Hz}, 1\text{H}, \text{CH}_2\text{OBn}), \ 3.56 \ (\text{dd}, J = 9.5, 3.1 \text{ Hz}, 1\text{H}, \text{CH}_2\text{OBn}), \ 3.61-3.70 \ (\text{m}, 1\text{H}, \text{CHOH}), \ 4.54 \ (\text{s}, 2\text{H}, \text{OCH}_3\text{Ph}), \ 5.00-5.09 \ (\text{m}, 2\text{H}, =\text{CH}_2), \ 5.75 \ (\text{ddd}, J = 17.4, 13.8, 7.8 \text{ Hz}, 1\text{H} =\text{CH}), \ 7.25-7.39 \ (\text{br m}, 5\text{H}, \text{ArH}); \ ^{13}\text{C NMR} \ (\text{CDCl}_3, \ 100.6 \text{ MHz}) \ \delta \ 16.1 \ (\text{q}), \ 41.5 \ (\text{d}), \ 73.2 \ (\text{t}), \ 73.8 \ (\text{t}), \ 73.9 \ (\text{d}), \ 115.5 \ (\text{t}), \ 128.1 \ (\text{d}), \ 128.2 \ (\text{d}), \ 128.9 \ (\text{d}), \ 138.4 \ (\text{s}), \ 140.8 \ (\text{d})

![OTBS PhCH2<CH3 114](image)

(3R,4S)-4-[[[1,1-Dimethylethyl)dimethylsilyloxy]-3-methyl-5-phenylmethoxy-1-pentene (114).$^{49}$ To a solution of 14.2 g (68.8 mmol) of alcohol 113 in 250 mL of DMF (from a freshly opened bottle) under argon at room temperature, was added 7.1 g (104.0 mmol) of imidazole, 843 mg (6.9 mmol) of DMAP, and 12.8 g (85.2 mmol) of TBSCI. The reaction mixture was stirred at room temperature for 16 h, diluted with 200 mL of water, and extracted with three 400-mL portions of ether-hexanes (1:1). The combined extracts were washed with three 100-mL portions of 1N HCl, 100 mL of brine solution, and dried (MgSO$_4$). Concentration in vacuo produced an oil that was
chromatographed over 600 g of silica gel (eluted with ethyl acetate-hexanes, 1:6) to give 22.0 g (98%) of silyl ether 114 as a colorless oil: \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) -0.02-0.02 (m, 6H, Si(CH\textsubscript{3})\textsubscript{2}), 0.85 (br s, 9H, SiC(CH\textsubscript{3})\textsubscript{3}), 0.96 (d, \( J = 6.9 \) Hz, 3H, CH\textsubscript{3}), 2.37 (dq, \( J = 12.4, 6.6 \) Hz, 1H, CH(CH\textsubscript{3})), 3.33 (dd, \( J = 9.7, 5.9 \) Hz, 1H, CH\textsubscript{2}OBn), 3.42 (dd, \( J = 9.7, 4.9 \) Hz, 1H, CH\textsubscript{2}OBn), 3.70 (dt, \( J = 5.6, 5.0 \) Hz, 1H, CH\textsubscript{2}OTBS), 4.46 (dd, \( J = 15.9, 12.1 \) Hz, 2H, OCH\textsubscript{2}Ph), 4.93-5.00 (m, 2H, =CH\textsubscript{2}), 5.79 (ddd, \( J = 17.3, 10.4, 7.4 \) Hz, 1H, =CH), 7.22-7.30 (m, 5H, ArH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100.6 MHz) \( \delta \) -4.3 (q), -3.8 (q), 14.7 (q), 18.6 (q), 26.3 (d), 41.6 (d), 73.6 (t), 73.7 (t), 75.3 (d), 114.4 (t), 127.9 (d), 128.0 (d), 128.7 (d), 138.9 (s), 142.1 (d).

\[
\text{OTBS}
\]
\[
\begin{array}{c}
\text{PhCH}_2\text{O} \\
\text{CH}_3 \\
\text{OH}
\end{array}
\]

\textbf{115}

\textbf{(3R,4S)-5-Benzylxy-4-(tert-butylidemethylsilanyloxy)-3-methylpentan-1-ol (115)}. To a 0 °C solution of 4.0 g (12.6 mmol) of 114 in 15 mL of dry THF, under an argon atmosphere, was added 37.8 mL (37.8 mmol) of a 1 M solution of BH\textsubscript{3} in THF, dropwise via cannula over 40 min. The reaction mixture was stirred for 2 h at 0 °C, warmed to ambient temperature for 2 h, and the solvent was removed in vacuo. The colorless oil was cooled to in an ice-water bath for 15 min, and 30 mL of absolute ethanol was added via addition funnel, followed by 15 mL of 2 N NaOH and 6 mL of 30% H\textsubscript{2}O\textsubscript{2}. The suspension was

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stirred for 30 min at 0 °C and 1 h at reflux. After cooling, the reaction mixture was reduced in vacuo to an approximate volume of 25 mL, and 25 mL of brine was added. The suspension was stirred at ambient temperature overnight, and was extracted with three 200-mL portions of ether. The combined ether layers were washed with 25 mL of water, 25 mL of brine, dried (MgSO₄), and concentrated in vacuo. The resulting residue was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 2.9 g (68%) of alcohol 115 as a pale yellow oil: IR (neat) 3362 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.55 (s, 3H, SiCH₃), 0.65 (s, 3H, SiCH₃), 0.88-0.90 (m, 12H, CH₃ and SiCH(CH₃)₂), 1.40-1.48 (m, 1H, RCH₂CH₂OH), 1.60-1.70 (m, 1H, RCH₂CH₂OH), 1.83 (ddq, J = 13.9, 7.0, 3.1 Hz, 1H, CHCH₃), 2.17 (br s, 1H, OH), 3.44 (dd, J = 9.7, 6.5 Hz, 1H, CH₂OBn), 3.48 (dd, J = 9.7, 4.6 Hz, 1H, CH₂OBn), 3.59-3.72 (m, 2H, CH₂OH), 3.79-3.82 (m, 1H, CHOTBS), 4.47 (d, J = 11.9 Hz, 1H, OCH₂Ph), 4.52 (d, J = 11.9 Hz, 1H, OCH₂Ph), 7.25-7.36 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ -4.5 (q), -3.9 (q), 16.1 (q), 18.6 (s), 26.3 (q), 35.4 (d), 36.9 (t), 62.1 (t), 73.0 (t), 73.8 (t), 75.5 (d), 127.9 (d), 128.0 (d), 128.7 (d), 138.8 (s); mass spectrum m/z (relative intensity) 361.21 (M+Na⁺, 100), 362.22 (26), 363.19 (8); exact mass calcd. for C₁₉H₃₆O₃SiNa⁺ m/z 361.2169, found m/z 361.2142.
(4S,5R)-5-Benzylxymethyl-4-methylidihydrofuran-2-one (117). To a solution of 6.7 g (17.8 mmol) of pyridinium dichromate in 15 mL of dry DMF, was added 2.0 g (5.9 mmol) of neat aldehyde 119 along with two 2-mL rinses of the syringe with DMF. The reaction mixture was stirred at room temperature for 48 h, diluted with 100 mL of water, and extracted with three 75-mL portions of ether-pentane (1:1). The combined organic phases were dried (MgSO4), concentrated in vacuo, dissolved in 220 mL of acetonitrile, and 6.6 mL of 48% HF was added. The reaction mixture was stirred at room temperature for 16 h, diluted with 220 mL of ethyl acetate, and washed with three 100-mL portions of saturated aqueous NaHCO3, 100 mL of water, and 100 mL of brine. The organic phase was dried (MgSO4), concentrated in vacuo, and the residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexanes, 1:1), to give 0.8 g (68%) of lactone 117 as a colorless oil: IR (neat) 1777 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.12 (d, J = 7.0 Hz, 3H, CH₃), 2.37 (dd, J = 17, 8.6 Hz, 1H, CH₂ O), 2.54 (dd, J = 17.0, 8.4 Hz, 1H, CH₂C=O), 2.67-2.78 (m, 1H, CHCH₃), 3.74 (d, J = 3.7 Hz, 2H, CH₂OBn), 4.0-4.57 (m, 3H, CO₂CH and OCH₂Ph), 7.27-7.36 (m, 5H, ArH); ¹³C NMR (CDCl₃, 125.8 MHz) δ 14.2 (q), 33.0 (d), 37.0 (t), 69.4 (t), 74.2 (t), 81.7 (d), 128.1 (d), 128.3 (d), 128.9 (d), 138.0 (s), 177.4 (s);
mass spectrum m/z (relative intensity) 243.10 (M+Na\textsuperscript{+}, 47), 244.10 (8), 257.1 (22), 258.08 (4); exact mass calcd. for C\textsubscript{13}H\textsubscript{18}O\textsubscript{3}Na\textsuperscript{+} m/z 243.0992, found m/z 243.0989.

(3R,4S)-5-BenzylOxy-4-(tert-butyldimethylsilyloxy)-3-methyl-pentanal (119). A dry 3-neck flask equipped with an addition funnel and argon atmosphere was charged with 3.55 g (8.37 mmol) of the Dess-Martin periodinane\textsuperscript{51,52} and 80 mL of dry dichloromethane. The addition funnel was charged with a solution of 2.36 g (6.98 mmol) of alcohol 115 in 70 mL of dry dichloromethane, and the solution was added to the stirred reaction mixture over 20 min at room temperature. The reaction mixture was stirred for an additional 1.5 h, diluted with 320 mL of ether, and washed with three 50-mL portions of 2N NaOH. The organic phase was dried (MgSO\textsubscript{4}) and concentrated in vacuo to give 2.24 g (95\%) of aldehyde 119 as a pale yellow oil. The material was used crude for subsequent reactions, however, analytically pure material was obtained by chromatography over silica gel (eluted with ethyl acetate-hexanes, 1:2): IR (neat) 1726 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \delta 0.03 (s, 3H, SiCH\textsubscript{3}), 0.04 (s, 3H, SiCH\textsubscript{3}), 0.87 (s, 9H, SiCH(CH\textsubscript{3})\textsubscript{3}), 0.91 (d, J = 6.7 Hz, 3H, CHCH\textsubscript{3}), 2.26 (ddd, J = 16.0, 8.1, 2.4 Hz, 1H, OCHCH\textsubscript{2}), 2.32-2.41 (m, 1H, CHCH\textsubscript{3}), 2.54 (ddd, J = 16.0, 7.2,
$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.38 (dd, $J = 9.6, 3.4$ Hz, 1H, CH$_2$OBn), 3.43 (dd, $J = 9.6, 3.4$ Hz, 1H, CH$_2$OBn), 3.79 (ddd, $J = 5.7, 5.7, 3.4$ Hz, 1H, CH$_2$OBn), 4.47 (d, $J = 12.0$ Hz, 1H, OCH$_2$Ph), 4.52 (d, $J = 12.0$ Hz, 1H, OCH$_2$Ph), 7.26-7.36 (m, 5H, ArH). 9.74 (app t, $J = 2.0$ Hz, 1H, CHO); $^{13}$C NMR (CDCl$_3$, 125.8 MHz) $\delta$ 45.1 (q), 14.7 (q), 18.6 (s), 26.3 (q), 32.2 (d), 48.3 (t), 72.8 (t), 73.8 (t), 74.3 (d), 128.0 (d), 128.1 (d), 128.8 (d), 138.6 (s); mass spectrum m/z (relative intensity) 359.20 (M+Na$^+$, 45), 360.22 (13), 375.19 (M+K$^+$23), 397.15 (14), 463.24 (23), 464.20 (7), 479.26 (9); exact mass calcd. for C$_{18}$H$_{32}$O$_3$SiNa$^+$ m/z 359.2013, found m/z 359.2021.


(4S,5R)-5-Benzylxoyethyl-4-methyltetrahydrofuran-2-ol (120). To a solution of 3.7 g (10.9 mmol) of aldehyde 119 in 356 mL of acetonitrile at 5 °C was added 15 mL of 48% HF, and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with 300 mL of dichloromethane and washed with three 100-mL portions of saturated aqueous NaHCO$_3$, 50 mL of water, 50 mL of brine, and dried (MgSO$_4$). The solvent was removed in vacuo and the residue was chromatographed over 120 g of silica gel eluted with ethyl acetate-hexanes, 1:1) to give 1.8 g (72%) of a 1.5:1 mixture of
anomeric lactols 120 as a colorless oil which solidified to a waxy white solid upon standing in the refrigerator: mp 42-45 °C; IR (neat) 3422 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major diastereomer) δ 0.89 (d, J = 7.1 Hz, 3H, CH₃), 1.72 (ddd, J = 12.9, 7.6, 5.3 Hz, 1H, HOCH₂CH₂), 1.94 (ddd, J = 12.9, 7.3, 2.0 Hz, 1H, HOCHCH₂), 2.45-2.56 (m, 1H, CHCH₃), 2.71-2.75 (m, 1H, OH), 3.40 (dd, J = 10.1, 6.1 Hz, 1H, CH₂OBn), 4.29 (ddd, J = 6.5, 6.4, 4.5 Hz, 1H, CH₂OBn), 4.45 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.52 (d J = 12.1 Hz, 1H, OCH₂Ph), 5.48-5.52 (m, 1H, OCHO), 7.20-7.32 (m, 5H, ArH); Representative peaks for the minor anomer: δ 1.01 (d, J = 6.6 Hz, 3H, CH₃), 4.49 (s, 2H, OCH₂Ph), 5.32-5.36 (m, 1H, OCHO);

¹³C NMR (CDCl₃, 100.6 MHz, major anomer) δ 14.60 (q), 33.7 (d), 42.3 (t), 70.6 (t), 73.9 (t), 79.8 (d), 98.4 (d), 128.0 (d), 128.4 (d), 128.8 (d), 138.7 (s); mass spectrum m/z (relative intensity) 245.11 (M+Na⁺, 36); exact mass calcd. for C₁₃H₁₈O₃Na⁺ m/z 245.1148, found m/z 245.1145.


![121](OBn)

(2R,3S)-2-Benzylxymethyl-3-methyl-2,3-dihydrofuran (121). To a −45 °C solution of 1.1 g (4.6 mmol) of lactol 120 in 34 mL of dry dichloromethane, under an argon atmosphere, was added 2.5 mL (18.4 mmol) of dry triethylamine followed by the dropwise addition of 445 µL (5.75 mmol) of methanesulfonyl
chloride. The reaction was stirred at -45 °C for 3 h, ambient temperature for 15 h, and reflux for 6 h. The cooled solution was diluted with 90 mL of ether-petroleum ether (1:1) and the resulting suspension was filtered through a thin pad of celite. The filter cake was rinsed with three 10-mL portions of petroleum ether, the filtrate was concentrated, and the residue was chromatographed over 80 g of silica gel (eluted with ether-petroleum ether, 1:4) to give 625 mg (67%) of dihydrofuran 121 as a colorless oil: IR (neat) 3089, 1614 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.79 (d, J = 7 Hz, 3H, CH₃), 2.79-2.88 (m, 1H, CH₂CH₃), 3.53-3.59 (m, 2H, CH₂OBn), 4.39-4.51 (m, 3H, OCHOBn and OCH₂Ph), 4.78 (app t, J = 2.7 Hz, 1H, OCH=), 6.15 (app t, J = 2.3 Hz, 1H, =CH), 7.11-7.23 (m, 5H, ArH); ¹³C NMR (CDCl₃, 125.8 MHz) δ 15.4 (q), 38.1 (d), 69.4 (t), 73.9 (t), 82.7 (d), 107.5 (d), 128.1 (d), 128.2 (d), 128.8 (d), 138.5 (s), 145.0 (d); mass spectrum m/z (relative intensity) 205.12 (M+H⁺ 11), 227.10 (M+Na⁺ 8), 431.22 (2(M+Na)⁺ 100); exact mass calcd. for C₁₃H₁₆O₂Na⁺ m/z 227.1042, found m/z 227.1020.

(4S,5R)-5-Benzyloxymethyl-4-methyltetrahydrofuran-2,3-diol (109). A flask equipped with magnetic stir bar was charged with 6.7 mL of tert-butyl alcohol, 22 mL water, 67 mL acetone, 1.83 g (15.8 mmol) of N-
methylmorpholine-N-oxide, 7.6 mL (0.30 mmol) of 1% aqueous OsO₄ (w/w), and the solution was purged with argon. The reaction mixture was cooled to approximately -5 °C, and to it was added a -5 °C solution of 3.06 g (15.0 mmol) of dihydrofuran 121 in 22 mL of acetone via cannula over about 2 min. The reaction mixture was stirred at -5 °C for 1 h, ambient temperature for 2 h, and 2.56 g (14.70 mmol) of sodium dithionite was added. After stirring for an additional 45 min, the reaction mixture was extracted with three 250-mL portions of ethyl acetate, and the combined extracts were washed with three 25-mL portions of water. The organic phase was dried (MgSO₄), concentrated in vacuo, and the residue was chromatographed over 100 g of silica (eluted with ethyl acetate-hexanes, 1:1) to give 3.2 g (90%) of a 3:1 mixture of anomeric diols 109 as a white solid: mp 64-66 °C; IR (thin film) 3384 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major isomer) δ 0.96 (d, J = 7.1 Hz, 3H, CH₃), 2.17-2.28 (m, 1H, CHCH₃), 2.62 (br d, J = 6.5 Hz, 1H, CHO₂), 3.37-3.46 (m, 2H, CH₂OBn), 3.81-3.83 (m, 1H, CHOH), 4.02-4.11 (m, 1H, OCH₂Ph), 4.31 (ddd, J = 5.0, 5.0, 4.0 Hz, 1H, OCH₂OBn), 4.42 (d, J = 12.0 Hz, 1H, OCH₂Ph), 4.47 (d, J = 12.2 Hz, 1H, OCH₂Ph), 5.30 (br d, J = 4.3Hz, 1H, HOCHO), 7.19-7.31 (m, 5H, ArH); diagnostic peaks for the minor isomer: δ 1.02 (d, J = 7.1 Hz, 3H, CH₃), 2.52 (br s, 1H, OH), 5.05 (dd, J = 9.5, 2.0 Hz, 1H, HOCHO); ¹³C NMR (CDCl₃, 125.8 MHz, major isomer) δ 11.9 (q), 41.0 (d), 70.6 (t), 73.9 (t), 78.7 (d), 81.5 (d), 96.1 (d), 128.1 (d), 128.6 (d), 129.1 (d), 138.4 (s); mass spectrum m/z (relative intensity) 261.10
(M+Na\(^+\) 65), 499.23 (77), 500.22 (21); exact mass calcd. for C\(_{13}\)H\(_{18}\)O\(_4\)Na\(^+\) m/z 261.1097, found m/z 261.1086.

Anal. calcd. for C\(_{13}\)H\(_{18}\)O\(_4\): C, 66.53; H, 7.61. Found: C, 65.76; H, 7.77.

(2R,3R,4S,5S)-5-Benzylxymethyl-2,2,6-trimethyltetrahydrofuro[2,3-d][1,3]dioxole (123). To a room temperature solution of 38.3 mg (0.16 mmol) of diol 109 in 2 mL of 2-methoxypropene was added 1 mg (5.8 µmol) of p-toluenesulfonic acid, and the reaction mixture was stirred for 14 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed over 2 g of silica gel (eluted with ether-petroleum ether, 1:1) to give 30.4 mg (72%) of acetonide 123 as a colorless oil: IR (neat) 1372, 1064-1097 cm\(^{-1}\); \(^1\)H NMR (C\(_6\)D\(_6\), 400 MHz) \(\delta\) 0.45 (d, \(J = 7.5\) Hz, 3H, CH\(_3\)), 1.08 (s, 3H, Me), 1.39 (s, 3H, Me), 2.70 (dq, \(J = 7.5, 4.4\) Hz, 1H, H\(_b\)), 3.32 (dd, \(J = 9.7, 6.5\) Hz, CH\(_2\)OBn), 3.49 (dd, 9.7, 6.1 Hz, 1H, CH\(_2\)OBn), 3.84 (d, \(J = 3.6\) Hz, 1H, H\(_c\)), 4.20 (d, \(J = 12.1\) Hz, 1H, OCH\(_2\)Ph), 4.29 (d, \(J = 12.1\) Hz, 1H, OCH\(_2\)Ph), 4.57 (dt, 6.2, 4.3 Hz, 1H, H\(_a\)), 5.57 (d, 3.6 Hz, 1H, H\(_d\)), 6.98-7.01 (m, 1H, p-ArH), 7.05-7.08 (m, 2H, m-ArH), 7.15-7.17 (m, 2H, o-ArH); \(^1\)C NMR (C\(_6\)D\(_6\), 100.6 MHz) \(\delta\) 10.6 (q), 26.4 (q), 27.1 (q), 41.1 (d), 69.2 (t), 73.5 (t), 78.4 (d), 86.7 (d), 105.1 (d), 111.0 (s), 127.9 (d), 128.3

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(2S,3S,4R)-1-Benzylloxy-3-methyl-6-phenyl-2-yl-3-methyl-hex-5-ene-2,4-diol (131). To a suspension of 2.33 g (6.0 mmol) of benzyltriphienylphosphonium bromide in 20 mL of dry dioxane (distilled from CaH₂), under an argon atmosphere, was added 670 mg (6.0 mmol) of potassium tert-butoxide. The reaction mixture was stirred at room temperature for 30 min, heated to 80 °C, and a solution of 726 mg (3.0 mmol) of diol 109, in 5 mL of dry dioxane, was added via syringe. The reaction mixture was stirred at reflux for 2 h, cooled to room temperature, and 2 mL of water was added. The reaction mixture was concentrated in vacuo, and the resulting paste was triturated with two 10-mL portions of ethyl acetate. The combined organic portions were concentrated and chromatographed over 140 g of silica gel (eluted with ethyl acetate-petroleum ether, 1:2) to give 761 mg (80%) of a 3:1 mixture of E and Z ene-diols 131 as a pale yellow oil. Although the mixture of isomeric 131 was used in subsequent reactions, analytically pure material could be obtained by careful selection of fractions from the column: IR (neat) 3406 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, E
isomer) δ 0.90 (d, J = 7.1 Hz, 3H, CH₃), 1.78-1.85 (m, 1H, CHCH₂), 2.6-3.0 (br s, 2H 2-OH's), 3.45-3.56 (m, 2H, CH₂OBn), 4.13 (ddd, J = 7.5, 4.5, 4.2 Hz, 1H, HOCHCH₂OBn), 4.50-4.60 (m, 3H, HOCHCH= and OCH₂Ph), 6.22 (dd, J = 16.0, 5.6 Hz, 1H, =CHCHOH), 6.62 (d, J = 15.9 Hz, 1H, PhCH=), 7.20-7.38 (m, 10H, 2-ArH's); diagnostic signals for the Z-isomer are: δ 1.04 (d, J = 7.1 Hz, 3H, CH₃), 5.79 (dd, J = 11.7, 9.0 Hz, 1H, =CHCHOH), 6.56 (d, J = 11.7 Hz, 1H, PhCH=);

C NMR (CDCl₃, 100.6 MHz) δ 7.1 (q), 40.6 (d), 73.0 (t), 73.9 (t), 74.4 (d), 76.3 (d), 126.8 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.9 (d), 129.0 (d), 130.6 (d), 132.2 (d), 137.3 (s), 138.2 (s); mass spectrum m/z (relative intensity) 335.16 M⁻Na⁺ 44; exact mass calcd. for C₂₀H₂₄O₃Na⁺ m/z 335.1618, m/z found ν 1616.

(2S,3S,4R)-1-Benzyloxy-3-methyl-8-phenylocta-5,7-diene-2,4-diol

To a suspension of 919 mg (2.0 mmol) of phosphonium bromide in 6.7 mL of dry dioxane (distilled from CaH₂), under an argon atmosphere, was added 224 mg (2.0 mmol) of potassium tert-butoxide. The reaction mixture was heated to 70 °C for 30 min, cooled to room temperature, and a solution of 239 mg (2.0 mmol) of diol 109, in 1.7 mL of dry dioxane, was added via syringe. The
reaction mixture was stirred at room temperature for 2 h, quenched with the addition of 2 mL of water, diluted with 50 mL of ethyl acetate, washed with three 10-mL portions of water, 10 mL of brine solution, and dried (MgSO₄). The solvent was removed in vacuo and the residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 270 mg (80%) of a 3:1 mixture of E and Z ene-diols 132 as a yellow oil. Although the mixture of isomeric 132 was used in subsequent reactions, analytically pure material could be obtained by careful selection of fractions from the column: IR (neat) 3416 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, E isomer) δ 0.86 (d, J = 7.2 Hz, 3H, CH₃), 1.69-1.75 (m, 1H, CHCH₃), 2.73 (br s, 1H, OH), 2.93 (br s, 1H, OH), 3.40-3.48 (m, 2H, CH₂OBn), 4.02-4.06 (m, 1H, HOCHCH₂OBn), 4.45-4.53 (m, 3H, Hα and OCH₂Ph), 5.81 (dd, J = 15.2, 5.7 Hz, 1H, Hβ), 6.43 (dd, J = 15.2, 11.4 Hz, 1H, Hc), 6.53 (d, J = 15.6 Hz, 1H, Ha), 6.77 (dd, J = 15.6, 11.4 Hz, 1H, Hb), 7.20-7.62 (m, 10H, ArH); diagnostic signals for the minor Z-isomer: δ 0.91 (d, J = 6.9 Hz, 3H, CH₃), 4.82 (dd, J = 8.2, 3.8 Hz, 1H, Hα), 5.47 (dd, J = 10.8, 8.2 Hz, 1H, Hb), 6.13 (t, J = 10.8 Hz, Hc); ¹³C NMR (CDCl₃, 125.8 MHz) δ 7.0 (q), 40.6 (d), 73.0 (t), 73.9 (t), 74.4 (d), 76.1 (d), 126.8 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.8 (d), 128.9 (d), 129.0 (d), 131.1 (d), 132.8 (d), 135.4 (d) 137.7 (s), 138.2 (s); mass spectrum m/z (relative intensity) 359.20 (43), 377.21 (22), 393.20 (18); exact mass calcd. for C₂₁H₂₆O₃Na⁺ m/z 361.177443, found m/z 359.19517.
(2S,3S,4R)-1-Benzylloxy-3-methyl-6-furan-2-yl-3-methylhex-6-ene-2,4-diol (133). To a suspension of 1.12 g (2.64 mmol) of phosphonium bromide in 26 mL of dry dioxane (distilled from CaH₂), under an argon atmosphere, was added 296 mg (2.64 mmol) of potassium tert-butoxide. The reaction mixture was stirred at room temperature for 30 min, heated to 80 °C, and a solution of 726 mg (3.0 mmol) of diol 109, in 9 mL of dry dioxane, was added via syringe. The reaction mixture was stirred at room temperature for 2 h, quenched with the addition of 2 mL of water, washed with three 10-mL portions of water, 10 mL of brine, and dried (MgSO₄). The solvent was removed in vacuo and the residue was chromatographed over 20 g of silica gel (eluted with ethyl acetate-hexanes, 1:4), to give 262 mg (97%) of a 5:1 mixture of E and Z ene-diols 133 as a pale yellow oil: IR (neat) 3405 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, E isomer) δ 0.86 (d, J = 7.2 Hz, 3H, CH₃), 1.69-1.75 (m, 1H, CHCH₃), 2.73 (br s, 1H, OH), 2.93 (br s, 1H, OH), 3.40-3.48 (m, 2H, CH₂Obn), 4.02-4.06 (m, 1H, HOCHCH₂OBn), 4.45-4.53 (m, 3H, H, and OCH₂Ph), 6.07 (dd, J = 15.9, 5.4 Hz, 1H, Ha), 6.13 (app d, J = 3.2 Hz, 1H, H), 6.30 (dd, J = 3.4, 2.0 Hz, 1H, Hb), 6.38 (dd, J = 15.9, 1.7 Hz, 1H, Hf), 7.20-7.32 (m, 6H, Hc and ArH); diagnostic signals for the Z-isomer: δ
0.94 (d, J = 7.1 Hz, 3H, CH₃), 5.12 (br d, J = 8.0 Hz, 1H, H₄), 5.56 (dd, J = 12.1, 8.0 Hz, 1H, H₆); $^{13}$C NMR (CDCl₃, 100.6 MHz) δ 6.9 (q), 40.4 (d), 73.0 (t), 73.9 (t), 74.5 (d), 75.8 (d), 108.2 (d), 111.7 (d), 118.8 (d), 128.2 (d), 128.2 (d), 128.9 (d), 129.9 (d), 138.2 (s), 142.2 (d) 153.1 (s); mass spectrum m/z (relative intensity) 325.14 (M+Na⁺ 37), 341.14 (72), 342.14 (16); exact mass calcd. for C₁₉H₂₂O₄Na⁺ m/z 325.141028, found m/z 325.14405.

![Chemical Structure](image)

(2S,3S,4R)-1-Benzyl-3-methyl-8-(2-furyl)octa-5,7-diene-2,4-diol (134). To a suspension of 454 mg (1.0 mmol) of phosphonium bromide in 7 mL of dry dioxane (distilled from CaH₂), under an argon atmosphere, was added 113 mg (1.0 mmol) of potassium tert-butoxide. The reaction mixture was heated to 60 °C for 20 min, cooled to room temperature, and a solution of 80 mg (0.34 mmol) of diol 109, in 1 mL of dry dioxane, was added via syringe. The reaction mixture was stirred at room temperature for 3 h, quenched with the addition of 1 mL of water, diluted with 30 mL of ethyl acetate, washed with three 5-mL portions of water, 5 mL of brine, and dried (MgSO₄). The solvent was removed in vacuo and the residue was chromatographed over 8 g of silica gel (eluted with ethyl acetate-hexanes, 1:3), to give 112 mg (95%) of a 6:1 mixture of
E and Z ene-diols 134 as a orange oil: IR (neat) 3418 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz, E isomer) δ 1.01 (d, J = 7.1 Hz, 3H, CH₃), 1.53-1.60 (m, 1H, CHCH₃), 2.49 (br s, 1H, OH), 2.56 (br s, 1H, OH), 3.26 (dd, J = 9.5, 4.5 Hz, 1H, CH₂OBn), 3.36 (dd, J = 9.5, 7.6 Hz, 1H, CH₂OBn), 3.96-4.00 (m, 1H, HOCHCH₂OBn), 4.27 (d, J = 12.0 Hz, 1H, OCH₂Ph), 4.32 (d, J = 12.0 Hz, 1H, OCH₂Ph), 4.37-4.39 (m, 1H, H₆), 5.67 (dd, J = 15.2, 5.2 Hz, 1H, H₆), 6.06 (d, J = 3.1 Hz, 1H, H₇), 6.14 (d, J = 3.2, 1.7 Hz, 1H, H₇), 6.27 (d, J = 15.6 Hz, 1H, H₇), 6.61 (d, J = 15.6, 11.2, 1.2 Hz, 1H, H₇), 6.94 (dd, J = 15.6, 10.9 Hz, 1H, H₇), 7.05-7.29 (m, 6H, Hb and ArH); diagnostic signals for minor isomer: δ 1.12 (d, J = 6.9 Hz, 3H, CH₃), 5.61 (dd, J = 10.9, 8.1 Hz, 1H, H₇), 5.79 (dd, J = 15.2, 5.5 Hz, 1H, H₇); ¹³C NMR (C₆D₆, 100.6 MHz) δ 6.8 (q), 40.3 (d), 73.0 (t), 73.4 (t), 74.3 (d), 75.7 (d), 108.5 (d), 111.8 (d), 120.0 (d), 127.3 (d), 128.6 (d), 128.7 (d), 129.6 (d), 130.2 (d), 136.4 (d), 138.7 (d), 142.2 (d) 153.9 (s); mass spectrum m/z (relative intensity) 349.14 (7), 351.15 (M+Na⁺ 35); exact mass calcd. for C₂₉H₂₄O₄Na⁺ m/z 351.1567, found m/z 351.1541.

(2R,3R,4S,5S,6R)-2-Benzylxoyethyl-3-methyl-6-phenyl-5-phenylseleneny ltetra-hydropyran-4-ol (135). To a −78 °C solution of 100 mg
(0.2 mmol) of 131 in 3 mL of dry dichloromethane was added to a room

temperature solution of 61.5 mg (0.32 mmol) of phenyl selenenyl chloride in 1 mL

dry dichloromethane. The reaction mixture was stirred at -78 °C for 2 h,

quenched with the addition of 1 mL of saturated aqueous NaHCO₃, and diluted

with 10 mL of dichloromethane. The layers were partitioned, the organic layer

was washed with 1 mL of saturated aqueous NaHCO₃, 1 mL of brine and dried

(MgSO₄). The solvent was evaporated to give a residue that was

chromatographed over 4 g of silica gel (eluted with ethyl acetate-hexanes, 3:7) to

give 91 mg (61%) of pyran 135 as a colorless oil: IR (neat) 3446 cm⁻¹; ¹H NMR

(CHCl₃, 500 MHz) δ 1.01 (d, J = 7.1 Hz, 3H, CH₃), 2.19-2.24 (m, 1H, CHCH₃),

4.19-4.28 (br s, 1H, OH), 3.49 (dd, J = 10.0, 6.2 Hz, 1H, CH₂OBn), 3.62-3.65 (m, 2H,

~SePh and CH₂OBn), 3.92 (br d, J = 1.8 Hz, 1H, CHOH), 4.49 (dt, J = 6.4, 2.0

Hz, 1H, CHCH₂OBn), 4.53 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.65 (d, J = 12.1, 1H,

OCH₂Ph), 4.85 (d, J = 11.2 Hz, 1H, CPh), 7.16-7.28 (m, 5H, ArH), 7.31-7.39 (m,

ArH), 7.42-7.45 (m, 2H, ArH); ¹³C NMR (CDCl₃, 125.8 MHz) δ 11.2 (q), 37.3

53.1 (d), 70.9 (t), 72.8 (d), 73.4 (d), 73.7 (t), 79.3 (d), 128.0 (d), 128.1 (d),

128.2 (d), 128.3 (d), 128.6 (d), 128.7 (d), 129.5 (d), 135.2 (d), 138.7 (s), 140.7

(s) one singlet and one doublet are not seen in the aromatic region of the

spectrum; mass spectrum m/z (relative intensity) 491.12 (M+Na⁺ 100); exact

mass calcd. for C₂₈H₂₆O₃SeNa⁺ m/z 491.1096, found m/z 491.1089.
To a −78 °C solution of 206 mg (0.68 mmol) of 133 in 7 mL of dry dichloromethane was added a room temperature solution of 137 mg (0.72 mmol) of phenylselenenyl chloride in 5 mL of dry dichloromethane, via syringe pump over 45 min. The reaction mixture was stirred at −78 °C for 2 h, quenched with the addition of 2 mL of saturated aqueous NaHCO₃ and diluted with 50 mL of ethyl acetate. The layers were partitioned, and the organic layer was washed with three 5-mL portions of saturated aqueous NaHCO₃, 5 mL of water, and 5 mL of brine. After drying (MgSO₄), the solution was concentrated to give a residue that was chromatographed over 22 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 217 mg (69%) of pyran 136 as a yellow oil: IR (neat) 3451 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.88 (d, J = 7.2 Hz, 3H, CH₃), 1.98-2.04 (m, 1H, CHCH₃), 2.58 (br s, 1H, OH), 3.31 (dd, J = 10.0, 5.9 Hz, 1H, CH₂OBn), 3.46 (dd, J = 10.0, 5.9 Hz, 1H, CH₂OBn), 3.78-3.81 (m, 2H, CHSePh and CHOH), 4.30 (dt, J = 6.5, 2.3 Hz, 1H, CHCH₂OBn), 4.36 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.51 (d, J = 12.1, 1H, OCH₂Ph), 4.77 (d, J = 11.2 Hz, 1H, CH-furyl), 6.20 (dd, J = 3.1, 1.9 Hz, 1H, 122
H₆), 6.3 (d, J = 3.1 Hz, 1H, H₆), 7.12-7.24 (m, 9H, H₆ and ArH), 7.27-7.30 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.0 (q), 37.2 (d), 49.3 (d), 70.9 (t), 72.1 (d), 72.6 (d), 73.6 (d), 73.8 (t), 110.1 (d), 110.5 (d), 127.8 (s), 128.0 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.5 (d), 135.3 (d), 138.6 (s), 142.7 (d), 152.7 (s); mass spectrum m/z (relative intensity) 481.09 (M+Na⁺, 37); exact mass calcd. for C₂₄H₂₆O₄SeNa⁺ m/z 481.0888, found m/z 481.0858.

![Image of compound 137]

(2R,3R,4S,5S,6R)-2-Benzylxymethyl-3-methyl-5-phenyl-selenenyl-6-styryltetra-hydropyran-4-ol (137). To a -78 °C solution of 665 mg (2.0 mmol) of 132 in 20 mL of dry dichloromethane was added a room temperature solution of 377 mg (2.0 mmol) of phenylselenenyl chloride in 7 mL of dry dichloromethane. The reaction mixture was stirred at -78 °C for 3 h, quenched by addition of 7 mL of saturated aqueous NaHCO₃ and diluted with 60 mL of ethyl acetate. The layers were partitioned, the organic layer was washed with 7 mL of saturated aqueous NaHCO₃, and 7 mL of brine. After drying (MgSO₄), the solution was concentrated to give a residue that was chromatographed over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 656 mg (65%) of
pyran 137 as a colorless oil: IR (neat) 3442, 3058 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.86 (d, J = 7.2 Hz, 3H, CH₃), 1.98-2.05 (m, 1H, CHCH₂), 2.59 (d, J = 1.9 Hz, 1H, OH), 3.36 (dd, J = 10.0, 5.6 Hz, 1H, CH₂OBn), 3.43 (dd, J = 11.1, 2.4 Hz, 1H, CHSePh), 3.52 (dd, J = 10.0, 7.1 Hz, 1H, CH₂OBn), 3.73 (d, J = 2.2 Hz, 1H, CHOH), 4.30 (dt, J = 7.5, 2.3 Hz, 1H, CHCH₂OBn), 4.41 (dd, J = 10.9, 7.4 Hz, 1H, H₂), 4.44 (d, J = 12.2, 1H, OCH₂Ph), 4.57 (d, J = 12.2 Hz, 1H, OCH₂Ph), 6.14 (dd, 15.8, 7.3, 1H, Hb), 6.64 (d, J = 15.8 Hz, 1H, Ha), 7.14-7.29 (m, 13H, ArH), 7.45 (dd, J = 7.9, 1.2 Hz, 2H, o-PhSe); ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.2 (q), 37.3 (d), 51.2 (d), 71.1 (t), 72.3 (d), 73.1 (d), 73.8 (t), 77.2 (d), 126.8 (s), 127.2 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.7 (d), 134.0 (d), 135.2 (d), 137.0 (s), 138.7 (s) one aromatic doublet is not seen in the spectrum; mass spectrum m/z (relative intensity) 517.12 (M+Na⁺ 39); exact mass calcd. for C₂₈H₃₀O₃SeNa⁺ m/z 517.1252, found m/z 517.1242.

Anal. calcd. for C₂₈H₃₀O₃Se: C, 67.28; H, 6.02. Found: C, 68.06; H, 6.32.
(2R,3R,4S,5S,6R)-2-Benzylxymethyl-6-(2-furan-2-yl)ethenyl-3-methyl-5-phenyl-selenenyltetrahydropyran-4-ol (138). To a -78 °C solution of 27 mg (0.08 mmol) of 134 in 0.8 mL of dry dichloromethane was added a room temperature solution of 16 mg (0.08 mmol) of phenylselenenyl chloride in 0.5 mL of dry dichloromethane. The reaction mixture was stirred at -78 °C for 30 min, quenched by addition of 0.5 mL of saturated aqueous NaHCO₃ and diluted with 20 mL of ethyl acetate. The layers were partitioned, and the organic layer was washed with two 5-mL portions of saturated aqueous NaHCO₃, 5 mL of water, and 5 mL of brine. After drying (MgSO₄), the solution was concentrated to give a residue that was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 12 mg (35%) of a 9:2 mixture of isomeric pyrans 138 as a red oil: IR (neat) 3444 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major isomer) δ 0.88 (d, J = 7.3 Hz, 3H, CH₃), 2.03-2.14 (m, 1H, CHCH₃), 2.60 (d, J = 1.9 Hz, 1H, OH), 3.39 (dd, J = 10.0, 5.4 Hz, 1H, CH₂OBn), 3.43 (dd, J = 11.1, 2.5 Hz, 1H, CHSePh), 3.51 (dd, J = 10.0, 7.1 Hz, 1H, CH₂OBn), 3.71 (dd, J = 4.5, 2.3 Hz, 1H, CHO), 4.32 (ddd, J = 7.0, 5.5, 2.4 Hz, 1H, CHCH₂OBn), 4.38 (dd, J = 11.2, 7.2 Hz, 1H, CH₂OBn).
Hz, 1H, H.), 4.48 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.61 (d, J = 12.1 Hz, 1H, OCH₂Ph), 6.20 (dd, J = 15.7, 7.1 Hz, 1H, H₆), 6.22 (d, J = 3.4 Hz, 1H, H₅), 6.34 (dd, J = 3.2, 1.8 Hz, 1H, H₅), 6.50 (d, J = 15.3 Hz, 1H, H₆), 7.21-7.32 (m, 9H, ArH), 7.50-7.54 (m, 2H, ArH); selected signals diagnostic for the minor isomer δ 2.78 (d, J = 1.4 Hz, 1H, OH), 3.65 (br s, 1H, CHOH), 5.65 (dd, J = 11.7, 8.7 Hz, 1H, H₄), 6.42 (d, J = 11.7 Hz, 1H, H₄). The ratio of isomers was established by integration of the resonances at δ 3.71 and 3.65; ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.1 (q), 37.1 (d), 71.1 (t), 72.0 (d), 73.1 (d), 73.7 (t), 76.4 (d), 108.9 (d), 111.6 (d), 121.9 (d), 127.2 (d), 127.8 (d), 128.0 (s), 128.1 (d), 128.4 (d), 128.8 (d), 129.7 (d), 135.2 (d), 138.7 (s), 142.5 (d), 152.7 (s); mass spectrum m/z (relative intensity) 507.10 (M⁺Na⁺ 13); exact mass calcd. for C₂₆H₂₉O₄SeNa⁺ m/z 507.1045, found m/z 507.1045.

![rac-139](image)

**(2R, 3 S)-3-Methyl-1-phenylmethoxy-4-penten-2-ol (rac-139)**. To a dry flask under a blanket of argon was added 21 mL (7 mmol) of a solution of crude aldehyde 111 in dichloromethane, and 30 mL of dry THF. The solution was concentrated in vacuo at 30 °C, to approximately 20 mL, and the dilution/concentration process was repeated two more times. To the resulting solution was added 1.81 g (14.0 mmol) of crotyl bromide and the solution was set
A separate flask was charged with 2.69 g (28.0 mmol) of ammonium(II) chloride, 87 mg (0.4 mmol) of nickel(II) chloride, heated with a flame while under vacuum (approximately 30 mm Hg), and cooled to room temperature under a blanket of argon. To this flask was added 20 mL of dry THF, and while the suspension was stirred at room temperature, the solution of crude aldehyde-acetyl bromide was added via cannula over 30 min. The resulting suspension was stirred for 18 h, 25 mL of water was added, and the phases were partitioned. The aqueous phase was extracted with three 25-mL portions of ether, and the combined extracts were washed with 20 mL of water, 20 mL of brine, dried (MgSO₄), and concentrated. The resulting residue was purified by chromatography over 75 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 1.1 g (76%) of rac-139 as a colorless oil: 'H NMR (CDCl₃, 250 MHz) δ 1.03 (d, J = 7.0 Hz, 3H, CH₃), 2.21 (br s, 1H, OH), 2.28-2.42 (m, 1H, CHCH₃), 3.42 (m, 1H, CH₂OBn), 3.54 (dd, J = 9.4, 3.2 Hz, 1H, CH₂OBn), 3.67-3.70 (m, 1H, CHO), 4.55 (s, 2H, OCH₂Ph), 5.04-5.10 (m, 2H, =CH₂), 5.75 (m, 1H, =CH), 7.25-7.39 (br m, 5H, ArH).

Representative procedure for the formation of Mosher esters 140-143. A dry flask was charged with 89.6 mg (0.38 mmol) of Mosher's acid and 4 mL of dry benzene was added. The solution was concentrated in vacuo, a dry magnetic stir bar was inserted, and an argon atmosphere was established. The flask was charged with 1.0 mL of dry dichloromethane, 44.3 µL (0.49 mmol) of oxalyl chloride, and 4.4 µL of dry DMF. The reaction mixture was stirred for 45
min at room temperature, cooled to 0 °C, and a vacuum was cautiously applied to evaporate volatile components. After stirring under reduced pressure (0.05 mm Hg) at ambient temperature for 30 min, the residue was dissolved in 2.2 mL of dry dichloromethane to provide a stock solution of acid chloride. To a flask containing a solution of 12.4 mg (0.06 mmol) of the homoallylic alcohol in 0.5 mL of dry dichloromethane was added 2 mg (0.16 mmol) of DMAP, 42 μL (0.30 mmol) of dry triethylamine, and the solution was cooled to 0 °C. To the reaction mixture was added 1.1 mL (0.19 mmol) of the stock solution of acid chloride, the cold bath was removed, and stirring was continued at room temperature for 14 h. The reaction mixture was diluted with 10 mL of dichloromethane and washed with two 10-mL portions of saturated aqueous ammonium chloride, two 10-mL portions of saturated aqueous sodium bicarbonate, and 10 mL of water. After drying (Na₂SO₄), the solvent was removed in vacuo and the residue was chromatographed over 1 g of silica gel (eluted with ethyl acetate-hexanes, 1:20), with care being taken to combine all fractions that contained diastereomeric products.
(αS)-α-Methoxy-α-trifluoromethylbenzeneacetic acid, (±)-(2S,3R)-3-methyl-1-phenylmethoxy-4-penten-2-ol ester (140 and 141). $^1$H NMR (CDCl$_3$, 250 MHz, diagnostic peaks for 140 and 141) δ 0.91 (d, $J = 7.0$ Hz, 3H, CH$_3$), 0.99 (d, $J = 7.0$ Hz, 3H, CH$_3$), 3.43 (s, 3H, OCH$_3$), 3.48 (s, 3H, OCH$_3$); $^{19}$F NMR (CDCl$_3$, 235.3 MHz, diagnostic peaks for 143) δ -70.5 (integral of 1), -70.2 (integral of 1). The ratio of isomers, and thus the ee, was determined by integration of the $^{19}$F spectra.

(αS)-α-Methoxy-α-trifluoromethylbenzeneacetic acid, (2R,3S)-3-methyl-1-phenylmethoxy-4-penten-2-ol ester (142). $^1$H NMR (CDCl$_3$, 250 MHz, major isomer 142) δ 0.88 (d, $J = 6.8$ Hz, 3H, CH$_3$), 2.42-2.53 (m, 1H, CHCH$_3$), 3.49 (s, 3H, OCH$_3$), 3.54-3.63 (m, 2H, CH$_2$OBn), 4.40 (d, $J = 11.8$ Hz, 1H, OCH$_2$Ph), 4.49 (d, $J = 11.8$ Hz, 1H, OCH$_2$Ph), 4.91-4.92 (m, 1H, =CH$_2$), 4.97-
4.98 (m, 1H, =CH2), 5.22 (dt, 6.8, 3.2 Hz, 1H, CHCO2R), 5.99 (ddd, J = 17.5, 10.0, 7.6 Hz, 1H, HC=CH2), 7.16-7.30 (m, 8H, ArH), 7.51-7.54 (d, J = 7.5 Hz, 2H, ArH); diagnostic peaks for the minor isomer 143: δ 0.99 (d, J = 6.8 Hz, 3H, CH3), 3.43 (s, 3H, OCH3); 19F NMR (CDCl3, 235.3 MHz) δ -70.1 (integral of 25), -70.5 (integral of 1).

![143](image)

(αS)-α-Methoxy-α-trifluoromethylbenzeneacetic acid, (2S,3R)-3-methyl-1-phenylmethoxy-4-penten-2-ol ester (143). 1H NMR (CDCl3, 400 MHz, diagnostic peaks for the major isomer 143) δ 0.99 (d, J = 6.8 Hz, 3H, CH3), 3.43 (s, 3H, OCH3); diagnostic peaks for the minor isomer 142: δ 0.88 (d, J = 6.8 Hz, 3H, CH3); 19F NMR (CDCl3, 235.3 MHz) δ -70.7 (integral of 4), -70.3 (integral of 1).

![ent-113](image)

(2R,3S)-3-Methyl-1-phenylmethoxy-4-penten-2-ol (ent-113). A 250 mL 3-neck flask equipped with magnetic stir bar, gas inlet adapter, and a gas
outlet adapter leading to a solution of saturated aqueous potassium iodide, was charged with 4.1 g (15 mmol) of 110 and 50 mL of dry dichloromethane. The solution was cooled in a dry-ice/acetone bath for 15 min under an atmosphere of O₂, and ozone was bubbled through the reaction mixture until a pale blue color was seen (approximately 15 min). The reaction mixture was purged of excess ozone by bubbling argon through the solution, and 8.5 mL (115 mmol) of dimethyl sulfide was added dropwise via addition funnel over 30 min. The solution was stirred at the cold bath temperature for 2.5 h, the cold bath was removed, and stirring continued for an additional 15 h at ambient temperature. The reaction mixture was washed with two 25-mL portions of saturated aqueous NaHCO₃ and two 25-mL portions of water. The organic phase was dried (MgSO₄) for two hours and diluted with 75 mL of dry THF. The resulting solution was concentrated in vacuo to a volume of approximately 50 mL (keeping the bath temperature below 30 °C), and the dilution-concentration process was repeated twice more to achieve a solution of the crude aldehyde 111 in approximately 50 mL of dry THF. A separate dry 250 mL 3-neck flask equipped with a magnetic stir bar, and rubber septum, was charged with 2.48 g (22.1 mmol) of potassium tert-butoxide and the flask was heated at 80 °C at 0.2 mm Hg for 40 h. After establishing a nitrogen atmosphere, 6 mL of dry THF was added and the solution was cooled to −78 °C. To the resulting suspension was added, via cannula, 3.9 mL (41.7 mmol) of condensed cis-2-butene, and 13.6 mL (21.8 mmol) of 1.6 M n-butyllithium solution in hexanes. The reaction mixture was warmed to −45 °C
(cyclohexane/CO₂) for 10 min, was cooled back to −78 °C, and a solution of 8.4 g (26.6 mmol) of (+)-B-methoxydiisopinocampheylborane in 27 mL of dry ether was added dropwise over 30 min. The reaction mixture was stirred for 30 min and 3.7 mL (23.3 mmol) of boron trifluoride-etherate was added over 3 min. The reaction mixture was stirred for 20 min, and the solution of the aldehyde, cooled to −78 °C, was added via cannula over 8 min. The reaction mixture was stirred for 3 h, warmed to 0 °C, and 40 mL of 2N aqueous NaOH was added, followed by the slow addition of 15 mL of 30% aqueous H₂O₂. The reaction mixture was stirred for 15 min, warmed to room temperature for 1 h, and 50 mL of brine was added. The resulting emulsion was well stirred for 1.5 h, the phases were partitioned, and the aqueous phase was extracted with three 50-mL portions of ether. The combined organic phases were washed with 50 mL of brine, dried (MgSO₄), and concentrated to give an oil which was chromatographed over 400 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 1.27 g (28%) of homoallylic alcohol ent-113 as a colorless oil: [α]₂⁰ -24.9, (c 1.13), CH₂Cl₂; [α]₂⁰ -23.7, (c 1.08), CHCl₃; H NMR (CDCl₃, 400 MHz) δ 1.09 (d, J = 6.7 Hz, 3H, CH₃), 2.25-2.53 (br m, 2H, CHCH₃ and OH), 3.39 (dd, J = 9.5, 7.6 Hz, 1H, CH₂OBn), 3.56 (dd, J = 9.5, 3.1 Hz, 1H, CH₂OBn), 3.61-3.70 (m, 1H, CHOH), 4.54 (s, 2H, OCH₂Ph), 5.00-5.09 (m, 2H, =CH₂), 5.75 (ddd, J = 17.4, 13.8, 7.8 Hz, 1H, =CH), 7.25-7.39 (br m, 5H, ArH); C NMR (CDCl₃, 100.6 MHz) δ 16.1 (q), 41.5 (d), 73.2 (t), 73.8 (t), 73.9 (d), 115.5 (t), 128.1 (d), 128.2 (d), 128.9 (d), 138.4.
5-Phenylsulfenyl-penta-2,4-dienal (152). To a room temperature solution of 2.52 g (15.2 mmol) of 3-phenylmercaptoacrolein (151) in 15.0 mL of dry THF was added 335 mg (1.4 mmol) of ZnBr$_2$ followed by the dropwise addition, over 14 min, of a solution of 5.0 mL (16.6 mmol) of $\alpha,\alpha'$-bis(trimethylsilyl)-tert-butylacetaldimine in 8 mL of dry THF. The reaction mixture was stirred for 1 h, a solution of 3.1 g (22.7 mmol) ZnCl$_2$ in 30 mL of water and 2 mL of ether was added, and stirring continued for an additional hour. The reaction mixture was filtered through a pad of celite, and the filtrate was extracted with two 35-mL portions of ether. The combined extracts were dried (MgSO$_4$), concentrated in vacuo, and the residue was chromatographed over 60 g of silica gel eluted with ethyl acetate-hexanes, 1:9 to give 1.7 g (60%) of the desired $\Delta^2$-dienal 152 as a red oil: IR (neat) 1675 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.96 (dd, $J = 15.3$, 8.0 Hz, 1H, $H_a$), 6.29 (dd, $J = 14.45$, 11.4 Hz, 1H, $H_c$), 7.06 (ddd, $J = 15.3$, 11.4 Hz, 1H, $H_b$), 7.04 (d, $J = 14.5$ Hz, 1H, $H_d$), 7.35-7.47 (m, 5H, ArH), 9.49 (d, $J = 8.0$ Hz, 1H, CHO); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 125.5, 129.2, 129.3, 130.1, 132.0, 132.6, 142.4, 150.6, 193.9.
2,2-Dimethyl-7-phenylsulfenylhepta-4,6-diene-1,3-diol (155). To a -70 °C solution of 268 mg (2.64 mmol) of diisopropylamine in 10 mL of dry THF was added dropwise 1.6 mL (2.56 mmol) of a 1.6 M solution of n-butyllithium in hexanes. The reaction mixture was stirred for 20 min and a solution of 293 mg (2.52 mmol) of ethyl isobutyrate in 5 mL of dry THF was added dropwise over 20 min. The reaction mixture was stirred at -70 °C for 20 min, warmed to -35 °C for 5 min, cooled back to -70 °C, and a solution of 413 mg (2.45 mmol) of aldehyde 152 in 5 mL of dry THF was added dropwise via syringe over 40 min. The reaction mixture was stirred for 20 min, 6 mL of saturated aqueous ammonium chloride was added, and the mixture was allowed to warm to room temperature. The reaction mixture was extracted with 50 mL of ethyl acetate and the extract was washed with two 5-mL portions of water and 5 mL of brine. After drying (MgSO₄), the solvent was removed in vacuo and the residue was dried under high vacuum (approximately 0.1 mm Hg) for 30 min. The residual 525 mg of crude β-hydroxy ester was dissolved in 11 mL of dry toluene. The reaction mixture was cooled to 0 °C and 5.1 mL (5.1 mmol) of a 1 M solution of DIBAL in hexanes was added dropwise over 20 min. The reaction mixture was stirred at 0
C for 40 min, 4 mL of ethanol was added slowly (about 20 min) followed by 40 mL of ethyl acetate and 10 mL of a solution of saturated aqueous sodium potassium tartarate. The biphasic mixture was stirred vigorously at room temperature for 1 h, the phases were partitioned, and the aqueous phase was extracted with two 10-mL portions of ethyl acetate. The combined organic phases were dried (MgSO₄) and concentrated to give a residue that was purified by chromatography (MPLC, column size B, eluted with ethyl acetate-hexanes, 1:3) to give 231 mg (36%) of diol 155 as a viscous oil: ¹H NMR (CDCl₃, 400 MHz) δ 0.87 (s, 3H, CH₃), 0.90 (s, 3H, CH₃), 2.62 (br s, 1H, OH), 2.67 (br s, 1H, OH), 3.46 (dd, J = 10.8, 3.4 Hz, 1H, CH₂OH), 3.55 (dd, J 10.8, 4.5 Hz, 1H, CH₂OH), 4.04 (dd, J = 6.9, 2.2 Hz, 1H, CHOH), 5.70 (dd, J = 14.6, 7.1 Hz, 1H, H₆), 6.25-6.43 (m, 3H, H₆, H₇, and H₈), 7.23-7.38 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 19.5, 22.7, 39.3, 72.3, 80.6, 127.4, 127.5, 129.5, 130.4, 131.3, 131.4, 131.9.

(±)-(2S,3S,4S)-5,5-Dimethyl-3-phenylselenenyl-2-(2-phenylsulfenyl-vinyl)tetrahydropyran-4-ol (156). To a -78 °C solution of 115 mg (0.44 mmol) of diol 155 in 4.4 mL of dry dichloromethane was added, dropwise over 5 min, a
solution of 85 mg (0.44 mmol) of phenylselenenyl chloride in 4.4 mL of dry dichloromethane. The reaction mixture was stirred at -78 °C for 2 h, and 1 mL of saturated aqueous sodium bicarbonate was added. After warming to room temperature, the phases were separated and the organic phase was washed with two 1-mL portions of saturated aqueous sodium bicarbonate, 1 mL of water, and 1 mL of brine. The organic phase was dried (Na₂SO₄), the solvent was removed in vacuo, and the residue was purified by chromatography (MPLC, lobar size A, eluted with ethyl acetate-hexanes, 1:9) to give 88 mg (45%) of pyran 156 contaminated with a small amount (ca 7%) of material suspected of being an isomer: IR (neat) 3454, 1579 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major) δ 0.95 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.61 (d, J = 2.4 Hz, 1H, OH), 3.35 (dd, J = 11.1, 1.0 Hz, 1H, H₄), 3.50-3.55 (m, 2H, CHO and CHSePh), 3.79 (d, J = 11.1 Hz, 1H, H₅), 4.26 (dd, J = 10.6, 7.5 Hz, 1H, H₆), 5.87 (dd, J = 15.1, 7.3 Hz, 1H, H₇), 6.60 (d, J = 15.1 Hz, 1H, H₈), 7.27-7.43 (m, 8H, ArH), 7.56-7.59 (m, 2H, ArH); some diagnostic signals for the impurity: δ 2.70 (d, J = 2.1 Hz, 1H, OH), 2.89-2.95 (m, 2H), 4.69 (dd, J = 11.1, 8.4 Hz, 1H, H₉); ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.9 (q), 24.0 (q), 36.7 (s), 52.7 (d), 72.0 (t), 74.2 (d), 76.2 (d), 127.4 (d), 128.1 (s), 128.4 (d), 128.7 (d), 129.5 (d), 129.8 (d), 130.4 (d), 130.8 (d), 134.8 (s), 135.0 (d); mass spectrum m/z 443.05; exact mass calcd. for C₂₁H₂₄O₂SSeNa⁺ m/z 443.0554, found m/z 443.0521.
5-(4-Methoxyphenyl)penta-2,4-dienal (165).\textsuperscript{57} To a suspension of 10 g (73.4 mmol) of potassium glutaraldehyde in 185 mL of dry THF was added 147 mg (1.2 mmol) of DMAP, 170 \( \mu \)L (1.2 mmol) of triethylamine, 11.6 g (76.7 mmol) of TBSCI, and the reaction mixture was stirred at room temperature for 12 h. A separate flask was charged with 2.0 g (83.6 mmol) of magnesium turnings, 26 mL of dry ether, and 2.5 mL (20.0 mmol) of neat \( \rho \)-bromoanisole. Once the reaction had initiated, as evidenced by self sustained reflux, a solution of 8.3 g (67.0 mmol) of \( \rho \)-bromoanisole in 26 mL of dry ether was added dropwise over 45 min. The reaction mixture was stirred at room temperature for 2 h and transferred, via cannula, to the solution of glutaraldehyde (previously cooled to 0°C) over 30 min. The reaction mixture was stirred at room temperature for 3 h, 100 mL of 3N aqueous HCl was added, and stirring continued for an additional 1.5 h. The reaction mixture was extracted with three 200-mL portions of ether, and the combined extracts were washed with two 50-mL portions of water, 50 mL of brine, and dried (MgSO\(_4\)). The solvent was removed in vacuo, and the residue was chromatographed over 500 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 8.9 g (65%) of aldehyde 165 as a yellow solid: mp 73-75 °C (lit.\textsuperscript{57} 72-73 °C); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \( \delta \) 3.7 (s, 3H, OCH\(_3\)), 6.10 (dd, \( J = 15.1, 8.1 \) \( \text{Hz} \))
7-(4-Methoxyphenyl)-2,2-dimethyl-3-(triethylsilanyloxy)hepta-4,6-dien-1-ol (167). To a -78 °C solution of 435 mg (4.30 mmol) of diisopropylamine in 43 mL of dry THF was added dropwise 2.0 mL (4.30 mmol) of a 2.1 M solution of n-butyllithium in hexanes. The reaction mixture was stirred for 15 min and 500 mg (4.30 mmol) of neat ethyl isobutyrate was added dropwise over about 2 min. The reaction mixture was stirred at -78 °C for 10 min, warmed to -45 °C for 5 min, cooled back to -78 °C, and a solution of 786 mg (4.18 mmol) of aldehyde 165 in 5 mL of dry THF was added dropwise via syringe over 5 min. The reaction mixture was stirred for 90 min, 898 mg (6.0 mmol) of neat TESCl was added in one portion, and the mixture was allowed to warm to ambient temperature over 1.5 h. The reaction mixture was washed with three 5-mL portions of aqueous saturated sodium bicarbonate and 10 mL of brine.
organic phase was dried (MgSO₄), the solvent was removed in vacuo, and the resulting 1.9 g of crude β-hydroxy ester was dissolved in 45 mL of dry toluene. The reaction mixture was cooled to -78 °C and 11 mL (11 mmol) of a 1 M solution of DIBAL in hexanes was added dropwise over 35 min. The reaction mixture was stirred at -78 °C for 1 h, 3 mL of ethanol was added slowly (over 20 min), and the solution was warmed to room temperature. To the reaction mixture was added 20 mL of a solution of saturated aqueous sodium potassium tartarate and 20 mL of ethyl acetate. The biphasic mixture was stirred vigorously at room temperature for 1.5 h, the phases were partitioned, and the aqueous phase was extracted with two 20-mL portions of ethyl acetate. The combined organic phases were dried (MgSO₄) and concentrated to give a residue that was purified by chromatography over 75 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 1.16 g (74%) of alcohol 167 as a pale yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 0.59 (q, J = 7.9 Hz, 6 H, Si(CH₂CH₃)₃), 0.80 (s, 3H, CH₃), 0.94 (t, J = 7.9 Hz, 9H, Si(CH₂CH₃)₃), 0.97 (s, 3H, CH₃), 3.13 (br t, J = 4.7 Hz, 1H, OH), 3.32 (dd, J = 10.8, 5.9 Hz, 1H, CH₂OH), 3.60 (dd, J = 10.8, 3.1 Hz, 1H, CH₂OH), 3.79 (s, 3H, OCH₃), 4.00 (d, J = 8.2 Hz, 1H, CHOTES), 5.76 (dd, J = 15.3, 8.2 Hz, 1H, H₄), 6.24 (dd, J = 15.2, 10.2 Hz, 1H, H₉), 6.48 (d, J = 15.6 Hz, 1H, H₉), 6.63 (dd, J = 15.6, 10.2 Hz, 1H, H₉), 6.84 (d, J = 8.9 Hz, 2 H, ArH), 7.33 (d, J = 8.9 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 5.4, 7.2, 21.1, 23.1, 39.8, 55.7, 71.5, 82.9, 114.5, 126.5, 128.0, 130.3, 132.6, 132.7, 133.1, 159.7.
(±)-(2S,3S,4S)-2[2(4-Methoxyphenylvinyl)5,5-dimethyl-3-phenylselenenyl]tetrahydropyran-4-ol (90). To a -78 °C solution of 256 mg (0.68 mmol) of alcohol 167 in 6 mL of dry dichloromethane was added, dropwise over 3 min, a solution of 130 mg (0.68 mmol) of phenylselenenyl chloride in 6 mL of dry dichloromethane. The reaction mixture was stirred at -78 °C for 35 min, and 1 mL of saturated aqueous sodium bicarbonate was added. After warming to room temperature, the reaction mixture was extracted with 30 mL of ethyl acetate, and the extract was washed with two 10-mL portions of saturated aqueous sodium bicarbonate, 10 mL of water, and 10 mL of brine. After drying (Na₂SO₄), the solvent was removed in vacuo and the residue was purified by chromatography over 20 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:9) to give 163 mg (57%) of pyran 90 contaminated with a small amount (ca 10%) of an isomer: ¹H NMR (CDCl₃, 400 MHz, major isomer) δ 0.92 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.56 (br s, 1H, OH), 3.34 (dd, J = 11.1, 1.0 Hz, 1H, H₄), 3.47 (br s, 1H, CHO), 3.62 (dd, J = 11.1, 2.4 Hz, 1H, H₄), 3.78-3.80 (m, 4H, CHSePh and OCH₃), 4.29 (dd, J = 10.6, 7.5 Hz, 1H, H₆), 6.04 (dd, J = 15.7, 7.5 Hz, 1H, H₆), 6.63 (d, J = 15.7 Hz, 1H, H₆), 6.80-6.86 (m, 2H, ArHOCH₃), 7.20-7.31 (m, ...
5H, ArH), 7.49-7.51 (m, 2H, ArH-ðCH3); 13C NMR (CDCl3, 100.6 MHz) δ 22.9, 24.0, 36.8, 52.7, 55.6, 72.1, 74.2 (d), 76.7, 114.2, 126.3, 128.2, 129.6, 129.7, 129.8, 133.5, 135.1, 159.7.

![Chemical structure](image)

(±)-(2S,4R)-2-[1'-Bromo-2'-hydroxy-2'-(4-methoxyphenyl)-ethyl]-5,5-dimethyl-3-phenylselenyltetrahydropyran-4-ol [stereochemistry at 1' and 2' not known] (168). To a 0 °C solution of 204 mg (0.49 mmol) of pyran 90 in 3 mL of acetone and 1.5 mL of water was added 88 mg (0.49 mmol) of N-bromosuccinimide. The reaction mixture was stirred for 10 min at 0 °C and 12 h at room temperature. The mixture was extracted with 30 mL of ethyl acetate. The organic extract was washed with two 10-mL portions of water, two 10-mL portions of brine, and dried (MgSO4). The solvent was removed in vacuo and the residue was chromatographed over 13 g of flash silica (eluted with ethyl acetate-hexanes, 1:9) to give 190 mg (75%) of bromohydrin 168 as a colorless oil: 1H NMR (CDCl3, 400 MHz) δ 0.82 (s, 3H, CH3), 0.96 (s, 3H, CH3), 2.56 (br s, 1H, OH), 3.27 (d, J = 10.5 Hz, 1H, Hδ), 3.38 (br s, 1H, CHOH), 3.55 (br s, 1H, OH), 3.65 (d, J = 10.5 Hz, 1H, Hδ), 3.70-3.74 (m, 4H, OCH3 and PhSeCH), 3.82 (dd, J = 11.1, 1.3 Hz, 1H, Hδ), 4.68 (dd, J = 6.4, 1.3 Hz, 1H, Hb), 4.99 (d, J = 6.4 Hz, 1H, Hα), 6.83 (d, J = 8.6 Hz, 2H, ArHOCH3), 7.18-7.25 (m, 5H, ArH), 7.51 (d, J = 9.5 Hz, 1H, ArH).
Hz, 2H, ArHOCH₃); ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.9, 23.6, 36.7, 52.5, 55.6, 60.7, 71.4, 73.0, 74.1, 76.6, 114.4, 127.4, 127.8, 128.7, 129.8, 134.1, 135.3, 159.7. This material was clearly a single diastereomer by ¹H and ¹³C NMR.

(±)-2[2'-Hydroxy-2'-{4-methoxyphenyl)ethyl]-5,5-dimethyl-tetrahydropyran-4-ol [stereochemistry at 2' not known] (169). To a solution of 212 mg (0.41 mmol) of pyran 168 in 10 mL of dry benzene at room temperature was added 1.08 g (3.7 mmol) of tri-n-butyltin hydride and 67 mg (0.41 mmol) of AIBN. The reaction flask was fitted with a reflux condenser and the reaction mixture was heated at reflux for 1 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was chromatographed over 50 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:2) to give 98 mg (85%) of 169 as a white solid: mp 118-123 °C; ¹H NMR (CDCl₃, 250 MHz) δ 0.85 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 1.46 (dt, J = 14.0, 2.9 Hz, 1H, H₂d), 1.83-2.00 (m, 3H, H₃d and H₃b), 3.31 (d, J = 11.4 Hz, 1H, H₃c), 3.57-3.61 (m, 2H, H₃e and CHOH), 3.79 (s, 3H, OHC₃), 3.86-3.96 (m, 1H, H₃c), 4.96 (dd, J = 6.4, 1.3 Hz, 1H, H₃a), 6.84-6.89 (m, 2H, ArH-OC₃), 7.24-7.29 (m, 2H, ArH-
OCH₃); \(^{13}\)C NMR (CDCl₃, 62.9 MHz) δ 22.1, 24.3, 34.8, 35.6, 44.0, 55.6, 69.7, 71.3, 72.4, 72.6, 114.1, 127.1, 137.2, 159.1.

(±)-(2S,4S)-(4-Hydroxy-5,5-dimethyltetrahydropyran-2-yl)-acetaldehyde (170). To a room temperature solution of 76.8 mg (0.27 mmol) of diol 169 in 2 mL of dry dichloromethane was added, in a dropwise manner, a solution of 146 mg (0.30 mmol) of bromine(I) hexafluorophosphate (161) in 2 mL of dry dichloromethane. The turbid reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo to give a residue that was chromatographed over 5 g of flash silica gel (eluted with ethyl acetate-hexanes, 4:6) to give product contaminated with residual collidine. The material was dissolved in 10 mL of ethyl acetate and washed with two 2-mL portions of 1 N aqueous HCl, two 2-mL portions of brine, and dried (MgSO₄). Removal of the solvent in vacuo gave 24 mg (52%) of aldehyde 170 as a colorless oil: IR (neat) 3436, 1723 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz) δ 0.84 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 1.59 (dt, J = 14.0, 2.8 Hz, 1H, H_c), 1.82 (dt, J = 14.0, 2.8, 1H, H_a), 1.89 (br s, 1H, OH), 2.43 (ddd, J = 16.1, 4.6, 1.9 Hz, 1H, H_d), 2.55 (ddd, J = 16.1, 8.1, 2.9 Hz, 1H, H_b), 3.23 (dd, J = 12.2, 1.0 Hz, 1H, H_d), 3.59-3.64 (m, 2H, H_c) and

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CJJOH), 4.12-4.24 (m, 1H, H₆), 9.76 (dd, J = 2.8, 1.8 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 100.6 MHz) δ 22.1 (q), 24.2, (q), 34.7 (s), 35.7 (t), 49.6 (t), 67.6 (d), 72.4 (d), 72.5 (t), 201.8 (d); mass spectrum m/z 195.10; exact mass calcd. for C₉H₁₆O₃Na⁺ m/z 195.0997, found m/z 195.1003.

(2'S,3'R,4S,5R)-3-[3'-Hydroxy-7-[4-methoxyphenyl)-2'-methylhepta-4,6-dienoyl]-4-methyl-5-phenyloxazolidin-2-one (172). To a 0 °C solution of 1.86 g (7.9 mmol) of propionyloxazolidinone 172b in 18 mL of dry dichloromethane was added a solution of 2.39 g (8.7 mmol) of freshly distilled (0.4 mm/ 43 °C) dibutylboron triflate in 8 mL of dry dichloromethane, keeping the internal temperature below 5 °C. To this solution was added, in the same manner, 1.23 g (9.5 mmol) of diisopropylethylamine, the reaction mixture was stirred at 0 °C for 30 min, cooled to −78 °C, and a solution of 1.67 g (8.9 mmol) of aldehyde 165 in 2.7 mL of dry dichloromethane was added via cannula over 20 min. The reaction mixture was stirred at −78 °C for 30 min, room temperature for 2.5 h, and after cooling to 0 °C, 9.5 mL of pH 7 phosphate buffer was added followed by a solution of 9.5 mL of H₂O₂ in 26 mL of methanol. The reaction mixture was stirred at 0 °C for 1.5 h and extracted with three 70-mL portions of ether. The combined extracts were washed with 40 mL of 5% aqueous sodium...
bicarbonate and two 20-mL portions of brine. After drying (MgSO₄), the solvent was removed in vacuo to give a yellow solid which was purified by crystallization (ethyl acetate-hexanes, 2:3) to give 2.3 g (70%) of a 22:1 diastereomeric mixture of hydroxy-imides 172 as a white solid. An additional 0.5 g (15%) of product was obtained by concentration of the mother liquor and chromatography of the residue over 50 g of silica gel (eluted with ethyl acetate-hexanes, 1:5): mp 155-157 °C; IR (KBr) 3428, 1779, 1686 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major isomer) δ 5.89 (d, J = 6.6 Hz, 3H, Me₆), 1.26 (d, J = 7.0 Hz, 3H, CH₃), 2.80 (br s, 1H, OH), 3.30-3.98 (m, 1H, CHCH₃), 3.91-3.98 (m, 1H, CHCH₃), 4.59 (t, J = 4.3 Hz, 1H, CHOH), 4.75-4.87 (d, J = 6.7, 6.6 Hz, 1H, CHMe₆), 5.66 (d, J = 7.3 Hz, 1H, CHPh), 5.77 (dd, J = 6.1, 6.2 Hz, 1H, H₆), 6.46 (ddd, J = 15.2, 10.3, 1.1 Hz, 1H, H₇), 6.52 (d, J = 15.2 Hz, 1H, H₈), 6.66 (dd, J = 15.6, 10.3, Hz, 1H, H₉), 6.85 (d, J = 8.7 Hz, 2H, ArH-OCH₃), 7.27-7.43 (m, 7H, ArH-OCH₃ and ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.6 (q), 14.8 (q), 43.4 (d), 55.2 (d), 55.7 (q), 73.1 (d), 79.4 (d), 114.5 (d), 126.0 (d), 126.5 (d), 128.0 (d), 129.1 (d), 129.2 (d), 130.3 (s), 131.9 (d), 132.6 (d), 133.3 (s), 133.5 (s), 153.1 (s), 159.7 (s), 176.6 (s); mass spectrum m/z 558.26; exact mass calcd. for C₂₅H₂₇NO₅Na⁺ m/z 444.1787, found m/z 444.1793.
(4S,5R)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (172b). To a -78 °C solution of 3.0 g (16.9 mmol) of 4-methyl-5-phenyloxazolidin-2-one in 35 mL of dry THF was added 7.7 mL (17.2 mmol) of 2.2 M n-butyllithium solution in hexanes, dropwise over 30 min. After stirring for 10 min, 1.5 mL (17.8 mmol) of neat propionyl chloride was added as quickly as possible, while keeping the internal temp below -60 °C, and the reaction mixture was then warmed to 0 °C and stirred for 1 h. Excess acid chloride was hydrolyzed by addition of 7 mL of 1M potassium carbonate, and after stirring for 1 h at room temperature, the reaction mixture was extracted with three 50-mL portions of dichloromethane. The combined extracts were washed with 25 mL of water, 25 mL of brine, dried (MgSO₄), and concentrated. The residue was chromatographed over 150 g of silica (eluted with ethyl acetate-hexanes, 1:3) to give 3.3 g (83%) of 172b as a pale yellow oil: \(^1\)H NMR (CDCl₃, 400 MHz) δ 0.89 (d, \( J = 6.6 \) Hz, 3H, CH₃), 1.18 (t, \( J = 7.4 \) Hz, 3H, CH₂CH₃), 2.83-3.09 (m, 2H, CH₂CH₂C=O), 4.76 (dq, \( J = 6.9, 6.7 \) Hz, 1H, CHCH₃), 5.66 (d, \( J = 7.3 \) Hz, 1H, CHPh), 7.28-7.45 (m, 5H, ArH); \(^{13}\)C NMR (CDCl₃, 100.6 MHz) δ 8.7, 15.0, 29.7, 55.2, 79.4, 126.1, 129.1, 129.2, 133.8, 139.2, 174.3.
To a 0 °C suspension of 953 mg (23.8 mmol) of sodium hydride (as a 60% suspension in mineral oil) in 17.5 mL of dry THF, was added dropwise a solution of 3.5 g (21.7 mmol) of 4-isopropyl-2-thioxothiazolidin-1-one in 17.5 mL of dry THF. The reaction mixture was stirred for 10 min, and 2.1 mL (23.8 mmol) of neat propionyl chloride was added dropwise over 5 min. The cold bath was removed and the reaction mixture was stirred at room temperature for 2 h, quenched by addition of 3.5 mL of 5% aqueous HCl, and extracted with three 25-mL portions of ethyl acetate. The combined extracts were washed with two 10-mL portions of water, two 10-mL portions of brine, dried (MgSO₄), and concentrated to give an oil that was chromatographed over 250 g of silica (eluted with ethyl acetate-hexanes, 1:9) to give 4.6 g (97%) of 173 as a yellow oil: 

\[ \text{H NMR (CDCl}_3, 400 MHz) \delta 0.91 (d, J = 7.0 \text{ Hz}, 3H, (CH}_3)_2\text{CH}, 0.10 (d, J = 7.0 \text{ Hz}, 3H, (CH}_3)_2\text{CH}, 1.10 (t, J = 7.5 \text{ Hz}, 3H, CH}_3\text{CH}_2), 2.30 (m, 1H, CH(CH}_3)_2), 2.97 (dd, J = 11.4, 1.2 \text{ Hz}, 1H, CH}_2\text{S}), 3.03-3.16 (m, 1H, CH}_3\text{CH}_2\text{C}=0), 3.21-3.37 (m, 1H, CH}_3\text{CH}_2\text{C}=0), 3.46 (dd, J = 11.4, 8.2 \text{ Hz}, 1H, CH}_2\text{S}), 5.10 (dt, J = 6.3, 1.2 \text{ Hz}, \text{H} \text{NMR (CDCl}_3, 400 MHz) \delta 0.91 (d, J = 7.0 Hz, 3H, (CH}_3)_2\text{CH}, 0.10 (d, J = 7.0 Hz, 3H, (CH}_3)_2\text{CH}, 1.10 (t, J = 7.5 Hz, 3H, CH}_3\text{CH}_2), 2.30 (m, 1H, CH(CH}_3)_2), 2.97 (dd, J = 11.4, 1.2 Hz, 1H, CH}_2\text{S}), 3.03-3.16 (m, 1H, CH}_3\text{CH}_2\text{C}=0), 3.21-3.37 (m, 1H, CH}_3\text{CH}_2\text{C}=0), 3.46 (dd, J = 11.4, 8.2 Hz, 1H, CH}_2\text{S}), 5.10 (dt, J = 6.3, 1.2 Hz,
(2'S,3'R,4R)-3'-Hydroxy-1-(4-isopropyl-2-thioxothiazolidin-3-yl)-7-(4-methoxyphenyl)-2'-methylhepta-4,6-dien-1-one (174). To a −70 °C solution of 8.51 g (20.4 mmol) of tin(II) triflate in 37 mL of dry dichloromethane was added 2.31 g (20.4 mmol) of neat N-ethylpiperidine, followed by a solution of 3.70 g (17.0 mmol) of thiazolidinethione 173 in 18 mL of dry dichloromethane, at a rate that maintained the reaction mixture temperature below −70 °C (about 20 min). The reaction mixture was stirred at −70 °C for 3.5 h, a solution of 3.20 g (17.0 mmol) of aldehyde 165 in 10 mL of dry dichloromethane was added over 10 min, and stirring continued for 1 h at −70 °C and 2 h at 0 °C. The reaction mixture was cooled to −30 °C, 5 mL of pH 7 phosphate buffer was added, and the solution was allowed to warm to room temperature. The suspension was filtered through a thin pad of celite, the filter cake was rinsed with two 15-mL portions of dichloromethane, and the filtrate was washed with two 20-mL portions of brine. After drying (Na₂SO₄), the solvent was removed in vacuo and the resulting red oil was chromatographed over 500 g of flash silica gel (eluted with ethyl acetate-
hexanes, 1:2), to give 5.42 g (79%) of a 95:5 mixture of diastereomeric hydroxy-
imides 174 as an orange foam: $[\alpha]^2_0 -176.4$, c 0.99, CHCl$_3$; IR (neat) 3504, 1686,
1604 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz, major isomer) $\delta$ 0.94 (d, $J = 7.0$ Hz, 3H,
CH(CH$_3$)$_2$), 1.02 (d, $J = 6.7$ Hz, 3H, CH(CH$_3$)$_2$), 1.16 (d, $J = 7.0$ Hz, 3H, CHCH$_2$),
2.25 (m, 1H, CH(CH$_3$)$_2$), 2.96 (dd, $J = 11.6$, 1.0 Hz, 1H, CH$_2$S), 2.99 (br s, 1H,
OH), 3.44 (dd, $J = 11.5$, 8.1 Hz, 1H, CH$_2$S), 3.77 (s, 3H, OCH$_3$), 4.68 (t, $J = 4.5$
Hz, 1H, CHOH), 4.90 (dq, $J = 6.9$, 3.4 Hz, 1H, CHCH$_3$), 5.16 (dt, $J = 6.6$, 1.0 Hz,
1H, CHN), 5.76 (dd, $J = 15.1$, 5.9 Hz, 1H, H$_d$), 6.39-6.49 (m, 2H, H$_a$ and H$_b$), 6.63
(dd, $J = 15.4$, 10.4 Hz, 1H, H$_b$), 6.80-6.84 (m, 2H, ArH-OCH$_3$), 7.28-7.31 (m, 2H,
ArH-OCH$_3$); diagnostic signals for the minor isomer: $\delta$ 1.15 (d, $J = 7.0$ Hz, 3H,
CHCH$_3$), 1.82-1.90 (m, 1H, CH(CH$_3$)$_2$), 5.42 (dd, $J = 11.0$, 8.5 Hz, 1H, H$_d$). The
ratio of diastereomers was calculated using the integrations at $\delta$ 1.15 and 1.16;
$^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 11.9 (q), 18.0 (d), 19.5 (q), 30.4 (t), 31.2 (d), 43.4
(d), 55.7 (q), 73.2 (d), 73.3 (d), 114.5 (d), 126.7 (d), 128.0 (d), 130.4 (s), 132.0
(d), 132.4 (d), 132.7 (d) 159.6 (s), 177.2 (s), 203.8 (s); mass spectrum $m/z$
(relative intensity) 428.13 (M+Na$^+$ 41); exact mass calcd. for C$_{21}$H$_{27}$NO$_3$S$_2$Na$^+$ $m/z$
428.1330, found $m/z$ 428.1302.
(2S,3R)-3-Hydroxy-7-(4-methoxyphenyl)-2-methylhepta-4,6-dienoic acid methoxymethyl amide (175). To a −10 °C suspension of 6.49 g (66.5 mmol) of N,O-dimethylhydroxylamine-hydrochloride in 18 mL of dry dichloromethane, was added 33.5 mL (67.0 mmol) of a 2 M solution of trimethylaluminum in hexanes, over 40 min, and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was cooled again to −10 °C, and a solution of 5.40 g (13.3 mmol) of thioimide 174 in 100 mL of dry dichloromethane was added dropwise via cannula over 100 min, and the reaction mixture was stirred at −5 °C for 3h. The reaction mixture was transferred via cannula to a rapidly stirred 0 °C emulsion comprised of 70 mL of dichloromethane in 140 mL of 0.5 M HCl. The resulting yellow solution was stirred at 0 °C for 30 min, the phases were partitioned, and the organic phase was washed with two 25-mL portions of water and two 25-mL portions of brine. The organic phase was dried (MgSO₄), the solvent was removed in vacuo, and the orange residue was chromatographed over 200 g of silica gel (eluted with ethyl acetate-hexanes, 1:2) to give 3.74 g (92%) of Weinreb amide 175 as a pale yellow solid: mp 74-77 °C; [α]DS²⁰ +32.4, c 1.12, CHCl₃; IR (neat) 3423, 1637, 1604.
\[ 1^1H \text{ NMR (CDCl}_3, 400 \text{ MHz}) \delta 1.18 (d, J = 7.1 \text{ Hz, } 3H, \text{ CH}_3), 2.98 (\text{ br s, CH}_3), 3.19 (s, 3H, NCH}_3), 3.70 (s, 3H, NOCH}_3), 3.79 (s, 3H, Ar-OCH}_3), 3.84 (\text{ br s, 1H, OH}), 4.52 (\text{ br t, J = 3.9 Hz, 1H, CH}_2\text{OH}), 5.71 (\text{ dd, J = 15.1, 5.8 Hz, } 1H, \text{ H}_d), 6.45 (\text{ ddd, J = 15.1, 10.5, 1.1 Hz, 1H, H}_c), 6.49 (d, J = 15.5 \text{ Hz, 1H, H}_a), 6.81-6.85 (m, 2H, Ar-OCH}_3), 7.29-7.33 (m, 2H, Ar-OCH}_3); 13^C \text{ NMR (CDCl}_3, 100.6 \text{ MHz}) \delta 11.2 (q), 32.3 (q), 40.1 (d), 55.7 (q), 62.0 (q), 72.6 (d), 114.4 (d), 126.7 (d), 127.9 (d), 130.4 (s), 132.0 (d), 132.5 (d), 152.6 (d) 159.6 (s), 178.0 (s); \text{ mass spectrum } \text{m/z (relative intensity) 328.16 M}^+\text{Na}^+ 81); \text{ exact mass calcd. for } C_{17}H_{23}NO_4Na^+ \text{ m/z 328.1519, found m/z 328.1551.} \]

For \text{calcd. for } C_{17}H_{23}NO_4: C, 66.86; H, 7.59; N, 4.59. \text{ Found: C, 66.18; H, 7.27; N = 63.}

\[ [\text{Benzyl}o\text{xy}methyl]\text{tributylstannane (182) \text{.}^{44} To a } 0 \text{ °C solution of 30.6 mL (218 mmol) of diisopropylamine in 400 mL of dry THF was added 82.2 mL (218 mmol) of a 2.43 M solution of n-butyllithium in hexanes. The reaction mixture was stirred for 5 min, 53.8 mL (200 mmol) of tri-n-butyltin hydride was added and stirring continued for another 15 min before the solution was cooled to \text{-78 °C. To this greenish solution was added 27.6 mL (200 mmol) of neat}} \]
A methylbenzyl ether, dropwise over about 5 min, and the reaction mixture was stirred for 40 min. After warming to room temperature, 1.2 L of hexanes was added, the solution was washed with two 100-mL portions of water, 100 mL of brine, and dried (Na₂SO₄). Removal of the solvent in vacuo gave a pale yellow oil which was chromatographed over 900 g of silica gel (eluted with hexanes), and this provided 54.9 g (63%) of stannane 182 as a colorless oil: ¹H NMR (CDCl₃, 250 MHz) δ 0.85-0.95 (m, 15H, n-Bu), 1.22-1.37 (m, 6H, n-Bu), 1.45-1.61 (m, 6H, n-Bu), 3.72-3.77 (m, 2H, SnCH₂), 4.31 (s, 2H, OCH₂ Ph), 7.27-7.36 (m, 5H, ArH).

![Chemical Structure](image)

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(2R,3R)-3-(tert-Butyldimethylsilyloxy)-7-(4-methoxyphenyl)-2-methylhepta-4,6-dienoic acid methoxymethyl amide (184). To a room temperature solution of 611 mg (2.0 mmol) of Weinreb amide 175 in 13 mL of dry DMF was added 356 mg (2.5 mmol) of TBSCI, 184 mg (2.7 mmol) of imidazole, and 24 mg (0.2 mmol) of DMAP. The reaction mixture was stirred for 18 h, poured into 13 mL of water, and the solution was extracted with three 30-mL portions of ether-hexanes, 1:1. The combined extracts were washed with two...
10-mL portions of 0.5 M HCl, 10 mL of water, 10 mL of brine, and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was chromatographed over 40 g of silica gel (eluted with ethyl acetate-hexanes, 1:3) to give 1.0 g (94%) of TBS-ether 184 as a white foam: mp 48-50 °C; IR (thin film) 1782, 1701, 1605 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.03 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃), 0.88 (d, J = 6.6 Hz, 3H, Me), 0.91 (s, 9H, SiC(CH₃)₃), 1.21 (d, J = 6.7 Hz, 3H, CH₃), 3.80 (s, 3H, OCH₃), 4.02 (dq, J = 6.7, 6.5 Hz, 1H, CH₂CH₃), 4.39 (t, J = 6.7 Hz, 1H, CH₂OTBS), 4.65 (dq, J = 7.0, 6.5 Hz, 1H, CHMe₂), 5.52 (d, J = 7.0 Hz, 1H, CHPh), 5.77 (dd, J = 15.2, 7.2 Hz, 1H, H₂), 6.29 (dd, J = 15.2, 10.3 Hz, 1H, H₂), 6.50 (d, J = 15.6 Hz, 1H, H₂), 6.64 (dd, J = 15.6, 10.3 Hz, 1H, H₂), 6.83-6.86 (m, 2H, ArH-OCH₃), 7.23-7.25 (m, 2H, ArH-OCH₃), 7.31-7.40 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ -4.5 (q), -3.7 (q), 13.1 (q), 14.7 (q), 18.5 (s), 26.2 (q), 45.2 (d), 55.6 (d), 55.7 (q), 75.7 (d), 79.3 (d), 114.5 (d), 126.0 (d), 126.5 (d), 127.9 (d), 129.0 (d), 129.1 (d), 130.3 (s), 131.9 (d), 132.6 (d), 133.6 (s), 134.1 (d), 153.2 (s), 159.7 (s), 174.9 (s); mass spectrum m/z 558.26; exact mass calcld. for C₃H₄O₄NO₃SiNa⁺ m/z 558.2652, found m/z 558.2643.
(2R,3R)-3-(tert-Butyldimethylsilyloxy)-7-(4-methoxyphenyl)-2-methylhepta-4,6-dienal (185). To a -78 °C suspension of 24 mg (0.6 mmol) of 95% LiAlH₄ in 2.5 mL of dry THF was added a solution of 208 mg (0.5 mmol) of Weinreb amide 184 in 2.5 mL of dry THF, dropwise over 25 min. The reaction mixture was stirred at -78 °C or 2 h, -20 °C for 5 min, and 1 mL of water was cautiously added. The resulting suspension was filtered through a pad of celite and the filtrate was extracted with 30 mL of THF. The extract was washed with 5 mL of brine, dried (MgSO₄), the solvent was removed in vacuo, and the residue was chromatographed over 10 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 141 mg (67%) of unreacted starting material and 30 mg (17%) of aldehyde 185 as an oil: IR (neat) 1726, 1604 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.04 (s, 3H, SiCH₃), 0.06 (s, 3H, SiCH₃), 0.89 (s, 9H, SiC(CH₃)₃), 1.09 (d, J = 7.0 Hz, 3H, CH₃), 2.47-2.53 (m, 1H, CHCH₃), 3.80 (s, 3H, OCH₃), 4.60 (ddd, J = 6.9, 4.5, 0.9 Hz, 1H, CHOTBS), 5.70 (dd, J = 15.2, 6.7 Hz, 1H, Hd), 6.33 (ddd, J = 15.2, 9.7, 0.9 Hz, 1H, Hc), 6.48 (d, J = 15.6 Hz, 1H, Ha), 6.62 (dd, J = 15.6, 9.7 Hz, 1H, Ha).
Hz, 1H, Hb) 6.83 (m, 2H, ArH-OCH3), 7.31-7.34 (m, 2H, ArH-OCH3), 9.78 (d, J = 1.4 Hz, 1H, CHO); 13C NMR (CDCl3, 100.6 MHz) δ -4.6 (q), -3.7 (q), 8.9 (q), 18.5 (s), 26.1 (q), 53.4 (d), 55.6 (q), 73.7 (d), 114.5 (d), 126.3 (d), 128.0 (d), 130.2 (s), 132.2 (d), 132.8 (d), 132.9 (d), 159.7 (s), 204.9 (d).

(3R,4R)-1-Benzyl-oxy-4-(tert-butyldimethylsilyloxy)-8-(4-methoxy-phenyl)-3-methylocta-5,7-dien-2-one (188). To a -78 °C solution of 308 mg (0.75 mmol) of stannane 182 in 2 mL of dry THF was added 469 µL (0.75 mmol) of a 1.6 M solution of n-butyllithium in hexanes, at a rate that kept the internal temperature below -65 °C. The reaction mixture was stirred for 30 min and a solution of Weinreb amide 184 in 2 mL of dry THF was added dropwise, again keeping the internal temperature below -65 °C. The reaction mixture was stirred at -78 °C for 2 h, 0.5 mL of saturated aqueous ammonium chloride was added, and after warming to room temperature, was extracted with 30 mL of ethyl acetate. The extract was washed with two 5-mL portions of water, two 5-mL portions of brine, and dried (Na2SO4). Removal of the solvent in vacuo gave a residue that was chromatographed over 20 g of silica gel (eluted with two void-
volumes of hexanes, followed by ethyl acetate-hexanes, 1:4) to give 69 mg (48%) of ketone 188: IR (neat) 1722, 1602 cm⁻¹; $^1$H NMR (CDCl₃, 500 MHz) δ 0.00 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.87 (s, 9H, SiC(CH₃)₃), 1.08 (d, $J = 7.0$ Hz, 3H, CH₃), 2.82 (dq, $J = 6.8, 6.7$ Hz, 1H, CHCH₃), 3.81 (s, 3H, Ar-OCH₃), 4.11 (d, $J = 17.6$ Hz, 1H, O=CH₂), 4.20 (d, $J = 17.6$ Hz, 1H, O=CH₂), 4.31 (t, $J = 7.6$ Hz, 1H, CHOTBS), 4.53 (d, $J = 12.0$ Hz, 1H, OCH₂Ph), 4.58 (d, $J = 12.0$ Hz, 1H, OCH₂Ph), 5.62 (dd, $J = 15.3, 7.4$ Hz, 1H, H₄), 6.22 (dd, $J = 15.3, 10.4$ Hz, 1H, H₅), 6.45 (d, $J = 15.6$ Hz, 1H, H₅), 6.57 (dd, $J = 15.6, 10.4$ Hz, 1H, H₆), 6.83 (m, 2H, ArH-OCH₃), 7.25-7.34 (m, 7H, ArH-OCH₃ and ArH); $^{13}$C NMR (CDCl₃, 125.8 MHz) δ -4.5 (q), -3.6 (q), 12.9 (q), 18.5 (s), 26.2 (q), 50.0 (d), 55.7 (q), 73.6 (t), 75.5 (d), 76.0 (t), 114.5 (d), 126.4 (d), 128.0 (d), 128.3 (d), 128.3 (d), 128.8 (d), 130.3 (s), 132.4 (d), 132.8 (d), 132.9 (d), 137.8 (s), 159.7 (s), 210.0 (s); mass spectrum m/z 503.26; exact mass calcd. for C₂₉H₄₀O₄SiNa⁺ m/z 503.2594, found m/z 503.2601. Continued elution of the column gave 12 mg (4%) of α-amino ketone 190 as a yellow oil:
(3R,4R)-4-(tert-Butyldimethylsilyl oxy)-1-methoxyamino-8-(4-methoxyphenyl)-3-methylocta-5,7-diene-2-one (190). IR (neat) 3323, 1664 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.07 (s, 3H, SiCH₃), 0.10 (s, 3H, SiCH₃), 0.92 (s, 9H, SiC(CH₃)₃), 1.13 (d, J = 7.0 Hz, 3H, CH₃), 2.54 (dq, J = 7.1, 4.8 Hz, 1H, CHCH₃), 3.30 (s, 3H, NOCH₃), 3.79 (s, 3H, Ar-OCH₃), 4.32 (dd, J = 6.8, 5.2 Hz, 1H, CHOTBS), 4.61 (dd, J = 10.4, 6.4 Hz, 1H, CH₂NH), 4.72 (dd, 10.4, 6.4 Hz, 1H, CH₂NH), 5.66 (dd, J = 15.1, 7.3 Hz, 1H, Hₐ), 6.28 (dd, J = 15.1, 10.1 Hz, 1H, Hₐ), 6.47 (d, J = 15.5 Hz, 1H, H₉), 6.59 (dd, J = 15.5, 10.1 Hz, 1H, H₉), 6.84 (d, J = 8.7 Hz, 2H, ArH-OCH₃), 7.01 (t, J = 7.2 Hz, 1H, NH), 7.30 (d, J = 8.8 Hz, 2H, ArH-OCH₃); ¹³C NMR (CDCl₃, 100.6 MHz) δ -4.6, -3.7, 13.2, 18.5, 26.2, 47.7, 55.6, 56.4, 71.6, 76.1, 114.5, 126.4, 128.0, 130.2, 131.3, 133.0, 133.2, 159.7, 174.7; mass spectrum m/z 419.25; exact mass calcd. for C₂₃H₃₇O₄NSi m/z 419.2492, found m/z 419.2478. Continued elution of the column gave 14 mg (5%) of methylamide 189 as an oil:
(3R,4R)-4-(tert-Butyldimethylsilanyloxy)-8-(4-methoxyphenyl)-3-methyl-1-methylaminocta-5,7-diene-2-one (189). IR (neat) 3314, 1648 cm⁻¹; 
'H NMR (CDCl₃, 250 MHz) δ 0.05 (s, 3H, SiCH₃), 0.08 (s, 3H, SiCH₃), 0.91 (s, SiC(CH₃)₃), 1.11 (d, J = 7.2 Hz, 3H, CH₃), 2.44 (dq, J = 7.0, 4.6 Hz, 1H, CH₂), 2.78 (d, J = 4.7 Hz, 3H, NCH₃), 3.80 (s, 3H, Ar-OCH₃), 4.33 (dd, J = 7.0, 3.2 Hz, 1H, ArH), 5.65 (dd, J = 15.1, 7.1 Hz, 1H, H₉, 6.18-6.23 (m, 1H, CHOTBS), 6.27 (dd, J = 15.1, 10.1 Hz, 1H, H₈), 6.45 (d, J = 15.5 Hz, 1H, H₇), 6.61 (d, J = 10.5 Hz, 1H, H₆), 6.84 (d, J = 8.7 Hz, 2H, ArH-OCH₃), 7.31 (d, J = 8.8 Hz, 2H, ArH-OCH₃); 
13C NMR (CDCl₃, 100.6 MHz) δ -4.6, -3.7, 12.9, 18.5, 26.2, 47.7, 55.7, 75.9, 77.7, 114.4, 126.5, 127.9, 130.3, 132.3, 132.6, 132.7, 159.6, 174.6; mass spectrum m/z 389.24; exact mass calcd. for C₉₃H₇₂O₃NSi m/z 389.2386, found m/z 389.2375
(2R,3R)-7-(4-Methoxyphenyl)-2-methyl-3-(triethylsilyloxy)-hepta-4,6-dienoic acid methoxymethyl amide (195). To a solution of 5.54 g (18.2 mmol) of Weinreb amide 175 in 80 mL of dry DMF was added 2.40 g (35.2 mmol) of imidazole and 4.08 g (27.0 mmol) of neat TESCl, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with the addition of 2 mL of saturated aqueous sodium bicarbonate, diluted with 75 mL of water, and extracted with three 150-mL portions of ether-hexanes (1:1). The combined extracts were washed with 50 mL of brine, dried (MgSO₄), and concentrated to give a residue that was purified by chromatography over 170 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:2). This gave 7.21 g (95%) of the desired silyl ether 195 as a yellow oil that solidified to a waxy solid upon standing at -20 °C: mp 37-39 °C; [α]_D^20 = -55.4, (c 1.42), CHCl₃; IR (neat) 1655, 1604 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.61 (q, J = 7.7 Hz, 6H, Si(CH₂CH₃)₃), 0.95 (t, J = 7.8 Hz, 9H, Si(CH₂CH₃)₃), 1.21 (d, J = 6.9 Hz, 3H, CHCH₃), 3.05 (br s, 1H, CHCH₃), 3.11 (s, 3H, NCH₃), 3.63 (s, 3H, NOCH₃), 3.79 (s, 3H, ArOCH₃), 4.28 (t, J = 8.0 Hz, 1H, CH₃Si(CH₂CH₃)₃), 5.73 (dd, J = 15.2, 7.3 Hz, 1H, H₆), 6.27 (dd, J = 15.2, 10.4 Hz, 1H, H₅), 6.44 (d, J = 15.6 Hz, 1H, H₄), 6.58 (dd, J =
Due to the complicating presence of amide rotamers, it was not possible to determine the multiplicity of the peaks in the spectrum; exact mass calcd. for $C_{23}H_{37}NO_{3}Si \text{ m/z} 419.2492$, found $m/z$ 419.2491.

(2R,3R)-1-Benzylloxy-8-(4-methoxyphenyl)-3-methyl-4-(triethyl-silanoxy)-octa-5,7-dien-2-one (196). To a $-78 \, ^\circ\text{C}$ solution of 6.17 g (14.31 mmol) of stannane 182 in 45 mL of dry THF was added 6.8 mL (9.54 mmol) of a 1.4 M solution of $n$-butyllithium in hexanes, dropwise at a rate such that the internal temperature was maintained below $-70 \, ^\circ\text{C}$. The reaction mixture was stirred at $-78 \, ^\circ\text{C}$ for 1 h, and to it was added a solution of 2.41 g (5.80 mmol) of protected Weinreb amide 195 in 8 mL of dry THF, as rapidly as possible, while keeping the internal temperature below $-75 \, ^\circ\text{C}$. The reaction mixture was stirred for 80 min, 15 mL of pH 7 phosphate buffer was added, and the solution was warmed to room temperature over about 30 min. The reaction mixture was
washed with two 15-mL portions of water, two 15-mL portions of brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The resulting yellow oil was extracted with three 25-mL portions of acetonitrile, the extracts were combined, the solvent was removed in vacuo, and the residue was chromatographed over 300 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 1.8 g (42%) of ketone 196 as a pale yellow oil: IR (neat) 1724, 1604 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.57 (q, J = 7.8 Hz, 6H, Si(CH$_2$CH$_3$)$_3$), 0.92 (t, J = 7.8 Hz, 9H, Si(CH$_2$CH$_3$)$_3$), 1.08 (d, J = 7.0 Hz, 3H, CH$_3$), 2.83 (dq, J = 6.9, 6.7 Hz, 1H, CHCH$_3$), 3.80 (s, 3H, Ar-OCH$_3$), 4.11 (d, J = 17.6 Hz, 1H, O=CCH$_2$), 4.20 (d, J = 17.6 Hz, 1H, O=CCH$_2$), 4.29 (t, J = 7.4 Hz, 1H, CHOSi(CH$_2$CH$_3$)$_3$), 5.63 (dd, J = 15.2, 7.6 Hz, 1H, H$_d$), 6.22 (dd, J = 15.2, 10.3 Hz, 1H, H$_c$), 6.45 (d, J = 15.6 Hz, 1H, H$_a$), 6.57 (dd, J = 15.6, 10.3 Hz, 1H, H$_b$), 6.85 (d, J = 8.7 Hz, 2H, ArH-OCH$_3$), 7.25-7.36 (m, 7H, ArH-OCH$_3$ and ArH). It should be noted that on occasion this material is contaminated with ca 5% of a retro-aldol byproduct with signals at: δ 2.01 (q, J = 7.4 Hz, 2H, O=CCH$_2$CH$_3$), 3.55 (s, 2H, O=CCH$_2$OBn), 4.13 (s, 2H, OCH$_2$Ph); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ 5.3 (t), 7.2 (q), 12.9 (q), 49.9 (d), 55.7 (q), 73.6 (t), 75.5 (d), 76.1 (t), 114.5 (d) 126.4 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.8 (d), 130.3 (s), 132.4 (d), 132.8 (d), 132.9 (d), 137.8 (s), 159.7 (s), 210.0 (s); mass spectrum m/z (relative intensity) 503.26 (M+Na$^+$ 39), 519.27 (M+K$^+$ 43); exact mass calcd. for C$_{29}$H$_{40}$O$_4$SiNa$^+$ m/z 503.2588, found m/z 503.2593.
(1R,2S,3R)-1-Benzyloxy-8-(4-methoxyphenyl)-3-methylocta-5,7-diene-2,4-diol (179). To a room temperature solution of 2.73 g (5.7 mmol) of ketone 196 in 48 mL of THF and 10 mL of water was added 442 µL (5.7 mmol) of neat trifluoroacetic acid and the reaction mixture was stirred for 1 h. To the reaction mixture was added 472 mg (5.7 mmol) of solid sodium bicarbonate, stirring continued for 30 min, 50 mL of toluene was added, and the solution was washed with three 20-mL portions of water and three 20-mL portions of brine. After drying (Na₂SO₄), the solution was concentrated to give a yellow oil which was dried under high vacuum (approximately 0.1 mm) for 30 min. The residue was dissolved in 55 mL of dry toluene and the solution was cooled to -78 °C. To this solution was added 10 mL of a solution of zinc borohydride over 20 min, the reaction mixture was stirred for 1 h, and 8 mL of pH 7 phosphate buffer was added. After warming to room temperature, the reaction mixture was extracted with 50 mL of ethyl acetate, and the extract was washed with three 20-mL portions of brine and dried (Na₂SO₄). The solvent was removed in vacuo, and the residue was chromatographed over 250 g of silica gel (eluted with ethyl
acetate-hexanes, 1:3) to give 2.36 g (ca 74%) of a 1:4 diastereomeric mixture of epoxides 179 as a waxy yellow solid. It should be noted that this material was contaminated with approximately 35% of triene 194. This material was used without further purification for subsequent reactions, however, analytically pure material could be obtained by recrystallization from benzene-hexanes (1:1): mp 39-91 °C; IR (neat) 3416, 1604, 1510 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major isomer) δ 0.94 (d, J = 7.1 Hz, 3H, CHCH₃), 1.72-1.79 (m, 1H, CHCH₃), 2.84 (br s, 2H, OH), 3.45-3.61 (m, 2H, CH₂OBn), 3.80 (s, 3H, OCH₃), 4.08-4.11 (m, 1H, H₁), 4.47-4.49 (m, 1H, H₂), 4.53 (d, J = 11.9 Hz, 1H, OCH₂Ph), 4.58 (d, J = 11.9 Hz, 1H, OCH₂Ph), 5.76 (dd, J = 15.2, 5.8 Hz, 1H, H₃), 6.40 (ddd, J = 15.1, 10.4, 0.9 Hz, 1H, H₄), 6.48 (d, J = 15.6 Hz, 1H, H₅), 6.65 (dd, J = 15.6, 10.4 Hz, 1H, H₆), 7.27-7.37 (m, 7H, Ar-OCH₃ and ArH); some diagnostic signals from the minor isomer are as follows: δ 0.88 (d, J = 7.1 Hz, 3H, CH₂), 1.88-1.96 (m, 1H, CHCH₃) 4.42 (d, J = 5.7 Hz, 1H, H₆), the ratio of diastereomers was determined by the integration of signals at δ 0.88 and 0.94; ¹³C NMR (CDCl₃, 100.6 MHz) δ 7.0 (q), 40.5 (d), 55.7 (q), 73.0 (t), 73.8 (t), 74.3 (d), 76.1 (d), 114.4 (d), 126.8 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.9 (d), 130.5 (s), 131.3 (d), 132.4 (d), 134.2 (d) 138.2 (s), 159.6 (s); mass spectrum m/z (relative intensity) 391.19 (M+Na⁺ 7); exact mass calcd. for C₂₃H₂₈O₄Na⁺ m/z 391.1880, found m/z 391.1877.
(2R,3R,4S,5S,6R)-2-Benzylmethyl-6-[2-(4-methoxyphenyl)vinyl]-3-methyl-5-phenylselenenyltetrahydropyran-4-ol (199) and
(1'R,2'S,2R,3R,4S,5S,6R,)-2-Benzylmethyl-6-[2'-hydroxy-2'-(4-methoxyphenyl)-1'-phenylselenenylethyl]-3-methyl-5-phenylselenenyltetrahydropyran-4-ol (206). To a -78 °C solution of 2.36 g (ca 6.4 mmol) of contaminated diol 179 in 30 mL of dry dichloromethane was added a solution of 1.34 g (7.0 mmol) of phenylselenenyl chloride in 10 mL of dry dichloromethane, dropwise over 5 min. The reaction mixture was stirred at -78 °C for 4 h, 5 mL of saturated sodium bicarbonate solution was added, and the reaction mixture was warmed to room temperature. The reaction mixture was extracted with 20 mL of ethyl acetate, and the extract was washed with 10 mL of saturated sodium bicarbonate, two 10-mL portions of water, and dried (Na₂SO₄). Removal of the solvent in vacuo gave a residue that was chromatographed using MPLC (self packed column; 150 g of flash silica gel, eluted with ethyl acetate-hexanes, 1:4), which gave 1.42 g (66%) of pyran 199 as a pale yellow oil, as well as 0.76 g (23%) of diol 206 as a single diastereomer, resulting from a second addition of...
the phenylselenenyl chloride to 199. 

Pyran 199: IR (neat) 3450, 1606 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.97 (d, \(J = 7.2\) Hz, 3H, CH\(_3\)), 2.09-2.15 (m, 1H, CH\(_2\)), 2.69 (d, \(J = 2.0\) Hz, 1H, OH), 3.46 (dd, \(J = 10.4, 5.6\) Hz, 1H, CH\(_3\)OBn), 3.55 (dd, \(J = 11.1, 2.5\) Hz, 1H, CHSePh), 3.63 (dd, \(J = 9.9, 6.9\) Hz, 1H, CH\(_2\)OBn), 3.82 (dd, \(J = 4.7, 2.5\) Hz, 1H, CHOH), 3.85 (s, 3H, OCH\(_3\)), 4.40 (dt, \(J = 5.4, 2.4\) Hz, 1H, CH\(_2\)OBn), 4.49 (dd, \(J = 10.9, 7.6\) Hz, 1H, H\(_a\)), 4.54 (d, \(J = 12.2\) Hz, 1H, OCH\(_2\)Ph), 4.68 (d, \(J = 12.2\) Hz, 1H, OCH\(_2\)Ph), 6.07 (dd, \(J = 15.7, 7.6\) Hz, 1H, H\(_b\)), 6.69 (d, \(J = 15.7\) Hz, 1H, H\(_a\)), 6.88 (d, \(J = 8.7\) Hz, 2H, ArH-CH\(_3\)); 13C NMR (CDCl\(_3\), 100.6 MHz) \(\delta\) 10.6 (q), 36.8 (d), 50.8 (d), 52.2 (q), 70.6 (t), 71.7 (d), 72.6 (d), 73.2 (t), 76.9 (d), 113.7 (d), 125.7 (d), 127.5 (s), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.2 (d), 129.2 (d), 129.3 (s), 133.2 (d), 134.7 (d), 138.2 (s), 159.2 (s); mass spectrum m/z (relative intensity) 547.14 (M+Na\(^+\) 24); exact mass calcd. for C\(_{29}\)H\(_{32}\)O\(_4\)SeNa\(^+\) m/z 547.1358, found m/z 547.1368.

Diol 208: IR (neat) 3450, 1610 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.83 (d, \(J = 7.2\) Hz, 3H, CH\(_3\)), 1.89-1.96 (m, 1H, CH\(_2\)), 2.55 (s, 1H, OH), 3.29 (dd, \(J = 10.0, 3.7\) Hz, 1H, CH\(_2\)OBn), 3.47 (dd, \(J = 10.0, 8.6\) Hz, 1H, CH\(_2\)OBn), 3.55 (br s, 1H, CHOH), 3.71 (s, 3H, OCH\(_3\)), 3.85 (d, \(J = 4.2\) Hz, 1H, H\(_b\)), 3.99 (d, \(J = 11.2\) Hz, 1H, H\(_a\)), 4.05 (dd, \(J = 11.2, 2.3\) Hz, 1H, H\(_b\)), 4.10 (d, \(J = 7.7\) Hz, 1H, OH\(_a\)), 4.15 (dt, \(J = 7.4, 3.4\) Hz, 1H, CH\(_2\)OBn), 4.46 (d, \(J = 12.0\) Hz, 1H, OCH\(_2\)Ph), 4.59 (d, 12.0, 1H, OCH\(_2\)Ph), 4.98 (dd, \(J = 7.7, 4.2\) Hz, 1H, H\(_b\)), 6.71 (d, \(J = 8.7\) Hz, 2H, ArH-CH\(_3\)), 7.07 (d, \(J = 8.6\) Hz, 2H, ArH-CH\(_3\)), 7.11-7.37 (m, 13H, ArH), 7.47 (br d, \(J = 6.6\) Hz, 2H, ArH); 13C NMR (CDCl\(_3\), 100.6 MHz) \(\delta\) 10.6 (q), 36.8 (d), 50.8 (d), 52.2 (q), 70.6 (t), 71.7 (d), 72.6 (d), 73.2 (t), 76.9 (d), 113.7 (d), 125.7 (d), 127.5 (s), 127.6 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.2 (d), 129.2 (d), 129.3 (s), 133.2 (d), 134.7 (d), 138.2 (s), 159.2 (s); mass spectrum m/z (relative intensity) 547.14 (M+Na\(^+\) 24); exact mass calcd. for C\(_{29}\)H\(_{32}\)O\(_4\)SeNa\(^+\) m/z 547.1358, found m/z 547.1368.
MHz) δ 11.5 (q), 37.1 (d), 50.7 (d), 56.1 (q), 57.7 (d), 71.8 (t), 72.1 (d), 74.1 (d),
74.3 (t), 75.1 (d), 77.1 (d), 114.6 (d), 127.5 (s), 127.9 (d), 128.3 (d), 128.5 (d),
129.1 (d), 129.3 (d), 130.0 (d), 130.4 (d), 130.8 (s), 135.3 (d), 135.4 (d), 135.7
(s), 139.1 (s), 159.6 (s), one downfield CH was obscured; mass spectrum m/z
(relative intensity) 721.09 (M+Na+ 100); exact mass calcd. for C₃₅H₃₆O₆Se₂Na+
m/z 721.0942, found m/z 721.0933.

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(2R,3R,4S,5S,6R)-2-Benzylxoxymethyl-6-[2-(4-methoxyphenyl)vinyl]-3-
methyl-5-phenylselenyltetrahydropyran-4-yl acetate (200). A dry flask was
charged with 335 mg (0.64 mmol) of pyran 199, 6 mL of neat acetic anhydride,
and 65 μL of dry pyridine. The reaction mixture was stirred at room temperature
under argon for 24 h, concentrated in vacuo, and the residue was dissolved in 50
mL of ethyl acetate. The solution was washed with two 3-mL portions of 0.5 M
HCl, two 10-mL portions of water, two 10-mL portions of brine, and dried
(MgSO₄). Removal of the solvent in vacuo gave a paste that was
chromatographed over 16 g of silica gel (eluted with ethyl acetate-hexanes, 1:2)
to provide 312 mg (86%) of acetate 200 as a yellow oil: IR (neat) 1743 cm⁻¹; ¹H
166
NMR (CDCl₃, 400 MHz) δ 0.87 (d, J = 7.2 Hz, 3H, CH₃), 1.75 (s, 3H, O=CCH₃), 2.18-2.25 (m, 1H, CHCH₃), 3.27-3.29 (m, 4H, OCH₃ and CH₂OBn), 3.45 (dd, J = 10.9, 3.1 Hz, 1H, CHSePh), 3.55 (dd, J = 9.6, 6.5 Hz, 1H, CH₂OBn), 4.29 (d, J = 12.2 Hz, 1H, OCH₂Ph), 4.32-4.37 (m, 2H, OCH₂Ph and CHCH₂OBn), 4.67 (dd, J = 10.5, 6.6 Hz, 1H, H₆), 5.53 (t, J = 2.8 Hz, 1H, CHOAc), 6.19 (dd, J = 15.8, 6.6 Hz, 1H, H₆), 6.66 (m, 2H, ArH-OCH₃), 6.80 (d, J = 15.8 Hz, 1H, H₆), 6.85-6.92 (m, 3H, ArH), 7.04-7.16 (m, 5H, ArH), 7.22-7.24 (m, 2H, ArH), 7.48-7.50 (m, 2H, ArH- OCH₃); ¹³C NMR (C₆D₆, 100.6 MHz) δ 10.7 (q), 20.7 (q), 36.4 (d), 48.4 (d), 55.0 (q), 70.9 (t), 73.8 (t), 74.1 (d), 77.2 (d), 79.8 (d), 114.4 (d), 126.9 (d), 128.0 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.6 (d), 130.2 (s), 130.4 (s), 132.8 (d), 135.2 (d), 139.0 (s), 160.1 (s), 169.5 (s); exact mass calcd. for C₃H₃O₅Se m/z 566.1566, found m/z 566.1606.

(1'R,2'S,2R,3R,4S,5S,6R)-2-Benzylxoyethyl-6-[1'-bromo-2'-hydroxy-2-4-methoxypheny]ethyl]-3-methyl-5-phenylselenyltetrahydropyran-4-yl acetate (201 and 201b). To a 0 °C solution of 297 mg (0.53 mmol) of pyran 200 in 5 mL of acetone and 2.5 mL of water was added 104 mg (0.57 mmol) of N-
bromosuccinimide. The reaction mixture was stirred for 1 h at 0 °C, 2 h at room temperature, and was extracted with 50 mL of ethyl acetate. The organic extract was washed with two 10-mL portions of water, two 10-mL portions of brine, and dried (Na₂SO₄). The solvent was removed in vacuo, and the residue was chromatographed over 400 mg of flash silica (eluted with ethyl acetate-hexanes, 1:2) to give 256 mg (69%) of a 1.7:1 mixture of separable diastereomeric bromohydrins 201 and 201b as colorless oils; major isomer (201): IR (neat) 3476, 1743 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz,) δ 0.73 (d, J = 7.1 Hz, 3H, CH₃), 1.49 (s, 3H, OC=OCH₃), 1.74-1.82 (m, 1H, CHCH₃), 3.00 (dd, J = 9.8, 3.6 Hz, 1H, CH₂OBn), 3.23 (s, 3H, OCH₃), 3.33 (dd, J = 9.8, 8.5 Hz, 1H, CH₂OBn), 3.86 (dd, J = 11.0, 3.1 Hz, CHSePh), 4.12 (br d, J = 7.5 Hz, 1H, OH), 4.16 (d, J = 11.8 Hz, 1H, OCH₂Ph), 4.20 (dt, J = 7.2, 3.4 Hz, 1H, CHCH₂OBn), 4.30 (app t, J = 12.0 Hz, 2H, ArHOCH₃), 5.09 (dd, J = 5.7, 1.4 Hz, 1H, Hₐ), 5.31 (t, J = 6.0 Hz, 1H, Hₐ), 5.39 (t, J = 3.1 Hz, 1H, CHOAc), 6.73 (d, J = 8.7 Hz, 2H, ArHOCH₃), 6.93-7.00 (m, 3H, ArH), 7.04-7.08 (m, 1H, ArH), 7.15-7.20 (m, 2H, ArH), 7.29-7.34 (m, 4H, ArH), 7.63-7.67 (m, 2H, ArHOCH₃); ¹³C NMR (C₆D₆, 100.6 MHz) δ 10.6 (q), 20.5 (q), 36.4 (d), 46.4 (d), 54.9 (q), 61.0 (d), 71.3 (t), 73.9 (t), 74.7 (d), 76.0 (d), 76.2 (d), 77.3 (d), 114.5 (d), 128.1 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.8 (d), 135.0 (s), 135.9 (d), 138.8 (s), 159.9 (s), 169.5 (s), one downfield singlet and one downfield doublet were not seen in the spectrum; mass spectrum m/z (relative intensity) 685.06 (M+Na⁺ 82); exact mass calcd. for C₃₁H₃₅BrO₆SeNa⁺ m/z 685.0674, found m/z 685.0637; minor isomer (201b): IR
(neat) 3477, 1744 cm$^{-1}$; $^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$ 0.91 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.64 (s, 3H, OC=OCH$_3$), 1.80 (br s, 1H, OH), 2.12-2.19 (m, 1H, CHCH$_3$), 3.27 (s, 3H, OCH$_3$), 3.33 (dd, $J = 9.9, 6.0$ Hz, 1H, CH$_2$OBn), 3.56 (dd, $J = 9.9, 6.5$ Hz, 1H, CH$_2$OBn), 4.31-4.40 (m, 3H, CHSePh, OCH$_2$Ph, and CHCH$_2$OBn), 4.47 (d, $J = 12.2$ Hz, 1H, OCH$_2$Ph), 4.91 (d, $J = 11.5$ Hz, 1H, H$_a$), 5.02 (d, $J = 9.7$ Hz, 1H, H$_b$), 5.30 (dd, $J = 9.7, 4.5$ Hz, 1H, H$_p$), 5.50-5.52 (m, 1H, CHOAc), 6.66 (d, $J = 8.7$ Hz, 2H, ArH-OCH$_3$), 6.87 (d, $J = 8.6$ Hz, 2H, ArH), 6.94-6.96 (m, 3H, ArH), 7.05-7.19 (m, 3H, ArH), 7.30-7.32 (m, 2H, ArH), 7.57-7.60 (m, 2H, ArH-OCH$_3$); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 10.5 (q), 20.6 (q), 36.6 (d), 47.1 (d), 55.0 (q), 57.7 (d), 70.7 (t), 73.8 (t), 75.0 (d), 76.3 (d), 77.4 (d), 83.5 (d), 114.3 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.9 (d), 129.9 (d), 130.3 (s), 135.1 (d), 135.5 (s), 139.2 (s), 160.2 (s), 169.6 (s); mass spectrum mlz (relative intensity) 685.06 (M+Na$^+$ 100); exact mass calcd. for C$_{31}$H$_{35}$BrO$_5$SeNa$^+$ mlz 685.0674, found mlz 685.0620.
(2'S,2R,3R,4R,6R)-2-Benzylxymethyl-6-[2'-hydroxy-2'-(4-methoxy-phenyl)-ethyl]-3-methyltetrahydropyran-4-yl acetate (202). To a room temperature solution of 25.7 mg (0.04 mmol) of bromohydrin 201 in 0.8 mL of dry benzene was added 54 µL (0.20 mmol) of neat tri-n-butyltin hydride followed by 60 µL (0.06 mmol) of a 1 M solution of triethylborane in hexanes. The reaction mixture was stirred for 1 h, diluted with 15 mL of hexanes, and 0.5 mL of saturated aqueous sodium bicarbonate solution was added. The phases were partitioned, the organic phase was concentrated in vacuo and the residue was chromatographed over 1 g of silica gel (eluted with three void-volumes of hexanes followed by 40% ethyl acetate-hexanes) to give 15.6 mg (93%) of alcohol 202 as a colorless oil: IR (neat) 3442, 1728 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz) δ 0.71 (d, J = 7.3 Hz, 3H, CH₃), 1.36 (br d, J = 14.6 Hz, 1H, Hd), 1.47 (br d, J = 14.6 Hz, 1H, H₄), 1.55 (s, 3H, O₂CH₃), 1.65-1.87 (m, 3H, CHCH₃ and H₃'s), 3.14 (br s, 1H, OH), 3.19 (dd, J = 9.8, 5.0, Hz, 1H, CH₂OBn), 3.30 (s, 3H, OCH₃), 3.46 (dd, J = 9.8, 7.5 Hz, 1H, CH₂OBn), 4.03 (ddt, J = 11.8, 9.0, 2.7 Hz, 1H, Hc), 4.17 (ddd, J = 7.4, 4.9, 2.5 Hz, 1H, CHCH₂OBn), 4.29 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.37 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.85 (dd, J = 5.6, 2.8 Hz, 1H, OCH₂Ph).
CfCl\(\text{OAc}\), 5.04 (br d, \(J = 7.4\) Hz, 1H, H\(_5\)), 6.79-6.89 (m, 2H, ArH-\(\text{OCH}_3\)), 7.05-7.08 (m, 3H, ArH), 7.31-7.33 (m, 4H, ArH and ArH-\(\text{OCH}_3\)); \(^{13}\text{C NMR (C}\_6\text{D}_6\), 100.6 MHz} \(\delta 10.9\) (q), 20.9 (q), 31.8 (t), 34.2 (d), 45.1 (t), 55.0 (q), 71.2 (d), 71.7 (t), 73.0 (d), 73.8 (t), 74.7 (d), 114.2 (d), 127.4 (d), 128.0 (d), 128.2 (d), 128.5 (d), 128.8 (d), 138.1 (s), 139.1 (s), 159.4 (s), 169.5 (s); mass spectrum \(m/z\) (relative intensity) 451.21 (M+\(\text{Na}^+\) 62); exact mass calcd. for C\(_{28}\)H\(_{32}\)BrO\(_4\)Na\(^+\) \(m/z\) 451.2091, found \(m/z\) 451.2081.

![Structure of compound 203](image)

\((2'R,2R,3R,4R,6R)-2\)-Benzyloxymethyl-6-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-3-methyltetrahydropyran-4-yl acetate (203). To a room temperature solution of 73.8 mg (0.06 mmol) of bromohydrin 201b in 1 mL of dry benzene was added 77 \(\mu\)L (0.28 mmol) of neat tri-\(n\)-butyltin hydride followed by 50 \(\mu\)L (0.05 mmol) of a 1 M solution of triethylborane in hexanes. The reaction mixture was stirred for 1 h, 0.5 mL of saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with 25 mL of hexanes. The extract was concentrated in vacuo and the residue was chromatographed over 5 g of silica gel (eluted with three void-volumes of
hexanes followed by 40% ethyl acetate-hexanes) to give 18 mg (74%) of alcohol 203 as a colorless oil: IR (neat) 3473, 1729 cm⁻¹; ¹H NMR (C₆D₆, 400 MHz) δ 0.66 (d, J = 7.2 Hz, 3H, CH₃), 1.28-1.39 (m, 2H, H₆), 1.46 (dt, J = 14.4, 2.7 Hz, 1H, H₆), 1.64-1.73 (m, 4H, CH₃ and OCOCH₃), 1.86 (dt, J = 14.3, 10.0 Hz, 1H, H₆), 3.11 (dd, J = 9.8, 4.4, Hz, 1H, CH₂OBn), 3.30-3.39 (m, 4H, Ar-OCH₃ and CH₂OBn), 3.91 (tt, J = 10.5, 2.9 Hz, 1H, Hc), 4.08 (d, J = 0.8 Hz, 1H, OH), 4.15 (dd, J = 7.7, 4.4, 2.5 Hz, 1H, CHCH₂OBn), 4.23 (d, J = 12.0 Hz, 1H, OCH₂Ph), 4.33 (d, J = 12.0 Hz, 1H, OCH₂Ph), 4.78 (dd, J = 5.7, 2.0 Hz, 1H, CH(OAc), 4.95 (dd, J = 9.6, 3.1 Hz, 1H, H₆), 6.79-6.89 (m, 2H, ArH-OCH₃), 7.05-7.08 (m, 1H, ArH), 7.31-7.42 (m, 2H, ArH), 7.39-7.42 (m, 2H, ArH-OCH₃); ¹³C NMR (C₆D₆, 100.6 MHz) δ 10.8 (q), 21.0 (q), 32.0 (t), 34.2 (d), 46.1 (t), 55.0 (q), 71.6 (t), 72.8 (d), 73.8 (t), 74.2 (d), 74.5 (d), 74.6 (d), 114.2 (d), 127.5 (d), 128.2 (d), 128.8 (d), 138.1 (s), 129.0 (s), 159.6 (s), 169.4 (s), one aromatic doublet is missing from the spectrum; mass spectrum m/z (relative intensity) 451.21 (M+Na⁺ 40); exact mass calcd. for C₂₅H₂₂BrO₅Na⁺ m/z 451.2091, found m/z 451.2070.
(2R,3R,4R,6R)-2-Benzylloxymethyl-3-methyl-6-(2-oxoethyl)-
tetrahydropyran-4-yl acetate (204). From 202: To a room temperature solution
of 66 mg (0.15 mmol) of alcohol 202 in 1.2 mL of dry dichloromethane was added
127 mg (0.26 mmol) of bis(2,4,6-trimethylpyridine) bromine(l)
hexafluorophosphate and the reaction mixture was stirred for 2 h. To the mixture
was added 50 mg of silica gel, the solvent was removed in vacuo, and the solid
residue was chromatographed over 5 g of flash silica gel (eluted with ethyl
acetate-hexanes 1:2.5) to give 20.2 mg (42%) of aldehyde 204 as a colorless oil.
No identifiable starting material was recovered: IR (neat) 1728 cm⁻¹; ¹H NMR
(CDCl₃, 400 MHz) δ 0.91 (d, J = 7.1 Hz, 3H, CH₃), 1.61-1.74 (m, 2H, Hc), 1.82-
1.88 (m, 1H, CH(CH₃)₂), 2.08 (s, 3H, OCOCH₃), 2.45 (ddd, J = 16.4, 4.7, 1.9 Hz,
1H, Ha), 2.59 (ddd, J = 16.4, 7.9, 2.7 Hz, 1H, Hₙ), 3.37 (dd, J = 10.1, 5.2 Hz, 1H,
CH₂OBn), 3.49 (dd, J = 10.1, 7.0 Hz, 1H, CH₂OBn), 4.08 (dt, J = 4.9, 2.4 Hz, 1H,
CH₃OBn), 4.27-4.28 (m, 1H, Hb), 4.47 (d, J = 12.7 Hz, 1H, OCH₂Ph), 4.58 (d,
J = 12.0 Hz, 1H, OCH₂Ph), 4.89 (dd, J = 5.7, 2.9 Hz, 1H, CHOAc), 7.27-7.37 (m,
5H, ArH), 9.80 (t, J = 2.1 Hz, 1H, CHO); ¹³C NMR (CDCl₃, 100.6 MHz) δ 10.9 (q),
21.7 (q), 31.4 (t), 33.7 (d), 49.7 (t), 68.8 (d), 71.3 (t), 72.8 (d), 73.9 (t), 74.6 (d),

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128.1 (d), 128.2 (d), 128.8 (d), 138.5 (d), 170.5 (s), 2.1.2 (d); mass spectrum m/z (relative intensity) 343.15 (M+Na+ 48); exact mass calcd. for C18H24O3Na+ m/z 343.1516, found m/z 343.1514.

From 203: To a room temperature solution of 17.7 mg (0.04 mmol) of alcohol 203 in 1 mL of dry dichloromethane was added 24.0 mg (0.05 mmol) of bis(2,4,6-trimethylpyridine) bromine(I) hexafluoro-phosphate and the reaction mixture was stirred for 2 h and 50 mg of silica gel was added. The solvent was removed in vacuo, and the solid was chromatographed over 1 g of flash silica gel (eluted with ethyl acetate-hexanes 1:2.5) to give 4.9 mg (38%) of aldehyde 204 as a colorless oil, and 8 mg (46%) of recovered alcohol 203. This material was spectroscopically identical to 204 prepared from alcohol 202.

(2R,3R,4S,5S,6R)-4-Benzyloxy-2-benzyloxymethyl-6-[2-(4-methoxy-phenyl)vinyl]-3-methyltetrahydropyran (207). To a solution of 335 mg (0.64 mmol) of hydroxypyran 199 in 1 mL of dry benzene was added 0.5 mL of 50% (w/w) aqueous NaOH, 11 mg (0.03 mmol) of tetrabutylammonium iodide, and
6.36 mg (1.92 mmol) of benzyl bromide. The reaction mixture was sonicated at 65 °C for 1 h, diluted with 50 mL of ethyl acetate, washed with three 10-mL portions of water, 10 mL of brine, and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was chromatographed over 20 g of flash silica gel eluted with ethyl acetate-hexanes, 1:9) to give 251 mg (64%) of benzyl protected 

bpen 207 as an oil: IR (neat) 1607, 1511 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.94 (t, J = 7.1 Hz, 3H, CH₃), 2.11-2.17 (m, 1H, CH₂CH₃), 3.30-3.36 (m, 2H, CH₂OBn and CHSePh), 3.49 (dd, J = 9.8, 6.7 Hz, 1H, CH₂OBn), 3.70 (s, 3H, OCH₃), 3.89 (dd, J = 7.1 Hz, 1H, CHOObn), 4.23 (dt, J = 6.4, 2.0 Hz, 1H, CHCH₂OBn), 4.42 (d, J = 12.2 Hz, 1H, OCH₂Ph), 4.48-4.54 (m, 3H, OCH₂Ph and Hc), 4.64 (d, J = 11.4 Hz, 1H, OCH₂Ph), 5.66 (dd, J = 15.8, 7.3 Hz, 1H, Hb), 6.53 (d, J = 15.8 Hz, 1H, ArH-OCH₃), 6.92 (d, J = 8.6 Hz, 2H, ArH-OCH₃), 7.05-7.11 (m, 3H, ArH), 7.16-7.32 (m, 8H, ArH), 7.36-7.38 (m, 4H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 9.5 (q), 32.1 (d), 48.4 (d), 53.9 (q), 69.3 (t), 70.6 (t), 71.4 (t), 72.1 (t), 78.5 (d), 81.6 (d), 112.3 (d), 124.9 (d), 125.7 (d), 126.0 (d), 126.4 (d), 126.5 (d), 126.6 (d), 126.9 (d), 127.0 (d), 127.1 (d), 127.6 (d), 128.3 (s), 129.5 (s), 131.4 (d), 133.1 (d), 133.6 (s), 137.0 (s), 157.8 (s); mass spectrum m/z 637.18; exact mass calcd. for C₃₆H₃₈O₆SeNa⁺ m/z 637.1827, found m/z 637.1824.
(2R,3R,4S,5S,6R)-2-(4-Benzyl-6-benzyl-5-methyl-3-phenylselenyltetrahydropyran-2-yl)-2'-bromo-1'-{(4-methoxyphenyl)-
ethanol (208). To a 0 °C solution of 279 mg (0.45 mmol) of pyran 207 in 4 mL of
acetone and 2 mL of water, was added 82 mg (0.46 mmol) of N-
chlorosuccinimide. The reaction mixture was stirred for 10 min at 0 °C and 10 h
at room temperature. The mixture was extracted with 50 mL of ethyl acetate.
The organic extract was washed with two 10-mL portions of water, two 10-mL
portions of brine, and dried (MgSO₄). The solvent was removed in vacuo, and
the residue was chromatographed over 20 g of flash silica (eluted with ethyl
acetate-hexanes, 1:4) to give 275 mg (86%) of a 5:1 mixture of diastereomeric
prochondin 208 as a viscous colorless oil: IR (neat) 3464, 1611 cm⁻¹; ¹H NMR
(C₆D₆, 400 MHz, major isomer) δ 0.82 (d, J = 7.1 Hz, 3H, CH₃), 1.72-1.78 (m, 1H,
CHCH₃), 3.11 (dd, J = 9.8, 4.1 Hz, 1H, CH₂OBn), 3.22 (s, 3H, OCH₃), 3.41 (dd, J
= 9.8, 8.5 Hz, 1H, CH₂OBn), 3.71 (t, 3.0 Hz, 1H, CH₂SePh), 4.13 (d, J = 7.9 Hz, 1H, OH), 4.20-4.49 (m, 6H, two OCH₂Ph's,
CHOBn, and H₂), 4.96 (dd, J = 5.4, 1.2 Hz, 1H, CHBr), 5.29 (dd, J = 7.9, 5.4 Hz,
¹H, H₂), 6.72 (d, J = 8.6 Hz, 2H, ArH-OCH₃), 6.94-7.31 (m, 15H, ArH), 7.65 (d, J
= 8.0 Hz, 2H, ArH-OCH$_3$); some diagnostic signals for the minor isomer are as follows: $\delta$ 0.98 (d, $J$ = 7.1 Hz, 3H, CH$_3$), 2.11-2.18 (m, 1H, CHCH$_3$), 3.26 (s, 3H, OCH$_3$), 5.23 (dd, $J$ = 9.9, 5.1 Hz, 1H, H$_a$), the ratio of diastereomers was determined from the integrations of the signals at $\delta$ 0.82 and 0.98; $^{13}$C NMR (C$_6$D$_6$, 100.6 MHz) $\delta$ 10.7 (q), 33.9 (d), 47.9 (d), 54.6 (q), 60.9 (d), 71.1 (t), 72.0 (t), 73.6 (t), 73.7 (d), 76.7 (d), 77.4 (d), 82.4 (d), due to interference of signals that arise from the NMR solvent, and the complicating presence of partially resolved signals from the minor diastereomer, only diagnostic signals upfield from 83 ppm are given. However, it should be noted that subsequent reduction of this material gave the alcohol expected for the reported compound.; mass spectrum m/z 733.08; exact mass calcd. for C$_{35}$H$_{35}$BrO$_5$SeNa$^+$ m/z 733.0873, found m/z 733.0807. The stereochemistry of the 1' bromide and 2' hydroxyl was not determined.

(2R,4R,5S,6R)-2-(4-Benzyl oxy-6-benzyloxymethyl-5-methyl-tetrahydro pyran-2-yl)-1'-(4-methoxyphenyl)ethanol (209). To a 0 °C solution of 100 mg (0.16 mmol) of pyran 207 in 1.6 mL of acetone and 0.8 mL of water,
was added 30 mg (0.17 mmol) of N-bromosuccinimide. The reaction mixture was stirred for 10 min at 0 °C and 3 h at room temperature. The mixture was extracted with 50 mL of ethyl acetate. The organic extract was washed with two 10-mL portions of water, two 10-mL portions of brine, and dried (MgSO₄). The solvent was removed in vacuo, and the residue was dried under high vacuum for 30 min before being dissolved in 2 mL of dry benzene. To this solution was added 248 mg (0.85 mmol) of tri-n-butyltin hydride followed by the dropwise addition of 0.16 mL (0.16 mmol) of a 1 M solution of triethylborane in hexanes. The reaction mixture was stirred for 1.5 h, diluted with 50 mL of ethyl acetate, and washed with two 5-mL portions of aqueous saturated sodium bicarbonate and 10 mL of brine. The organic phase was dried (Na₂SO₄), the solvent was removed in vacuo, and the residue was extracted with three 10-mL portions of acetonitrile. The combines extracts were concentrated and the residue was chromatographed over 5 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 60 mg (78%) of alcohol 209 as a viscous colorless oil: IR (neat) 3464 cm⁻¹; 'H NMR (CDCl₃, 400 MHz) δ 0.84 (d, J = 7.1 Hz, 3H, CH₃), 1.51-1.59 (m, 1H, H₂), 1.63-1.70 (m, 1H, H₄), 1.77-1.93 (m, 3H, H₅ and CH₂CH₂), 3.36 (dd, J = 10.0, 4.4 Hz, 1H, CH₂OBn), 3.46-3.55 (m, 2H, CH₂OBn and CHOObn), 3.74 (s, 3H, OCH₃), 3.89 (d, J = 5.9 Hz, 1H, OH), 3.93-3.99 (m, 1H, CHCH₂OObn), 4.10-4.13 (m, 1H, Hₚ), 4.33-4.59 (m, 4H, two OCH₂Ph's), 4.88-4.95 (m, 1H, Hₜ), 6.77-6.83 (m, 2H, ArH-OCH₃), 7.19-7.34 (m, 12H, ArH and ArH-OCH₃); ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.5 (q), 31.3 (t), 33.5 (d), 43.9 (t), 55.6 (q), 70.5 (t), 71.8 (d), 71.7
(d), 71.9 (t), 73.8 (t), 74.3 (d), 77.6 (d), 114.0 (d), 114.1 (d), 127.2 (d), 127.6 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.8 (d), 137.2 (s), 138.7 (s), 139.2 (s), 158.9 (s); mass spectrum m/z 499.25; exact mass calcd. for C_{30}H_{38}O_{3}Na^{+} m/z 499.2455, found m/z 499.2457.

\[
\begin{align*}
\text{H}_{2}\text{CH}_{2}\text{CO} & \\
\text{H}_{2} & \\
\text{H}_{2} & \\
\text{OCH}_{2}\text{Phi} & \\
\text{OCH}_{2}\text{Phi} & \\
\end{align*}
\]

(2S,4R,5S,6R)-(4-Benzyl oxy methyl-5-methyl tetrahydro pyran -2-yl)- ethyl acetate (211). To a solution of 10 mg (0.03 mmol) of aldehyde 210 in 0.5 mL of absolute ethanol was added 4 mg (0.04 mmol) of solid sodium bicarbonate. The reaction mixture was stirred at room temperature for 10 h, the solvent was removed in vacuo, and the solid residue was suspended in 0.5 mL (7.0 mmol) of DMSO. To this suspension was added 250 μL (2.6 mmol) of acetic anhydride and the reaction mixture was stirred for 10 h, during which time the solids dissolved. The reaction mixture was quenched with 1 mL of a solution of sodium ethoxide in ethanol (prepared by the careful addition of 1 mL of absolute ethanol to 100 mg of oil free sodium metal), and after stirring for 30 min, 2 mL of water was added followed by 20 mL of ethyl acetate. The solution was washed with two 2-mL portions of water and 5 mL of brine. To the solution was added 10 mg of silica gel, the solvent was removed in vacuo and the solid residue was
chromatographed over 2 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give an undetermined amount of ester 211: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.86 (d, $J = 7.2$ Hz, 3H, CH$_3$), 1.22 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$), 1.58 (dt, $J = 14.3$, 2.8 Hz, 1H, H$_a$), 1.78 (br d, $J = 14.3$ Hz, 1H, H$_a$), 2.56 (dd, $J = 14.9$, 7.2 Hz, 1H, H$_a$), 3.38 (dd, $J = 10.2$, 5.3 Hz, 1H, CH$_2$OBn), 3.48-3.54 (m, 2H, CH$_2$OBn and CHO$_3$), 4.11 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$), 4.20-4.27 (m, 2H, H$_a$ and CHCH$_2$OBn), 4.47 (d, $J = 12.1$ Hz, 1H, OCH$_2$Ph), 4.54 (s, 2H, OCH$_2$Ph), 4.60 (d, $J = 12.1$ Hz, 1H, OCH$_2$Ph), 7.26-7.324 (m, 10 H, ArH); $^{13}$C NMR (CDCl$_3$, 125.8 MHz) $\delta$ 10.9 (q), 14.2 (q), 30.9 (t), 33.0 (d), 41.5 (t), 60.4 (t), 69.6 (d), 70.1 (t), 71.1 (t), 71.2 (t), 73.2 (d), 77.2 (d), 127.3 (d), 127.4 (d), 127.5 (d), 127.7 (d), 128.2 (d), 128.3 (d), 138.5 (s), 138.8 (s), 171.1 (s); mass spectrum $m/z$ 435.21; exact mass calcd. for C$_{25}$H$_{32}$O$_5$Na$^+$ $m/z$ 435.2147, found $m/z$ 435.2144.

![Chemical Structure](image)

**212**

(2'S,2R,3S,4R,6S)-2-Benzylxoxymethyl-6-[2'-hydroxy-2'-{4-methoxyphenyl}ethyl]-3-methyltetrahydropyran-4-ol (212). To a room temperature solution of 800 mg (1.15 mmol) of bis-selenide 206 in 15 mL of dry benzene was added 1.51 g (4.40 mmol) of tri-$n$-butyltin hydride followed by the

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dropwise addition of 1.15 mL (1.15 mmol) of a 1 M solution of triethylborane in hexanes. The reaction mixture was stirred for 1.5 h, diluted with 50 mL of ethyl acetate, and washed with two 5-mL portions of aqueous saturated sodium bicarbonate and 10 mL of brine. The organic phase was dried (Na$_2$SO$_4$), the solvent was removed in vacuo, and the residue was extracted with three 20-mL portions of acetonitrile. The combined extracts were concentrated and the residue was chromatographed over 50 g of flash silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 353 mg (79%) of diol 212 as a white solid: mp 92-94 °C; IR (thin film) 3412, 1612 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.90 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.42 (br d, $J = 14.0$ Hz, 1H, H$_a$), 1.66-1.70 (m, 1H, CHCH$_3$), 1.75-1.87 (m, 2H, H$_a$ and H$_b$), 1.93-2.03 (m, 2H, H$_b$ and OH), 3.43 (dd, $J = 10.0$, 4.4 Hz, 1H, CH$_2$OBn), 3.60 (dd, $J = 10.0$, 7.9 Hz, 1H, CH$_2$OBn), 3.82 (s, 3H, OCH$_3$), 3.85 (br s, 1H, OH), 4.03 (dt, $J = 9.1$, 2.4 Hz, 1H, H$_a$), 4.15-4.20 (m, 2H, H$_b$ and CH$_2$OBn), 4.57 (d, $J = 12.0$ Hz, 1H, OCH$_2$Ph), 4.65 (d, $J = 12.0$ Hz, 1H, OCH$_2$Ph), 4.98-5.02 (m, 1H, H$_a$), 6.87 (d, $J = 8.6$ Hz, 2H, ArH), 7.30-7.42 (m, 7H, ArH); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 11.4 (q), 33.2 (t), 35.8 (d), 44.1 (t), 55.7 (q), 70.5 (d), 70.6 (d), 71.5 (d), 72.0 (t), 73.7 (d), 73.8 (t), 114.0 (d), 127.2 (d), 128.1 (d), 128.2 (d), 128.8 (d), 137.2 (s), 138.6 (d), 158.9 (s); mass spectrum $m/z$ 409.20; exact mass calcd. for C$_{23}$H$_{30}$O$_5$Na$^+$ $m/z$ 409.1985, found $m/z$ 409.1997.
(2R,3S,4R,6S)-2-Benzylxomethyl-6-(5,5-dimethyl[1,3]dioxan-2-ylmethyl)-3-methyltetrahydropyran-4-ol (213). To a solution of 204 mg (0.53 mmol) of diol 206 in 3 mL of dry dichloromethane was added a solution of cis 2,4,6-trimethyl-pyridine) bromine(I) hexafluorophosphate in 5 mL of dry dichloromethane, dropwise over 1 h. The reaction mixture was stirred for 3 h, diluted with 15 mL of dichloromethane, and washed with two 5-mL portions of 0.5 N aqueous HCl and two 5-mL portions of brine. To the solution of crude aldehyde was added 312 mg (3.0 mmol) of 2,2-dimethylpropane-1,3-diol and 2 mg of p-toluenesulfonic acid. The reaction mixture was stirred for 10 h, concentrated in vacuo, and the residue was chromatographed over 25 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to give 71 mg (36%) of acetal 213 as an oil: IR (neat) 3462 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.68 (s, 3H, Me₃), 0.86 (d, J = 7.1 Hz, 3H, CH₃), 1.16 (s, 3H, Me₃), 1.48-1.52 (m, 2H, H₂ and OH), 1.60-1.65 (m, 3H, CH₂CH₃, H₂ and H₂), 1.85 (ddd, J = 14.1, 8.5, 3.3 Hz, 1H, H₃), 3.36-3.43 (m, 3H, two H₂'s and CH₂OBn), 3.52-3.57 (m, 3H, two H₂'s and CH₂OBn), 3.87 (dd, J = 5.2, 2.4 Hz, 1H, CHOH), 3.92-4.00 (m, 1H, H₄), 4.15 (dt, 5.1, 2.4 Hz,
(2S,4R,5S,6R)-2-(4-Benzyl-6-benzylomethyl-5-methyltetrahydropyran-2-ylmethyl)-5,5-dimethyl[1,3]dioxane (214). To a 0 °C suspension of 8.4 mg (0.21 mmol) of sodium hydride (as a 60% dispersion in mineral oil) in 4 mL of dry DMF was added dropwise over 5 min, a solution of 71 mg (0.19 mmol) of alcohol 213 in 2 mL of dry DMF. The reaction mixture was stirred at 0 °C for 1 h, 97.5 mg (0.57 mmol) of neat benzyl bromide was added, and stirring continued for 18 h. The reaction was quenched with the addition of 1 mL of water and extracted with three 15-mL portions of ether-hexanes (1:1). The combined extracts were dried (Na₂SO₄), concentrated in vacuo, and the residue was chromatographed over 10 of silica gel (eluted with ethyl acetate-hexanes, 4.51 (d, J = 12.1 Hz, 1H, OCH₂Ph), 4.60-4.63 (m, 2H, OCH₂Ph and H₆), 7.26-7.35 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100.6 MHz) δ 11.3 (q), 22.2 (q), 23.4 (q), 30.5 (s), 34.9 (t), 36.8 (d), 41.9 (t), 68.8 (d), 70.9 (d), 71.6 (t), 73.3 (d), 73.5 (t), 77.6 (t), 77.7 (t), 100.0 (d), 127.9 (d), 128.0 (d), 128.7 (d), 139.0 (s); mass spectrum m/z 387.21; exact mass calcd. for C₂₁H₂₅O₅Na⁺ m/z 387.2142, found m/z 387.2129.
(4R,5S,6R)-2-(4-Benzylxyloxy-6-benzylxomethyl-5-methyltetra-hydropyran-2-yl)-1-(4-methoxyphenyl)ethanone (215). To a room temperature solution of 128 mg (0.30 mmol) of the Dess-Martin periodinane in 2.5 mL of dry dichloromethane was added a solution of 120 mg (0.25 mmol) of alcohol 214 in 2 mL of dry dichloromethane over 5 min. The reaction mixture was stirred for 2 h,
diluted with 30 mL of ether, and washed with three 2-mL portions of 2 N NaOH, two 5-mL portions of water, and two 5-mL portions of brine. The solution was dried (Na₂SO₄), concentrated in vacuo, and the residue was chromatographed over 5 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to give 65 mg (74%) of ketone 215 as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 0.90 (s, 3H, CH₃), 1.63 (dt, J = 11.6, 2.6 Hz, 1H, Hc), 1.97-2.03 (m, 2H, CHCH₃ and Hd), 3.01 (dd, J = 15.7, 7.1 Hz, 1H, Ha), 3.36 (dd, J = 15.7, 5.7 Hz, 1H, Ha), 3.44 (dd, J = 10.2, 5.0 Hz, 1H, CH₂OBn), 3.53-3.60 (m, 2H, CH₂OBn, CHOBn), 3.90 (s, 3H, OCH₃), 4.31 (dt, J = 4.9, 2.3 Hz, 1H, CHCH₂OBn), 4.42-4.68 (m, 5H, two OCH₂Ph's and Hb), 6.94-6.98 (m, 2H, ArHOCH₃), 7.32-7.42 (m, 10H, ArH), 8.0-8.02 (m, 2H, ArHOCH₃); ¹³C NMR (CDCl₃, 100.6 MHz) δ 10.9 (q), 30.8 (t), 33.3 (d), 44.8 (t), 55.3 (q), 69.6 (d), 69.9 (t), 71.3 (t), 73.1 (t), 73.8 (d), 76.6 (d), 113.5 (d), 127.2 (d), 127.3 (d), 127.4 (d), 127.6 (d), 128.2 (d), 128.3 (d), 130.4 (s), 130.5 (d), 138.4 (s), 138.8 (s), 163.3 (s), 196.6 (s)
LIST OF REFERENCES


(20) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. The desso-martin periodinane: 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one. Organic Syntheses 2000, 77, 141-152.


Homoallylic alcohol 113 has reportedly been prepared in 70% yield using this method.


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APPENDIX

SELECTED $^1$H AND $^{13}$C NMR SPECTRA
113 JU-2-213
(CDCl₃, 100.6 MHz)
114 JU-2-216
(CDCl₃, 100.6 MHz)

PhCH₂O

OTBS

CH₃
207
121 JU-2-279
(CDCl₃, 125.8 MHz)
131 JU-2-203
(CDCl₃, 100.6 MHz)
133 JU-3-155

(CDCl₃, 100.6 MHz)
137 JU-3-51
(CDC\textsubscript{3}, 100.6 MHz)
142 JU-3173
(CDCl₃, 236.3 MHz)
152 JU-3-206
(CDC\textsubscript{3}, 100.6 MHz)
156 JU-3-217
(CDC\textsubscript{3}, 100.6 MHz)
168 JU-4-14
(CDCl₃, 100.6 MHz)
170 JU-4-18
(CDC\textsubscript{3}, 100.6 MHz)
172b JU-4-21
(CDCl₃, 100.6 MHz)
174 JU-4-108
(CDCl₃, 100.6 MHz)
175 JU-4-110
(CDCl₃, 100.6 MHz)
184 JU-4-52
(CDCl₃, 100.6 MHz)
185 JU-4-53
(CDCl₃, 100.6 MHz)
188 JU-4-39
(CDCl₃, 500 MHz)
188 JU-4-39
(CDCls, 125.8 MHz)
195 JU-4-139  
(CDCl\textsubscript{3}, 100.6 MHz)
196 JU-4-113
(CDCl₃, 100.6 MHz)
PhSe'\[\text{HO}]

199 JU-4-229
(CDCl₃, 100.6 MHz)
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202 JU-179
(C₆D₆, 400 MHz)
202 JU-4-179 (C₆D₆, 100.6 MHz)
203  JU-4-180
(C6D6, 100.6 MHz)
207 JU-4-223
(CDCl₃, 100.6 MHz)
208 JU-4-231
(C₆D₆, 400 MHZ)
\[ \text{H}_2\text{CO} - \text{Br} - \text{O} - \text{CH}_2\text{Ph} \]

208 JU-4-231

\((\text{C}_6\text{D}_6, 100.6 \text{ MHz})\)
209 JU-4-224
(CDCl₃, 100.6 MHz)
211 JU-4-226
(CDCl₃, 400 MHz)
211 JU-4-226
(CDCl₃, 100.6 MHz)
**212 JU-4-212**
*(CDCl₃, 100.6 MHz)*
214 JU-4-217
(CDCl₃, 100.6 MHz)
215 JU-4-236
(CDC\textsubscript{3}, 400 MHz)