Enantioselective Total Synthesis of (-)-Monic Acid C via Carbosulfenylation of a Dihydropyran

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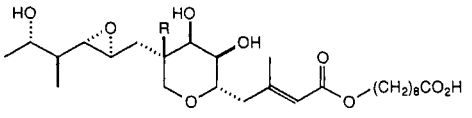
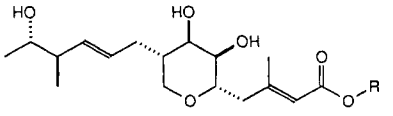
A stereoselective synthesis of (-)-monic acid C (**5**) was accomplished in a linear sequence of 22 steps beginning from dihydropyran and with (-)-1-borneol as a chiral auxiliary. 2-(1-Bornyloxy)pyrans **10** and **11** were converted via trans epoxides **12** and **13** to hydroxy selenides **16** and **17**. Selenide **16** was transformed to vinyl ether **20**, which underwent Claisen rearrangement to **22**. The latter, after oxidation to carboxylic acid **24**, was treated with stannic chloride to give the γ-lactone **26**. A parallel sequence from **17** brought this selenide, via **29** and its Claisen rearrangement product **31**, into convergence with **26**. Carbosulfenylation of **26** in the presence of 2-(trimethylsiloxy)propene was accompanied by elimination and led to **33** and its trans isomer **34**. Cis hydroxylation of **33**, protection of the resulting diol, and Horner–Emmons condensation of **41** with *tert*-butyl dimethylphosphonoacetate gave **43**. Attachment of the second side chain of **5** was effected by means of a Julia olefination of **46** with sulfone **65**, prepared from ethyl (2*S*,3*S*)-3-hydroxy-2-methylbutanoate. The resulting substituted tetrahydropyran **68**, after removal of the three protecting groups, yielded **5**.

The pseudomonic acids A–D (**1**–**4**)[1] are a family of antimicrobial agents produced by submerged cultures of *Pseudomonas fluorescens* (NCIB 10586). They have potent activity against Gram-positive bacteria and mycoplasma pathogens[2] and have been shown to be competitive inhibitors of isoleucyl-*t*RNA synthetase.[3] Studies of the interaction of pseudomonic acid A (**1**) with *E. coli* ileu-*t*RNA synthetase[4] have led to the proposal that the terminus of the epoxide chain, which has the same carbon skeleton as L-isoleucine, competes with this amino acid for the single isoleucine binding site on the enzyme.[5] Pseudomonic acids have a much lower affinity for mammalian ileu-*t*RNA synthetase than for the microbial enzyme, thus accounting for the low toxicity of the antiobiotic in mammals.[6]



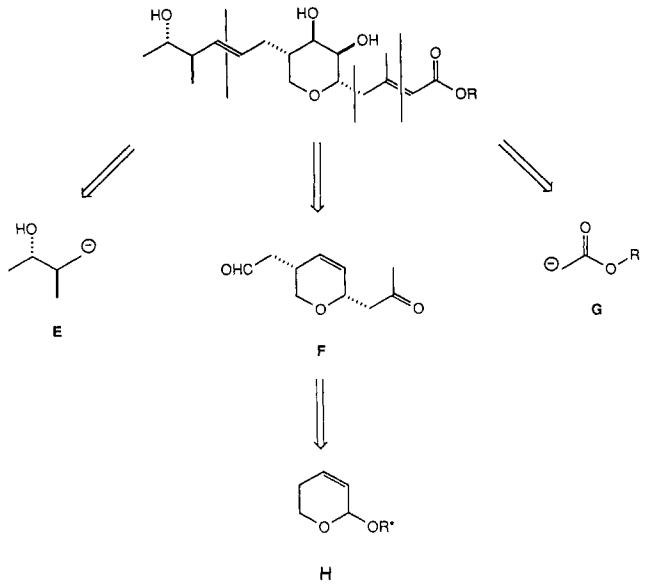
1, R = H (Pseudomonic acid A)
2, R = OH (Pseudomonic acid B)



3, R = $(CH_2)_8CO_2H$ (Pseudomonic acid C)
4, R = $(CH_2)_4CH{=}CH(CH_2)_2CO_2H$ (Pseudomonic acid D)
5, R = H (Monic acid C)

The structural, stereochemical, and biological characteristics of pseudomonic acids have stimulated much chemical interest, and there are at least 16 complete or formal syntheses of pseudomonic acids in the literature.[7]

Scheme I



These syntheses, almost exclusively, have been directed toward the A or C series. Moreover, while some are enantioselective, most of these routes rely on sugar derivatives as the source of asymmetry.

From a practical standpoint, a synthesis of nonracemic **3** is especially attractive since this substance is chemically stable and retains antibacterial activity over a broad pH range. In contrast, pseudomonic acid A shows rapid loss of activity outside pH 4–9, a property that is associated with intramolecular attack on the epoxide by the C-7 hydroxyl substituent.[8]

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(4) Hughes, J.; Mellows, G. *Biochem. J.* **1980**, *191*, 209.

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(6) Sutherland, R.; Comber, K. R.; Mizen, L. W.; Slocombe, B.; Clayton, J. P. *16th Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting*; Abstract 52, 1976.

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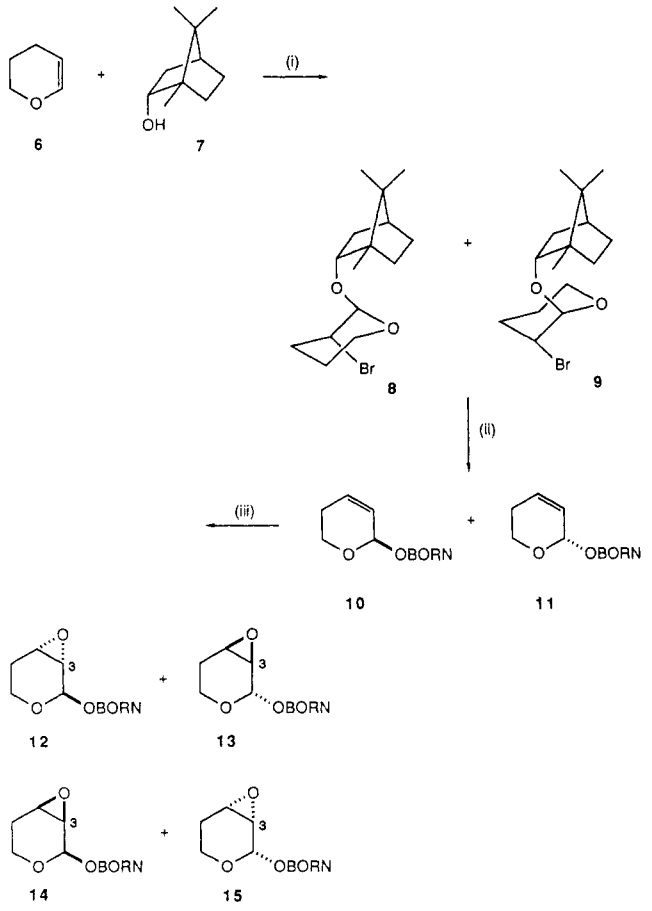
Scheme II[a]



[a] Reagents: (i) Br_2, $C_6H_5NMe_2$, CH_2Cl_2, −78 → 0 °C, 6 h; (ii) DBU, 95 °C, 20 h; (iii) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 48 h.

We describe herein a synthesis of the natural (−) enantiomer of monic acid C (**5**) from three primary subunits (E–G) as depicted in Scheme I.[9] The absolute stereochemistry of F is established in this plan through an asymmetric functionalization of dihydropyran H using (−)-borneol as chiral auxiliary. The convergence of subunit F with a five-carbon segment E, derived from ethyl (2*S*,3*S*)-3-hydroxy-2-methylbutanoate, and a three-carbon species, derived from acetone, sets in place all six stereogenic centers of **5**.

The synthesis of (−)-monic acid from an achiral starting material (dihydropyran, **6**) must entail an enantioselective step if optical resolution is to be avoided. It is generally recognized that there is strategic advantage to effecting enantioselection at an early stage in a synthetic sequence, and it was hoped that a chiral acetal derived from **6** with a nonracemic alcohol would provide a means for achieving this goal. The literature offers no guidance on the feasibility of asymmetric induction using this methodology, and estimates of the energy difference between diastereomeric transition states leading to acetalization with several chiral alcohols were too inaccurate to allow a reliable prediction to be made. In the event, acetalization of **6** with (−)-1-borneol (**7**) and several other nonracemic alcohols resulted in no significant stereoselection (Scheme II). Nevertheless, this reaction, through a subsequent separation of diastereomers, did afford access to a key synthetic intermediate for **5** in homochiral form.

The reaction of **6** with bromine in methanol is known to give the trans bromo acetal almost exlusively.[10] When an analogous reaction of **6** was carried out with (−)-1-borneol (**7**) in the presence of *N*,*N*-dimethylaniline,[11] two stereoisomeric bornyl bromotetrahydropyranyl ethers, **8** and **9**, were obtained in high yield and approximately equal amounts. Subsequent results confirmed that each of these isomers was the result of trans addition to **6**, but it was not possible at this stage to assign configuration unambiguously. Exposure of **6** to other chiral alcohols, including 8-phenylmenthol and nopinol, gave tetrahydropyranyl ethers with similar lack of stereoselectivity.

Since **8** and **9** could not be separated, the mixture was subjected to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in order to effect elimination of hydrogen bromide. The resulting olefins **10** and **11**, obtained as a 1:1 mixture, were separable by high-performance liquid chromatography, but, for practical reasons, we again elected to carry this mixture forward. Our intent at this point was to use the double bond of **10** and **11** to install the hexenyl side chain of **5** at the C-5 position of the tetrahydropyran and then introduce the butenoate appendage in a second allylic functionalization. The relatively bulky bornyl substituent was expected to provide a steric bias that would induce the correct configuration at the incipient stereogenic center.

Our first move toward this objective involved epoxidation of the mixture of **10** and **11** with *m*-chloroperbenzoic acid. This gave a 3:1 mixture of trans and cis epoxides, which were easily separated (as pairs of diastereomers) by flash chromatography. The major, trans epoxy acetal, consisting of **12** and **13**, could be distinguished from the cis epoxides, **14** and **15**, by comparison of the chemical shift of H-3 in the ^1H NMR spectra of the stereoisomers. Specifically, H-3 appeared as a doublet (J = 4 Hz) at δ 2.95 in the trans epoxide whereas the cis epoxide showed H-3 as a broadened multiplet at lower field ($\delta \sim 3.3$). These observations agree with the findings of Sweet and Brown.[12]

Attempts to effect elimination of epoxides **12** and **13** with strong, sterically demanding bases did not lead to the desired allylic alcohol, and an indirect method for this transformation was therefore devised. When it was found that the diastereomeric mixture of **12** and **13** underwent clean, regioselective opening at C-4 in the presence of sodium phenylselenide[13] to give **16** and **17** (Scheme III), and that these hydroxy selenides were easily separated by chromatography, a means was at hand not only for segregating the two stereochemical series but for emplacing the requisite functionality on the tetrahydrofuran ring as well. Each hydroxy selenide was separately subjected to excess hydrogen peroxide in the presence of ethanolic sodium carbonate at reflux to give the expected allylic alcohols **18** and **19**,[14] accompanied by small quantities of epoxides **12** and **13**. It was subsequently found that, if sodium borate was substituted for sodium carbonate as the base for elimination of the intermediate selenoxide, epoxide formation could be completely suppressed.

It was not possible at this juncture to ascertain the absolute configuration of diastereomeric alcohols **18** and **19**, but it was recognized that an opportunity lay ahead on the synthetic pathway to **5** for their correlation with a substance of established stereochemistry. After a determination of which member of the pair possessed the desired

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(9) Preliminary communication: Kuroda, C.; Theramongkol, P.; Engebrecht, J. R.; White, J. D. *J. Org. Chem.* **1986**, *51*, 956.
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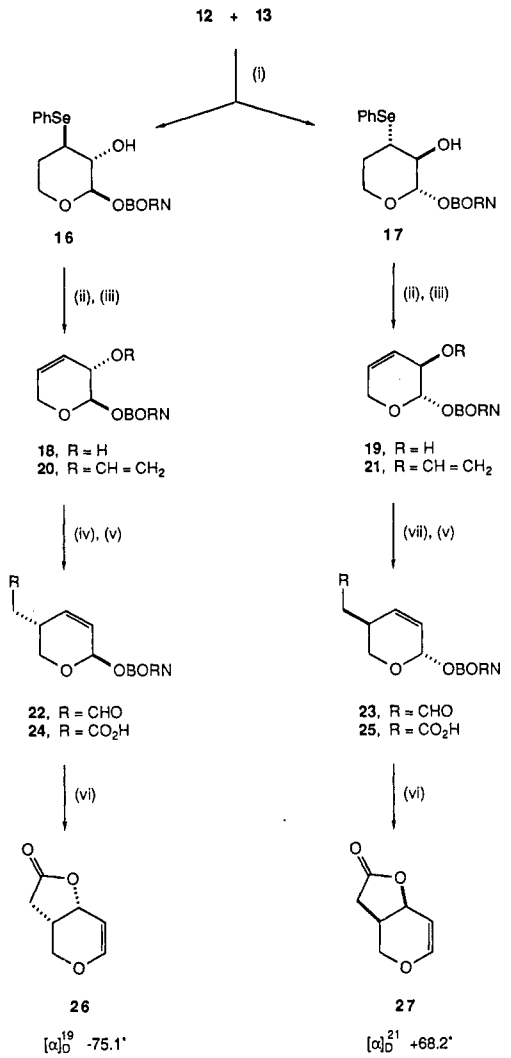
(14) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979.

Scheme III[a]

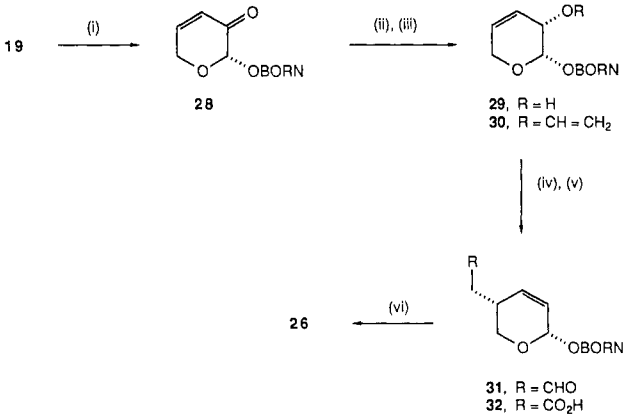


[a] Reagents: (i) PhSeSePh, $NaBH_4$, LiBr, EtOH–THF, reflux, 2 h; (ii) 30% H_2O_2, $NaHCO_3$, EtOH–THF, 0 → 40 °C, 3 h; (iii) CH_2=CHOEt, $Hg(OCOCF_3)_2$, reflux, 72 h; (iv) Pyrex helices, 250 °C, flow rate 0.16 mL/s; (v) $AgNO_3$, KOH, EtOH–H_2O, 0.5 h; (vi) $SnCl_4$, CH_2Cl_2, −78 °C, 0.5 h; (vii) Pyrex helices, 185 °C.

hydroxyl configuration, our objective would then be to converge the unwanted alcohol with the main pathway through an oxidation–reduction sequence. Etherification of **18** and **19** separately with ethyl vinyl ether in the presence of mercuric trifluoroacetate as catalyst afforded vinyl ethers **20** and **21**, together with minor quantities of the ethoxyethyl ethers. Pyrolysis of **20** and **21** at 250 °C in a continuous-flow system resulted in their smooth conversion via Claisen rearrangement to aldehydes **22** and **23**, in which the configuration at C-3 of the tetrahydropyran ring has been transferred with complete integrity to the new stereogenic center bearing the acetaldehyde appendage. Aldehydes **22** and **23** were somewhat unstable, and initial attempts to oxidize them to acids with chromium oxidants met with disappointing results. However, silver(I) oxide, prepared and used in situ,[15] converted **22** and **23** to the crystalline carboxylic acids **24** and **25** in excellent yield.

With the crucial C-5 stereochemistry of the tetrahydropyran in place the bornyl auxiliary was no longer needed, and the next stage called for its removal via a process that would lead to an oxoallyl cation. It was expected that this cation would undergo intramolecular attack by the carboxyl function to yield γ-lactones **26** and **27**, pivotal intermediates in our plan for introduction of the second (C-2) side chain of monic acid as well as stereochemical correlation with a substance of known configuration. In the event, dilute solutions of acids **24** and **25** in dichloromethane underwent clean conversion to lactones **26** and **27** in the presence of stannic chloride, and, in addition, (−)-1-borneol was recovered from the reaction in sufficient quantity for recycling. A comparison of the optical rotation as well as infrared and NMR spectra of **26** with data on the same lactone provided by Dr. G. W. Fleet and prepared independently by him from D-arabinose[7f] left no doubt that these materials were identical in all respects, including absolute configuration.

Scheme IV[a]



[a] Reagents: (i) MnO_2, CH_2Cl_2, room temperature, 4 h; (ii) $(iBu)_2AlH$, toluene, −78 °C; (iii) CH_2=CHOEt, $Hg(OCOCF_3)_2$; (iv) Pyrex helices, 280 °C; (v) $AgNO_3$, KOH, EtOH–H_2O; (vi) $SnCl_4$, CH_2Cl_2, −78 °C.

With **26** confirmed as the correct enantiomer for our route to monic acid, we sought a means for bringing the parallel series from **17** into stereoconvergence with this material. Allylic alcohol **19** appeared to be an ideal substrate for this purpose, since facile oxidation would be expected to lead to a ketone, reduction of which would take place from the face opposite the bulky bornyloxy substituent. This would afford a diastereomer of **18** in which the allylic alcohol would again be positioned to set configuration at C-5 of the tetrahydropyran through a Claisen rearrangement. Thus, oxidation of **19** with manganese dioxide[16] furnished **28**, and reduction of this ketone with diisobutylaluminum hydride[17] gave the expected alcohol **29** as the sole product (Scheme IV). A sequence analogous to that employed with **18** led to vinyl ether **30** and, after pyrolysis, to **31**. The somewhat lower yield observed in the Claisen rearrangement of **30**, as compared with **20**, appears to be associated with the higher temperature needed for the reaction and a consequent competing elimination to an unstable pyran. In any event, **31** was oxidized in nearly quantitative yield to carboxylic acid **32**, which, upon exposure to stannic chloride, yielded **26** identical in all respects, including optical rotation, with the lactone obtained from **18**.

Introduction of the monic acid side chain at C-2 of the tetrahydropyran was initially envisioned via a S_N2' displacement (perhaps catalyzed by a Lewis acid) of the allylic

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(17) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213.

Table I. Carbosulfenylation of 26 with RSCl-$ZnBr_2$ and 2-(Trimethylsiloxy)propene

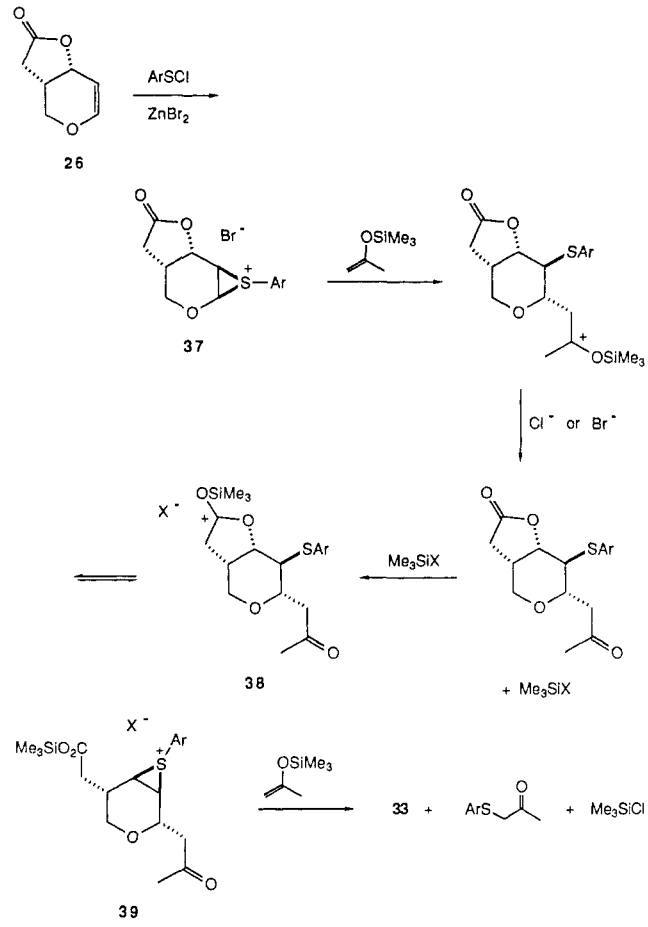
R	solvent	temp, °C	yield, % (33 + 34)	ratio 33:34
Ph	CH_2Cl_2	−78	86	51:49
Ph	CH_2Cl_2	−92	60	54:46
Ph	CH_2Cl_2–pentane	−78	37	50:50
Ph	CH_2Cl_2–CH_3CN	−78	0	
o-(Me_2CH)-C_6H_4	CH_2Cl_2	−78	63	50:50
o-$O_2NC_6H_4$	CH_2Cl_2	−78	72	57:43
p-$MeOC_6H_4$	CH_2Cl_2	−78	50	55:45
2,4-$(O_2N)_2$-C_6H_3	CH_2Cl_2	−78	47	59:41
Ph_3C	CH_2Cl_2	−78	97	76:24

lactone. While this process, if it had been successful, would have correctly sited the double bond in the tetrahydropyran for subsequent hydroxylation, the cis stereochemistry of the side chains in monic acid mandates that the S_N2' displacement of **26** occur in a syn fashion at the endo face of the bicyclic framework. In practice, this approach failed to yield satisfactory results due, in part, to the availability of alternative sites in **26**, including the lactone carbonyl, for nucleophilic attack.

We therefore turned to an indirect method for accomplishing this substitution that had encouraging precedence in work reported by Paterson.[18] Carbosulfenylation of **26** was expected to occur readily at the electron-rich double bond, and, if this took place at the exo face of the bicycle, entry of the nucleophile at the endo C-2 terminus of the intermediate sulfonium species was assured. To our surprise, the reaction of **26** with benzenesulfenyl chloride, 2-[(trimethylsilyl)oxy]propene, and a catalytic quantity of zinc bromide gave a product which, although it clearly had incorporated the acetonyl moiety, contained no sulfur. Closer inspection revealed that the sulfenylation–alkylation had been followed by an unanticipated elimination of the sulfenyl lactone to give a mixture of the two carboxylic acids **33** and **34**. Unfortunately, the bonus that had accrued in this process was offset by the discovery that the stereoselectivity was negligible. Methyl esters **35** and **36**, obtained from their parent acids with diazomethane, were found to be present in a nearly 1:1 ratio by HPLC analysis. Modification of the sulfenylating agent in the form of substitution on the aromatic ring was generally deleterious, as seen from Table I. However, triphenylmethanesulfenyl chloride markedly improved both the yield and stereoselectivity of the acetonylation of **26**, and a carefully optimized procedure gave a 97% yield of a 3:1 mixture of **33** and **34**, respectively.

A plausible view of the mechanism of the conversion of **26** to **33** is presented in Scheme V. The necessity for a catalytic quantity of zinc bromide, without which only **26** is recovered, appears to be associated with preactivation of the sulfenyl halide. The requirement for at least 2 equiv (4 is optimum) of the enol ether reflects its probable secondary role as a nucleophile in trapping the sulfonium ion after its extrusion from **39**. This would lead to α-(phenylthio)acetone as a byproduct of the reaction, which was, in fact, detected. The mechanism proposed in Scheme V is also consistent with the observation that a full equivalent of the sulfenyl chloride is required (ruling out halide attack on **38** or episulfonium ion **39** to regenerate a catalytic sulfenyl system). Finally, the putative role of trimethylsilyl chloride, generated in situ from the reaction of the silyl enol ether with chloride ion, in assisting the lactone elimination is based on the finding that the product before

Scheme V



aqueous workup is the trimethylsilyl ester of **33**. The choice of a silyl enol ether as the partner for **26** was therefore felicitous in several respects: it reacts with **37** at carbon and with **39** at sulfur,[19] yet it does not compete with **26** for the sulfenyl halide. The predominance of **33** when triphenylmethanesulfenyl chloride is used may be simply a steric effect manifested as a preference by the bulkier electrophile for exo attack on **26**. Alternatively, a variant of the mechanism shown in Scheme V, in which trityl cation is generated and perhaps becomes an electrophilic participant, can be envisioned. We have no evidence for the latter option, however.

Hydroxylation of the double bond of **35** was accomplished with catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide as the principal oxidant[20] and afforded a single, crystalline diol **40** in high yield (Scheme VI). The stereochemistry of this diol was assumed to be as shown, based upon osmylation at the more exposed β face of the double bond in the cis 2,5-disubstituted pyran **35**. The diol was protected as its cyclohexylidene derivative **41**, prepared by treatment of **40** with 1,1-dimethoxycyclohexane in the presence of an acidic catalyst. A small quantity of the dimethyl ketal **42** was also produced in this reaction. The keto function of **41** was elaborated to the α,β-unsaturated carboxylate side chain of monic acid C by a Horner–Emmons condensation with the sodium salt of *tert*-butyl dimethylphosphonoacetate,[21] which afforded a 7:1 mixture of *E* (**43**) and *Z* (**44**) isomers, respectively. These

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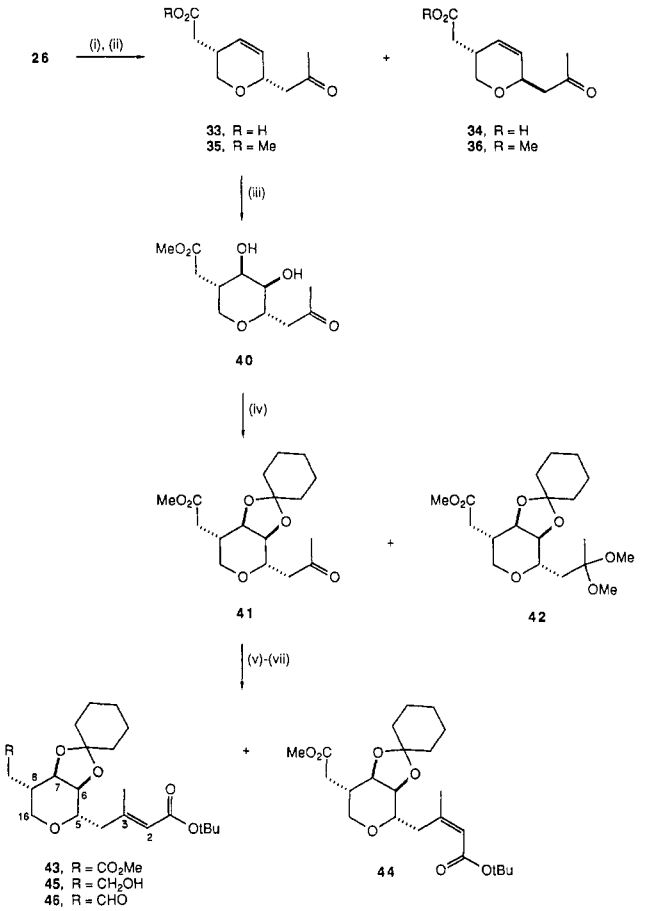
Scheme VI[a]



[a] Reagents: (i) Ph_3CSCl, $CH_2{=}C(Me)OSiMe_3$, $ZnBr_2$ (cat.), CH_2Cl_2, -78 °C, 1.5 h; (ii) CH_2N_2, Et_2O-EtOH, room temperature, 8 h; (iii) OsO_4 (cat.), *N*-methylmorpholine *N*-oxide, *t*-BuOH-THF-H_2O, room temperature, 72 h; (iv) 1,1-dimethoxycyclohexane, *p*-TsOH (cat.), room temperature, 0.5 h; (v) $(MeO)_2POCH_2CO_2tBu$, NaH, LiBr, THF, room temperature, 17 h; (vi) Li(*n*-Bu)(iBu)$_2$AlH, THF, -78 °C, 1.5 h; (vii) pyridinium chlorochromate, 4-Å molecular sieves, CH_2Cl_2.

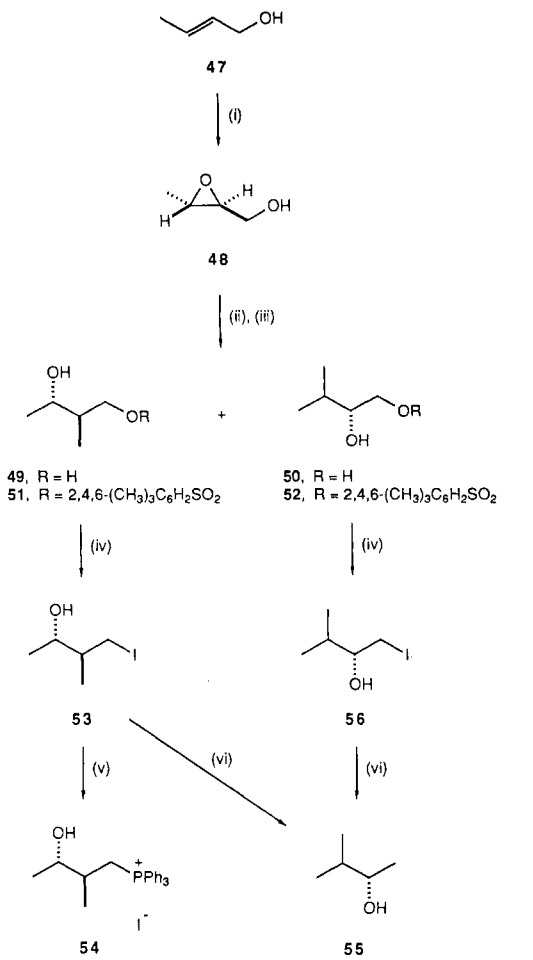
esters were readily separated by chromatography, and it was found that the yield of **43** could be augmented by irradiation of **44** with a 450-W Hanovia lamp, which gave a 1:1 mixture of the two isomers.

Attachment of the left side chain (C-11–C-14) of monic acid to **43** necessitated a trans olefination, for which either a Schlosser-modified Wittig reaction[22] or Julia elimination[23] of a β-hydroxy sulfone was projected. For either process it was necessary to replace the methyl ester of **43** by an aldehyde while leaving the *tert*-butyl ester unmolested. The ate complex prepared from diisobutylaluminum hydride and *n*-butyllithium[24] afforded a convenient means for accomplishing this transformation. Reduction of **43** with this reagent led to a mixture of the primary alcohol **45** and the aldehyde **46**, which, without separation, was oxidized with pyridinium chlorochromate to **46** in excellent yield. This aldehyde afforded a convenient check point at which to verify structure and configuration, and salient ^{1}H NMR data are collected in Table II. The trans, cis, trans arrangement of substituents on

Table II. ^{1}H NMR Data for 46 (400 MHz, $CDCl_3$)

proton	chemical shift, ppm	multiplicity	coupling constant, Hz
H_2	5.65	s	
H_4	2.55	dd	17, 6
$H_{4'}$	2.75	dd	17, 10
H_5	3.44	dt	9, 3
H_6	3.66	dd	9, 5
H_7	4.02	dd	5, 2
H_8	2.67	m	
H_9	2.17	dd	15, 10
$H_{9'}$	2.48	d	15
H_{16}ax	3.57	d	12
H_{16}eq	3.76	dd	12, 3
$C(CH_3)_3$	1.47	s	
CH_3	2.15	s	
CHO	9.80	d	1

Scheme VII[a]



[a] Reagents: (i) *t*-BuOOH, $Ti(OiPr)_4$, (+)-DIPT, CH_2Cl_2, -20 °C, 20 h; (ii) $Me_2(CN)CuLi_2$, THF, -20 °C, 2 h; (iii) 2,4,6-$Me_3C_6H_2SO_2Cl$, pyridine, -20 °C, 3 days; (iv) NaI, Me_2CO, reflux, 7 h; (v) Ph_3P, MeCN, reflux, 36 h; (vi) $NaBH_4$, DMSO, room temperature, 10 h.

the tetrahydropyran is confirmed by $J_{5,6}$ (9.0 Hz), $J_{6,7}$ (4.8 Hz), and $J_{7,8}$ (2.2 Hz) couplings, while the negligible coupling between H-8 and H-16$_{axial}$ suggests that the aldehyde chain in **46** is axial. The stereochemical assignment made to **46** was strongly supported by comparison of its ^{1}H NMR spectrum with that of the analogous ethyl ester. The latter was first obtained as a racemate in the course of Kozikowski's synthesis[7a] of **5** and was later prepared in optically active form by Fleet.[7f]

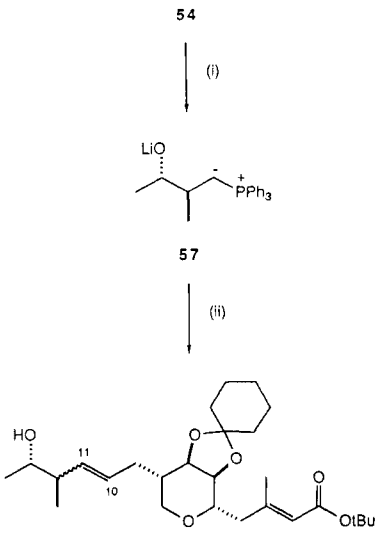
The (2*S*,3*S*)-phosphonium salt **54** required for Wittig reaction with **46** was prepared from *trans*-2-buten-1-ol (**47**).

(22) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311. For a comprehensive mechanistic analysis of this and other variations of the Wittig reaction, see: Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664.

(23) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833.

(24) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

Scheme VIII[a]



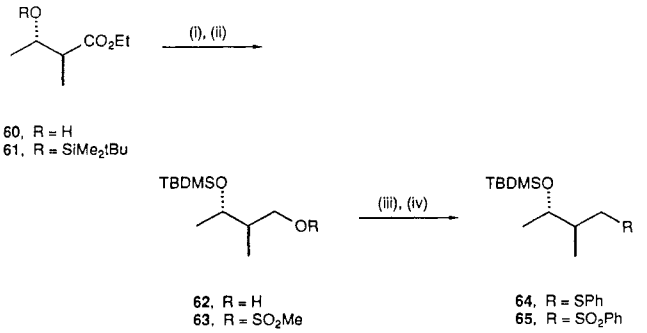
[a] Reagents: (i) *n*-BuLi (2 equiv), LiBr, 0 → 22 °C, 0.5 h; (ii) **46**, THF, −45 → −30 °C, 2 h.

Asymmetric epoxidation[25] of **47** with *tert*-butyl hydroperoxide in the presence of titanium isopropoxide and (+)-diisopropyl L-tartrate gave **48** (Scheme VII), and treatment of this epoxide with lithiocyanomethylcuprate[26] afforded a 1:1 mixture of (2*R*,3*S*)-2-methylbutane-1,3-diol (**49**) and (2*R*)-3-methyl-butane-1,2-diol (**50**) in high yield. This mixture, which could not be separated by chromatography, was converted to the corresponding mono 2,4,6-trimethylbenzenesulfonates **51** and **52** by selective sulfonation of the primary hydroxyl groups of **49** and **50**. Sulfonates **51** and **52** were readily separated by column chromatography, and **51** was then subjected to displacement by iodide. The resulting iodo alcohol **53** proved to be unstable and was reacted promptly with triphenylphosphine to furnish the phosphonium salt **54**.

The configuration of **53** was verified, and an estimate of the optical efficiency of the asymmetric epoxidation of **47** was derived from reduction of **53** with sodium borohydride to the known (*S*)-3-methyl-2-butanol (**55**).[27] This correlation confirmed that the sequence from **48** leads to **54** in an enantiomeric excess of 95%. The sulfonate **52** was also converted to **55** by reaction with sodium iodide followed by reduction of the resulting iodo alcohol **56** with sodium borohydride.

The Wittig reaction of **46** with γ-oxidoylide **57**, prepared from **54** with 2 equiv of base, was explored under a variety of conditions, but, as was anticipated from results obtained by Kozikowski in a similar coupling of racemic partners,[7a] the efficiency of this process was disappointingly low. An optimized protocol, in which **57** was generated with 2 equiv of butyllithium at −45 °C and allowed to react with **46** for 2 h at −30 °C before being warmed to room temperature, afforded a 37% yield of olefins consisting of a 57:43 mixture of *E* (**58**) and *Z* (**59**) isomers (Scheme VIII). Although **58** and **59** could be separated on a column of silica gel impregnated with 10% silver nitrate, this route was judged

Scheme IX[a]



[a] Reagents: (i) $(iBu)_2AlH$, toluene, −78 °C, 1 h; (ii) $MeSO_2Cl$, pyridine, room temperature, 20 h; (iii) PhSH, tBuOK, DMF, room temperature, 1.5 h; (iv) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, room temperature, 4.5 h.

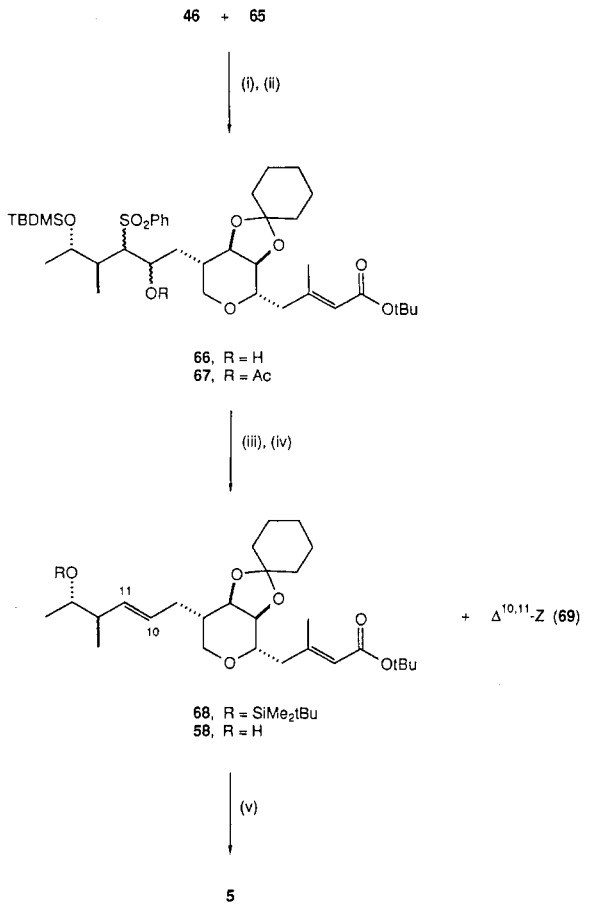
unacceptable as a means for installing the left side chain of monic acid C. We therefore decided to explore a different strategy in which side-chain coupling was effected between **46** and the anion of a sulfone. It was expected on the basis of substantial precedent established by Julia[28] that reductive elimination of the derived β-acetoxy sulfone would lead to the *E* olefin of monic acid. This approach had, in fact, been investigated by Keck in his synthesis of pseudomonic acid C but was abandoned in favor of a scheme that reversed the aldehyde and sulfone components.[7j] Williams was similarly unsuccessful in his efforts to apply Julia methodology to this problem, although he was able to adapt an alternative protocol for elimination of his intermediate β-hydroxy sulfone.[7l]

Sulfone **65** was prepared from ethyl (2*S*,3*S*)-3-hydroxy-2-methylbutyrate (**60**)[29] by following the route outlined by Keck[30] (Scheme IX). Thus, protection of **60** as its *tert*-butyldimethylsilyl ether **61**, followed by reduction of the ester, furnished **62**, which was converted to mesylate **63**. Treatment of **63** with sodium benzenesulfinate did not lead to **65**, but the reaction of **63** with sodium thiophenoxide effected clean displacement to give **64**, which was oxidized in high yield to **65**. The anion of **65**, obtained with butyllithium, condensed smoothly with **46** and produced a pair of stereoisomeric hydroxy sulfones **66** (Scheme X). This mixture was acetylated, and the acetoxy sulfones **67** were reacted with sodium amalgam to give *E* olefin **68** and its *Z* isomer **69** in the ratio 17:3, respectively. The major product **68** was separated from **69** and unreacted **66** by chromatography on silica gel and was subjected to tetra-*n*-butylammonium fluoride to give **58**, identical with material obtained previously from the Wittig reaction of **46**.

The final transformation of **58** to **5** required hydrolysis of the cyclohexylidene ketal and conversion of the *tert*-butyl ester to a carboxylic acid. It was found that these two operations could be accomplished consecutively by first exposing **58** to trifluoroacetic acid in dichloromethane (which cleaved the ester) and then to 50% aqueous trifluoroacetic acid. Monic acid C (**5**) was obtained as a glass in 93% yield by this protocol, but, although its properties were in good agreement with those reported,[1d] we were unable to secure a specimen of naturally derived material for direct comparison. Consequently, a sample of natural monic acid A (**70**) was degraded to **5** by protection of **70** as its acetonide **71**, deoxygenation of the epoxide to **72** with

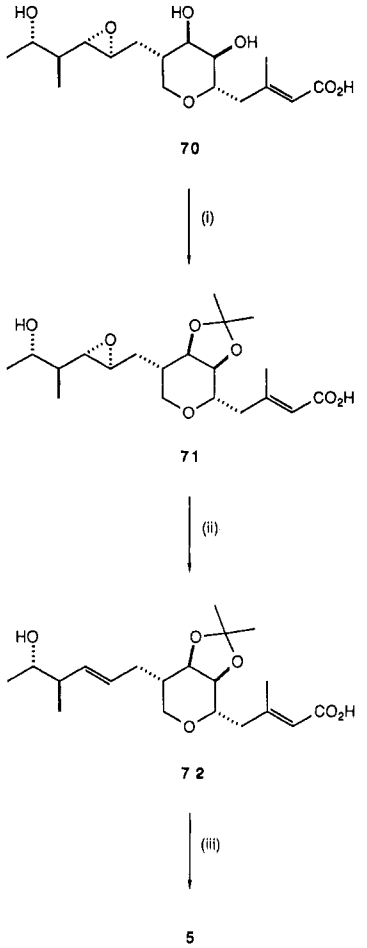
(25) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.
(26) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.
(27) Meek, A. G.; Martin, Z. Z.; Nadworny, H. A.; Silver, M. S. *J. Org. Chem.* **1976**, *41*, 323.
(28) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.
(29) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825.
(30) Experimental details for these transformations were inadvertently omitted from ref 7j and are therefore included herein.

Scheme X[a]



[a] Reagents: (i) *n*-BuLi, THF, −65 °C, 1 h; (ii) Ac_2O, pyridine, room temperature, 10 h; (iii) Na(Hg), Na_2HPO_4, EtOAc–MeOH, −20 °C, 11 h; (iv) *n*-Bu_4NF, THF, room temperature, 24 h; (v) CF_3CO_2H, CH_2Cl_2, 0 °C, 1 h, then 50% $CF_3CO_2H(H_2O)$, room temperature, 0.75 h.

Scheme XI[a]



[a] Reagents: (i) 2,2-$(MeO)_2CMe_2$, *p*-TsOH (cat.), EtOAc; (ii) $KHCO_3$, KSeCN, $Me_2C(OH)Et$-H_2O (9:1), reflux, 41 h; (iii) 80% $AcOH(H_2O)$, room temperature, 15 h.

potassium selenocyanate, and, finally, removal of the acetonide (Scheme XI). Our synthetic monic acid C (**5**) was identical with the substance obtained from **70** by comparison of infrared and ^1H and ^{13}C NMR spectra and optical rotation. Monic acid C has been converted to pseudomonic acid C (**3**),[7a] and the latter, through its methyl ester, has been further elaborated to pseudomonic acid A (**1**).[1d] Synthesis of **5** thus constitutes a formal synthesis of these related materials.

Experimental Section

Melting points were obtained on a hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 727B or a Nicolet Model 5-DXB spectrometer. ^1H NMR spectra were determined at 80 or 400 MHz. Low- and high-resolution mass spectra (MS) were obtained at an ionization potential of 70 eV. Optical rotations were measured in 1-dm cells of 1-mL capacity.

Analytical thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F254, layer thickness 0.2 mm) manufactured by E. Merck and Co. Column chromatography was carried out with Merck silica gel 60 (230–400 mesh ASTM). Alumina refers to Brockmann Activity I neutral aluminum oxide manufactured by M. Woelm. For high-performance liquid chromatography (HPLC) a system equipped with two semipreparative silica (μ-Porasil) columns and a refractive index detector was employed. The purity of all title compounds was verified to be ≥95% by HPLC, ^1H NMR, or ^{13}C NMR analyses.

For reactions requiring dry solvents, THF and ether were distilled from sodium benzophenone ketyl under N_2; CH_2Cl_2 was distilled from CaH_2. All solvents for extraction and chromatography were distilled prior to use. Starting materials were obtained from commercial suppliers and used without purification.

3-Bromo-2-(1-bornyloxy)tetrahydropyran (8 and 9). To a cooled, stirred solution of 3,4-dihydro-2*H*-pyran (**6**, 56.2 g, 0.668 mol) in CH_2Cl_2 (500 mL) at −78 °C was added dropwise a solution of Br_2 (101.7 g, 0.635 mol) in CH_2Cl_2 (250 mL). After being stirred for 15 min, the light yellow solution was treated with *N*,*N*-dimethylaniline (78.6 g, 0.648 mol). The temperature was raised to 0 °C, and a solution of (−)-1-borneol (**7**, 20.0 g, 0.13 mol) in CH_2Cl_2 (300 mL) was added slowly. The mixture was stirred for 30 min, allowed to warm to room temperature, and stirred for a further 6 h. Concentration of the mixture under reduced pressure gave a dark blue viscous liquid, which was triturated three times with Et_2O. The ethereal layers were combined, washed with dilute aqueous Na_2CO_3 and water, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a yellow liquid, which was fractionally distilled through a Vigreux column under reduced pressure (ca. 2–3 Torr). When the column head temperature reached approximately 50 °C, the distillation was discontinued and the dark residue was cooled to room temperature and diluted with hexane. The hexane solution was washed once with water, dried over anhydrous Na_2SO_4, and concentrated to give a light yellow liquid. This was distilled in a Kugelrohr apparatus to afford 33.6 g (82% from borneol) of **8** and **9** as a light yellow liquid: bp 84 °C (0.05 Torr); IR (neat) 1060, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (2 × 6 H, s), 0.88 (3 H, s), 0.90 (3 H, s), 3.3–4.1 (2 × 4 H, m), 4.51 (1 H, d, J = 5 Hz), 4.57 (1 H, d, J = 5 Hz); MS, m/e (relative intensity) 237 (2, $[M - Br]^+$), 165 (54), 137 (74), 84 (100); HRMS 237.1771 ($[M - Br]^+$, calcd for $C_{15}H_{25}BrO_2$ 237.1854).

2-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran (10 and 11). A mixture of **8** and **9** (9.40 g, 29.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (11.27 g, 74.0 mmol) was heated at 95–100 °C under a N_2 atmosphere for 20 h. The resulting brown solid was

cooled to room temperature, slurried with ether (60 mL), and filtered. The solid residue was washed well with ether, and the filtrate was washed with three portions of water and dried over anhydrous Na_2SO_4. The solution was concentrated to give a light yellow oil, which was chromatographed on silica (130 g) with hexane and hexane–AcOEt (20:1 and 10:1) as eluents. This afforded 6.9 g (99%) of a mixture of **10** and **11** as a clear colorless liquid: IR (neat) 1650, 1080, 1020, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (9 H, s), 0.85 (6 H, s), 0.87 (3 H, s), 3.5–4.2 (2 × 3 H, m), 4.88 (2 × 1 H, br s), 5.70 (2 × 1 H, br d, J = 10 Hz), 5.95 (2 × 1 H, dd, J = 10.5 Hz); MS, m/e (relative intensity) 153 (20), 109 (42), 83 (100).

***trans*-2-(1-Bornyloxy)-3,4-epoxytetrahydropyran (12 and 13).** To a stirred solution of the mixture of **10** and **11** (3.55 g, 0.015 mol) in CH_2Cl_2 (75 mL) was added *m*-chloroperbenzoic acid (4.96 g, 0.023 mol) portionwise at room temperature. After being stirred for 48 h, the mixture was filtered, and the solid residue was washed with cold CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to one-third of the original volume and filtered again. The crystalline residue was washed with a small amount of cold CH_2Cl_2, and dimethyl sulfide (0.5 mL) was added to the filtrate, which was stirred for 30 min. The resulting suspension was filtered through Celite, and the residue was washed with CH_2Cl_2. Concentration of the combined filtrates gave a viscous liquid, which was filtered through a short column of alumina (Activity I) with 1:1 AcOEt–hexane as eluent. The combined fractions afforded a light yellow liquid after evaporation of the solvent, which was subjected to column chromatography on silica (120 g) with hexane–AcOEt (20:1) as eluent, to give 2.21 g (61%) of an oily mixture of **12** and **13** and 0.798 g (22%) of **14** and **15**.

12 and 13: IR (neat) 1050, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.87 (3 H, s), 2.97 and 3.03 (1 H, d, J = 4 Hz), 3.30 and 3.33 (2 H, m), 3.65 and 3.66 (1 H, dd, J = 10, 6 Hz), 3.85 and 4.02 (1 H, br d, J = 10 Hz), 4.87 and 4.91 (1 H, s); MS, m/e (relative intensity) 252 (0.4, M^+), 169 (3), 153 (14), 137 (22), 109 (68), 99 (72), 41 (100). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.60.

14 and 15: IR (neat) 1050, 1010, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.87 (3 H, s), 2.9–3.5 (3 H, m), 3.5–4.3 (2 H, m), 4.90 and 4.95 (each $^1/_2$ H, s); MS, m/e (relative intensity) 252 (1, M^+), 169 (7), 153 (16), 137 (29), 109 (89), 99 (100); HRMS 252.1657 (calcd for $C_{15}H_{24}O_3$ 252.1675).

2(*R*)-(1-Bornyloxy)-3(*R*)-hydroxy-4(*R*)-(phenylseleno)-tetrahydropyran (16) and 2(*S*)-(1-Bornyloxy)-3(*S*)-hydroxy-4(*S*)-(phenylseleno)tetrahydropyran (17). To a stirred solution of diphenyl diselenide (2.38 g, 7.63 mmol) in EtOH–THF (1:1, 100 mL) was added $NaBH_4$ (0.598 g, 15.8 mmol) portionwise at room temperature. Anhydrous LiBr (1.2 g, 13.9 mmol) was added in one portion to the solution, which was vigorously stirred for 30 min. To the light yellow slurry was added the mixture of **12** and **13** (3.5 g, 13.9 mmol), and the mixture was heated to mild reflux for 2 h, cooled to room temperature, and concentrated under reduced pressure to half of the original volume. The slurry was filtered, and the solid was washed with Et_2O, dissolved in H_2O (25 mL), and extracted twice with Et_2O. The combined ethereal layers were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed to give a viscous yellow oil. Chromatographic separation on silica (200 g), with hexane–AcOEt (20:1, 10:1, 5:1, successively) as eluent, afforded 2.70 g (48%) of the less polar hydroxy selenide (**16**) as an oil and 2.76 g (49%) of crystalline **17**, respectively.

16: $[\alpha]^{21}_D$ −62.8° (*c* 3.48, $CHCl_3$); IR (neat) 3500, 1580, 1240, 1140, 1050, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (6 H, s), 0.90 (3 H, s), 2.57 (1 H, d, J = 2 Hz), 2.9–3.6 (3 H, m), 3.7–4.1 (2 H, m), 4.20 (1 H, d, J = 7 Hz), 7.2–7.7 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 13.5, 18.5, 19.4, 26.5, 27.8, 32.1, 37.0, 43.8, 44.7, 47.1, 49.2, 63.5, 72.9, 85.6, 105.2, 127.3, 127.6, 128.6 (×2), 135.6 (×2); MS, m/e (relative intensity) 410 (1, M^+), 257 (4), 253 (12), 209 (19), 157 (23), 137 (100); HRMS 410.1359 (calcd for $C_{21}H_{30}O_3Se$ 410.1360).

17: mp 84.0–84.5 °C (from AcOEt–hexane); $[\alpha]^{21}_D$ +25.1° (*c* 3.34, $CHCl_3$); IR (Nujol) 3425, 1580, 1190, 1000, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (6 H, s), 0.90 (3 H, s), 2.54 (1 H, d, J = 3 Hz), 2.9–3.6 (3 H, m), 3.7–4.1 (2 H, m), 4.22 (1 H, d, J = 6 Hz), 7.1–7.7 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 13.3, 18.7, 19.6,26.6, 28.1, 32.0, 35.9, 43.8, 44.9, 47.8, 48.9, 63.2, 72.8, 82.5, 102.1, 127.7, 127.9, 128.8 (×2), 135.6 (×2); MS, m/e (relative intensity) 253 (2, $[M - SePh]^+$), 209 (4), 137 (100). Anal. Calcd for $C_{21}H_{30}O_3Se$: C, 61.61; H, 7.39. Found: C, 61.46; H, 7.14.

2(*R*)-(1-Bornyloxy)-3(*S*)-hydroxy-3,6-dihydro-2*H*-pyran (18). To a stirred solution of **16** (2.35 g, 5.74 mmol) in EtOH–THF (1:1, 40 mL) was added 260 mg of $NaHCO_3$ followed by 6.5 mL of 30% aqueous H_2O_2 dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, at room temperature for 2 h, and at 40 °C for 3 h. The solvent was removed azeotropically with benzene under reduced pressure, and the resultant syrupy residue was diluted with EtOH (20 mL). The mixture was heated to mild reflux for 8.5 h and concentrated, and the residue was diluted with H_2O and extracted with Et_2O. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated to give an oily residue, which was chromatographed on silica (100 g). Elution with hexane–AcOEt (10:1) gave 0.12 g (8%) of **12**. Subsequent elution with hexane–AcOEt (5:1) gave 1.26 g (87%) of **18**: mp 68.5–69.5 °C; $[\alpha]^{21}_D$ +123.5° (*c* 2.14, $CHCl_3$); IR (film) 3450, 1040, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s), 0.87 (6 H, s), 3.89 (2 H, m), 4.15 (2 H, m), 4.62 (1 H, d, J = 4 Hz), 5.85 (2 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.5, 19.5, 26.5, 27.9, 36.9, 44.8, 47.4, 49.2, 60.9, 65.1, 84.3, 102.2, 124.9, 128.2; MS, m/e (relative intensity) 153 (5), 137 (100), 81 (96). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.56.

2(*S*)-(1-Bornyloxy)-3(*R*)-hydroxy-3,6-dihydro-2*H*-pyran (19). By the same procedure as described for **18**, **17** (2.61 g, 6.36 mmol) afforded, after chromatography on silica (80 g), 95 mg (6%) of epoxide **13** and 1.26 g (79%) of **19**: mp 104.5–105.0 °C; IR (Nujol) 3450, 1060, 1040, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (9 H, s), 3.6–4.4 (4 H, m), 4.70 (1 H, d, J = 3 Hz), 5.87 (2 H, AB q, J = 10 Hz); MS, m/e (relative intensity) 153 (4), 137 (100), 81 (99). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.22; H, 9.58.

2(*S*)-(1-Bornyloxy)-3-oxo-3,6-dihydro-2*H*-pyran (28). To a stirred suspension of activated MnO_2 (1.5 g) in CH_2Cl_2 (100 mL) was added **19** (125 mg, 0.495 mmol) at room temperature. After 2.5 h, additional MnO_2 (0.75 g) was added, and the mixture was stirred for a further 1.5 h. The suspension was filtered through Celite, and the filtrate was concentrated to dryness to give 107 mg (86%) of **28** as a crystalline solid, which was homogeneous according to TLC: mp 71–72 °C; $[\alpha]^{21}_D$ −192.0° (*c* 0.53, $CHCl_3$); IR (Nujol) 1690, 1040, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (6 H, s), 0.89 (3 H, s), 4.10 (1 H, ddd, J = 10, 4, 2 Hz), 4.25 (1 H, ddd, J = 19, 4, 2 Hz), 4.55 (1 H, dt, J = 19, 2 Hz), 4.83 (1 H, s), 6.12 (1 H, br d, J = 10 Hz), 7.00 (1 H, ddd, J = 10, 4, 2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.8, 19.7, 26.5, 28.0, 35.6, 45.1, 48.0, 49.2, 59.6, 82.8, 96.6, 124.9, 147.4, 188.9; MS, m/e (relative intensity) 137 (72), 81 (45), 68 (100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.07; H, 8.99.

2(*S*)-(1-Bornyloxy)-3(*S*)-hydroxy-3,6-dihydro-2*H*-pyran (29). To a stirred solution of **28** (606 mg, 2.42 mmol) in dry toluene (80 mL, freshly distilled from sodium) at −78 °C under N_2 was added dropwise a solution of diisobutylaluminum hydride (1.5 M in toluene, 2.5 mL, 3.75 mmol). After the mixture was stirred for 1 h at −78 °C, MeOH was added and the mixture was allowed to warm to room temperature. The resulting slurry was filtered through Celite, and the residue was washed well with MeOH. The combined filtrate was evaporated under reduced pressure and was chromatographed on silica (30 g), with hexane–AcOEt (12:1) as eluent, to give 538 mg (88%) of **29** as a colorless oil: $[\alpha]^{21}_D$ −122.1° (*c* 1.26, $CHCl_3$); IR (neat) 3500, 1095, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (6 H, s), 0.88 (3 H, s), 3.7–4.3 (4 H, m), 4.90 (1 H, d, J = 4 Hz), 5.75 (2 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.8, 19.6, 26.7, 28.2, 35.9, 45.1, 47.9, 49.1, 59.7, 64.2, 81.1, 94.5, 126.4, 126.6; MS, m/e (relative intensity) 234 (0.2, $[M - H_2O]^+$), 153 (10), 137 (100). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.46; H, 9.73.

2(*R*)-(1-Bornyloxy)-3(*S*)-(vinyloxy)-3,6-dihydro-2*H*-pyran (20). To a stirred solution of **18** (400 mg, 1.585 mmol) in ethyl vinyl ether (35 mL, distilled from CaH_2) under N_2 was added mercuric trifluoroacetate (51.3 mg, 0.12 mmol). The mixture was heated to mild reflux for 24 h, after which another portion of mercuric trifluoroacetate (ca. 40 mg) and ethyl vinyl ether (15 mL) were added. After 72 h half of the solvent was removed by distillation at atmospheric pressure and was replaced by fresh ethyl vinyl ether (ca. 25 mL) along with additional quantities of

mercuric trifluoroacetate (ca. 40 mg). Refluxing was continued for an additional 24 h, and the mixture was cooled to room temperature. Anhydrous K_2CO_3 (500 mg) was added to the vigorously stirred mixture during 30 min, which was then filtered and concentrated. The resultant light yellow oil was chromatographed on silica (30 g). Elution with hexane–AcOEt (20:1) gave 316 mg (78% based on consumed starting material) of **20** as a colorless oil, and further elution with hexane–AcOEt (3:1) gave 32 mg of **18**.

20: $[\alpha]^{21}_D$ +136.2° (*c* 1.40, $CHCl_3$); IR (neat) 1630, 1610, 1180, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (9 H, s), 3.89 (1 H, ddd, *J* = 10, 4, 2 Hz), 4.07 (1 H, dd, *J* = 7, 2 Hz), 4.15 (3 H, m), 4.32 (1 H, dd, *J* = 14, 2 Hz), 4.74 (1 H, d, *J* = 3 Hz), 5.80 (1 H, br d, *J* = 11 Hz), 5.97 (1 H, br d, *J* = 11 Hz), 6.40 (1 H, dd, *J* = 14, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.6, 19.5, 26.5, 28.0, 37.1, 44.9, 47.4, 49.3, 60.8, 71.9, 84.6, 88.3, 100.1, 121.9, 129.8, 150.5; MS, *m/e* (relative intensity) 153 (5), 137 (45), 109 (42), 81 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.48; H, 9.59.

2(*S*)-(1-Bornyloxy)-3(*S*)-(vinyloxy)-3,6-dihydro-2*H*-pyran (30). By the same procedure as described for **20**, **29** (602 mg, 2.39 mmol) and mercuric trifluoroacetate (total of 121 mg) in ethyl vinyl ether afforded, after chromatography on silica (30 g) with the same eluents, 371 mg (70% based on consumed starting material) of **30** as an oil and 123 mg of recovered **29**.

30: $[\alpha]^{19}_D$ −92.4° (*c* 0.56, $CHCl_3$); IR (neat) 1640, 1610, 1180, 1100, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.88 (3 H, s), 3.8–4.2 (3 H, m), 4.03 (1 H, dd, *J* = 7, 2 Hz), 4.35 (1 H, dd, *J* = 14, 2 Hz), 4.45 (1 H, m), 4.98 (1 H, d, *J* = 4 Hz), 5.79 (2 H, AB q, *J* = 11 Hz), 6.44 (1 H, dd, *J* = 14, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.8, 19.6, 26.6, 28.0, 35.3, 45.0, 47.8, 49.0, 60.1, 71.0, 81.3, 88.6, 93.4, 122.9, 128.2, 150.5; MS, *m/e* (relative intensity) 153 (1), 137 (5), 109 (25), 96 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.65; H, 9.65.

2(*S*)-(1-Bornyloxy)-3(*R*)-(vinyloxy)-3,6-dihydro-2*H*-pyran (21). By the same procedure as described for the conversion of **18** to **20**, **19** (362 mg, 1.43 mmol) and mercuric trifluoroacetate (total of 126 mg) in ethyl vinyl ether afforded, after chromatography on silica (30 g) with hexane–AcOEt (20:1 and 10:1) as eluents, 317 mg (79%) of **21** as a colorless oil: $[\alpha]^{21}_D$ −187.0° (*c* 2.00, $CHCl_3$); IR (neat) 1630, 1610, 1175, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (9 H, s), 4.05 (1 H, m), 4.07 (1 H, dd, *J* = 7, 2 Hz), 4.12 (2 H, m), 4.32 (1 H, dd, *J* = 14, 2 Hz), 4.78 (1 H, d, *J* = 3 Hz), 5.80 (1 H, br d, *J* = 11 Hz), 5.95 (1 H, br d, *J* = 11 Hz), 6.42 (1 H, dd, *J* = 14, 7 Hz); MS, *m/e* (relative intensity) 153 (4), 137 (64), 81 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.49; H, 9.62.

[2(*R*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetaldehyde (22). A 21-cm Pyrex column packed with glass helices (prewashed with dilute aqueous NH_4OH and dried at 150 °C) and equipped with an injection adapter at the top and a receiving adapter with a 50-mL flask at the bottom, was heated to 250–255 °C by two Nichrome coils wound around the column. With the receiving flask submerged in a dry ice–acetone bath and a dry stream of N_2 passing through the column at a rate of 0.16 mL/s, **20** (288 mg, 1.036 mmol) was introduced dropwise through the injection port on to the column head via syringe. After addition was complete the column was allowed to cool to room temperature and was washed with AcOEt. The resulting solution was combined with the pyrolysate collected in the receiving flask and was concentrated to give a light yellow oil. This was chromatographed on silica (21g), using hexane–AcOEt (20:1 and 6:1) as eluents, to yield 270 mg (94%) of **22** as a colorless oil: $[\alpha]^{21}_D$ −80.1° (*c* 3.34, $CHCl_3$); IR (neat) 2700, 1725, 1650, 1035, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (9 H, s), 2.60 (2 H, br s), 3.50 (1 H, d, *J* = 11 Hz), 3.83 (1 H, ddd, *J* = 10, 4, 2 Hz), 4.07 (1 H, dd, *J* = 11, 3 Hz), 4.85 (1 H, d, *J* = 3 Hz), 5.77 (1 H, dd, *J* = 10, 3 Hz), 5.95 (1 H, dd, *J* = 10, 4 Hz), 9.75 (1 H, t, *J* = 1 Hz); MS, *m/e* (relative intensity) 153 (32), 141 (40), 137 (40), 109 (87), 95 (100). A semicarbazone derivative of **22** was prepared: mp 161–162 °C. Anal. Calcd for $C_{18}H_{29}O_3N_3$: C, 64.45; H, 8.71. Found: C, 64.53; H, 8.80.

[2(*S*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetaldehyde (31). By the same procedure as described for **22**, **30** (24.5 mg, 0.088 mmol) was pyrolyzed at 280 °C. After chromatography of the pyrolysate on silica (1 g), elution with hexane–AcOEt (20:1) gave 2.7 mg of recovered **30**, and elution with hexane–AcOEt (10:1) gave 11.2 mg (51% based on consumed starting material) of **31**: mp 74.0–75.5 °C; $[\alpha]^{20}_D$ −72.3° (*c* 0.16, $CHCl_3$); IR (Nujol) 1715, 1035, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (9 H, s), 2.90 (1 H, m), 3.56 (1 H, dd, *J* = 11, 9 Hz), 3.70 (1 H, dd, *J* = 11, 6 Hz), 4.01 (1 H, ddd, *J* = 10, 4, 2 Hz), 4.93 (1 H, m), 5.74 (1 H, dd, *J* = 10, 2 Hz), 5.80 (1 H, d, *J* = 10 Hz), 9.80 (1 H, t, *J* = 1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.9, 19.9, 26.8, 28.4, 29.4, 36.2, 45.2, 45.3, 47.9, 48.9, 62.0, 81.4, 92.3, 127.7, 131.8, 200.3; MS, *m/e* (relative intensity) 234 (1), 153 (56), 109 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.47; H, 9.36.

[2(*S*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*S*)-yl]acetaldehyde (23). By the same procedure as described for the conversion of **20** to **22**, **21** (315 mg, 1.13 mmol) was pyrolyzed at 180–185 °C to afford, after chromatography on silica (20 g) with hexane–AcOEt (20:1) as eluent, 232 mg (74%) of **23** as a colorless oil: $[\alpha]^{21}_D$ +27.7° (*c* 3.06, $CHCl_3$); IR (neat) 2700, 1720, 1035, 1015, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.86 (3 H, s), 3.50 (1 H, d, *J* = 11 Hz), 4.00 (1 H, m), 4.10 (1 H, dd, *J* = 11, 4 Hz), 4.87 (1 H, d, *J* = 3 Hz), 5.73 (1 H, dd, *J* = 11, 3 Hz), 5.96 (1 H, dd, *J* = 11, 5 Hz), 9.75 (1 H, t, *J* = 1 Hz); MS, *m/e* (relative intensity) 153 (51), 109 (100).

[2(*R*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetic Acid (24). To a stirred solution of **22** (240 mg, 0.862 mmol) in EtOH (4.2 mL) at room temperature was added a solution of $AgNO_3$ (356 mg, 2.1 mmol) in H_2O (0.45 mL). Aqueous KOH solution (4.77 mL, 1 M) was introduced dropwise to the mixture, which deposited a copious black precipitate. The suspension was vigorously stirred for 30 min and was filtered through Celite, which was washed well with H_2O. The combined filtrates were extracted once with Et_2O, and the extract was discarded. The aqueous layer was acidified to pH 6 with solid $NaHSO_4$ and was extracted twice with Et_2O. The combined ethereal layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give 236 mg (93%) of **24** as a colorless waxy solid: mp 60–63 °C; $[\alpha]^{21}_D$ −73.9° (*c* 1.40, $CHCl_3$); IR (Nujol) 3300–2400, 1700, 1040, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (9 H, s), 3.60 (1 H, d, *J* = 11 Hz), 3.85 (1 H, ddd, *J* = 10, 4, 2 Hz), 4.05 (1 H, dd, *J* = 11, 3 Hz), 4.87 (1 H, d, *J* = 3 Hz), 5.80 (1 H, dd, *J* = 11, 3 Hz), 6.00 (1 H, dd, *J* = 11, 4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.6, 19.6, 26.6, 28.1, 30.6, 36.1, 37.5, 45.0, 47.2, 49.2, 60.7, 84.6, 95.1, 126.8, 130.6, 177.4; MS, *m/e* (relative intensity) 153 (36), 141 (79), 109 (100). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.55; H, 8.98.

[2(*S*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetic Acid (32). By the same procedure as described for **24**, **31** (29.6 mg, 0.106 mmol) was treated with $AgNO_3$ (44 mg, 0.26 mmol) and aqueous KOH (0.6 mL, 1M) in EtOH to afford 30.2 mg (96%) of **32** as a crystalline solid: mp 106–109 °C; $[\alpha]^{20}_D$ −62.6° (*c* 0.23, $CHCl_3$); IR (Nujol) 3300–2400, 1720, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (9 H, s), 3.59 (1 H, t, *J* = 11 Hz), 3.75 (1 H, dd, *J* = 11, 6 Hz), 4.01 (1 H, ddd, *J* = 10, 4, 2 Hz), 4.94 (1 H, br s), 5.74 (1 H, dd, *J* = 10, 2 Hz), 5.86 (1 H, d, *J* = 10 Hz), 8.25 (1 H, br); ^{13}C NMR ($CDCl_3$) δ 13.6, 18.9, 19.9, 26.8, 28.4, 31.2, 35.5, 36.2, 45.2, 47.9, 48.9, 61.9, 81.3, 92.2, 127.3, 131.6, 177.0; MS, *m/e* (relative intensity) 153 (15), 141 (33), 119, (77), 85 (100). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.54; H, 8.95.

[2(*S*)-(1-Bornyloxy)-5,6-dihydro-2*H*-pyran-5(*S*)-yl]acetic Acid (25). By the same procedure as described for the conversion of **22** to **24**, **23** (210 mg, 0.754 mmol) was treated with $AgNO_3$ (299 mg, 1.76 mmol) and aqueous KOH (4 mL, 1 M) in EtOH to afford 209 mg (94%) of **25** as a crystalline solid: mp 98–99 °C; $[\alpha]^{21}_D$ +22.8° (*c* 2.30, $CHCl_3$); IR (Nujol) 3300–2400, 1710, 1630, 1040, 805, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (6 H, s), 0.87 (3 H, s), 3.62 (1 H, d, *J* = 11 Hz), 3.9–4.2 (2 H, m), 4.88 (1 H, d, *J* = 3 Hz), 5.74 (1 H, dd, *J* = 10, 3 Hz), 5.96 (1 H, dd, *J* = 10, 4 Hz), 9.22 (1 H, br); MS, *m/e* (relative intensity) 153 (54), 141 (85), 109 (100). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.12; H, 9.02.

3a(*S*),7a(*S*)-Dihydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one (26). A. From 24. To a stirred solution of **24** (336 mg, 1.142 mmol) in dry CH_2Cl_2 (65 ml) at −78 °C under argon was added dropwise anhydrous $SnCl_4$ (103 μL, 0.880 mmol). After being stirred for 30 min, the reaction mixture was quenched by addition of Et_3N (0.80 mL) and was allowed to warm to room temperature. Anhydrous K_2CO_3 (0.5 g) was added, and vigorous stirring was continued for 10 min. The mixture was diluted with Et_2O and was filtered through Celite, which was washed well with Et_2O. The fitrate was evaporated under reduced pressure to give a

copious amount of a white solid. This solid was rinsed with several portions of Et_2O, filtered again, and washed with Et_2O. The filtrate was evaporated, and the residual light brown oil was chromatographed on silica (16 g). Elution with hexane–AcOEt (6:1) gave 152 mg (86%) of (−)-1-borneol and then elution with hexane–AcOEt (3:1) gave 134 mg (84%) of **26** as a colorless liquid, which spontaneously crystallized. Recrystallization of **26** from pentane–Et_2O gave colorless needles: mp 51.0–51.5 °C; $[\alpha]^{19}_D$ −75.1° (*c* 0.24, $CHCl_3$); IR (Nujol) 1760, 1640, 1240, 1160, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (1 H, dd, *J* = 12, 9 Hz), 4.06 (1 H, dd, *J* = 12, 4 Hz), 4.88 (1 H, t, *J* = 4 Hz), 5.05 (1 H, dd, *J* = 7, 4 Hz), 6.67 (1 H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8, 33.2, 64.3, 71.2, 99.2, 149.2, 175.3; MS, *m/e* (relative intensity) 140 (100, M^+), 112 (41), 95 (79), 81 (77); HRMS 140.0464 (calcd for $C_7H_8O_3$ 140.0473).

B. From 32. By the same procedure as described above, **32** (30.1 mg, 0.102 mmol) was treated with $SnCl_4$ (10 μL, 0.09 mmol) to afford, after chromatography on silica (6 g), 11.5 mg (73%) of 1-borneol and 10.2 mg (71%) of **26**.

3a(*R*),7a(*R*)-Dihydro-4*H*-furo[3,2-*c*]pyran-2(3*H*)-one (27). By the same procedure described for the conversion of **24** to **26**, a solution of **25** (100 mg, 0.340 mmol) in CH_2Cl_2 (20 mL) was treated with anhydrous $SnCl_4$ (28 μL, 0.255 mmol). Workup and column chromatography on silica (3.5 g) gave 37.0 mg (78%) of **27**: mp 48–49 °C; $[\alpha]^{21}_D$ +68.2° (*c* 0.22, $CHCl_3$); IR (film) 1770, 1640, 1240, 1160, 960 cm^{-1}; ^1H NMR ($CDCl_3$) and mass spectra were identical with those reported above for **26**.

[2(*S*)-(2-Oxopropyl)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetic Acid (33) and [2(*R*)-(2-Oxopropyl)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetic Acid (34). To a stirred solution of **26** (74.3 mg, 0.530 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C was added dropwise a solution of triphenylmethanesulfenyl chloride (164 mg, 0.528 mmol) in CH_2Cl_2 (3 mL). After 10 min of stirring, a solution of isopropenyl trimethylsilyl ether (1.0 mL, 2.04 mmol) in CH_2Cl_2 was added dropwise followed by a catalytic amount (ca. 20 mg) of $ZnBr_2$. The mixture was stirred at −78 °C for 1.5 h, and saturated aqueous $NaHCO_3$ was added. The mixture was allowed to warm to room temperature and washed twice with CH_2Cl_2. The organic layer was extracted twice with saturated aqueous $NaHCO_3$, which was again washed with CH_2Cl_2. The combined aqueous layers were acidified to pH 2 with dilute HCl and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and concentrated to give 101.9 mg (97%) of an oily mixture of **33** and **34**, which was used in the next step without further purification: IR (neat) 3700–2400, 1715, 1165, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (3 H, s), 3.38 (0.3 H, dd, *J* = 11, 8 Hz), 3.79 (1.4 H, br s), 4.01 (0.3 H, dd, *J* = 11, 5 Hz), 4.55 (1 H, br t, *J* = 6 Hz), 5.72 (1 H, d, *J* = 11 Hz), 5.87 (1 H, br d, *J* = 11 Hz), 9.26 (1 H, br); MS, *m/e* (relative intensity) 198 (3, M^+), 183 (3), 138 (100).

Methyl [2(*S*)-(2-Oxopropyl)-5,6-dihydro-2*H*-pyran-5-(*R*)-yl]acetate (35) and Methyl [2(*R*)-(2-Oxopropyl)-5,6-dihydro-2*H*-pyran-5(*R*)-yl]acetate (36). To a solution of the mixture of **33** and **34** (99.1 mg, 0.500 mmol) in a minimum quantity of EtOH was added an excess of CH_2N_2 in Et_2O. The mixture was left standing overnight at room temperature, and the resultant colorless solution was evaporated under reduced pressure. The residue was chromatographed on silica (2.5 g), with hexane–AcOEt (10:1 and 3:1) as eluents, to yield 100.3 mg (95%) of a 3:1 mixture of **35** and **36** as a colorless liquid. These were separated by HPLC, with use of a μ-Porasil column and hexane–AcOEt (3:1) as eluent, to give pure **35** and **36** as colorless liquids.

35: $[\alpha]^{18}_D$ −65.4° (*c* 0.21, $CHCl_3$); IR (neat) 1740, 1720, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (3 H, s), 3.69 (3 H, s), 3.74 (2 H, m), 4.53 (1 H, br t, *J* = 6 Hz), 5.63 (1 H, dd, *J* = 11, 1.5 Hz), 5.84 (1 H, br d, *J* = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 30.7, 31.3, 37.5, 48.8, 51.5, 67.2, 70.8, 128.4, 130.0, 172.5, 206.2; MS, *m/e* (relative intensity) 212 (8, M^+), 197 (3), 155 (19), 138 (100); HRMS 212.1058 (calcd for $C_{11}H_{16}O_4$ 212.1048).

36: $[\alpha]^{19}_D$ −72.6° (*c* 0.18, $CHCl_3$); IR (neat) 1735, 1710, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (3 H, s), 3.34 (1 H, dd, *J* = 11, 8 Hz), 3.69 (3 H, s), 3.99 (1 H, dd, *J* = 11, 5 Hz), 4.53 (1 H, m), 5.72 (2 H, AB q, *J* = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8, 31.3, 36.2, 48.5, 51.6, 67.7, 70.4, 128.8, 129.6, 172.1, 206.3; MS, *m/e* (relative intensity) 212 (6, M^+), 197 (3), 155 (24), 138 (100); HRMS 212.1058 (calcd for $C_{11}H_{16}O_4$ 212.1048).

Methyl [2(*S*)-(2-Oxopropyl)-3(*R*),4(*R*)-dihydroxytetrahydropyran-5(*S*)-yl]acetate (40). To a stirred solution of *N*-methylmorpholine *N*-oxide (80.0 mg, 0.522 mmol) in *t*-BuOH–THF–H_2O (3 mL, 10:3:1) at room temperature was added a solution of osmium tetraoxide (150 μL, 0.0148 mmol, 2.5 w/v in *t*-BuOH). A solution of **35** (75.1 mg, 0.354 mmol) in 2 mL of *t*-BuOH–THF–H_2O (10:3:1) was introduced, and the reaction mixture was stirred for 72 h. At this point $NaHCO_3$ (50 mg) and Florisil (600 mg) were added, and the mixture was stirred for an additional 45 min and then filtered. The solid was washed well with *t*-BuOH–THF–H_2O, and the filtrate was concentrated under reduced pressure. The residual material was triturated with saturated aqueous NaCl and extracted thoroughly with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a light yellow solid, which was chromatographed on silica (2.5 g) with $CHCl_3$–EtOH (10:1) as eluent to afford 81.9 mg (94%) of **40** as colorless crystals. Recrystallization of **40** from pentane–Et_2O gave **40** as fine needles: mp 97.0–97.5 °C; $[\alpha]^{20}_D$ +25.1° (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.22 (3 H, s), 3.69 (3 H, s), 3.2–4.1 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 30.8, 33.8, 38.4, 47.0, 51.8, 65.2, 69.1, 70.1, 72.9, 172.7, 208.3; MS, *m/e* (relative intensity) 244 (9, $[M - 2H]^+$), 228 (30, $[M - H_2O]^+$), 211 (46), 171 (87), 154 (88), 97 (100). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.68; H, 7.38.

Methyl [2(*S*)-(2-Oxopropyl)-3(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-5(*S*)-yl]acetate (41). A stirred suspension of **40** (80.5 mg, 0.327 mmol) in 1,1-dimethoxycyclohexane (3 mL) containing a catalytic amount of *p*-toluenesulfonic acid (1.9 mg) was stirred at room temperature for 12 h. Anhydrous K_2CO_3 (ca. 50 mg) was added, and, after 30 min of vigorous stirring, the mixture was filtered and the residue was washed with AcOEt. The filtrate was evaporated under reduced pressure to leave a light yellow oil, which was chromatographed on silica (2.5 g). Elution with hexane–AcOEt (6:1) gave 15.9 mg (13%) of dimethoxy acetal **42**, and elution with hexane–AcOEt (3:1) gave 92.9 mg (87%) of **41** as a colorless oil: $[\alpha]^{19}_D$ −4.5° (*c* 0.22, $CHCl_3$); IR (neat) 1740, 1720, 1165, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (3 H, s), 3.69 (3 H, s), 3.2–4.3 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.0, 25.0, 30.8, 33.7, 35.1, 35.6, 38.1, 46.9, 51.8, 66.5, 73.1, 74.9, 75.1, 109.9, 172.3, 206.5; MS, *m/e* (relative intensity) 326 (99, M^+), 283 (38), 211 (65), 193 (100); HRMS 326.1736 (calcd for $C_{17}H_{26}O_6$ 326.1729).

***tert*-Butyl 4-[3(*S*),4(*R*)-(Cyclohexylidenedioxy)-5(*S*)-[(methoxycarbonyl)methyl]tetrahydropyran-2(*S*)-yl]-3-methyl-2(*E*)-butenoate (43).** To a stirred, hexane-washed suspension of sodium hydride (12.5 mg as a 50% suspension in mineral oil, 0.521 mmol) in dry THF (1 mL) at 0 °C under argon was added dropwise a solution of *tert*-butyl dimethylphosphonoylacetate (147.5 mg, 0.604 mg) in THF (0.3 mL). After 10 min at 0 °C, the mixture was warmed to room temperature and stirred for an additional 30 min. A solution of LiBr (42.3 mg, 0.487 mmol) in THF (0.3 mL) was added, and the resultant slurry was stirred for 5 min and then cooled to 0 °C. A solution of **41** (44.7 mg, 0.137 mmol) in THF (0.5 mL) was added dropwise, and stirring was continued at 0 °C for 10 min and then at room temperature for 17 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted thrice with Et_2O. The ethereal layer was dried over anhydrous Na_2SO_4 and concentrated to give an oily residue, which was chromatographed on silica (3 g). Elution with hexane–AcOEt (10:1) gave a mixture of **43** and **44**, and elution with hexane–AcOEt (3:1) gave recovered **41** (13.1 mg). The mixture of **43** and **44** was separated by a second chromatography on silica (1.5 g), with hexane–AcOEt (20:1) as eluent, and afforded 31.5 mg (77%) of crystalline **43** and 4.4 mg (11%) of oily **44**. *Z* isomer **44** was dissolved in hexane–Et_2O (1:1), and the solution was irradiated with a 450-W Hanovia mercury lamp through Pyrex to yield a 1:1 mixture of **43** and **44**, which were separated as described above.

43: mp 60.5–63.0 °C; $[\alpha]^{19}_D$ −4.8° (*c* 0.11, $CHCl_3$); UV (MeOH) λ_{max} 218 nm (ε 18000); IR (film) 1740, 1705, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (9 H, s), 2.15 (3 H, d, *J* = 1 Hz), 3.3–3.9 (4 H, m), 3.69 (3 H, s), 4.07 (1 H, br d, *J* = 4 Hz), 5.65 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 18.7, 23.7, 24.0, 25.0, 28.2 (×3), 33.7, 35.1, 35.6, 38.2, 44.2, 51.8, 66.5, 73.7, 75.0, 76.8, 79.5, 109.7, 119.4, 154.4, 166.1, 172.4; MS, *m/e* (relative intensity) 424 (58, M^+), 381 (33), 367 (53), 171 (100); HRMS 424.2498 (calcd for $C_{23}H_{36}O_7$ 424.2461).

44: $[\alpha]^{19}_D$ −9.6° (*c* 0.05, $CHCl_3$); UV (MeOH) λ_{max} 214 nm (ε 25000); IR (neat) 1740, 1710, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47

(9 H, s), 1.91 (3 H, d, J = 1.5 Hz), 3.3–3.9 (4 H, m), 3.69 (3 H, s), 4.05 (1 H, br d, J = 5 Hz), 5.67 (1 H, br s); MS, m/e (relative intensity) 424 (13, M^+), 368 (23), 325 (40), 155 (100).

[2(*S*)-(2-Methyl-3-(*tert*-butoxycarbonyl)-2(*E*)-propenyl)-3(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-5(*S*)-yl]acetaldehyde (46). To a stirred solution of **43** (19.4 mg, 0.059 mmol) in dry THF (0.7 mL) at −78 °C under argon was added dropwise a solution of the ate complex (0.24 mL, 0.091 mmol, 0.38 M in THF) prepared from *n*-butyllithium and diisobutylaluminum hydride. After 1.5 h of stirring at −78 °C, the reaction mixture was quenched with MeOH (0.7 mL) and stirred for 15 min. Saturated aqueous Na_2SO_4 was added, and the mixture was allowed to warm to room temperature and filtered through Celite. The Celite was washed well with Et_2O, and the filtrate was dried over anhydrous Na_2SO_4 and concentrated to give a mixture of **45** and **46** as an oil, which was used without further purification.

To a stirred solution of the mixture of **45** and **46** obtained above in dry CH_2Cl_2 (0.8 mL) was added powdered 4-Å molecular sieves (100 mg) and pyridinium chlorochromate (19.6 mg, 0.091 mmol) at room temperature. After 45 min of vigorous stirring, the reaction mixture was diluted with Et_2O and was filtered through Celite. The Celite was washed well with Et_2O, and the filtrate was concentrated under reduced pressure to give a brown liquid, which was passed through a short column of silica, with Et_2O as eluent. The eluate was concentrated, and the resultant oil was chromatographed on silica (0.8 g), with hexane–AcOEt (10:1) as eluent, to give 14.4 mg (80% from **43**) of **46** as a colorless oil: $[\alpha]^{21}_D$ −6.1° (c 0.80, $CHCl_3$); IR (neat) 2725, 1730, 1705, 1650, 730 cm^{-1}; ^1H NMR ($CDCl_3$), see Table II; ^{13}C NMR ($CDCl_3$) δ 18.7, 23.7, 24.0, 25.0, 28.3 (×3), 31.3, 35.6, 38.2, 44.2, 44.8, 66.6, 73.7, 75.1, 76.8, 79.6, 109.8, 119.5, 154.3, 166.1, 200.1; MS, m/e (relative intensity) 394 (55, M^+), 338 (23), 295 (35), 227 (30), 57 (100); HRMS 394.2399 (calcd for $C_{22}H_{34}O_6$ 394.2355).

(2*S*,3*S*)-2,3-Epoxybutanol (48). To a 500-mL flask equipped with a magnetic stir bar and charged with 200 mL of dry CH_2Cl_2 at −23 °C was added via syringe 5.94 mL (5.68 g, 20 mmol) of titanium tetraisopropoxide, followed by 4.20 mL (4.68 g, 20 mmol) of (+)-diisopropyl L-tartrate. The mixture was stirred for 5 min, and 1.7 mL (1.44 g, 20 mmol) of crotyl alcohol, followed by a solution of anhydrous *tert*-butyl hydroperoxide (ca. 11 mL, 3.67 M, ca. 40 mmol) in CH_2Cl_2, was added. The resulting mixture was kept at −20 °C for 20 h. To this cold mixture was added an equal amount of Et_2O (ca. 200 mL), and the mixture was stirred until a homogeneous solution was obtained. A saturated aqueous solution of Na_2SO_4 (6 mL) was then added with vigorous stirring. The resulting slurry was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residual oil was chromatographed on silica, with Et_2O–petroleum ether (35–60 °C) (8:2) as eluent, to yield 1.01 g (58%) of **48** as an oil. An analytically pure sample was obtained by gas–liquid chromatography on a 6 ft × 0.25 in. column of 7.5% TCEP on Chromosorb W at 110 °C: $[\alpha]^{20}_D$ −50.0° (c 0.52, benzene) [lit.[31] $[\alpha]^{20}_D$ −49° (c 5, benzene)]; IR (neat) 3540, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, d, J = 5 Hz), 2.4 (1 H, br s), 2.95 (2 H, m), 3.75 (2 H, dd, J = 12, 3 Hz); ^{13}C NMR ($CDCl_3$) δ 17.2, 42.0, 49.6, 61.7; MS, m/e (relative intensity) 60 (8, $[M - CO]^+$), 45 ((72), 43 (100), 31 (43).

(2*R*,3*S*)-2-Methyl-1,3-butanediol (49) and (2*R*)-3-Methyl-1,2-butanediol (50). Cupric cyanide (3.58 g, 40 mmol) was azeotropically dried with two 15-mL portions of toluene under a continuous stream of N_2. Dry THF (40 mL) was added, and the slurry was cooled to −78 °C. Methyllithium (51.7 mL, 80 mmol, 1.55 M in Et_2O) was added dropwise to produce a pale green solution, which was allowed to warm to −20 °C, and a solution of **48** (0.88 g, 10 mmol) in THF (4 mL) at 0 °C was added dropwise. An additional quantity of THF (2 mL) was added, and the mixture was stirred at −20 °C for 2 h. The reaction was quenched with 50 mL of a 9:1 saturated aqueous NH_4Cl–NH_4OH solution and stirred for 30 min at room temperature. Saturated aqueous NaCl (25 mL) was added, the layers were separated, and the aqueous phase was extracted with three 100-mL portions of Et_2O. The combined organic extracts were dried over anhydrous K_2CO_3, and the solvent was removed in vacuo to give 0.955 g (92%) of an approximately 1:1 mixture of **49** and **50** as an oil. These diols were separated by conversion to their monotriphenylmethyl ethers with triphenylmethyl chloride and DMAP in CH_2Cl_2. Chromatography on silica and elution with hexane–AcOEt (4:1) gave (2*R*,3*S*)-2-methyl-1-(triphenylmethoxy)-3-butanol followed by (2*R*)-3-methyl-1-(triphenylmethoxy)-2-butanol. Hydrogenolysis of these ethers over 10% Pd/C in EtOH at 32 psig for 12 h afforded **49** and **50**.

49: $[\alpha]^{20}_D$ + 3.5° (c 1.7, EtOH); IR (neat) 3400, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, d, J = 8 Hz), 1.23 (3 H, d, J = 6 Hz), 1.65 (1 H, m), 2.55 (1 H, br s), 2.95 (1 H, br s), 3.70 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.0, 41.8, 68.1, 73.7; MS, m/e (relative intensity) 86 (4, $[M - H_2O]^+$), 71 (17), 58 (21), 45 (71), 43 (100).

50: $[\alpha]^{20}_D$ −6.4° (c 1.46, cyclohexane) [lit.[32] $[\alpha]^{20}_D$ −6.3° (c 2.0, cyclohexane)]; IR (neat) 3420, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 4 Hz), 0.98 (3 H, d, J = 4 Hz), 1.65 (1 H, m), 2.80 (2 H, br s), 3.50 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 18.2, 18.7, 30.9, 64.9, 77.3; MS, m/e (relative intensity) 105 (59, M + 1), 87 (88), 73 (93), 43 (91).

(2*S*,3*R*)-3-Methyl-4-[[(2,4,6-trimethylphenyl)sulfonyl]oxy]butan-2-ol (51) and (3*R*)-2-Methyl-4-[[(2,4,6-trimethylphenyl)sulfonyl]oxy]butan-3-ol (52). To a solution of **49** and **50** (0.608 g, 5.8 mmol) in 30 mL of pyridine at −20 °C was added a solution of mesitylenesulfonyl chloride (1.54 g, 6.96 mmol, 1.2 equiv) in 10 mL of pyridine, which was precooled to −20 °C before addition. The mixture was kept in a freezer at −20 °C for 3 days, the pyridine was then removed in vacuo, and the residue was extracted into Et_2O. The ethereal extract was concentrated in vacuo to give an oil, which was purified by chromatography on silica. Elution with petroleum ether (35–60 °C)–Et_2O (4:1) gave 0.596 g (36%) of **51** and 0.799 g (48%) of **52** as oils.

51: $[\alpha]^{20}_D$ +10.7° (c 1.24, EtOH); IR (neat) 3500, 3030, 1350, 1170, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6 Hz), 1.15 (3 H, d, J = 7 Hz), 1.80 (1 H, m), 2.27 (3 H, s), 2.60 (6 H, s), 3.65 (1 H, br s), 3.95 (3 H, m), 6.92 (2 H, s); ^{13}C NMR ($CDCl_3$) δ 13.4, 20.5, 20.8, 21.0, 22.6, 40.4, 68.5, 71.6, 131.8, 139.9, 143.3; MS, m/e (relative intensity) 286 (43, M^+), 200 (100), 91 (55), 45 (90).

52: $[\alpha]^{20}_D$ −2.6° (c 1.18, EtOH); IR (neat) 3600, 3010, 1345, 1165, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 8 Hz), 0.91 (3 H, d, J = 8 Hz), 1.68 (1 H, m), 2.28 (3 H, s), 2.62 (6 H, s), 3.55 (1 H, br s), 3.95 (3 H, m), 6.92 (2 H, s); ^{13}C NMR ($CDCl_3$) δ 17.5, 18.6, 21.0, 22.5, 30.6, 71.7, 74.2, 131.7, 139.9, 143.8; MS, m/e (relative intensity) 286 (18, M^+), 184 (76) 120 (80), 119 (100), 91 (49), 43 (57).

(2*S*,3*S*)-1-Iodo-2-methyl-3-butanol (53). A solution of **51** (290 mg, 1.07 mmol) and sodium iodide (1.5 g, 10 equiv) in acetone (20 mL) was refluxed for 7 h. The solvent was removed under reduced pressure to give a red-orange solid. The solid was triturated with Et_2O, and the solvent was removed in vacuo to yield **53** as a red oil. This material was used without further purification.

(2*S*)-1-Iodo-3-methyl-2-butanol (56). A solution of **52** (290 mg, 1.07 mmol) and NaI (1.5 g, 10 equiv) in acetone (20 mL) was refluxed for 7 h. The solvent was removed under reduced pressure to give a red-orange solid. The solid was triturated with Et_2O, and the ethereal solution was passed through Celite to yield a yellow solution. The Et_2O was removed in vacuo to give **56** as a red oil, which was used without further purification.

((2*S*,3*S*)-3-Hydroxy-2-methylbutyl)triphenylphosphonium Iodide (54). Crude **53** obtained above was dissolved in 35 mL of CH_3CN, and triphenylphosphine (4.2 g, 16 mmol, 5 equiv) was added. The mixture was refluxed for 36 h, and most of the solvent (25 mL) was removed by distillation to leave a colorless precipitate. The solid was washed by decantation with Et_2O (3 × 40-mL portions) to furnish 1.40 g (95% based on **51**) on **54** as a colorless solid. A sample of **54** was recrystallized from MeOH: mp 252–254 °C dec $[\alpha]^{20}_D$ −2.1° (c 1.26, CH_3CN); IR (KBr) 3400, 1100, 745 cm^{-1}; ^1H NMR (CD_3OD) δ 0.68 (3 H, d, J = 7 Hz), 1.11 (3 H, d, J = 5 Hz), 2.0 (1 H, br s), 3.6 (4 H, m), 7.25 (15 H, m); ^{13}C NMR (CD_3OD) δ 17.4, 20.5, 26.3, 37.3, 72.4, 120.8, 131.5, 135.0, 136.2; MS, m/e (relative intensity) 348 (0.4,

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$[M - HI]^+$, 271 (100), 262 (73), 201 (70), 183 (72), 77 (37). Anal. Calcd for $C_{23}H_{26}OPI$: C, 58.00, H, 5.46. Found: C, 58.05; H, 5.26.

(2*S*)-3-Methyl-2-butanol (55). A. From 53. To a stirred solution of crude **53**, obtained from **51** as described above, in 3 mL of DMSO was added $NaBH_4$ (104 mg, 5 equiv), and the mixture was stirred overnight at room temperature. With vigorous stirring, 3 mL of saturated aqueous NaCl was slowly added, and the mixture was stirred for 30 min. This solution was extracted thrice with 20-mL portions of Et_2O, the ethereal extract was dried over anhydrous Na_2SO_4, and the solvent was removed by distillation. The residual oil was passed through a column of silica, eluting with Et_2O–petroleum ether (35–60 °C) (1:1), to give partially purified **55**. This material was further purified by gas–liquid chromatography on a 5 ft × 0.25 in. column of 1.5% OV-101 on Chromosorb G at 40 °C to yield 16.6 mg (33% from **51**) of **55**: $[\alpha]^{20}_D$ +5.00° (*c* 1.66, EtOH) [lit.[27] $[\alpha]^{20}_D$ + 5.34° (*c* 5, EtOH)]; IR (neat) 3400, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 7 Hz), 0.93 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 1.35 (1 H, br s), 1.63 (1 H, m), 3.53 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 17.7, 18.1, 20.1, 35.1, 72.8; MS, *m/e* (relative intensity) 87 (1, $M^+ - 1$), 55 (16), 45 (100).

B. From 56. A solution of crude **56** in 3 mL of DMSO was reduced with $NaBH_4$ (37 mg, 5 equiv) as described for **53** to give 65.2 mg (39% from **52**) of **55**: $[\alpha]^{20}_D$ + 4.8° (*c* 1.53, EtOH). The spectral properties of this material matched those of **55** prepared from **53**.

***tert*-Butyl 4-{5(*S*)-[5(*S*)-Hydroxy-4(*R*)-methylhex-2-(*E*)-enyl]-3(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-2(*S*)-yl}-3-methyl-2(*E*)-butenoate (58) and *tert*-Butyl 4-{5(*S*)-[5(*S*)-Hydroxy-4(*R*)-methylhex-2(*Z*)-enyl]-3(*S*),4-(*R*)-(cyclohexylidenedioxy)tetrahydropyran-(2*S*)-yl}-3-methyl-2(*E*)-butenoate (59).** To a slurry of **54** (34.4 mg, 0.072 mmol) in THF (200 μL) at 0 °C was added a solution of *n*-butyllithium (120 μL, 0.144 mmol, 1.2 M in hexane) dropwise over 2 min. The resulting yellow-orange solution was stirred vigorously at 0 °C for 20 min and then at room temperature for 10 min, after which a solution of lithium bromide (4.3 mg, 0.072 mmol) in THF (200 μL) was added. The mixture was cooled to −45 °C, and a solution of **46** (19 mg, 0.048 mmol) in THF (200 μL) was added. After 2 h at −30 °C, the mixture was quenched with acetic acid (4.7 mg, 0.072 mmol), diluted with Et_2O (3 mL), and vigorously stirred for 5 min. The resulting slurry was filtered through Celite, which was washed well with Et_2O (2 mL). The filtrate was evaporated under reduced pressure to give a colorless oil, which was taken up into Et_2O (6 mL). The ethereal extract was washed with H_2O (1 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil, which was chromatographed on silica (1.5 g) with hexane–AcOEt (8:1) as eluent. The major fraction, consisting of a mixture of **58** and **59**, was rechromatographed on 10% silver nitrate impregnated silica (1.2 g), with hexane–AcOEt (8:1 and then 5:1) as eluent, to give 4.75 mg (21%) of **58** and 3.55 mg (16%) of **59**.

58: $[\alpha]^{23}_D$ +3.5° (*c* 0.20, $CHCl_3$); IR (neat) 3500, 1705, 1650, 1140, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 6.7 Hz), 1.16 (3 H, d, J = 6.3 Hz), 1.47 (9 H, s), 2.16 (3 H, s), 2.48 (2 H, br d, J = 14.5 Hz), 3.42 (1 H, dt, J = 2.9, 9.2 Hz), 3.55 (1 H, t, J = 6.2 Hz), 3.6–3.7 (3 H, m), 4.05–4.15 (2 H, m), 5.44 (1 H, dd, J = 15.3, 8.2 Hz), 5.52 (1 H, dt, J = 15.3, 7.1 Hz), 5.67 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 16.6, 18.8, 20.3, 23.7, 24.1, 25.0, 28.3, 34.0, 35.6, 36.8, 38.2, 44.1, 44.8, 66.4, 71.0, 73.8, 75.1, 76.6, 77.2, 79.5, 109.3, 119.3, 129.6, 134.7, 154.6, 166.2; MS, *m/e* (relative intensity) 464 (35, M^+), 421 (45), 407 (59), 364 (72), 57 (100); HRMS 464.3163 (calcd for $C_{27}H_{44}O_6$ 464.3138).

59: IR (neat) 3500, 1710, 1650, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 6.8 Hz), 1.19 (3 H, d, J = 6.2 Hz), 1.47 (9 H, s), 1.70–1.41 (10 H, m), 2.01 (1 H, m), 2.15 (3 H, d, J = 1.1 Hz), 2.21–2.17 (2 H, m), 2.30 (1 H, m), 2.46 (2 H, m), 3.42 (1 H, dt, J = 2.9, 9.0 Hz), 3.52 (1 H, m), 3.60 (1 H, d, J = 12.2 Hz), 3.66 (1 H, dd, J = 2.9, 11.7 Hz), 3.69 (1 H, dd, J = 5.0, 8.8 Hz), 4.10 (1 H, m, J = 2.4 Hz), 5.36 (1 H, t, J = 10.8 Hz), 5.54 (1 H, dt, J = 7.3, 10.9 Hz), 5.65 (1 H, s); MS, *m/e* 464 (M^+), 421, 407, 364.

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-butanol (62). To a solution of **60**[29] (317.5 mg, 2.17 mmol) in dry DMF (7 mL, distilled over 4 Å molecular sieves) was added imidazole (1.00 g, 14.7 mmol) and *tert*-butyldimethylsilyl chloride (955 mg, 6.34 mmol), and the mixture was stirred at room temperature for 21 h. Water (10 mL) was added, and the mixture was extracted with 4 × 15 mL of Et_2O. The ethereal extract was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The resultant oil was passed through silica (10 g) and was eluted with hexane–AcOEt (10:1) to give **61**, which was taken up in dry toluene (50 mL). To this solution at −78 °C was added dropwise a solution of diisobutylaluminum hydride (9 mL, 1.0 M in hexane), and the mixture was stirred for 1 h. A further quantity (10 mL) of the hydride solution was then added, and, after stirring for 1 h at −78 °C, the reaction mixture was quenched with MeOH (6 mL) and allowed to warm to room temperature. Saturated aqueous NaCl (5 mL) was added, and the mixture was extracted with Et_2O. The ethereal extract was dried over anhydrous Na_2SO_4, the solvent was removed by distillation, and the residual oil was chromatographed on silica (10 g). Gradient elution with hexane–AcOEt (starting at 20:1) afforded 159.6 mg (34% from **60**) of **62** as a colorless oil: $[\alpha]^{21}_D$ +25.0° (*c* 0.20, $CHCl_3$); IR (neat) 3350, 1255, 1035, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (6 H, s), 0.90 (9 H, s), 0.97 (3 H, d, J = 7 Hz), 1.21 (3 H, d, J = 6 Hz), 2.77 (1 H, m), 3.4–3.9 (3 H, m); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.3, 14.6, 17.9, 22.1, 25.8 (×3), 41.7, 65.8, 73.9; MS, *m/e* (relative intensity) 161 (28), 160 (32), 159 (20), 158 (21), 74 (100). Anal. Calcd for $C_{11}H_{26}O_2Si$: C, 60.49; H, 12.00. Found: C, 60.66; H, 11.81.

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylbutyl Methanesulfonate (63). To a solution of **62** (159.6 mg, 0.731 mmol) in pyridine (5 mL, freshly distilled from CaO) was added methanesulfonyl chloride (1 mL), and the mixture was stirred for 20 h at room temperature. Water (10 mL) was added, and the solution was extracted four times with Et_2O. The extract was dried over anhydrous Na_2SO_4 and concentrated to a yellow oil, which was chromatographed on silica (10 g). Elution with hexane–AcOEt (10:1) gave 192.2 mg (89%) of **63** as a pale yellow oil: $[\alpha]^{21}_D$ +29.0° (*c* 0.22, $CHCl_3$); IR (neat) 1365, 1180, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.90 (9 H, s), 0.99 (3 H, d, J = 7 Hz), 1.16 (3 H, d, J = 6 Hz), 1.89 (1 H, sept, J = 6 Hz), 3.00 (3 H, s), 3.75 (1 H, quint, J = 6 Hz), 4.10 (1 H, dd, J = 7, 10 Hz), 4.31 (1 H, dd, J = 5, 10 Hz); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 13.5, 18.0, 21.2, 25.8 (×3), 37.1, 40.7, 69.4, 72.1; MS, *m/e* (relative intensity) 239 (3, $[M - (CH_3)_3C]^+$, 195 (4), 171 (6), 159 (14), 153 (100).

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-(phenylthio)butane (64). Thiophenol (495 mg, 4.5 mmol) was added to a stirred solution of potassium *tert*-butoxide (507 mg, 4.52 mmol) in dry DMF (5 mL) at room temperature. The mixture was cooled to 0 °C, and a solution of **63** (185.0 mg, 0.624 mmol) in DMF (1.4 mL) was added. The mixture was stirred at room temperature for 1.5 h, H_2O was added, and the solution was extracted four times with Et_2O. The extract was dried over anhydrous Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica (10 g). Elution with hexane–Et_2O (100:1) yielded 170.8 mg (88%) of **64** as an oil: $[\alpha]^{21}_D$ +39° (*c* 0.305, $CHCl_3$); IR (neat) 1590, 1250, 1105, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s), 0.05 (3 H, s), 0.89 (9 H, s), 1.00 (3 H, d, J = 7 Hz), 1.11 (3 H, d, J = 6 Hz), 1.75 (1 H, m), 2.61 (1 H, dd, J = 9, 13 Hz), 3.20 (1 H, dd, J = 5, 13 Hz), 3.75 (1 H, quint, J = 6 Hz), 7.11–7.34 (5 H, m); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.3, 15.3, 18.1, 20.4, 25.9 (×3), 36.7, 40.5, 71.4, 125.4, 128.5 (×2), 128.8 (×2), 137.5; MS, *m/e* (relative intensity) 310 (2, M^+), 295 (2), 253 (100), 167 (27). Anal. Calcd for $C_{17}H_{30}OSSi$: C, 65.74; H, 9.74. Found: C, 65.91; H, 10.07.

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-1-(phenylsulfonyl)butane (65). *m*-Chloroperbenzoic acid (590 mg) was added in one lot to a solution of **64** (170.8 mg, 0.550 mmol) in CH_2Cl_2 (9 mL), and the mixture was stirred at room temperature for 4.5 h. The precipiate was filtered off and was washed with CH_2Cl_2. The filtrate was washed successively with aqueous $NaHSO_3$, aqueous $NaHCO_3$, and H_2O and was dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded an oil, which was chromatographed on silica (10 g). Elution with hexane–AcOEt (10:1) furnished 176.3 mg (94%) of **65** as a colorless oil: $[\alpha]^{22}_D$ +15.0° (*c* 0.225, $CHCl_3$); IR (neat) 1450, 1305, 1150, 1085, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 (3 H, s), 0.01 (3 H, s), 0.83 (9 H, s), 1.02 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 2.00 (1 H, m), 2.82 (1 H, dd, J = 9, 14 Hz), 3.34 (1 H, dd, J = 3, 14 Hz), 3.65 (1 H, dq, J = 4, 6 Hz), 7.54–7.68 (3 H, m), 7.90–7.94 (2

H, m); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.3, 17.0, 17.9, 20.7, 25.7 (×3), 36.0, 58.3, 71.4, 127.9 (×2), 129.2 (×2), 133.5, 140.1; MS, *m/e* (relative intensity) 327 (3, $[M - CH_3]^+$, 285 (100), 199 (15), 159 (40), 135 (65). Anal. Calcd for $C_{17}H_{30}O_3SSi$: C, 59.60; H, 8.83. Found: C, 59.74; H, 9.09.

***tert*-Butyl 4-{5(*S*)-[3-(Phenylsulfonyl)-5(*S*)-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-4(*R*)-methylhexyl]-3-(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-2(*S*)-yl}-3-methyl-2(*E*)-butenoate (66).** To a solution of **65** (32.0 mg, 0.0934 mmol) in dry THF (1.5 mL) at −65 °C under argon was added *n*-BuLi (1.2 mL, 0.096 mmol, 0.08 M solution in hexane–THF), and the mixture was stirred for 10 min. To the resulting yellow solution was added a solution of **46** (16.0 mg, 0.041 mmol) in THF, and stirring was continued at −65 °C for 1 h. Aqueous NaCl was added, and the mixture was allowed to warm to room temperature and extracted with Et_2O four times. The ethereal extract was dried over anhydrous Na_2SO_4 and concentrated to give an oily residue, which was chromatographed on silica (1 g). Successive elution with 10:1 and 6:1 hexane–AcOEt gave 25.1 mg (84%) of **66** (mixture of two diastereomers) as a viscous oil: IR (neat) 3500, 1710, 1650, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (6 H, s), 0.83 (9 H, s), 1.48 (9 H, s), 2.15 (3 H, d, J = 1 Hz), 3.1–4.5 (8 H, m), 5.64 (1 H, br s), 7.4–8.0 (5 H, m); MS, *m/e* (relative intensity) 736 (1, M^+), 662 (8), 623 (11), 605 (11), 548 (19), 394 (97), 159 (100).

***tert*-Butyl 4-{5(*S*)-[5(*S*)-[(*tert*-Butyldimethylsilyl)-oxy]-4(*R*)-methyl-2(*E*)-hexenyl]-3(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-2(*S*)-yl}-3-methyl-2(*E*)-butenoate (68).** To a solution of **66** (24.5 mg, 0.033 mmol) in dry pyridine (1 mL) was added 0.5 mL of acetic anhydride, and the mixture was stirred overnight at room temperature. To this mixture was added MeOH (1 mL) and, after 30 min, saturated aqueous $NaHCO_3$ (3 mL). The mixture was stirred for an additional 2.5 h, H_2O was added, and the solution was extracted with Et_2O. The ethereal extract was dried over anhydrous Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica (1 g). Successive elution with 10:1 and 3:1 hexane–AcOEt yielded 24.0 mg (93%) of **67** as a pale yellow oil. This material, which appeared as three spots on TLC, was used in the next step without further purification.

A solution of **67** obtained above (24.0 mg, 0.031 mmol) in AcOEt (1 mL) containing Na_2HPO_4 (340 mg) was cooled to −20 °C, and 6% sodium amalgam (1.14 g) and MeOH (1 mL) were added. This mixture was stirred at −20 °C for 3 h, and then a further quantity of sodium amalgam (0.27 g) was added. After 6 h at −20 °C, a final addition of sodium amalgam (0.20 g), Na_2HPO_4 (100 mg), and MeOH (0.5 mL) was made, the mixture was stirred for 2 h, and AcOEt was added. The mixture was allowed to warm to room temperature and was filtered by suction through silica with AcOEt. The filtrate was dried over anhydrous Na_2SO_4 and concentrated, and the oily residue was chromatographed on silica (1 g). Elution with hexane–AcOEt (20:1) gave 10.8 mg (79%) of a 17:3 mixture of **68** and **69** as a colorless oil, and subsequent elution with hexane–AcOEt (3:1) gave 5.5 mg of recovered **67**. Separation of **68** and **69** was carried out by HPLC with use of a μ-Porasil column and hexane–AcOEt (20:1) as eluent.

68: an oil; $[\alpha]^{21}_D$ −1.2° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 1700, 1650, 1265, 1145, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (3 H, s), 0.03 (3 H, s), 0.88 (9 H, s), 0.95 (3 H, d, J = 6.8 Hz), 1.02 (3 H, d, J = 6.1 Hz), 1.47 (9 H, s), 2.16 (3 H, s), 2.48 (1 H, br d, J = 13.7 Hz), 3.41 (1 H, dt, J = 2.8, 9.2 Hz), 3.6–3.7 (4 H, m), 4.11 (1 H, dd, J = 1.8, 4.7 Hz), 5.39 (1 H, dd, J = 6.1, 15.5 Hz), 5.43 (1 H, dd, J = 6.8, 15.5 Hz), 5.67 (1 H, s); MS, *m/e* (relative intensity) 578 (1, M^+), 534 (3), 521 (5), 479 (6), 465 (7), 159 (100); HRMS 578.4032 (calcd for $C_{33}H_{58}O_6Si$ 578.4002).

69: an oil; ^1H NMR ($CDCl_3$) δ 0.04 (6 H, s), 0.89 (9 H, s), 0.94 (3 H, d, J = 6.9 Hz), 1.04 (3 H, d, J = 6.4 Hz), 1.47 (9 H, s), 2.16 (3 H, d, J = 0.9 Hz), 2.47 (1 H, br d, J = 14.2 Hz), 3.40 (1 H, dt, J = 2.7, 9.1 Hz), 3.6–3.7 (4 H, m), 4.09 (1 H, br d, J = 4.5 Hz), 5.38 (1 H, dd, J = 7.0, 11.0 Hz), 5.43 (1 H, dd, J = 8.7, 11.0 Hz), 5.66 (1 H, s).

***tert*-Butyl 4-{5(*S*)-[5(*S*)-Hydroxy-4(*R*)-methyl-2(*E*)-hexenyl]-3(*S*),4(*R*)-(cyclohexylidenedioxy)tetrahydropyran-2(*S*)-yl}-3-methyl-2(*E*)-butenoate (58).** To a solution of **68** (4.4 mg, 7.6 μmol) in dry THF (0.3 mL) under argon was added a solution of tetra-*n*-butylammonium fluoride in THF (50 μL, 1.0 M), and the mixture was stirred for 12 h at room temperature. A further 40 μL of tetra-*n*-butylammonium fluoride solution was added, and stirring was continued for another 12 h. Water was added, the mixture was extracted four times with CH_2Cl_2, and the extract was dried over anhydrous Na_2SO_4 and concentrated. The oily residue was chromatographed on silica (0.2 g), with hexane–AcOEt (10:1 → 3:1) as eluent, to afford 3.0 mg (85%) of **58** identical with material prepared from **54**.

4-{5(*S*)-[5(*S*)-Hydroxy-4(*R*)-methyl-2(*E*)-hexenyl]-3-(*R*),4(*R*)-dihydroxytetrahydropyran-2(*S*)-yl}-3-methyl-2-(*E*)-butenoic Acid (Monic Acid C) (5). A. From 58. To a solution of trifluoroacetic acid (20 μL) in CH_2Cl_2 (50 μL) at 0 °C was added a solution of **58** (2.9 mg, 6.25 μmol) in CH_2Cl_2 (200 μL). The mixture was stirred for 1 h and then was warmed to room temperature. After the solution was stirred for 3 h, 50% aqueous AcOH (350 μL) was added to the solution, and stirring was continued for 7 h. The solvent was removed in vacuo, and the residue was taken up into 50% aqueous trifluoroacetic acid (350 μL). After being stirred for 45 min, the mixture was concentrated to yield 2.7 mg of a colorless oil, which was chromatographed on silica (0.4 g). Gradient elution with $CHCl_3$–MeOH (40:1 → 5:1) gave 1.9 mg (93%) of **5** as a glassy solid: $[\alpha]^{24}_D$ −5.8 (*c* 0.12, H_2O); IR (KBr) 3400, 1690, 1640, 1240 cm^{-1}; ^1H NMR (D_2O) δ 0.84 (3 H, d, J = 6.9 Hz), 0.99 (3 H, d, J = 6.2 Hz), 1.94 (3 H, s), 2.19 (1 H, dd, J = 10.2, 15.0 Hz), 2.50 (1 H, br d, J = 14.9 Hz), 3.40–3.48 (2 H, m), 3.56 (1 H, t, J = 6.1 Hz), 3.65 (1 H, dd, J = 3.0, 11.9 Hz), 3.74–3.83 (2 H, m), 5.35 (2 H, m), 5.68 (1 H, s); ^{13}C NMR (D_2O) δ 16.1, 18.5, 19.5, 32.2, 41.2, 42.3, 43.9, 65.0, 68.9, 70.1, 71.9, 74.8, 119.6, 128.9, 135.2. These spectral data were identical with those obtained for **5** prepared from monic acid A (**70**) as described below.

B. From 71. A solution of **71** (7.2 mg, 0.02 mmol) in 80% aqueous AcOH (250 μL) was allowed to stand at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica (0.7 g), with a gradient elution of $CHCl_3$–MeOH (100:1 → 10:1), to give 6.2 mg (97%) of **5**: $[\alpha]^{23}_D$ −6.7° (*c* 0.52, H_2O).

6,7-*O*-Isopropylidenemonic Acid C (71). To a stirred suspension of monic acid A (**70**, 34.4 mg, 0.1 mmol) in AcOEt (500 μL) was added 2,2-dimethoxypropane (500 μL) and a few crystals of *p*-toluenesulfonic acid. After 1 h the solution was diluted with AcOEt and washed with saturated aqueous NaCl (1 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. The residue was taken up into 50% aqueous MeOH (400 μL), and $KHCO_3$ (10 mg) was added. The solution was evaporated to dryness in vacuo, and potassium selenocyanate (43.2 mg, 0.3 mmol) and a mixture of 2-methyl-2-butanol and H_2O (9:1; 1.5 mL) was added. The mixture was refluxed for 24 h, after which another portion of potassium selenocyanate (17 mg) was added, and the mixture was refluxed for an additional 17 h. The suspension was filtered, and the filtrate was diluted with AcOEt (4 mL) and extracted with water (4 × 1 mL). The cold (0 °C) aqueous extract was acidified to pH 2 with $NaHSO_4$ and reextracted with AcOEt (4 × 1 mL). The organic extract was dried over anhydrous $MgSO_4$, concentrated, and chromatographed on silica (3 g), with AcOEt–hexane (1:1 and 3:1) as eluent, to give 29.4 mg (80%) of **71** as a colorless viscous liquid: IR (neat) 3600–2400, 1700, 1640, 1060, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (3 H, d, J = 7 Hz), 1.16 (3 H, d, J = 6 Hz), 1.35 (3 H, s), 1.50 (3 H, s), 4.15 (1 H, dd, J = 5, 2 Hz), 5.45 (2 H, m), 5.77 (1 H, br s).

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