Total Synthesis of Tetronomycin

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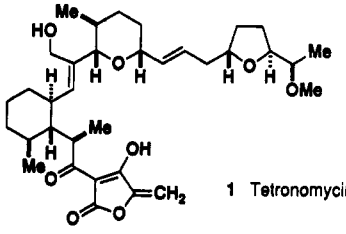
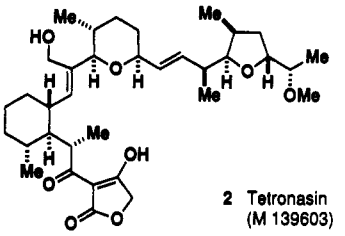
The first total synthesis of (+)-tetronomycin (1), a novel tetronic acid ionophore antibiotic, has been achieved through the synthesis and assemblage of the four cyclic segments **4**, **5**, **7**, and **8**. Construction of the C_5–C_{13} cyclohexyl portion **5** involves as the key step either a Beckmann fragmentation of the bicyclic ketone oxime **45** or an L-Selectride-mediated reductive annulation of the nona-2,7-dienoate **53**. The C_{14}–C_{28} polyether fragment **6** was constructed by a BF_3-catalyzed coupling reaction of the C_{14}–C_{22} allylsilane **7** and the C_{23}–C_{28} tetrahydrofuran **8** which were derived, respectively, from L-ascorbic acid or (*R*)-3-hydroxyisobutyrate and L-rhamnal. The union of **5** and **6** by an aldol condensation, followed by photoisomerization of the derived diastereomeric α,β-unsaturated esters, provided (*Z*)-**61**, which was converted to the aldehyde **63**. Subsequent acylation of the tetronate **4** with **63** via an aldol reaction–oxidation sequence afforded the protected tetronomycin **64**. Final deprotection provided synthetic tetronomycin, which was characterized as its sodium salt.

Tetronomycin (**1**)[1] and tetronasin (**2**)[2] are novel acyltetronic acid ionophore antibiotics[3] isolated from closely related strains of *Streptomyces* in the early 1980s by Sandoz (Swiss) and ICI (U.K.) scientists, respectively. The structures of the two molecules, as determined by X-ray analysis by the same groups, are quite similar, but interestingly each of the common 10 chiral centers have opposite absolute configurations.[4] Also notable in the tetronomycin structure is that its tetronic acid moiety has a rare γ-methylene substituent.[5]



1 Tetronomycin

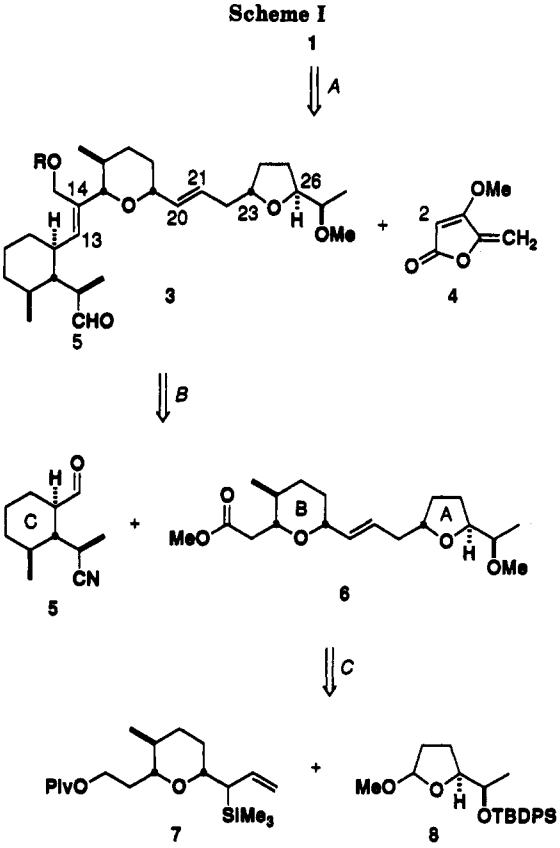


2 Tetronasin (M 139603)

Tetronomycin is active against Gram-positive bacteria and several *Mycoplasma* and *Neisseria* species, the spectrum being similar to other polyether natural products.[1] Tetronasin (M139603) has been reported to promote ruminant growth more effectively than currently available ionophores.[6]

Owing to the unusual structural features in **1** and **2**, as exemplified by the presence of the cyclohexyl and acyltetronic acid moieties which are not found in other polyether ionophores, their total synthesis has been the subject of considerable interest in recent years.[7] In this paper we describe the first total synthesis of tetronomycin as its sodium complex.[8]

Scheme I



(1) Keller-Juslén, C.; King, H. D.; Kuhn, M.; Loosli, H. R.; Pache, W.; Petcher, T. J.; Weber, H. P.; Wartburg, A. *J. Antbiot.* **1982**, *35*, 142–150.

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(4) For determination of the absolute configurations through the synthesis of oxidative degradation products, see refs 7j,o.

(5) The same α-acyl-γ-methylenetetronic acid structure has been found with agglomerins [Terui, Y.; Sakazaki, R.; Shoji, J. *J. Antibiot.* **1990**, *43*, 1245–1253] and with dehydrocarolic acid (hydrated form): Jacobsen, J. P.; Reffstrup, T.; Cox, R. E.; Holker, J. S. E.; Boll, P. M. *Tetrahedron Lett.* **1978**, 1081–1084.

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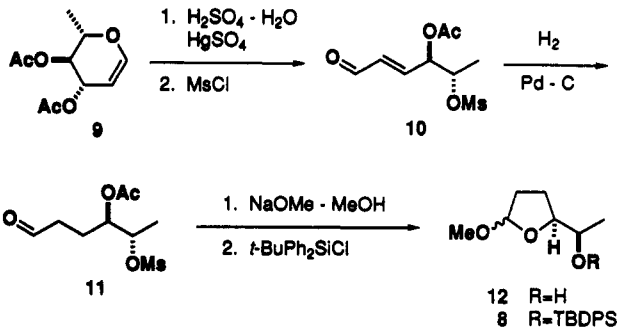
Scheme II



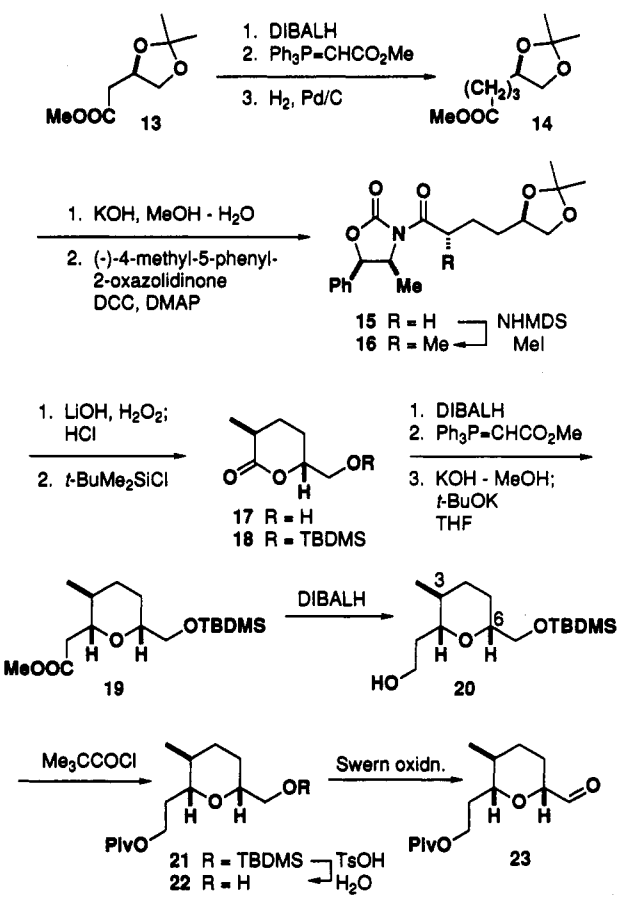
Synthesis Plan. The two double bonds (C_{13}–C_{14} and C_{20}–C_{21}) and the C_2–C_5 acyl linkage are readily identifiable disconnection points (Scheme I). Of these, the acyl bond formation via an aldol reaction of tetronate **4** with tricyclic aldehyde **3** (transform A) was delayed to a late stage of the synthesis due to the sensitivity of the α-acyl-γ-methylenetetronic acid residue (even when O-protected). The ABC ring system **3** was expected to arise via an aldol coupling between a cyclohexyl aldehyde subunit **5** and a heterocyclic fragment **6** (transform B). As an access to the AB ring system **6**, we envisaged a Lewis acid-catalyzed coupling of 2-methoxytetrahydrofuran **8** and 2-(1-(trimethylsilyl)-2-propen-1-yl)tetrahydropyran **7** (transform C), by which the trans geometry of the C_{20}–C_{21} double bond as well as the C_{23}/C_{26} trans stereochemistry in the tetrahydrofuran ring could be secured in one step. With regard to the synthesis of **5**, we planned to execute two approaches that will be described later.

The Tetrahydrofuran Subunit. As the starting material for preparation of the tetrahydrofuran **8**, we selected L-rhamnal diacetate (**9**) which has the requisite five-carbon chain. The C_4 and C_5 chiralities of **9** can produce those of **8** by inversion of the configurations.

Perlin hydrolysis[9] of **9** followed by O-mesylation afforded (4*R*,5*S*)-4-acetoxy-5-mesyloxy-2(*E*)-hexenal (**10**) in 82% yield (Scheme II). It was catalytically hydrogenated to **11** (98% yield), which on treatment with MeONa (1.2 equiv) in methanol provided 2-methoxytetrahydrofuran **12** via a methoxide-induced cyclization of a (4*R*,5*R*)-epoxide intermediate. The volatile product **12** was used without purification and treated with *tert*-butyldiphenylsilyl (TBDPS) chloride to furnish the tetrahydrofuran subunit **8** in 69% overall yield, as an anomeric mixture.

The Tetrahydropyran Subunit. The cis tetrahydropyranyl aldehyde **23**, which we used as a precursor to the allylsilane **7** (vide infra), was prepared by two routes. The first one (Scheme III) starts with methyl (*R*)-3,4-(isopropylidenedioxy)butyrate (**13**) which is easily derived from L-ascorbic acid.[10] Bishomologation of **13** by way of the conventional three-step reaction afforded **14** in 92% overall yield. This ester was hydrolyzed, and the crude carboxylic acid was condensed with (−)-4-methyl-5-phenyl-2-oxazolidinone in the presence of *N,N*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to give imide **15** (76% overall yield). Enolate methylation of **15** according to Evans' protocol[11] proceeded in an 8:1 stereoselectivity (97% yield). Since it was difficult to isolate the major, desired diastereomer **16** in a pure state, the epimeric mixture was used for subsequent transformations. Removal of the chiral auxiliary by treatment with LiOOH[12] followed by in situ lactonization afforded hydroxy δ-lactone **17**, which was O-silylated with *tert*-butyldimethylsilyl (TBDMS) chloride to provide **18** (a mixture with the α-methyl epimer) in 81% yield. Transformation of **18** into *cis*-(tetrahydropyranyl)acetic acid ester **19** was initiated by diisobutylaluminum hydride (DIBALH) reduction, followed by a Wittig reaction of the resulting lactol with $Ph_3P{=}CHCOOMe$.[13] The crude ζ-hydroxy-α,β-unsaturated ester was first treated with methanolic KOH to effect hydropyran ring closure.[13a]. The reaction product, which showed two major spots on TLC due to the C_2 epimers, was exposed to 0.2 equiv of *t*-BuOK in tetrahydrofuran (THF) at room temperature to effect equilibration,[13a,c] producing a mixture of **19** and its C_3 epimer (88:12 ratio) in 67% yield from **18**.[14] Chromatographic separation of the C_3 stereoisomers was achieved after ester reduction with DIBALH, providing **20** (88%) and (3*R*)-**20** (ca. 10%). Esterification of **20** with pivaloyl chloride in the presence of DMAP afforded **21**, whose ^1H NMR spectrum showed axial/axial couplings of $J_{2,3}$ = 9.3 and $J_{5,6}$ = 10.7 Hz. Lastly, **21** was desilylated to **22**, $[\alpha]_D$

Scheme III



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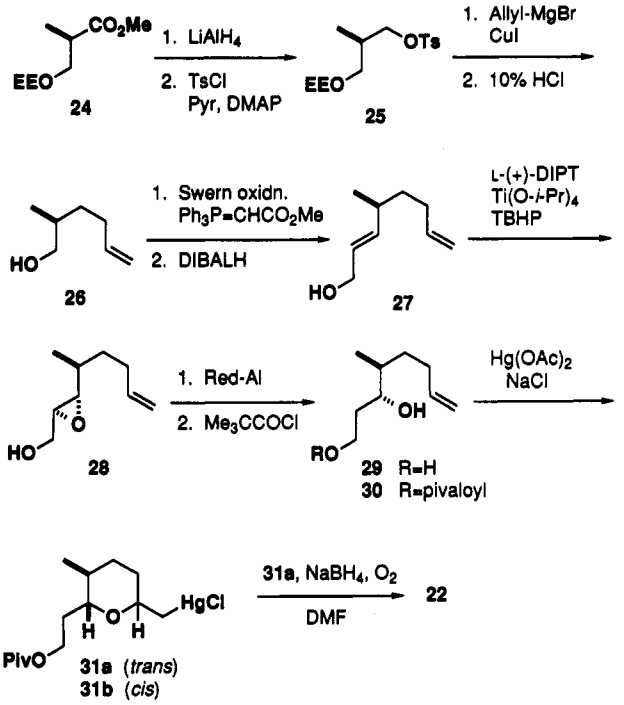
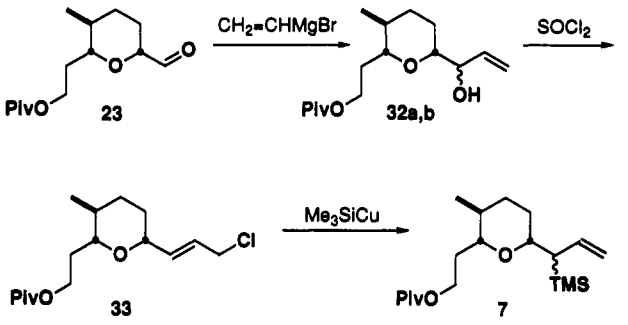
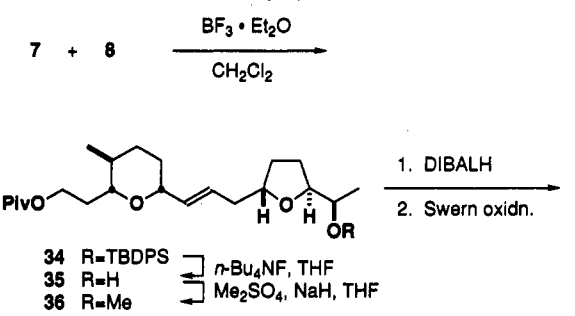
Scheme IV

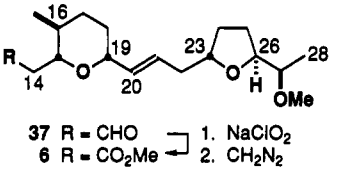


Scheme V



Scheme VI





37 R = CHO, 6 R = CO_2Me ← 1. $NaClO_2$ 2. CH_2N_2

+40.9°, and then it was subjected to Swern oxidation,[15] providing aldehyde **23** (88% overall yield).

A more expedient route to **22** utilizes methyl (*R*)-3-hydroxy-2-methylpropionate as the starting material (Scheme IV). Ester reduction of the 1-ethoxyethyl ether **24** with $LiAlH_4$ followed by O-tosylation gave **25** (95% yield). Reaction of the tosylate with allylmagnesium bromide (2 equiv) in the presence of CuI (0.5 equiv) in ether[16] afforded 2-methyl-5-hexenol (**26**) after removal of the EE moiety (80% overall yield). The alcohol **26** was then converted to bishomologated allyl alcohol **27** by a conventional procedure: one-pot Swern oxidation/stabilized ylid Wittig olefination[17] (89%); ester reduction with DIBALH (87%). Sharpless asymmetric epoxidation of **27** using diisopropyl L-(+)-tartrate[18] afforded epoxide **28** in 88% yield. Exposure of **28** to sodium bis(2-methoxyethoxy)aluminum hydride [Red-Al (Aldrich)],[19] followed by the selective trimethylacetylation of the resultant diol **29** produced **30** in 78% overall yield. Internal alkoxymercuration[20] of **30** with $Hg(OAc)_2$ in CH_2Cl_2, followed by NaCl treatment, afforded the desired 2,6-*cis*-tetrahydropyran **31a** (80% yield) along with the minor trans isomer **31b** (18% yield). Treatment of **31a** with $NaBH_4$ in *N,N*-dimethylformamide (DMF) in the presence of oxygen (Whitesides' method)[21] furnished **22**, $[\alpha]^{24}_D$ +38.4°, in 78% yield.

Transformation of the aldehyde **23** into allylsilane **7** was achieved straightforwardly according to the method of Smith[22] (Scheme V). Thus a Grignard reaction of **23** with vinylmagnesium bromide gave vinyl alcohol **32** in 76% yield as a 65:35 mixture of the carbinol epimers, which upon treatment with $SOCl_2$ afforded the S_N' chlorination product **33** (76% yield). Treatment of the allyl chloride **33** with (trimethylsilyl)copper generated from hexamethyldisilane (MeLi/HMPA, CuI–Me_2S) provided allylsilane **7** in 96% yield as an inseparable 88:12 mixture of diastereomers.

The Polyether Fragment. Coupling of **7** with **8** proceeded nicely in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C (Scheme VI).[23] The reaction product isolated in 92% yield was deduced by ^1H NMR analysis to be exclusively the (*E*)-olefin and a 95:5 mixture of the desired **34** and its C_{23} epimer. The mixture was readily separated by MPLC after desilylation. The pure hydroxy compound **35** (79% yield) was O-methylated with Me_2SO_4–NaH to give **36** in 89% yield. The pivaloyl protecting group was then removed by DIBALH reduction, and Swern oxidation of the liberated alcohol furnished aldehyde **37** in 93% yield. Lastly, **37** was subjected to $NaClO_2$ oxidation[24] followed

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(23) Reaction of allyltrimethylsilane with **8** under the same conditions proceeds with a 97:3 trans stereoselectivity.[7a] For other examples for allylation of 5- and 6-membered lactols and their O-derivatives with allyltrimethylsilane, see: Brücker, C.; Lorey, H.; Reissig, H. U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 556–557. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383–2386. Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1984**, *25*, 2085–2088. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.
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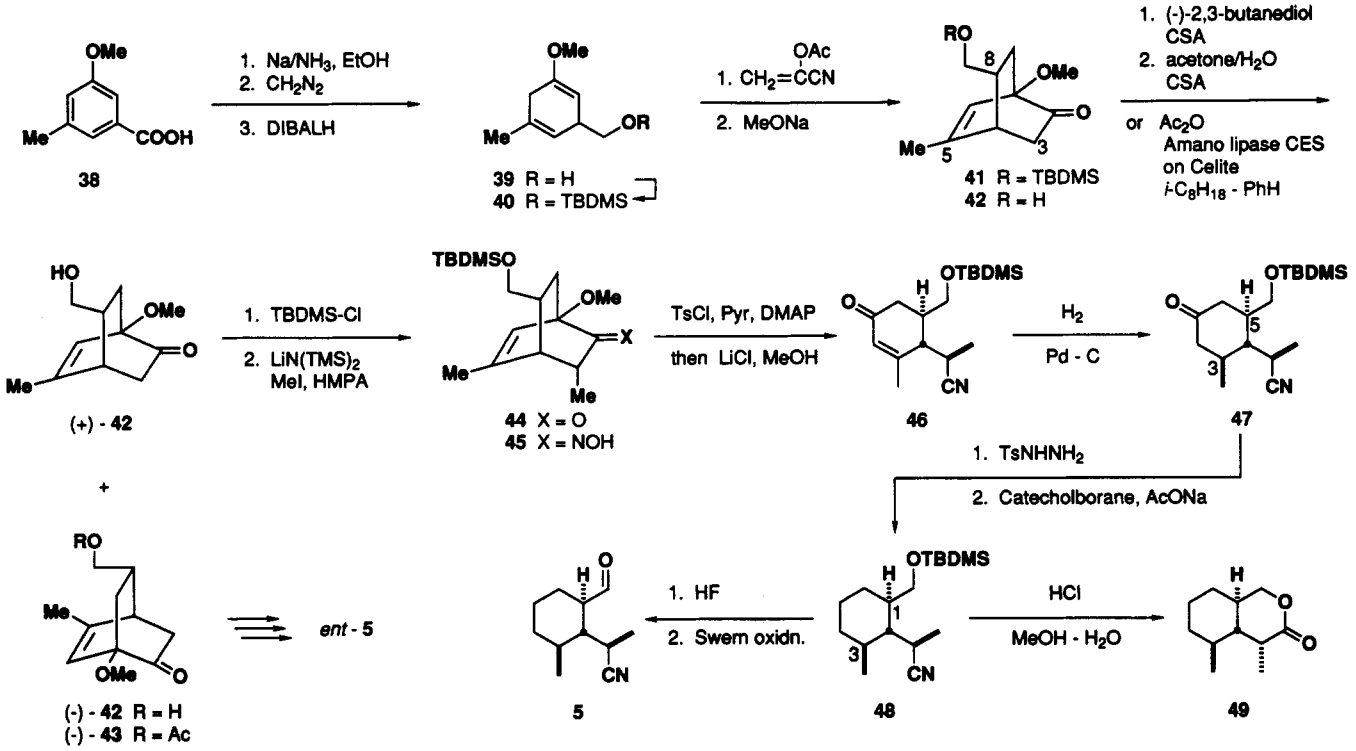
Scheme VII



by esterification with diazomethane providing **6** in 93% overall yield.

Cyclohexane Subunit. We have prepared the C-ring unit **5** having nitrile and aldehyde functionalities through two conceptionally different approaches. Our initial plan for establishing the four contiguous stereocenters in **5** called for a Beckmann fragmentation[25] of a bicyclic ketone oxime **45** to cyclohexenone **46** and its stereoselective hydrogenation (Scheme VII). We also intended to obtain both enantiomers (**5** and **ent-5**) by optical resolution of an appropriate intermediate.

Diels–Alder reaction of cyclohexadiene **40**, derived from 3-methoxy-5-methylbenzoic acid (**38**), with α-acetoxyacrylonitrile[26] followed by treatment of the cycloadduct with 1.1 equiv of NaOMe in MeOH afforded a 4:1 mixture of bicyclic ketone (±)-**41** and its C_8 epimer in 68% yield. These diastereomers could be separated by HPLC. The stereochemistry of the major product **41**, resulting from the approach of the dienophile to the less hindered face of **40**, was confirmed at a later stage of the synthesis. For a large-scale experiment, separation of the C_8 epimers was conveniently carried out by desilylation followed by fractional crystallization of the resulting hydroxy ketone (±)-**42**.

Resolution of racemic **42** was first performed via ketalization with (2*R*,3*R*)-butanediol. Care should have been taken with this acid-catalyzed reaction to minimize the tetrahydrofuran ring formation arising from attack of the hydroxyl oxygen at C_5. An alternative resolution method utilizing an enzyme-catalyzed enantioselective O-acetylation[27] turned out to be practical as a large-scale procedure. Thus treatment of (±)-**42** with acetic anhydride (2 equiv) in isooctane–benzene (9:4) in the presence of Amano lipase CES (*Pseudomonas* sp.) on Celite (23 °C, 9 h) afforded (+)-**42** (65% ee, 48% yield) and enantiomeric *O*-acetate (−)-**43** (63% ee, 52% yield).[28] The optical purity of (+)-**42** was readily enhanced to 98% (ca. 25% yield) by a single recrystallization from ether.

Enolate methylation of (+)-**41** using lithium hexamethyldisilazane (LHMDS) and MeI (THF/HMPA) proceeded slowly but in a highly stereoselective manner[29] affording **44** in 77% yield, the major byproduct being the α,α-dimethylated ketone. The orientation of the methyl group adjacent to the ketone carbonyl was determined by difference NOE experiments that indicated a syn arrangement of C_3-H and C_8-H. Beckmann fragmentation[29] of the oxime **45** was carried out by treatment in CH_2Cl_2 with excess amounts of tosyl (Ts) chloride and pyridine in the presence of DMAP catalyst, then addition of LiCl after complete formation of *O*-tosylate (as judged by TLC), afforded **46** in 73% yield. This enone was catalytically hydrogenated to give **47** in 72% yield. The next step, deoxygenation of the ketone **47**, was achieved via a catecholborane reduction of its tosylhydrazone (Kabalka's method)[30] to provide **48** in 82% yield. The relative and absolute configurations of **48** were determined by the production of δ-lactone **49** and by comparison of its ^{1}H NMR and optical rotation, $[\alpha]_D$ = +95.9°, with those of a sample obtained by an oxidative degradation of **1**.[7c] Finally, desilylation of **48** followed by Swern oxidation furnished the C-ring unit **5** (94.5% overall yield). The enantiomer of **5**, **ent-5**, which can be utilized in the synthesis of **2**, was prepared from (−)-**43** using the same sequence of reactions.[7c]

The second, more convenient route to **5** that we have investigated involves as a key step an L-Selectride-mediated reductive annulation of 1-*tert*-butyl 9-methyl (*S*)-

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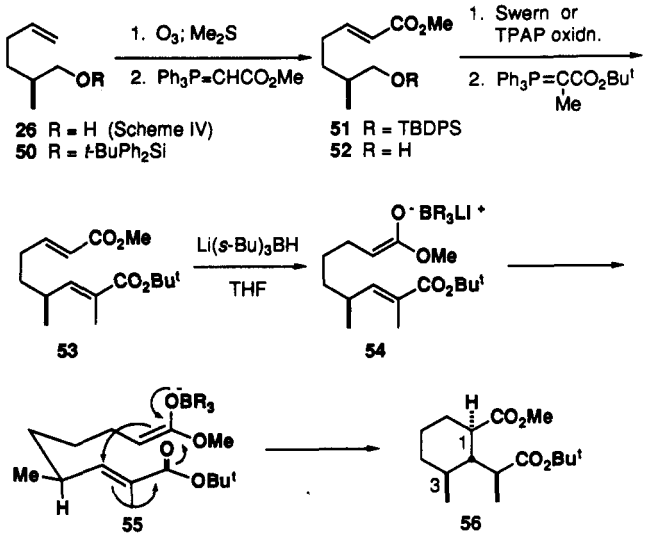
Scheme VIII

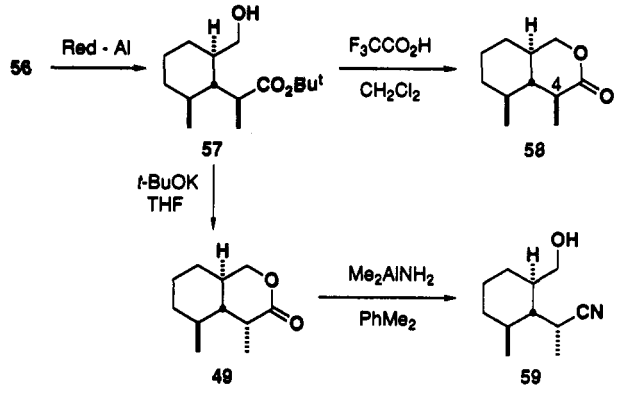


2,4-dimethyl-2,7-nonadienedioate (**53**) (Scheme VIII). It was envisaged that the precedented 1,4-addition[31] of the hydride reagent should occur at the less hindered, upper conjugated ester site, generating the (*Z*)-enolate **54**,[32] which in turn would undergo an internal Michael addition via a chairlike transition state **55**, to provide cyclohexane derivative **56** with the desired trans/trans ring stereochemistry. The stereochemical outcome of the α-methyl group of the propionate side chain was difficult to predict, but this center could be equilibrated, if necessary.

The nonadienoate **53** was prepared from (*S*)-2-methyl-5-hexenol (**26**), an intermediate in the synthesis of the tetrahydropyran unit **22** (Scheme IV). The unsaturated alcohol **26** was protected as the *tert*-butyldiphenylsilyl ether **50** (99.5%) and then exposed to O_3 in CH_2Cl_2–MeOH (−60 °C) to give 5-[(*tert*-butyldiphenylsilyl)oxy]-4-methylpentanal (73%)[33] after Me_2S treatment and deacetalization (TsOH–H_2O). Wittig reaction of the aldehyde with Ph_3P=CHCOOMe in refluxing benzene afforded **51** in 85% yield (*E*/*Z* ratio = 20:1), which was then desilylated to **52** (94%). This hydroxy ester was converted to the corresponding aldehyde by catalytic Pr_4NRuO_4 (TPAP) oxidation[34] and then reacted with Ph_3P=C(Me)COO-*t*-Bu in MeCN to furnish **53**, $[\alpha]^{26}_D$ +39.5°,[35] in 72% overall yield. Reaction of **53** with L-Selectride in THF at −25 °C followed by a MeOH quench produced cyclohexane diester **56** as the single stereoisomer in 52–61% yield. The trans/trans relationship of the adjacent ring substituents was revealed by ^{1}H NMR analysis, which showed vicinal coupling constants of $J_{1,2}$ = 11.3 and $J_{2,3}$ = 10.9 Hz. The undesired (*S*) configuration at the propionate side chain was assigned from the result of subsequent transformations.

Selective reduction of the methyl ester group in **56** was nicely achieved with $NaAl(OCH_2CH_2OMe)_2H_2$ (Red-Al) in THF at 0 °C affording δ-hydroxy *tert*-butyl ester **57** in 89% yield (Scheme IX). The use of DIBALH proved less effective in terms of selectivity. Treatment of **57** with trifluoroacetic acid (TFA) in CH_2Cl_2 produced lactone **58** which proved to be the C_4 epimer of **49** by ^{1}H NMR

Scheme IX



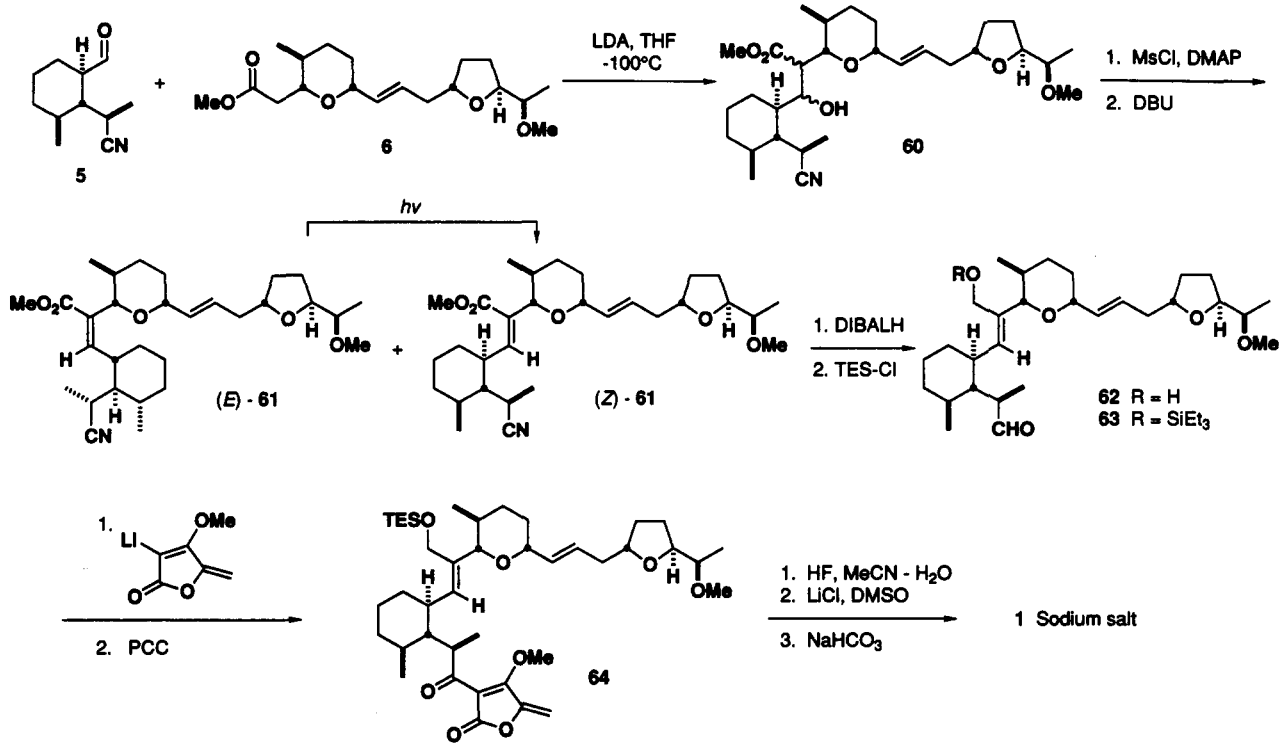
analysis. On the other hand, *t*-BuOK-induced lactonization in THF followed by in situ equilibration of the C_4 center at ambient temperature provided **49** in 86% yield. Finally, treatment of **49** with 4 equiv of Me_2AlNH_2[36] in xylene (ca. 100 °C) provided hydroxy nitrile **59** in 73–77% yield.

Total Synthesis of Tetronomycin. The lithium enolate of **6** generated by treatment with lithium diisopropylamide (LDA) in THF at ca. −100 °C was reacted with freshly prepared aldehyde **5** for 30 min to afford β-hydroxy ester **60** in quantitative yield as a mixture of diastereomers (predominantly two isomers by TLC) (Scheme X). In order to achieve a high yield in this aldol reaction, it is important to keep the reaction temperature as low as −100 °C. At higher temperatures a pyran ring opening via a β-elimination occurs as expected,[37] resulting in a substantial decrease of the yield. Dehydration of **60** was carried out by O-mesylation followed by exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The α,β-unsaturated ester product isolated in 91% overall yield was found by ^{1}H NMR to be predominantly (*E*)-ester [(*E*)-**61**/(*Z*)-**61** = 95:5]. This undesired but not unexpected stereochemical result led us to perform on *E* to *Z* isomerization. Conventional thiol- or disulfide-catalyzed isomerization techniques[38] proved totally ineffective. The isomerization was realized by irradiation with a low-pressure Hg lamp in acetone,[39] giving a 42:58 ratio of *Z*/*E* esters (25% isolated yield of (*Z*)-**61**).

The final stage of the total synthesis, construction of the acyltetronic acid structure, was initiated by DIBALH reduction of the ester and nitrile groups of (*Z*)-**61**. The resulting hydroxy aldehyde **62** was converted to its triethylsilyl (TES) ether **63** (55% overall yield), and then it was subjected to an aldol reaction with 4-methoxy-5-methylene-2(5*H*)-furanone (**4**)[40] under controlled conditions. Thus α-lithio tetronate (3 equiv), generated by treatment of **4** with LDA (THF) at −100 °C, was allowed to react with **63** in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) at the same temperature. The

(31) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200.
(32) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678–5680 and references cited therein.
(33) Protection of **26** as its *tert*-butyldimethylsilyl ether produced a complex mixture of products.
(34) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.
(35) An 8% smaller value, $[\alpha]^{24}_D$ +36.2°, was obtained by use of Swern protocol in the oxidation of **52** (87% overall yield).
(36) (a) Wood, J. L.; Khatri, N. A.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 4907–4910. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49–53. (c) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174.
(37) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843–846.
(38) (a) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123–1125. (b) Gais, H.-J. *Angew. Chem., Int. Ed. Engl.* **1984**, 143–145. (c) Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1–7.
(39) Duhaime, R. M.; Lombardo, D. A.; Skinner, I. A.; Weedon, A. C. *J. Org. Chem.* **1985**, *50*, 873–879.
(40) Takeda, K.; Yanao, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135–4137.
(41) Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318–6320.

Scheme X



carbinol product obtained in 63% yield was exposed to pyridinium chlorochromate (PCC) in CH_2Cl_2 to furnish acyltetronate **64** in 26% yield from **63**. Finally, desilylation with HF, followed by removal of the *O*-methyl protecting group by treatment with LiCl in dimethyl sulfoxide (DMSO), Li/Na exchange with $NaHCO_3$, and chromatographic purification, provided tetronomycin sodium salt (36% overall yield). The synthetic sodium complex prepared by this route had a mp of 187–189 °C after crystallization from *i*-Pr_2O/Et_2O. The reported mp is 107–110 °C.[1] However, the melting point of the actual material for which this value was reported was raised to our value by recrystallization from the same solvent system. Both samples proved to be identical by comparison of IR, ^1H NMR, and mass spectra and optical rotations.

Experimental Section

General. Air- and moisture-sensitive reactions were carried out under inert atmospheres (N_2 or Ar). When necessary, solvents and reagents were dried in the traditional fashion prior to use. Routine monitoring of reactions was performed using precoated silica gel TLC plates (Merck 60 F_{254}). Spots were visualized by UV and/or spraying an acetone solution of $KMnO_4$ and heating with a heat gun. The normal processing of organic extracts consisted of washing the extract with brine, drying over $MgSO_4$, filtration, and concentration with a rotary evaporator. Flash chromatography was performed employing EM Reagents 40–63-μm silica gel or Wako 20–40-μm silica gel with the amount and solvent system indicated. Medium-pressure chromatography (MPLC) was performed with a KUSANO prepacked column (2.2 × 20 cm, 10-μm silica gel). Analytical gas–liquid chromatography (GC) was carried out with a 4-mm × 2-m column packed with 1.5% OV-17 on Chromosorb W or with a 0.2-mm × 25-m capillary column (SE-52). Boiling points and melting points are uncorrected. IR spectra were obtained with KBr pellets or as films. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Optical rotations were determined with a digital polarimeter in $CHCl_3$ except where noted. Low- and high-resolution MS (EI) data were obtained at 70 eV. Elemental analyses were performed at the Instrument Center of this university.

(*E*)-(4*R*,5*S*)-4-Acetoxy-5-(methanesulfonyloxy)-2-hexenal (10). To a stirred solution of **9** (970 mg, 4.5 mmol) in dioxane (1 mL) were added 5 mM H_2SO_4 (10 mL) and $HgSO_4$ (20 mg, 0.07 mmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was neutralized by addition of saturated $NaHCO_3$ and extracted with AcOEt (10 mL × 4). The combined extracts were washed with brine (5 mL × 3), dried, and concentrated to give a colorless oil (770 mg). This material[9] was dissolved in dry CH_2Cl_2 (5 mL) and, after addition of DMAP (109 mg, 0.9 mmol) and pyridine (0.91 mL, 11 mmol), the mixture was ice-cooled and $MeSO_2Cl$ (0.69 mL, 9.0 mmol) was added. The solution was allowed to warm to room temperature and stirred for 3 h. After addition of AcOEt (40 mL), the whole was washed with a 1:1 H_2O/brine (10 mL × 2) and then with brine, dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 50 g, 2:3 AcOEt/hexane) to give **10** (929 mg, 82%) as a solid, which was recrystallized from *i*-Pr_2O/CH_2Cl_2 as colorless needles: mp 66–67 °C; R_f = 0.26 (1:1 AcOEt/hexane); $[\alpha]^{27}_D$ −22.4° (*c* 3.49); IR (KBr) 1737, 1692 cm^{-1}; ^1H NMR (270 MHz) δ 1.45 (3 H, d, *J* = 6.6 Hz), 2.18 (3 H, s), 3.06 (3 H, s), 5.04 (1 H, qd, *J* = 6.6, 3.3 Hz), 5.61 (1 H, ddd, *J* = 6.1, 3.3, 1.5 Hz), 6.32 (1 H, ddd, *J* = 15.9, 7.6, 1.5 Hz), 6.75 (1 H, dd, *J* = 15.9, 6.1 Hz), 9.62 (1 H, d, *J* = 7.6 Hz); Ms *m/e* 251 (M^+ + 1), 85 (base peak). Anal. Calcd for $C_9H_{14}O_6S$: C, 43.19; H, 5.64. Found: C, 42.90; H, 5.74.

(4*R*,5*S*)-4-Acetoxy-5-(methanesulfonyloxy)hexanal (11). A solution of **10** (129 mg, 0.5 mmol) in AcOEt (5 mL) was stirred under H_2 for 4 h after addition of 10% Pd/C (12 mg). Usual workup afforded **11** (128 mg, 98%) as a colorless oil which solidified on standing. An analytical sample was obtained by recrystallization from *i*-Pr_2O/CH_2Cl_2 as colorless needles: mp 55 °C; R_f = 0.24 (1:1 AcOEt/hexane); $[\alpha]^{27}_D$ +34.7° (*c* 2.71); IR (KBr) 1737, 1716 cm^{-1}; ^1H NMR (270 MHz) δ 1.44 (3 H, d, *J* = 6.6 Hz), 2.10 (3 H, s), 2.56 (2 H, tt, *J* = 7.1, 1.0 Hz), 3.04 (3 H, s), 4.89–4.97 (2 H, m), 9.78 (1 H, t, *J* = 1.0 Hz); MS *m/e* 209 (M^+ − Ac), 69 (base peak). Anal. Calcd for $C_9H_{16}O_6S$: C, 42.84; H, 6.39. Found: C, 42.82; H, 6.42.

(2*R*,*S*,5*S*)-5-[1(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-2-methoxytetrahydrofuran (8). A stirred solution of **11** (845 mg, 3.4 mmol) in dry MeOH (35 mL) was ice-cooled, and a 2 M methanolic solution of MeONa (2 mL, 4 mmol) was added. The mixture was allowed to warm to 5 °C, and then stirring at the same temperature was continued for 9.5 h. After neutralization with saturated NH_4Cl, the mixture was concentrated and extracted with Et_2O (20 mL × 3). The combined extracts were washed with brine (5 mL), dried, and concentrated. The residual crude **12** was dissolved in dry DMF (3 mL), and to the solution were added imidazole (520 mg, 7.6 mmol) and *tert*-butyldiphenylsilyl chloride (0.81 mL, 3.1 mmol). After being stirred at room temperature

for 1 h, the reaction mixture was diluted with AcOEt (40 mL), washed with brine (5 mL × 4), dried, and conentrated. The residual oil was subjected to chromatography (silica gel, 80 g, 1:19 AcOEt/hexane) to give 8 (883 mg, 69%), a 7:3 mixture of anomers which could be separated by MPLC.

(+)-8 (major isomer): oil; R_f = 0.38 (1:9 AcOEt/hexane); $[\alpha]^{24}_D$ +65.3° (c 3.44); ^{1}H NMR (270 MHz) δ 0.99 (3 H, d, J = 6.1 Hz), 1.05 (9 H, s), 3.32 (3 H, s), 3.87–3.98 (2 H, m), 4.95 (1 H, d, J = 4.4 Hz); ^{13}C NMR (67.8 MHz) δ 19.37 (s), 20.13 (q), 24.06 (t), 27.03 (q), 32.08 (t), 54.48 (q), 70.93 (d), 82.53 (d), 105.34 (d), 127.44 (d), 129.48 (d), 129.51 (d), 134.11 (s), 134.83 (s), 135.96 (d), 136.05 (d); MS m/e 353 (M^+ – OMe), 213 (base peak). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.62; H, 8.39.

(–)-8 (minor isomer): oil; R_f = 0.31 (1:9 AcOEt/hexane); $[\alpha]^{25}_D$ –60.7° (c 3.64); ^{1}H NMR (270 MHz) δ 1.05 (9 H, s), 1.10 (3 H, d, J = 6.1 Hz), 3.21 (3 H, s), 3.73 (1 H, quint, J = 6.1 Hz), 3.89 (1 H, m), 4.91 (1 H, m); ^{13}C NMR (50 MHz) δ 19.35 (s), 20.87 (q), 27.00 (q), 27.00 (t), 32.87 (t), 54.47 (q), 73.24 (d), 85.10 (d), 105.11 (d), 127.52 (d), 129.53 (d), 134.08 (s), 134.81 (s), 135.94 (d); MS m/e 353 (M^+ – OMe), 213, 71 (base peak). Anal. Calcd for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.82; H, 8.28.

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-butanoic Acid, Methyl Ester (14). To a stirred and cooled (–100 °C) solution of **13** (7.9 g, 45 mmol) in dry Et_2O (200 mL) was added a 0.94 M hexane solution of DIBALH (50 mL, 47 mmol) over 5 min. After continued stirring at –70 °C for 5 min, the reaction mixture was quenched with MeOH (50 mL) and then stirred at room temperature for 1.5 h before addition of Celite. The suspension was filtered and washed with Et_2O. The filtrate was concentrated to give an aldehyde corresponding to **13**. It was dissolved in dry MeCN (200 mL) containing Ph_3P=CHCOOMe (18.2 g, 54.5 mmol), and the solution was heated under reflux for 1 h before evaporation of the solvent. The residue was extracted with hexane/Et_2O to remove Ph_3PO, and the extract was subjected to chromatography (silica gel, 200 g, 1:4 AcOEt/hexane) to give the Wittig reaction product (8.6 g, 95%) as a 3:1 mixture of (*E*)/(*Z*) esters: R_f = 0.36 and 0.46 (1:2 AcOEt/hexane); δ 6.94 and 6.33 for H-3, respectively. A solution of the hexenoate diastereomers (15.7 g, 79.8 mmol) in AcOEt (500 mL) was shaken under H_2 (1 atm) after addition of 10% Pd/C (1.6 g). After 4 h when the hydrogenation was completed, the catalyst was removed by filtration. Concentration of the filtrate afforded a crude oil which was purified by silica gel chromatography (1:4 AcOEt/hexane) providing **14** (15.2 g, 97%) as a colorless oil: bp 63–65 °C (0.03 Torr); R_f = 0.38 (1:2 AcOEt/hexane); $[\alpha]^{26}_D$ –14.4° (c 2.89); IR (film) 1740 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.35 and 1.40 (each 3 H, s), 2.37 (2 H, t, J = 7.0 Hz), 3.52 (1 H, t, J = 6.6 Hz), 3.67 (3 H, s), 4.04–4.12 (2 H, m); ^{13}C NMR (50 MHz) δ 21.25 (t), 25.69 (q), 26.93 (q), 32.97 (t), 33.84 (t), 51.52 (q), 69.35 (t), 75.61 (d), 108.8 (s), 173.8 (s); MS m/e 187 (M^+ – Me), 85 (base peak). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 58.10; H, 8.78.

(4*S*,5*R*)-3-[(*R*)-5,6-(Isopropylidenedioxy)hexanoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one (15). To a solution of **14** (15.7 g, 77.5 mmol) in MeOH (160 mL) was added KOH (10.2 g) dissolved in water (40 mL), and the mixture was stirred at room temperature for 0.5 h. The bulk of MeOH was evaporated, and the residue was extracted with CH_2Cl_2 (100 mL × 3). The aqueous layer was neutralized (pH 4) with 10% HCl under ice cooling and then extracted with AcOEt (200 mL × 3). The combined extracts were washed with brine (100 mL × 3), dried, and concentrated to give a crude acid (13.7 g) as a pale yellow oil. To a solution of this material in CH_2Cl_2 (400 mL) were added (4*S*,5*R*)-(–)-4-methyl-5-phenyl-2-oxazolidinone (12.9 g, 72.9 mmol), DMAP (4.1 g, 36 mmol), and DCC (18.5 g, 90 mmol). The mixture was stirred at room temperature for 1 d and then heated at reflux for 2.5 h. The reaction mixture was cooled, filtered, and concentrated. The solid residue was subjected to chromatography (silica gel, 600 g, 1:9 AcOEt/hexane). The homogeneous eluates, R_f = 0.36 (1:1 AcOEt/hexane), were combined and recrystallized from *i*-Pr_2O/CH_2Cl_2 to give **15** (20.3 g, 76%): mp 128–129 °C (colorless plates); $[\alpha]^{26}_D$ –41.2° (c 2.85); ^{1}H NMR (270 MHz) δ 0.90 (3 H, d, J = 6.7 Hz), 1.36 and 1.41 (each 3 H, s), 3.54 (1 H, t, J = 7.3 Hz), 4.06 (1 H, dd, J = 7.3, 6.1 Hz), 4.13 (1 H, dq, J = 7.3, 6.1 Hz), 4.76 (1 H, quint, J = 6.7 Hz), 5.67 (1 H, d, J = 6.7 Hz); MS m/e 346 (M^+ – 1), 332 (base peak). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.84; H, 7.34; N, 4.15.

(4*S*,5*R*)-4-Methyl-3-[(2*S*,5*R*)-2-methyl-5,6-(isopropylidenedioxy)hexanoyl]-5-phenyl-1,3-oxazolidin-2-one (16). To a stirred and cooled (–80 °C) solution of **15** (8.04 g, 23.2 mmol) in dry THF (240 mL) was added a 0.78 M THF solution of $NaN(TMS)_2$ (30 mL, 23.4 mmol) over 10 min, and stirring of the mixture at the same temperature was continued for 1 h. Methyl iodide (3.1 mL, 46.3 mmol) was then added to the enolate solution, and the mixture was allowed to warm to –35 °C over a 1-h period. The reaction mixture was quenched by addition of saturated NH_4Cl (50 mL) and extracted with AcOEt (100 mL × 3). The combined extracts were successively washed with saturated NH_4Cl (50 mL × 2) and brine (50 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 350 g, 1:4 AcOEt/hexane) to give 8.12 g (97%) of a mixture of **16** and (2′*R*)-**16** (8:1 ratio by ^{1}H NMR analysis) as a pale yellow oil, R_f = 0.41 (1:9 AcOEt/benzene). This mixture was used in the next step. An analytical sample of **16** was obtained by MPLC: IR (film) 1782, 1699 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.88 (3 H, d, J = 6.7 Hz), 1.22 (3 H, d, J = 6.8 Hz), 1.39 and 1.42 (each 3 H, s), 3.54 (1 H, t, J = 6.4 Hz), 3.75 (1 H, sextet, J = 6.8 Hz), 4.76 (1 H, quint, J = 6.7 Hz), 5.66 (1 H, d, J = 6.7 Hz); MS m/e 362 (M^+ + 1), 346 (base peak). Anal. Calcd for $C_{20}H_{27}O_5N$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.53; H, 7.69; N, 3.90.

(3*S*,6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-methyltetrahydropyran-2-one (18). To a stirred and ice-cooled solution of the preceeding imide (7.27 g, 20 mmol) was added 30% H_2O_2 (9.1 mL, 80 mmol) and LiOH/H_2O (1.68 g, 40 mmol). After additional stirring for 30 min, the mixture was treated with 1.5 M Na_2SO_3 (120 mL) for 30 min, followed by removal of the bulk of THF solvent. The residual aqueous layer was acidified (pH 1) with HCl after extraction with CH_2Cl_2 (100 mL × 3) and then subjected to a continuous extraction with CH_2Cl_2. The crude **17** obtained by removal of the solvent was dissolved in dry CH_2Cl_2 (100 mL), and to the solution were added imidazole (1.7 g, 25 mmol) and TBDMS-Cl (1.9 g, 12.6 mmol) under ice cooling. After an additional stirring at room temperature for 1 h, the reaction mixture was quenched with saturated NH_4Cl (40 mL) and extracted with CH_2Cl_2 (40 mL × 4). The extract was concentrated after drying, and the residual oil was subjected to chromatography (silica gel, 80 g, 1:9 AcOEt/hexane) to give a white solid (2.84 g, 81%), R_f = 0.47 (1:2 AcOEt/hexane). This product was shown by ^{1}H NMR analysis to be a 8:1 mixture of **18** and (**3*R***)-**18**: IR (film) 1727 cm^{-1}; ^{1}H NMR (for **18**, 270 MHz) δ 0.07 (s), 0.89 (s), 1.30 (d, J = 7.1 Hz), 2.43 (dqd, J = 12.7, 7.1, 6.1 Hz), 3.70 and 3.74 (each dd, J = 11.0, 4.2 Hz), 4.34 (dq, J = 10.8, 4.2 Hz); MS m/e 201 (M^+ – C_4H_9), 75 (base peak). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.53; H, 10.10.

(2*R*,3*S*,6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-[(methoxycarbonyl)methyl]-3-methyltetrahydropyran (19). A 0.95 M hexane solution of DIBALH (45 mL, 42.8 mmol) was added dropwise to a stirred and cooled (–40 °C) solution of **18** (9.03 g containing ca. 10% (**3*R***)-**18**, 35.0 mmol) in Et_2O (250 mL). After an additional 30 min, the reaction mixture was quenched by addition of MeOH (45 mL) and filtered after addition of Celite and Et_2O. Concentration of the filtrate afforded a crude lactol (9.2 g). It was dissolved in dry MeCN (300 mL) containing Ph_3P=CHCOOMe (17.5 g, 42 mmol), and the mixture was heated under reflux for 18 h before evaporation of the solvent. The residue was extracted with hexane/Et_2O to remove Ph_3PO. Concentration of the extract followed by chromatography of the residual oil (silica gel, 300 g, 1:4 AcOEt/hexane) afforded the Wittig product (10.5 g). This material was dissolved in a mixture of KOH (2.2 g, 1 equiv) and dry MeOH (350 mL), and the solution was stirred at room temperature for 3.5 d when the starting material was not detected by TLC. A solution of NH_4Cl (2.2 g) in H_2O (30 mL) was added to the reaction mixture, and the bulk of MeOH was removed in vacuo. The residue was extracted with AcOEt (100 mL × 3), and the combined extracts were washed with brine, dried, and concentrated. The residual oil was dried by azeotropic distillation with benzene and dissolved in dry THF (360 mL). To the solution was added *t*-BuOK (700 mg, 0.2 equiv), and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt (500 mL), washed sequentially with saturated NH_4Cl (100 mL) and brine (100 mL × 2), dried, and concentrated. The residue was subjected to chromatography (silica gel, 400 g, 1:9 AcOEt/hexane) to afford 7.03 g (67%) of

a mixture of **19** and (**3*R***)-**19** (88:12) as a pale yellow oil: R_f = 0.36 (1:9 AcOEt/hexane); ^{1}H NMR (for **19**, 270 MHz) δ 0.03 and 0.04 (each s), 0.84 (d, J = 6.4 Hz), 0.88 (s), 2.38 (dd, J = 14.9, 9.0 Hz), 2.62 (dd, J = 14.9, 3.4 Hz), 3.47 (dd, J = 10.3, 5.6 Hz), 3.63 (dd, J = 10.3, 5.4 Hz), 3.68 (s). Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.69; H, 10.10.

(2*R*,3*S*,6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-(2-hydroxyethyl)-3-methyltetrahydropyran (20). To a stirred and cooled (−70 °C) solution of **19** (7.03 g contaminated with (**3*R***)-**19**, 22.2 mmol) in Et_2O (60 mL) was added dropwise a 0.95 M hexane solution of DIBALH (55 mL, 2.4 equiv). After the addition was completed, the reaction mixture was allowed to warm to −20 °C over 1 h, and then MeOH (60 mL) was added. After being stirred at room temperature for 1 h, the mixture was filtered through a Celite pad. The filtrate and ether washings were combined and concentrated. The residue was subjected to chromatography (silica gel, 300 g, 1:4 AcOEt/hexane) to give **20** (5.63 g, 88%) and a mixture of **20** and (**3*R***)-**20** (0.67 g). MPLC of the mixture (1:3 AcOEt/hexane) afforded analytically pure sample of the epimer.

For **20**: oil; R_f = 0.36 (1:3 AcOEt/hexane); $[\alpha]^{25}_D$ +16.2° (c 3.40); IR (film) 3450 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.05 (6 H, s), 0.82 (3 H, d, J = 6.6 Hz), 0.89 (9 H, s), 3.21 (1 H, td, J = 9.5, 2.7 Hz), 3.50 (1 H, dd, J = 10.3, 4.6 Hz), 3.59 (1 H, dd, J = 10.3, 6.8 Hz), 3.77–3.82 (2 H, m); ^{13}C NMR (50 MHz) δ −5.46 (q), −5.31 (q), 17.68 (q), 18.34 (s), 25.90 (q), 28.08 (t), 32.16 (t), 34.49 (t), 35.21 (d, C-3), 62.21 (t), 66.57 (t), 78.31 (d), 85.20 (d); MS m/e 289 (M^+ + 1), 75 (base peak). Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.28; H, 11.22.

For (**3*R***)-**20**: oil; R_f = 0.32 (1:3 AcOEt/hexane); $[\alpha]^{26}_D$ +17.5° (c 3.53); IR (film) 3420 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.05 and 0.06 (each 3 H, s), 0.89 (9 H, s), 0.96 (3 H, d, J = 6.8 Hz), 1.88 (1 H, dddd, J = 19.4, 10.5, 9.2, 4.5 Hz), 2.60 (1 H, br s, OH), 3.43–3.86 (6 H, m); ^{13}C NMR (50 MHz) δ −5.46 (q), −5.31 (q), 11.93 (q, Me-3), 18.34 (s), 22.26 (t), 25.90 (q), 30.56 (t), 31.43 (d, C-3), 35.13 (t), 62.75 (t), 66.65 (t), 79.01 (d), 81.62 (d); MS m/e 231 ($M^+ - C_4H_9$), 95 (base peak). Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.44; H, 11.30.

(2*R*,3*S*,6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (21). To a solution of **20** (1.78 g, 6.2 mmol) in CH_2Cl_2 (60 mL) were added Et_3N (1.3 mL, 9.3 mmol) and DMAP (150 mg). The mixture was stirred at room temperature, and Me_3CCOCl (0.91 mL, 7.4 mmol) was added dropwise. After additional stirring for 2 h, the mixture was washed with brine (10 mL × 4) and dried. The solvent was evaporated, and the residue was subjected to chromatography (silica gel, 60 g, 1:19 AcOEt/hexane) to give **21** (2.26 g, 98%) as a colorless oil: R_f = 0.50 (1:9 AcOEt/hexane); $[\alpha]^{26}_D$ +46.3° (c 1.29); ^{1}H NMR (270 MHz) δ 0.05 (6 H, s), 0.83 (3 H, d, J = 6.4 Hz), 0.89 (9 H, s), 1.19 (9 H, s), 1.99 (1 H, dddd, J = 14.4, 8.1, 7.4, 2.6 Hz, CH-2), 3.01 (1 H, td, J = 9.3, 2.6 Hz, H-2), 3.32 (1 H, dtd, J = 10.7, 5.6, 2.3 Hz, H-6), 3.47 and 3.66 (each 1 H, dd, J = 10.3, 5.6 Hz, CH-6), 4.15 (1 H, ddd, J = 10.7, 8.1, 6.4 Hz, CHOPiv), 4.23 (1 H, ddd, J = 10.7, 7.4, 4.6 Hz, CHOPiv); MS m/e 373 (M^+ + 1), 121 (base peak). Anal. Calcd for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.87. Found: C, 64.68; H, 10.71.

(2*R*,3*S*,6*R*)-6-(Hydroxymethyl)-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (22). (a) From **21** (Scheme III). To a solution of **21** (370 mg, 0.99 mmol) in a mixture of acetone (9 mL) and water (1 mL) was added $TsOH/H_2O$ (50 mg). After being stirred for 3 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$, and then the bulk of acetone was evaporated. The residual aqueous layer was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (5 mL × 3), dried, and concentrated to give **22** (306 mg, 100%) as a colorless oil: R_f = 0.30 (2:3 AcOEt/hexane); $[\alpha]^{25}_D$ +40.9° (c 3.67); IR (film) 3454, 1728 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.85 (3 H, d, J = 6.4 Hz), 1.20 (9 H, s), 1.65 (1 H, dddd, J = 14.1, 9.5, 6.1, 4.3 Hz), 1.95 (1 H, br s, OH), 2.05 (1 H, dddd, J = 14.1, 8.9, 7.0, 2.6 Hz), 3.03 (1 H, td, J = 9.5, 2.6 Hz), 3.38 (1 H, dddd, J = 10.5, 7.2, 3.5, 2.2 Hz), 3.50 (1 H, dd, J = 11.2, 7.2 Hz), 3.54 (1 H, dd, J = 11.2, 3.5 Hz), 4.16 (1 H, ddd, J = 10.8, 7.0, 4.3 Hz), 4.32 (1 H, ddd, J = 10.8, 8.9, 6.1 Hz); ^{13}C NMR (50 MHz) δ 17.61 (q), 27.22 (q), 27.51 (t), 32.30 (t), 35.30 (t), 38.71 (s), 60.90 (t), 66.22 (t), 78.15 (d), 79.75 (d), 178.62 (s); MS m/e 259 (M^+ + 1), 125 (base peak). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.80; H, 10.02.

(b) From **31a** (Scheme IV). A solution of **31a** (240 mg, 0.42 mmol) in oxygen-saturated DMF (2 mL) was added dropwise over 20 min to a solution of recrystallized $NaBH_4$ (24 mg, 0.63 mmol) in DMF (2 mL) which was stirred under bubbling of oxygen at room temperature. Five minutes after the addition was completed, the reaction mixture was diluted with Et_2O (30 mL), washed with 5% $KHSO_4$ (10 mL) and brine (10 mL × 2), dried, and concentrated. The residue was subjected to chromatography (silica gel, 6 g, 1:3 AcOEt/hexane) to give **22** as an oil (100 mg, 78%), $[\alpha]^{24}_D$ +38.4° (c 1.26). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.97; H, 10.28.

(2*R*,3*S*,6*R*)-6-Formyl-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (23). Oxalyl chloride (0.13 mL, 1.5 mmol) was added dropwise to a stirred and cooled (−80 °C) solution of DMSO (0.14 mL, 2.0 mmol) in CH_2Cl_2 (10 mL). After an additional stirring for 10 min, a solution of **22** (306 mg) in CH_2Cl_2 (5 mL) was added to the mixture. The reaction mixture was allowed to warm to −40 °C over 40 min and then after addition of Et_3N (1 mL, 7.2 mmol) brought to −10 °C over 1 h. The mixture was treated with brine (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed with brine (10 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 17 g, 1:4 AcOEt/hexane) to afford **23** (224 mg, 88% from **21**) as a colorless oil: R_f = 0.32 (1:2 AcOEt/hexane); $[\alpha]^{26}_D$ +119.7° (c 1.40); IR (film) 1725 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.86 (3 H, d, J = 6.4 Hz), 1.20 (9 H, s), 2.06 (1 H, dddd, J = 14.4, 8.1, 7.3, 2.4 Hz), 3.12 (1 H, td, J = 9.3, 2.4 Hz), 3.74 (1 H, dd, J = 11.4, 2.7 Hz), 4.21 (1 H, ddd, J = 10.8, 8.1, 6.1 Hz), 4.29 (1 H, ddd, J = 10.8, 7.3, 5.0 Hz), 9.63 (1 H, s); MS m/e 257 (M^+ + 1), 125 (base peak). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.57; H, 9.58.

(2*S*)-1-[(1*RS*)-1-Ethoxyethyl]-3-[(4-methylbenzenesulfonyl)oxy]-2-methylpropane (25). The crude **24**, obtained by treatment of 2.36 g (20 mmol) of (*R*)-methyl 3-hydroxy-2-methylpropionate ($[\alpha]^{24}_D$ −26.1° (c 4.19, MeOH)) with $EtOCH{=}CH_2$ (9.6 mL) and PPTS (520 mg) in CH_2Cl_2 (20 mL) at room temperature for 15 min, was dissolved in Et_2O (12 mL), and the solution was added to a stirred and ice-cooled suspension of $LiAlH_4$ (760 mg, 20 mmol) in Et_2O (50 mL). After 10 min, the reaction mixture was quenched with wet Et_2O and then treated with aqueous Rochelle salt. The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried, and concentrated. The residue was purified by chromatography (silica gel, 50 g, 1:2 AcOEt/hexane) to afford (2*S*)-3-(1-ethoxyethyl)-2-methylpropanol (3.08 g, 95%) as an oil, R_f = 0.36 (1:1 AcOEt/hexane). This material was dissolved in CH_2Cl_2 (60 mL), and to the solution were added Et_3N (4 mL) and DMAP (490 mg). The mixture was stirred at room temperature for 4 h after addition of TsCl (4.33 g, 22.7 mmol) at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed sequentially with water (30 mL × 3) and brine (20 mL), dried, and concentrated. The residue was purified by chromatography (silica gel, 200 g, 1:4 AcOEt/hexane) to give **25** (5.92 g, 99%) as a pale yellow oil: R_f = 0.32 (1:4 AcOEt/hexane); ^{1}H NMR (270 MHz) δ 0.93 (3 H, d, J = 6.8 Hz), 1.17 (3 H, t, J = 7.1 Hz), 1.22 (3 H, d, J = 5.4 Hz), 2.02–2.11 (1 H, m), 2.45 (3 H, s), 3.22–3.33 (1 H, m), 3.35–3.63 (3 H, m), 3.92–4.06 (2 H, m), 4.57 (1 H, m). Anal. Calcd for $C_{15}H_{24}O_5S$: C, 56.94; H, 7.65. Found: C, 56.68; H, 7.78.

(2*S*)-2-Methyl-5-hexenol (26). To a stirred and ice-cooled solution of **25** (1.9 g, 6 mmol) in dry Et_2O (30 mL) was added CuI (570 mg, 3 mmol) followed by dropwise addition of 0.72 M ethereal solution of $CH_2{=}CHCH_2MgBr$ (17 mL, 12.2 mmol) over a 5-min period. The resulting black heterogeneous mixture was allowed to warm to room temperature. After being stirred for 6 h, the reaction mixture was poured into a mixture of 28% NH_4OH and saturated NH_4Cl (1:2, 240 mL), and the whole was stirred for 45 min. The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL × 3). The combined ether extracts were washed with brine (50 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 50 g, 1:49 AcOEt/hexane) to give the EE ether of **26** as an oil (949 mg): R_f = 0.47 (1:9 AcOEt/hexane); bp 92–98 °C (17 Torr). This material was dissolved in THF (15 mL), and the solution was ice cooled and treated with 10% HCl (3 mL) for 5 h. The mixture

was then neutralized by addition of $NaHCO_3$ (830 mg), and the bulk of THF was evaporated. The residue was extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine (5 mL), dried, and concentrated. Distillation (Kugelrohr) of the residue afforded **26** (509 mg, 88%) as an oil: bp 80–85 °C (18 Torr); R_f = 0.43 (1:2 AcOEt/hexane); $[\alpha]^{24}_D$ −12.0° (*c* 5.56); IR (film) 3340, 1641 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.93 (3 H, d, *J* = 6.6 Hz), 1.14–1.28 (1 H, m), 1.46–1.72 (3 H, m), 1.98–2.21 (2 H, m), 3.44 (1 H, dd, *J* = 10.5, 6.4 Hz), 3.52 (1 H, dd, *J* = 10.5, 5.9 Hz), 4.95 (1 H, ddt, *J* = 10.2, 2.1, 1.2 Hz), 5.02 (1 H, dq, *J* = 17.2, 2.1 Hz), 5.82 (1 H, ddt, *J* = 17.2, 10.2, 6.7 Hz); ^{13}C NMR (67.8 MHz) δ 16.47 (q), 31.22 (t), 32.34 (t), 35.24 (d), 68.10 (t), 114.41 (t), 138.94 (d).

(*S*)-4-Methyl-2,7-octadien-1-ol (27). Oxalyl chloride (0.21 mL, 2.41 mmol) was added dropwise to a stirred and cooled (−80 °C) solution of DMSO (0.23 mL, 3.26 mmol) in CH_2Cl_2 (20 mL). After 10 min, a solution of **26** (184 mg, 1.61 mmol) in CH_2Cl_2 (3 mL) was introduced, and the mixture was stirred at −80 to −70 °C for 1 h before addition of Et_3N (1.0 mL, 7.17 mmol). The mixture was allowed to warm to −30 °C over 30 min, and then a solution of Ph_3P=CHCOOMe (1.61 g, 4.83 mmol) in CH_2Cl_2 (6 mL) was added. The reaction mixture was allowed to warm to room temperature over 2 h and, after continued stirring at the same temperature for 19 h, poured into brine (10 mL). The whole was extracted with CH_2Cl_2 (10 mL × 3), and the combined extracts were washed with water (10 mL × 2) and then with brine (10 mL), dried, and concentrated. Chromatography of the residue (silica gel, 30 g, 1:19 AcOEt/hexane) afforded methyl (*S*)-(*E*)-4-methyl-2,7-octadienoate (240 mg, 89%) as an oil: R_f = 0.46 (1:9 AcOEt/hexane); $[\alpha]^{24}_D$ +49.4° (*c* 1.77); IR (film) 1725, 1654 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.06 (3 H, d, *J* = 7.3 Hz), 2.34 (1 H, septet, *J* = 7.3 Hz), 3.73 (3 H, s), 4.96 (1 H, ddt, *J* = 10.3, 2.1, 1.2 Hz), 5.01 (1 H, dq, *J* = 17.1, 2.1 Hz), 5.76 (1 H, ddt, *J* = 17.1, 10.3, 7.3 Hz), 5.79 (1 H, d, *J* = 15.9 Hz), 6.86 (1 H, dd, *J* = 15.9, 7.3 Hz).

A stirred solution of the above octadienoate (240 mg) in Et_2O (10 mL) was cooled to −80 °C, and to the solution was added a 0.93 M hexane solution of DIBALH (3.8 mL, 3.53 mmol). After 10 min, the reaction mixture was quenched with MeOH (4 mL) followed by addition of Celite and Et_2O. The whole was filtered, and the filtrate was concentrated. Chromatography of the residue (silica gel, 6 g, 1:5 AcOEt/hexane) afforded **27** (173 mg, 87%) as an oil: R_f = 0.25 (1:4 AcOEt/hexane); IR (film) 3330 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.00 (3 H, d, *J* = 6.6 Hz), 1.34–1.43 (2 H, m), 1.67 (1 H, br, OH), 2.00–2.09 (2 H, m), 2.17 (1 H, septet, *J* = 6.6 Hz), 4.10 (2 H, dm, *J* = 4.6 Hz), 4.94 (1 H, ddt, *J* = 10.3, 2.1, 1.2 Hz), 5.00 (1 H, dq, *J* = 17.1, 2.1 Hz), 5.55 (1 H, dd, *J* = 15.6, 6.6 Hz), 5.62 (1 H, dt, *J* = 15.6, 4.9 Hz), 5.80 (1 H, ddt, *J* = 17.1, 10.3, 6.6 Hz); ^{13}C NMR (50 MHz) δ 20.36 (q), 31.50 (t), 35.88 (d), 35.88 (t), 63.66 (t), 114.37 (t), 127.54 (d), 138.54 (d), 138.89 (d).

(2*R*,3*S*,4*S*)-2,3-Epoxy-4-methyl-7-octen-1-ol (28). To a stirred and cooled (−20 °C) suspension of powdered 4-Å molecular sieves (530 mg) in CH_2Cl_2 (40 mL) were added (+)-diisopropyl tartrate (2.31 mL, 10.9 mmol) and, 10 min later, Ti(O-*i*-Pr)$_4$ (3.2 mL, 10.9 mmol). After 10 min, a 3 M solution of *t*-BuOOH in 2,2,4-trimethylpentane (7.3 mL, 21.8 mmol) was added, and the mixture was stirred at −20 °C for 10 min. A solution of **27** (1.52 g, 10.9 mmol) in CH_2Cl_2 (10 mL) was then added over 5 min, and the mixture was stirred at −20 °C for 7 h before addition of Me_2S (1.6 mL, 21.8 mmol). The reaction mixture was allowed to warm to room temperature and then kept at the same temperature for 1 h. After addition of triethanolamine (2.2 mL, 16.4 mmol), the mixture was filtered through a column of silica gel (80 g). The filtrate and ether washings were combined and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution was stirred for 1 h after addition of water (40 mL) and 30% NaOH in brine (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). Concentration of the combined organic layers followed by chromatography (silica gel, 50 g, 1:2 AcOEt/hexane) afforded **28** (1.49 g, 88%) as a colorless oil: R_f = 0.22 (1:2 AcOEt/hexane); $[\alpha]^{24}_D$ −28.5° (*c* 2.81). IR (film) 3421, 1639 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.95 (3 H, d, *J* = 6.6 Hz), 2.79 (1 H, dd, *J* = 7.1, 2.4 Hz), 2.94 (1 H, dt, *J* = 4.6, 2.4 Hz), 3.62 (1 H, ddd, *J* = 12.5, 7.5, 4.6 Hz), 3.92 (1 H, ddd, *J* = 12.5, 5.5, 2.4 Hz), 4.96 (1 H, ddt, *J* = 10.3, 2.0, 1.1 Hz), 5.03 (1 H, dq, *J* = 17.1, 2.0 Hz), 5.82 (1 H, ddt, *J* = 17.1, 10.3, 6.6 Hz). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.92; H, 10.59.

(3*R*,4*S*)-4-Methyl-1-(trimethylacetoxy)-7-octen-3-ol (30). To a stirred and ice-cooled solution of **28** (2.04 g, 13.1 mmol) in THF (70 mL) was added a 70% toluene solution of Red-Al (7.7 mL, 26.7 mmol). After continued stirring for 5 h, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with AcOEt (50 mL × 3). The combined extracts were washed with brine (20 mL), dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 80 g, AcOEt) to give diol **29** (1.83 g, 88%) as a colorless oil: R_f = 0.41 (AcOEt); ^{1}H NMR (270 MHz) δ 0.91 (3 H, d, *J* = 6.8 Hz), 4.96 (1 H, ddt, *J* = 10.3, 2.1, 1.2 Hz), 5.02 (1 H, dq, *J* = 17.1, 2.1 Hz), 5.81 (1 H, ddt, *J* = 17.1, 10.3, 6.6 Hz).

To a solution of the above diol **29** (1.83 g, 11.6 mmol) in CH_2Cl_2 (10 mL) containing DMAP (283 mg) and Et_3N (2.4 mL, 17.2 mmol) was added Me_3CCOCl (1.5 mL, 12.2 mmol) under stirring and ice cooling. After being stirred at the same temperature for 2 h, the reaction mixture was sequentially washed with water (40 mL) and brine (40 mL × 2), dried, and concentrated. The residue was subjected to chromatography (silica gel, 100 g, 1:4 AcOEt/hexane) to give **30** (2.51 g, 89%) as a colorless oil: R_f = 0.30 (1:4 AcOEt/hexane); $[\alpha]^{24}_D$ +8.45° (*c* 1.42). Optical purity of this sample was shown to be >92% ee by the ^{1}H NMR and GC analyses of the (*S*)-(−)-α-cyano-α-fluorophenylacetate:[41] IR (film) 3448, 1725 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.91 (3 H, d, *J* = 6.8 Hz), 1.21 (9 H, s, *t*-Bu), 1.81 (1 H, dddd, *J* = 14.4, 8.6, 5.4, 2.4 Hz), 3.51 (1 H, ddt, *J* = 12.5, 4.9, 2.4 Hz), 4.16 (1 H, dt, *J* = 11.0, 5.4 Hz), 4.36 (1 H, ddd, *J* = 11.0, 8.6, 4.9 Hz), 4.95 (1 H, ddt, *J* = 10.3, 2.1, 1.3 Hz), 5.02 (1 H, dq, *J* = 16.8, 2.1 Hz), 5.81 (1 H, ddt, *J* = 16.8, 10.3, 6.6 Hz). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.53; H, 11.08.

(2*R*,2*S*,6*R*,*S*)-6-[(Chloromercurio)methyl]-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (31a,b). To a stirred solution of **30** (1.0 g, 4.1 mmol) in CH_2Cl_2 (40 mL) was added powdered $Hg(OAc)_2$ (2.0 g, 6.2 mmol). After 10 min, the resulting homogeneous mixture was treated with brine (4 mL) under vigorous stirring. The layers were separated, and the organic layer was washed with brine (10 mL × 2), dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 120 g, 1:4 AcOEt/hexane) to give **31a** (2,6-cis, 1.57 g, 80%) and **31b** (2,6-trans, 0.36 g, 18%).

31a: oil; R_f = 0.32 (1:4 AcOEt/hexane); IR (film) 1718 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.83 (3 H, d, *J* = 6.3 Hz), 1.20 (9 H, s), 2.06 (1 H, dd, *J* = 11.8, 6.2 Hz), 2.30 (1 H, dd, *J* = 11.8, 5.0 Hz), 3.05 (1 H, td, *J* = 9.3, 2.4 Hz), 3.64 (1 H, m), 4.17–4.23 (2 H, m); ^{13}C NMR (50 MHz) δ 17.53 (q), 27.24 (q), 32.30 (t), 32.81 (t), 34.63 (d), 36.17 (t), 38.70 (s), 39.10 (t), 61.14 (t), 76.18 (d), 80.26 (d), 178.42 (s). A 6.5% NOE was observed between C_2-H (δ 3.05) and C_6-H (δ 3.64).

31b: oil; R_f = 0.24 (1:4 AcOEt/hexane); IR (film) 1718 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.99 (3 H, d, *J* = 6.6 Hz), 1.21 (9 H, s), 2.23 (1 H, dd, *J* = 12.0, 5.6 Hz), 2.29 (1 H, dd, *J* = 12.0, 8.3 Hz), 3.50 (1 H, quint, *J* = 4.6 Hz), 4.06–4.19 (2 H, m), 4.24 (1 H, ddd, *J* = 10.9, 6.8, 5.0 Hz); ^{13}C NMR (50 MHz) δ 18.29 (q), 25.67 (t), 27.24 (q), 30.66 (t), 31.39 (t), 32.41 (d), 37.64 (t), 38.74 (s), 61.22 (t), 69.52 (d), 73.74 (d), 178.43 (s).

(2*R*,3*S*,6*R*)-6-[(1*R*,*S*)-1-Hydroxy-2-propen-1-yl]-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (32a,b). To an ice-cooled solution of **23** (519 mg, 2.03 mmol) in Et_2O (12 mL) was added dropwise a 1 M THF solution of CH_2=CHMgBr (3 mL). After the addition was completed, the reaction mixture was stirred at room temperature for 1.5 h. It was then treated with saturated NH_4Cl (2 mL) and water (5 mL), and layers were separated. The aqueous layer was extracted with Et_2O (5 mL × 4), and the combined organic layers were washed with brine (5 mL × 2). After being dried, the solution was concentrated, and the residue was subjected to chromatography (silica gel, 17 g, 1:7 AcOEt/hexane) to give **32** (1:1.8 diastereomeric mixture; 440 mg, 76%). This mixture which was directly used in the next step could be separated by MPLC.

32a (major, more polar isomer): R_f = 0.45 (1:2 AcOEt/hexane); IR (film) 3482, 1728 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.83 (3 H, d, *J* = 6.6 Hz), 1.20 (9 H, s), 2.02 (1 H, dddd, *J* = 15.9, 8.4, 7.2, 2.6 Hz), 3.05 (1 H, td, *J* = 9.5, 2.6 Hz), 3.33 (1 H, ddd, *J* = 11.1, 3.6, 2.8 Hz), 4.09–4.33 (3 H, m), 5.19 (1 H, dt, *J* = 10.6, 1.6 Hz), 5.30

(1 H, dt, J = 17.3, 1.6 Hz), 5.87 (1 H, ddd, J = 17.3, 10.6, 6.3 Hz); MS m/e 227 ($M^+ - C_4H_9$), 125 (base peak). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.38; H, 9.82.

32b (minor, less polar isomer): R_f = 0.50 (1:2 AcOEt/hexane); IR (film) 3528, 1728 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.84 (3 H, d, J = 6.6 Hz), 1.20 (9 H, s), 2.05 (1 H, dddd, J = 14.7, 8.8, 6.8, 2.6 Hz), 2.27 (1 H, br, OH), 3.04 (1 H, td, J = 9.3, 2.6 Hz), 3.13 (1 H, ddd, J = 9.3, 6.8, 2.0 Hz), 3.91 (1 H, br t, J = 6.8 Hz), 4.17 (1 H, ddd, J = 11.0, 6.8, 4.4 Hz), 4.28 (1 H, ddd, J = 11.0, 8.8, 6.1 Hz), 5.21 (1 H, dt, J = 10.5, 1.3 Hz), 5.35 (1 H, dt, J = 17.2, 1.3 Hz), 5.80 (1 H, ddd, J = 17.2, 10.5, 6.8 Hz); MS m/e 285 (M^+ + 1), 125, 55 (base peak). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.36; H, 10.00.

(2*R*,3*S*,6*R*)-6-(3-Chloro-1-propen-1-yl)-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (33). To a stirred and ice-cooled solution of **32a,b** (823 mg, 2.90 mmol) in Et_2O (30 mL) was added $SOCl_2$ (0.4 mL, 5.7 mmol). After continued stirring at room temperature for 7 h, the reaction mixture was concentrated and Et_2O (20 mL) was added before the mixture was poured into ice–water. The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL × 3). The combined extracts were sequentially washed with saturated $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL × 2). Removal of the solvent followed by chromatography (silica gel, 35 g, 1:19 AcOEt/hexane) afforded **33** (667 mg, 76%) as an oil: R_f = 0.40 (1:9 AcOEt/hexane); $[\alpha]^{26}_D$ +69.2° (*c* 1.61); IR (film) 1727 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.84 (3 H, d, J = 6.4 Hz), 1.19 (9 H, s), 2.01 (1 H, dtd, J = 14.2, 7.7, 2.6 Hz), 3.07 (1 H, td, J = 9.3, 2.6 Hz), 3.80 (1 H, dm, J = 10.9 Hz), 4.05 (2 H, d, J = 5.7 Hz), 4.17 (1 H, ddd, J = 10.7, 7.7, 6.6 Hz), 4.25 (1 H, ddd, J = 10.7, 7.7, 5.1 Hz), 5.77 (1 H, dd, J = 15.4, 3.4 Hz), 5.84 (1 H, dd, J = 15.4, 5.7 Hz); MS m/e 267 (M^+ - Cl), 57 (base peak). Anal. Calcd for $C_{16}H_{27}O_3Cl$: C, 63.46; H, 8.99. Found: C, 63.68; H, 8.99.

(2*R*,3*S*,6*R*)-3-Methyl-2-[2-(trimethylacetoxy)ethyl]-6-[1-(trimethylsilyl)-2-propen-1-yl]tetrahydropyran (7). To a stirred and ice-cooled mixture of $(Me_3Si)_2$ (0.08 mL, 0.4 mmol) and dry HMPA (0.5 mL) was added dropwise a 1.5 M ethereal solution of MeLi (0.27 mL, 0.4 mmol). After 8 min, a solution of CuI (76 mg, 0.4 mmol) in Me_2S (0.5 mL) was introduced via a cannula. After 6 min, the mixture was cooled to −60 °C after addition of Et_2O (1 mL). Then a solution of **33** (49 mg, 0.16 mmol) in Et_2O (1 mL) was added, and stirring was continued for 1 at the same temperature. The reaction mixture was poured into a mixture of 28% NH_4OH (15 mL) and saturated NH_4Cl (30 mL), and the whole was extracted with Et_2O (10 mL × 4). The combined extracts were washed with brine (10 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 7 g, 1:39 AcOEt/hexane) to give **7** as a colorless oil: R_f = 0.58 (1:9 AcOEt/hexane); IR (film) 1731 cm^{-1}; ^{1}H NMR (for major isomer, 270 MHz) δ 0.05 (9 H, s), 0.80 (3 H, d, J = 6.4 Hz), 1.19 (9 H, s), 2.98 (1 H, td, J = 9.0, 2.2 Hz), 3.42 (1 H, dt, J = 11.0, 2.7 Hz), 4.11 (1 H, ddd, J = 10.8, 8.8, 6.4 Hz), 4.26 (1 H, ddd, J = 10.8, 7.1, 4.6 Hz), 4.80 (1 H, ddd, J = 17.1, 2.4, 1.0 Hz), 4.90 (1 H, dd, J = 10.5, 2.4 Hz), 5.84 (1 H, dt, J = 17.1, 10.5 Hz); ^{13}C NMR (50 MHz) δ −2.16 (q), 17.87 (q), 27.27 (q), 31.56 (t), 32.41 (t), 33.30 (t), 34.78 (d), 38.68 (s), 41.96 (d), 61.39 (t), 79.50 (d), 80.41 (d), 112.97 (t), 136.91 (d), 178.49 (s); MS m/e 325 (M^+ – Me), 57 (base peak). Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.65. Found: C, 67.08; H, 10.73.

(2*R*,3*S*,6*R*)-6-[(*E*)-3-[(2*S*,5*S*)-5-(1(*R*)-hydroxyethyl)-tetrahydrofuran-2-yl]-1-propenyl]-3-methyl-2-[2-(trimethylacetoxy)ethyl]tetrahydropyran (35). $BF_3{\cdot}OEt_2$ (0.04 mL, 0.22 mmol) was added dropwise to a stirred and cooled (−80 °C) solution of **8** (84 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). After 5 min, a solution of **7** (73 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was allowed to warm to −20 °C over 1.5 h. An additional $BF_3{\cdot}Et_2O$ (0.01 mL) was added at this point, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then treated with saturated $NaHCO_3$ (1 mL) and brine (1 mL), and the layers were separated. The organic layer combined with AcOEt extracts of the aqueous layer (10 mL × 3) was washed with brine (3 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 13 g, 1:9 AcOEt/hexane) to give an oil (127 mg, 93%), a 95:5 mixture of **34** and its *cis*-tetrahydrofuran isomer (by ^{1}H NMR): R_f = 0.50 (1:4 AcOEt/hexane); IR (film) 1728 cm^{-1}; ^{1}H NMR (for **34**, 270 MHz) δ 0.83 (d, J = 6.4 Hz), 0.93 (d, J = 6.4 Hz), 1.05 (s), 1.19 (9 H, s), 2.14 (dt, J = 14.1, 6.6 Hz), 2.30 (dt, J = 14.1, 5.9 Hz), 3.05 (td, J = 9.3, 2.4 Hz), 3.83 (td, J = 6.8, 5.0 Hz), 4.17 (ddd, J = 10.9, 8.5, 7.1 Hz), 4.24 (ddd, J = 10.9, 7.8, 5.2 Hz), 5.54 (dd, J = 15.6, 4.9 Hz), 5.60 (ddd, J = 15.6, 6.6, 5.9 Hz); MS m/e 620 (M^+), 199 (base peak).

Bu_4NF-induced desilylation of the above product (220 mg, 0.35 mmol) by the usual procedure followed by MPLC (1:2 AcOEt/hexane) provided **35** (111 mg, 83%) as an oil: R_f = 0.40 (1:1 AcOEt/hexane); $[\alpha]^{26}_D$ +37.5° (*c* 0.84); IR (film) 3448, 1728 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.84 (3 H, d, J = 6.4 Hz, Me-16), 1.12 (3 H, d, J = 6.4 Hz, Me-27), 1.19 (9 H, s, *t*-Bu), 2.18 (1 H, ddd, J = 13.8, 6.6, 6.2 Hz, H-22), 2.35 (1 H, dt, J = 13.8, 6.2 Hz, H-22), 3.05 (1 H, td, J = 9.3, 2.4 Hz, H-15), 3.73 (1 H, ddd, J = 11.0, 4.9, 2.0 Hz, H-19), 3.87 (1 H, td, J = 8.0, 3.7 Hz, H-26), 3.95 (1 H, m, H-23), 4.04 (1 H, dq, J = 8.0, 6.4 Hz, H-27), 4.20 (1 H, ddd, J = 12.5, 9.6, 1.7 Hz, CH-14), 4.21 (1 H, ddd, J = 12.5, 8.6, 2.0 Hz, CH-14), 5.57 (1 H, dd, J = 15.6, 4.9 Hz, H-20), 5.63 (1 H, dt, J = 15.6, 6.2 Hz, H-21); MS m/e 382 (M^+), 115 (base peak). Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.08; H, 10.01. Found: C, 68.79; H, 9.91.

36 (*O*-Methyl Ether of 35). To a stirred and ice-cooled suspension of NaH (93 mg, of 60% reagent in oil, 2.3 mmol) in THF (1.5 mL) was added a solution of **35** (111 mg, 0.29 mmol) in THF (1.5 mL) followed by Me_2SO_4 (0.11 mL, 1.2 mmol). After continued stirring for 1 h at room temperature, the reaction mixture was poured onto ice–water, and the whole was extracted with AcOEt (10 mL × 4). The combined extracts were washed with brine (5 mL × 3), dried, and concentrated. The residue was dissolved in Et_2O (30 mL) and treated with Et_3N (0.4 mL) overnight to remove excess Me_2SO_4. The solution was processed as usual, and crude product was purified by chromatography (silica gel, 7 g, 1:7 AcOEt/hexane) to provide **36** (102 mg, 89%) as a colorless oil: R_f = 0.38 (1:3 AcOEt/hexane); $[\alpha]^{26}_D$ +38.0° (*c* 1.05); IR (film) 1728 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.83 (3 H, d, J = 6.1 Hz, Me-16), 1.12 (3 H, d, J = 6.3 Hz, Me-27), 1.19 (9 H, s, *t*-Bu), 2.15 (1 H, ddd, J = 13.9, 7.3, 6.0 Hz, H-22), 2.36 (1 H, dt, J = 13.9, 6.0 Hz, H-22), 3.05 (1 H, td, J = 9.3, 2.4 Hz, H-15), 3.34 (1 H, qd, J = 6.3, 4.9 Hz, H-27), 3.37 (3 H, s, OMe), 3.72 (1 H, ddd, J = 10.8, 5.0, 2.1 Hz, H-19), 3.90 (1 H, dt, J = 7.3, 4.9 Hz, H-26), 3.99 (1 H, ddt, J = 8.0, 7.3, 6.0 Hz, H-23), 4.17 (1 H, ddd, J = 10.5, 8.3, 7.9 Hz, CH-14), 4.24 (1 H, ddd, J = 10.5, 7.8, 5.1 Hz, CH-14), 5.53 (1 H, dd, J = 15.9, 5.0 Hz, H-20), 5.63 (1 H, dt, J = 15.9, 6.0 Hz, H-21); MS m/e 396 (M^+), 129 (base peak). Anal. Calcd for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17. Found: C, 69.42; H, 10.12.

Aldehyde 37. A stirred solution of **36** (231 mg, 0.58 mmol) in Et_2O (6 mL) was cooled at −80 °C, and a 0.95 M hexane solution of DIBALH (0.92 mL, 0.87 mmol) was added dropwise. After 5 min, the reaction mixture was quenched with MeOH (1 mL) and stirred at room temperature for 1 h. Filtration after addition of Celite and Et_2O followed by evaporation afforded a crude oil which was purified by chromatography (silica gel, 7 g, 1:1 AcOEt/hexane) to give a hydroxy compound (179 mg, 99%): R_f = 0.35 (2:1 AcOEt/hexane); $[\alpha]^{27}_D$ +18.0° (*c* 1.46); IR (film) 3452 cm^{-1}; MS m/e 312 (M^+), 129 (base peak).

To a solution of DMSO (0.08 mL, 1.13 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (0.07 mL, 0.79 mmol) at −80 °C. After 10 min, to this mixture was added the hydroxy compound (prepared in the above experiment) (170 mg, 0.54 mmol) in CH_2Cl_2 (2 mL) via a cannula. The resulting mixture was allowed to warm to −60 °C over 1 h and then treated with Et_3N (0.54 mL) for 30 min at −40 °C. Brine (5 mL) was then added, and the whole was extracted with CH_2Cl_2 (5 mL × 4). The combined extracts were washed with brine (5 mL × 3), dried, and concentrated. The residual crude aldehyde was purified by chromatography (silica gel, 7 g, 1:3 AcOEt/hexane) to give **37** (157 mg, 94%): R_f = 0.35 (1:2 AcOEt/hexane); $[\alpha]^{26}_D$ +15.0° (*c* 1.16); IR (film) 1727 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.84 (3 H, d, J = 6.4 Hz), 1.12 (3 H, d, J = 6.3 Hz), 2.15 (1 H, dt, J = 13.7, 6.8 Hz), 2.35 (1 H, dt, J = 13.7, 5.6 Hz), 2.50 (1 H, ddd, J = 15.9, 8.5, 3.1 Hz), 2.63 (1 H, ddd, J = 15.9, 3.7, 2.0 Hz), 3.34 (1 H, qd, J = 6.3, 4.6 Hz), 3.37 (3 H, s), 3.53 (1 H, td, J = 8.5, 3.7 Hz), 3.89 (1 H, td, J = 7.1, 4.6 Hz), 3.98 (1 H, tt, J = 6.8, 5.6 Hz), 5.54 (1 H, dd, J = 15.9, 5.1 Hz), 5.62 (1 H, ddd, J = 15.9, 6.8, 5.6 Hz), 9.82 (1 H, dd, J = 3.1, 2.0 Hz); MS m/e 310 (M^+), 251, 129 (base peak). Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.36; H, 9.54.

Polyether Fragment 6. To a stirred mixture of **37** (140 mg, 0.45 mmol) and 2-methyl-2-butene (0.72 mL) in *t*-BuOH (5 mL) was added a solution of $NaClO_2$ (59 mg) and $NaH_2PO_4 \cdot 2H_2O$ (53 mg) in water (1.5 mL). After being stirred at room temperature for 20 min, the reaction mixture was diluted with AcOEt (30 mL) and washed with brine (4 mL × 3). The organic solvent was evaporated after drying to give the corresponding carboxylic acid. This material was dissolved in Et_2O (10 mL) and treated with excess ethereal CH_2N_2. The Et_2O solution was washed with brine (5 mL × 3), dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 7 g, 1:3 AcOEt/hexane) to afford **6** (142 mg, 93%) as a colorless oil: R_f = 0.49 (1:1 AcOEt/hexane); $[\alpha]^{26}_D$ +24.5° (*c* 1.43). IR (film) 1742 cm^{-1}; ^1H NMR (270 MHz) δ 0.84 (3 H, d, *J* = 6.4 Hz, Me-16), 1.12 (3 H, d, *J* = 6.4 Hz, Me-27), 2.14 (1 H, dt, *J* = 13.7, 7.0 Hz, H-22), 2.35 (1 H, dt, *J* = 13.7, 5.9 Hz, H-22), 2.43 (1 H, dd, *J* = 14.9, 8.8 Hz, H-14), 2.63 (1 H, dd, *J* = 14.9, 3.7 Hz, H-14), 3.33 (1 H, qd, *J* = 6.4, 4.6 Hz, H-27), 3.37 (3 H, s, OMe-27), 3.48 (1 H, td, *J* = 9.3, 3.7 Hz, H-15), 3.68 (3 H, s, COOMe), 3.79 (1 H, ddd, *J* = 11.1, 4.8, 2.2 Hz, H-19), 3.89 (1 H, ddd, *J* = 7.6, 6.6, 4.6 Hz, H-26), 3.98 (1 H, ddt, *J* = 7.9, 7.0, 5.9 Hz, H-23), 5.53 (1 H, dd, *J* = 15.6, 4.8 Hz, H-20), 5.57 (1 H, ddd, *J* = 15.6, 7.0, 5.9 Hz, H-21); ^{13}C NMR (50 MHz) δ 15.57 (q), 17.60 (q), 26.99 (t), 31.25 (t), 31.98 (t), 32.58 (t), 35.12 (d), 38.63 (t), 39.30 (t), 51.51 (q), 57.03 (q), 78.86 (d), 80.11 (d), 81.92 (d), 127.11 (d), 133.29 (d), 172.43 (s); MS *m/e* 340 (M^+), 97 (base peak). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.05; H, 9.55.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-methoxy-5-methyl-1,4-cyclohexadiene ((±)-40). A solution of **38** (10.0 g, 60 mmol) in dry EtOH (100 mL) was added to stirred liquid ammonia (500 mL), and then Na (6.23 g) was added portionwise (ca. 0.5 g) over a 1-h period. The reaction mixture was treated with NH_4Cl (14.5 g), and excess ammonia was allowed to evaporate. To the residue were added Et_2O (50 mL) and water (50 mL), and the mixture was carefully neutralized with 10% HCl under ice cooling and then brought to pH 5 with saturated KH_2PO_4. The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL × 6). The combined organic layers were washed with brine (50 mL × 3), dried, and concentrated to give the corresponding 1,4-dihydrobenzoic acid as a solid. This material dissolved in Et_2O (60 mL) was treated with an ethereal CH_2N_2 (generated from 18.8 g of *N*-methyl-*N*-nitrosourea) to give crude methyl ester after usual workup. A solution of the ester in Et_2O (150 mL) was cooled at −50 °C, and a 1 M hexane solution of DIBALH (170 mL) was added over 20 min. After additional stirring at the same temperature for 1.5 h, the reaction mixture was quenched with MeOH (150 mL) and stirred at room temperature for 1.5 h. The mixture was filtered through a Celite pad followed by washing with Et_2O. The combined filtrates were concentrated, and the residue was dissolved in AcOEt (100 mL). The solution was washed with brine (10 mL × 4), dried, and concentrated to give crude **39** (8.28 g) as a pale yellow oil. A solution of this material in CH_2Cl_2 (220 mL) was stirred for 15 min after addition of imidazole (8.05 g, 118 mmol) and TBDMS-Cl (8.91 g, 59 mmol). The mixture was sequentially washed with water (20 mL × 2) and brine (20 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 200 g, 1:49 AcOEt/hexane) to give **40** (12.4 g, 77% from **38**) as a colorless oil: R_f = 0.39 (1:19 AcOEt/hexane); ^1H NMR (270 MHz) δ 0.06 (6 H, s), 0.91 (9 H, s), 1.72 (3 H, br s), 2.59 and 2.62 (each 1 H, br s), 3.00 (1 H, m), 3.41 (1 H, dd, *J* = 9.3, 7.1 Hz), 3.49 (1 H, dd, *J* = 9.3, 6.8 Hz), 3.56 (3 H, s), 4.67 (1 H, br d *J* = 3.7 Hz), 5.40 (1 H, m); MS *m/e* 268 (M^+), 211, 123 (base peak); HRMS calcd for $C_{15}H_{28}O_2Si$ 268.1857, found 268.1872.

(1*R,4*R**,8*S**)-8-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one ((±)-41) and Its (8*R**)-Isomer.** Into a Ar-flushed pressure bottle containing a solution of **40** (15.24 g, 56.9 mmol) in dry chlorobenzene (25 mL) were added 2-acetoxyacrylonitrile (9.48 g, 85.3 mmol), 2,6-di-*tert*-butylcresol (150 mg), and dichloromaleic anhydride (30 mg). The mixture was then heated at 150 °C for 24 h. Evaporation of the solvent followed by chromatography (silica gel, 600 g, 1:4 AcOEt/hexane) of the residue afforded the Diels–Alder adduct as a pale yellow oil (14.8 g). A portion of this material (1.66 g, 4.38 mmol) was dissolved in MeOH (45 mL), and the solution was treated with 2.0 M MeONa in MeOH (2.4 mL) under ice cooling for 50 min. The mixture was concentrated, and the residue was extracted with AcOEt (20 mL × 3) after addition of brine (10 mL). The combined extracts were washed with saturated NH_4Cl (5 mL) and then with brine (5 mL × 3), dried, and concentrated to give a ca. 4:1 mixture of (±)-**41** and its C_8 epimer (1.33 g): R_f = 0.42 (1:4 AcOEt/hexane). Analytical samples of the diastereomers were obtained by MPLC (1:39 AcOEt/benzene).

(±)-**41**: IR (film) 1730 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 (6 H, s), 0.90 (9 H, s), 1.14 (1 H, dd, *J* = 12.4, 4.8 Hz, H-7), 1.87 (3 H, d, *J* = 1.7 Hz), 1.97 (1 H, dd, *J* = 12.4, 10.3 Hz, H-7), 2.07 (1 H, dd, *J* = 18.2, 2.3 Hz, H_{exo}-3), 2.14–2.26 (1 H, m, H-8), 2.18 (1 H, dd, *J* = 18.2, 3.5 Hz, H_{endo}-3), 2.86 (1 H, m, H-4), 3.20 (1 H, t, *J* = 9.8 Hz, CH-8), 3.40 (1 H, dd, *J* = 9.8, 6.0 Hz, CH-8), 3.49 (3 H, s), 5.85 (1 H, br s, H-6); MS *m/e* 310 (M^+), 253, 137 (base peak); HRMS calcd for $C_{17}H_{30}O_3Si$ 310.1962, found 310.1965.

8-*epi*-(±)-**41**: IR (film) 1734 cm^{-1}; ^1H NMR (270 MHz) δ 0.04 (6 H, s), 0.89 (9 H, s), 1.33 (1 H, dd, *J* = 12.3, 5.5 Hz, H-7), 1.85–2.12 (2 H, m, H-7, H-8), 1.88 (3 H, d, *J* = 1.7 Hz), 2.03 (1 H, ddd, *J* = 18.9, 3.3, 1.5 Hz, H_{endo}-3), 2.35 (1 H, dd, *J* = 18.9, 2.0 Hz, H_{exo}-3), 2.68 (1 H, m, H-4), 3.45 (1 H, dd, *J* = 10.3, 8.8 Hz, CH-8), 3.48 (3 H, s), 3.68 (1 H, dd, *J* = 10.3, 5.4 Hz, CH-8), 5.80 (1 H, br s, H-6); MS *m/e* 310 (M^+), 253, 137, 123 (base peak); HRMS calcd for $C_{17}H_{30}O_3Si$ 310.1962, found 310.1964.

(1*R,4*R**,8*S**)-8-(Hydroxymethyl)-1-methoxy-5-methylbicyclo[2.2.2]oct-5-en-2-one ((±)-42).** Crude (±)-**41** (8.75 g, 28.2 mmol) obtained in the preceding experiment was dissolved in MeCN (70 mL), and the solution was stirred under ice cooling after addition of 5% HF/MeCN (70 mL). After 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ (20 mL) and solid $NaHCO_3$ (10 g) and then concentrated. The residue was extracted with CH_2Cl_2 (40 mL × 3). The combined extracts were processed in the usual way, and the resulting oil (5.99 g) which solidified on standing was crystallized from *i*-Pr_2O/Et_2O, providing (±)-**42** (2.66 g, 48%) as colorless cubes: mp 82–84 °C; R_f = 0.33 (9:1 AcOEt/hexane); IR (KBr) 3470, 1730 cm^{-1}; ^1H NMR (270 MHz) δ 1.24 (1 H, dd, *J* = 12.4, 4.8 hz), 1.64 (1 H, s, OH), 1.90 (3 H, d, *J* = 1.7 Hz), 2.03 (1 H, dd, *J* = 12.4, 10.1 Hz), 2.12 (1 H, dd, *J* = 18.3, 2.4 Hz), 2.20 (1 H, dd, *J* = 18.3, 3.4 Hz), 2.86 (1 H, m), 3.33 (1 H, td, *J* = 9.8, 5.4 Hz), 3.48 (1 H, ddd, *J* = 9.8, 6.0, 4.5 Hz), 3.50 (3 H, s), 5.88 (1 H, br s); MS *m/e* 196 (M^+), 137 (base peak). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.04; H, 8.14.

Resolution of (±)-42. (a) To a solution of (±)-**42** (98 mg, 0.5 mmol) and 2(*R*),3(*R*)-butanediol (45 mg, 0.5 mmol) in dry benzene (3 mL) was added CSA (12 mg), and the solution was heated at reflux. After 4 h, the reaction mixture was processed by the usual manner followed by flash chromatography (silica gel, 17 g, 3:2 AcOEt/hexane) to give a 1:1 mixture of diastereomeric ketals (111 mg, 83%), R_f = 0.38 (1:2 hexane/AcOEt). The ketal mixture (382 mg from repeated experiments) was separated by MPLC (1:2:2 MeCN/CH_2Cl_2/hexane), yielding the less polar ketal of (+)-**42** (176 mg) (HRMS calcd 268.1673, found 268.1665) and the more polar ketal of (−)-**42** (112 mg) (HRMS found 268.1677). Treatment of each isomer with CSA (10 mg) in acetone/H_2O (3:2, 5 mL) at reflux for 20 h followed by usual workup and chromatography (1:1 AcOEt/hexane) afforded (+)-**42** (84%) and (−)-**42** (82%), respectively, whose spectral data were identical with those of the racemate.

(+)-**42**: mp 109–111 °C (colorless plates from *i*-Pr_2O/AcOEt); $[\alpha]^{27}_D$ +426° (*c* 0.72). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.17.

(−)-**42**: mp 110–112 °C (colorless plates from *i*-Pr_2O/AcOEt); $[\alpha]^{27}_D$ −419° (*c* 1.38). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.22; H, 8.17.

(b) To a solution of (±)-**42** (3.06 g, 15.6 mmol) in a mixture of isooctane (700 mL) and benzene (330 mL) were added freshly distilled acetic anhydride (2.9 mL) and Amano lipase CES on Celite (9.0 g containing 2.25 g of the enzyme), and the suspension was stirred at room temperature (ca. 23 °C). After 5 h by which time the acetylation had progressed to ca. 50% as determined by GC analysis (OV-17 packed column, 155 °C), the mixture was filtered through a Celite pad. The filtrate was stirred for 2 h after addition of K_2CO_3. The solvent was evaporated, and the residue was subjected to chromatography (silica gel, 220 g, 1:1 AcOEt/hexane) to give, in the order of elution, (−)-**43** (1.75 g, 74% ee)

and (+)-42 (1.56 g, 70% ee). Recrystallization of the latter hydroxy compound from Et_2O afforded a first crop of 99% ee (754 mg, 25% yield), $[\alpha]^{28}_D$ +415° (c 1.16). The same procedure for the acetate (−)-43 to remove crystalline racemate provided an oily sample of 90% ee (1.45 g, 39% yield), $[\alpha]^{28}_D$ −310° (c 2.08), which on treatment with 2% methanolic KOH followed by usual workup afforded (−)-42 of 94% ee, $[\alpha]^{26}_D$ −397° (c 0.62).

(1*S*,3*R*,4*R*,8*R*)-8-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-methoxy-3,5-dimethylbicyclo[2.2.2]oct-5-en-2-one (44). To an ice-colled solution of (+)-42 (97% ee, 1.87 g, 9.6 mmol) and imidazole (1.43 g, 21 mmol) in dry CH_2Cl_2 (50 mL) was added TBDMS-Cl (1.58 g, 10.5 mmol), and the mixture was stirred at room temperature for 1 h. Standard workup of the reaction mixture followed by chromatographic purification (silica gel, 170 g, 1:4 AcOEt/hexane) afforded (+)-41 (2.97 g, 99%) as a colorless oil: bp 75–85 °C (0.01 Torr) (ot); $[\alpha]^{26}_D$ +263° (c 2.78). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.66; H, 9.77.

A solution of the above (+)-41 (627 mg, 2.0 mmol) in THF (15 mL) was stirred under cooling at −80 °C, and a 1.0 M hexane solution of LHMDS (7.3 mL) was added dropwise over 10 min. After additional stirring at −50 to −60 °C for 1 h, the mixture was recooled to −80 °C before addition of MeI (0.41 mL, 6.1 mmol) and HMPA (1.1 mL, 6.1 mmol). The stirred reaction mixture was kept at −35 °C until no starting material was detected on TLC (ca. 24 h). The reaction was quenched with saturated NH_4Cl (10 mL) followed by extraction of the aqueous layer with AcOEt (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried, and concentrated to give an oil, which was subjected to MPLC (20-μm silica gel, 170 g, 1:4 AcOEt/hexane) providing 44 (448 mg, 69%) and unreacted starting material (76 mg). An analytical sample was obtained by distillation (Kugelrohr): bp 79–89 °C (0.01 Torr) (ot); $[\alpha]^{24}_D$ +239° (c 2.41); IR (film) 1732 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 (6 H, s), 0.90 (9 H, s), 1.10 (3 H, d, J = 7.2 Hz), 1.11 (1 H, dd, J = 12.5, 4.9 Hz), 1.87 (3 H, d, J = 1.7 Hz), 1.98 (1 H, dd, J = 12.5, 10.0 Hz), 2.06 (1 H, qd, J = 7.2, 2.2 Hz), 2.70 (1 H, dd, J = 4.4, 2.2 Hz), 3.22 (1 H, t, J = 9.8 Hz), 3.38 (1 H, dd, J = 9.8, 6.1 Hz), 3.48 (3 H, s), 5.79 (1 H, br s); MS *m/e* 325 (M^+ + 1), 150 (base peak). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.52; H, 10.06.

Oxime 45 was obtained as an oil (98% yield) by treatment with NH_2OH·HCl (4.5 equiv) and pyridine (20 equiv) in refluxing CH_2Cl_2 for 15 h, followed by chromatographic purification: R_f = 0.32 (1:2 AcOEt/hexane); IR (film) 3341, 1645 cm^{-1}; MS *m/e* 339 (M^+) 282, 190.

(4*S*,5*S*)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-[(1*R*)-1-cyanoethyl]-3-methylcyclohex-2-en-1-one (46). To a solution of 45 (2.13 g, 6.3 mmol) in CH_2Cl_2 (50 mL) were added DMAP (34 mg) and pyridine (5.1 mL). The mixture was stirred at −80 °C, and after addition of TsCl (4.05 g, 25.1 mmol) the temperature was allowed to rise to room temperature over a 1-h period. After complete formation of oxime tosylate as observed by TLC, the mixture was treated with LiCl (1.1 g) and MeOH (1.6 mL) overnight. An additional amount of MeOH (7.7 mL) was then added, and stirring at room temperature was continued for 2 weeks. The reaction mixture was concentrated, and AcOEt (50 mL) and water (30 mL) were added. The layers were separated, and the aqueous layer was extracted with AcOEt (30 mL × 3). Combined organic layers were sequentially washed with water (30 mL), saturated $CuSO_4$ (50 mL × 3), and brine (30 mL × 3). Concentration of the extract after drying gave a crude oil, which was subjected to chromatography (silica gel, 200 g, 1:3 AcOEt/hexane) to afford 46 (1.40 g, 72.5%) as a colorless oil. An analytical sample was obtained by distillation (Kugelrohr): bp 135–145 °C (0.02 Torr) (ot); $[\alpha]^{26}_D$ +1.07° (c 2.15); IR (film) 2240, 1673 cm^{-1}; ^1H NMR (270 MHz) δ 0.02 and 0.03 (each 3 H, s), 0.88 (9 H, s), 1.42 (3 H, d, J = 7.1 Hz), 2.07 (3 H, d, J = 1.0 Hz), 2.30 (1 H, d, J = 16.1 Hz, H_{ax}-6), 2.48 (1 H, m, H-5), 2.52 (1 H, dd, J = 16.1, 6.3 Hz, H_{eq}-6), 2.69 (1 H, br d, J = 5.9 Hz, H-4), 3.00 (1 H, qd, J = 7.1, 5.9 Hz, CH-4), 3.47 (1 H, dd, J = 10.0, 7.8 Hz, CH-5), 3.56 (1 H, dd, J = 10.0, 5.6 Hz, CH-5), 6.01 (1 H, br s, H-2); MS *m/e* 250 (M^+ − C_4H_9, base peak). Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.51; N, 4.55. Found: C, 66.04; H, 9.55; N, 4.57.

(3*S*,4*S*,5*S*)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-[(1*R*)-1-cyanoethyl]-3-methylcyclohexan-1-one (47). Catalytic hydrogenation of 46 (1.88 g) using 10% Pd/C (0.4 g) and H_2 (1 atm) in EtOH (200 mL) afforded a crude oil which was purified by chromatography (silica gel, 170 g, 1:3 AcOEt/hexane) to yield 47 in 72% yield: R_f = 0.33 (1:3 AcOEt/hexane); $[\alpha]^{26}_D$ +7.80° (c 3.72); IR (film) 2237, 1718 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 and 0.06 (each 3 H, s), 0.89 (9 H, s), 1.06 (3 H, d, J = 6.6 Hz), 1.37 (3 H, d, J = 7.3 Hz), 1.67 (1 H, td, J = 8.1, 2.7 Hz), 2.16 (1 H, dd, J = 15.5, 9.2 Hz), 2.33 (1 H, dd, J = 16.7, 8.1 Hz), 2.41 (1 H, dd, J = 16.7, 6.4 Hz), 2.52 (1 H, dd, J = 15.5, 4.0 Hz), 3.13 (1 H, qd, J = 7.3, 2.7 Hz), 3.58 (1 H, dd, J = 10.5, 3.4 Hz), 3.74 (1 H, dd, J = 10.5, 4.0 Hz); MS *m/e* 252 (M^+ − C_4H_9), 167, 75 (base peak). Anal. Calcd for $C_{17}H_{31}NO_2Si$: C, 65.97; H, 10.09; N, 4.53. Found: C, 66.22; H, 10.09; N, 4.56.

(1*R*,2*S*,3*S*)-1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-[(1*R*)-1-cyanoethyl]-3-methylcyclohexane (48). A solution of 47 (804 mg, 2.6 mmol) and $TsNHNH_2$ (509 mg, 2.7 mmol) in dry EtOH (35 mL) was heated under reflux for 1.5 h. The resulting crude tosylhydrazone obtained by evaporation of the solvent was dissolved in dry $CHCl_3$ (50 mL), and to the solution was added at −20 °C a 1.0 M THF solution of catecholborane (3.25 mL). After continued stirring at −10 °C for 45 min, the mixture was treated with powdered $AcONa·3H_2O$ (1.06 g, 7.8 mmol) followed by refluxing for 2 d. The reaction mixture was sequentially washed with 2% AcOH (50 mL × 2), saturated $NaHCO_3$ (30 mL), and brine (30 mL × 2). Evaporation of the solvent after drying afforded a crude oil which was purified by chromatography (silica gel, 80 g, 1:19 AcOEt/hexane) to provide 48 (627 mg, 82%) as a colorless oil: R_f = 0.28 (1:19 AcOEt/hexane); $[\alpha]^{26}_D$ −5.29° (c 1.14); IR (film) 2236, 838 cm^{-1}; ^1H NMR (270 MHz) δ 0.05 (6 H, s), 0.89 (9 H, s), 1.02 (3 H, d, J = 6.3 Hz), 1.33 (3 H, d, J = 7.3 Hz), 3.22 (1 H, qd, J = 7.3, 1.2 Hz), 3.65 (2 H, m); MS *m/e* 295 (M^+), 238 (base peak). Anal. Calcd for $C_{17}H_{33}NOSi$: C, 69.09; H, 11.25; N, 4.74. Found: C, 68.83; H, 11.27; N, 4.79.

(4*R*,4a*R*,5*S*,8a*R*)-4,5-Dimethyl-3-oxoperhydroisochroman (49). (a) From 48 (Scheme VII). To a solution of 48 (39 mg) in MeOH (1.5 mL) were added 37% HCl (0.5 mL) and water (0.5 mL), and the mixture was stirred for 2 d at room temperature. After being quenched with saturated $NaHCO_3$ (5 mL), the mixture was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (5 mL × 3), dried, and concentrated. The residue was subjected to chromatography (silica gel, 7 g, 1:4 AcOEt/hexane) to give 49 (21 mg, 89%) as a colorless oil: R_f = 0.40 (1:2 AcOEt/hexane); $[\alpha]^{27}_D$ +95.9° (c 1.39); IR (film) 1733 cm^{-1}; ^1H NMR (270 MHz) δ 0.81–1.08 (2 H, m, H_{ax}-6 and H-7), 0.88 (3 H, d, J = 6.7 Hz, Me-5), 1.23 (3 H, d, J = 7.6 Hz, Me-4), 1.26 (1 H, td, J = 11.0, 4.9 Hz, H-4a), 1.32–1.45 (2 H, m, H-5 and H-8), 1.66–1.92 (4 H, m), 2.89 (1 H, qd, J = 7.6, 4.9 Hz, H-4), 3.79 (1 H, t, J = 11.2 Hz, H_{ax}-1), 4.30 (1 H, dd, J = 11.2, 5.3 Hz, H-1); MS *m/e* 182 (M^+), 96 (base peak). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.54; H, 9.97.

(b) From 57 (Scheme IX). A freshly prepared solution of *t*-BuOK from K (20 mg) and *t*-BuOH (0.55 mL) was added over 5 min to an ice-cooled and stirred solution of 57 (106 mg, 0.414 mmol) in THF (2 mL). After being stirred at room temperature for 20 h, the mixture was quenched with saturated NH_4Cl (2 mL), and the whole was extracted with AcOEt (7 mL × 3). The aqueous layer was brought to pH 2 (HCl) and reextracted with AcOEt (7 mL × 3). The combined extracts were washed with brine, dried, and concentrated. Flash chromatography of the residue (silica gel, 7 g, 1:5 AcOEt/hexane) afforded a mixture of 49 and 58 (23:1 by capillary GC, 71 mg) which was separated by HPLC (5-μm silica gel, 1:9 AcOEt/hexane) yielding 49 (64.5 mg, 86%), $[\alpha]^{24}_D$ +95.4° (c 2.35), and 58 (2.5 mg 3%).

(1*R*,2*S*,3*S*)-1-Formyl-2-[(1*R*)-1-cyanoethyl]-3-methylcyclohexane (5). An ice-cooled solution of 48 (775 mg, 2.6 mmol) in MeCN (8 mL) was treated with 5% HF in MeCN (8 mL) for 45 min. After addition of saturated $NaHCO_3$ (16 mL), the mixture was extracted with AcOEt (30 mL × 4). The combined extracts were washed with brine, dried, and concentrated. The residual oil (59, 473 mg) was dried by an azeotropic distillation with benzene and used in the next step.

To a stirred, cooled (−85 °C) solution of DMSO (0.37 mL, 5.3 mmol) in CH_2Cl_2 (25 mL) was added oxalyl chloride (0.34 mL, 3.9 mmol) dropwise. After 20 min at this temperature, a solution of the preceding compound in CH_2Cl_2 (3 mL) was added and the mixture was stirred for 1 h at −60 to −80 °C, and then Et_3N (2.7 mL, 19 mmol) was added. The slurry was stirred at −60 °C for

50 min before addition of brine (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL × 3). The combined organic layers were successively washed with water (50 mL) and brine (50 mL), dried, and concentrated. The residue was purified by chromatography (silica gel, 33 g, 1:5 AcOEt/hexane) to give **5** (44 mg, 94.5%) as an oil: R_f = 0.24 (1:5 AcOEt/hexane); IR (film) 2236, 1721 cm^{-1}; ^1H NMR (270 MHz) δ 1.06 (3 H, d, J = 6.4 Hz), 1.38 (3 H, d, J = 7.3 Hz), 2.38 (1 H, tdd, J = 7.6, 4.5, 3.2 Hz), 2.89 (1 H, qd, J = 7.3, 1.5 Hz), 9.65 (1 H, d, J = 3.2 Hz); MS m/e 179 (M^+), 150, 55 (base peak).

(*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-methyl-1-hexene (50). Treatment of **26** (2.85 g, 25.0 mmol) in CH_2Cl_2 (85 mL) with *t*-$BuPh_2SiCl$ (8.45 mL, 32.5 mmol) and imidazole (5.11 g, 75.0 mmol) at room temperature for 40 min afforded **50** (8.76 g, 99.5%) after chromatography (silica gel, 180 g, 1:49 AcOEt/hexane): bp 115–7 °C (0.01 Torr) (ot); R_f = 0.40 (1:49 AcOEt/hexane); $[\alpha]^{24}_D$ −0.23° (*c* 3.00); IR (film) 1640, 1560 cm^{-1}; ^1H NMR (270 MHz) δ 0.93 (3 H, d, J = 6.8 Hz), 1.05 (9 H, s), 3.45 (1 H, dd, J = 9.9, 6.2 Hz), 3.52 (1 H, dd, J = 9.9, 5.6 Hz), 4.92 (1 H, ddt, J = 10.3, 2.0, 1.2 Hz), 4.98 (1 H, dq, J = 17.1, 2.0 Hz), 5.79 (1 H, ddt, J = 17.1, 10.3, 6.6 Hz). Anal. Calcd for $C_{23}H_{32}OSi$: C, 78.35; H, 9.15. Found: C, 78.43; H, 9.09.

(*E*)-(*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-2-heptenoic Acid, Methyl Ester (51). A solution of **50** (9.49 g, 27.0 mmol) in a mixture of CH_2Cl_2 (100 mL) and MeOH (20 mL) was cooled to −60 °C, and a stream of ozone gas was passed through the stirred solution. After no starting material was detected by TLC (ca. 1 h), excess ozone in the solution was removed by bubbling with N_2. After addition of Me_2S (19.8 mL, 270 mmol) at −70 °C, the mixture was allowed to warm to room temperature over 1 h and then concentrated. The residue (mostly dimethylacetal) was dissolved in acetone (100 mL), and after addition of TsOH (10 g) and water (10 mL) the mixture was stirred at room temperature for 30 min. It was concentrated and extracted with AcOEt (60 mL × 3). The combined extracts were successively washed with saturated $NaHCO_3$ (30 mL × 2) and brine (10 mL), dried, and concentrated. The residue was subjected to chromatography (silica gel, 200 g, 1:19 AcOEt/hexane) to give 5-[(*tert*-butyldiphenylsilyl)oxy]-4-methylpentanal (7.01 g, 73%) as a colorless oil. A solution of this aldehyde (19.8 mmol) and Ph_3P=CHCOOMe (19.8 g, 59.3 mmol) in dry benzene (180 mL) was stirred and refluxed for 1.5 h. The reaction mixture was concentrated, and the residue was treated with Et_2O (10 mL) and hexane (200 mL). Insoluble solid was removed by filtration, and the filtrate was concentrated. The residue was subjected to chromatography (silica gel, 200 g, 1:19 AcOEt/hexane) to afford **51** (6.90 g, 85%) and less polar (*Z*)-isomer (305 mg, 4%). An analytical sample of **51** was obtained by distillation (Kugelrohr): bp 145–50 °C (0.02 Torr) (ot); R_f = 0.34 (1:9 AcOEt/hexane); $[\alpha]^{24}_D$ −0.089° (*c* 3.52); IR (film) 1726, 1657 cm^{-1}; ^1H NMR (270 MHz) δ 0.92 (3 H, d, J = 6.6 Hz), 1.05 (9 H, s), 3.48 (2 H, d, J = 5.9 Hz), 3.73 (3 H, s), 5.80 (1 H, dt, J = 15.6, 1.6 Hz), 6.96 (1 H, dt, J = 15.6, 7.0 Hz). Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.20; H, 8.60.

(*E*)-(*S*)-7-Hydroxy-6-methyl-2-heptenoic Acid, Methyl Ester (52). A solution of **51** (7.42 g, 18.1 mmol) in 5% HF/MeCN (75 mL) was stirred at room temperature. After 3 h, the mixture was diluted with Et_2O (700 mL), washed with saturated $NaHCO_3$ (60 mL × 2) and then with brine (30 mL), dried, and concentrated. The residue was subjected to chromatography (silica gel, 180 g, 2:3 AcOEt/hexane) to afford **52** (2.92 g, 94%) as a colorless oil: bp 85–7 °C (0.007 Torr) (ot); R_f = 0.33 (1:1 AcOEt/hexane); $[\alpha]^{25}_D$ −13.8° (*c* 2.56); IR (film) 3428, 1725, 1655 cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (3 H, d, J = 6.6 Hz), 1.50 (1 H, s, OH), 3.46 (1 H, dd, J = 9.8, 5.1 Hz), 3.52 (1 H, dd, J = 9.8, 4.9 Hz), 3.73 (3 H, s), 5.84 (1 H, dt, J = 15.6, 1.5 Hz), 6.98 (1 H, dt, J = 15.6, 7.0 Hz). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.62; H, 9.57.

(*E,E*)-(*S*)-2,4-Dimethyl-2,7-nonadienedioic Acid, 1-*tert*-Butyl 9-Methyl Diester (53). (a) Oxalyl chloride (0.57 mL, 6.55 mmol) was added to a stirred and cooled (−80 °C) solution of DMSO (0.62 mL, 8.73 mmol) in CH_2Cl_2 (30 mL). After continued stirring for 25 min at −60 to −55 °C, a solution of **52** (750 mg, 4.37 mmol) in CH_2Cl_2 (4 mL) was added via a cannula (an additional 2 mL of the solvent was used for rinsing). The reaction mixture was allowed to warm to −25 °C over 1 h and then treated with Et_3N (3.0 mL, 21.8 mmol). After being stirred at −20 to −10 °C, the reaction mixture was quenched by addition of brine (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic phases were washed with brine (10 mL), dried, and concentrated. The residue was subjected to chromatography (silica gel, 50 g, 1:4 AcOEt/hexane) to give methyl 6-methyl-7-oxo-2-heptenoate (720 mg, 97%) as an oil: R_f = 0.40 (1:2 AcOEt/hexane); IR (film) 1724, 1658 cm^{-1}; ^1H NMR (270 MHz) δ 1.14 (3 H, d, J = 7.1 Hz), 1.51 and 1.91 (each 1 H, dq, J = 14.0, 7.0 Hz), 2.27 (2 H, qd, J = 7.0, 1.7 Hz), 2.39 (1 H, qtd, J = 7.1, 6.9, 1.6 Hz), 3.73 (3 H, s), 5.86 (1 H, dt, J = 15.7, 1.7 Hz), 6.94 (1 H, dt, J = 15.7, 7.0 Hz), 9.63 (1 H, d, J = 1.6 Hz).

To a solution of the above aldehyde (720 mg, 4.24 mmol) in dry MeCN (10 mL) was added Ph_3P=CH(Me)COO-*t*-Bu (3.0 g, 8.5 mmol), and the mixture was stirred under reflux for 2 h. The mixture was concentrated, and the residue was treated with Et_2O (5 mL) and hexane (15 mL). Insoluble solid material was removed by filtration, and the filtrate was concentrated. The residue was subjected to chromatography (silica gel, 50 g, 1:9 AcOEt/hexane) to afford **53** (1.08 g, 90%) as a colorless oil: R_f = 0.47 (1:4 AcOEt/hexane); $[\alpha]^{24}_D$ +36.2° (*c* 1.64).

(b) *n*-Pr_4NRuO_4 (328 mg, 0.933 mmol) was added to a stirred and cooled (0 °C) solution of **52** (3.21 g, 18.7 mmol) and *N*-methylmorpholine oxide (3.28 g, 28.0 mmol) in CH_2Cl_2 (180 mL) containing powdered 4-Å molecular sieves (9.5 g). After continued stirring at room temperature for 2 h, the mixture was filtered through a column of silica gel (70 g). The filtrate and CH_2Cl_2 washings were combined and concentrated. Reaction of the residual pale yellow oil (2.73 g) with Ph_3P=CH(Me)COO-*t*-Bu (20 g) in refluxing MeCN (50 mL) followed by the workup as described above afforded **53** (3.79 g, 72% from **52**): $[\alpha]^{26}_D$ +39.2° (*c* 1.68); IR (film) 1727, 1706, 1657 cm^{-1}; ^1H NMR (270 MHz) δ 1.01 (3 H, d, J = 6.8 Hz), 1.49 (9 H, s), 1.78 (3 H, d, J = 1.5 Hz), 2.08–2.24 (2 H, m), 2.41–2.57 (1 H, m), 3.73 (3 H, s), 5.81 (1 H, dt, J = 15.7, 1.6 Hz), 6.40 (1 H, dq, J = 10.0, 1.5 Hz), 6.94 (1 H, dt, J = 15.7, 7.0 Hz); ^{13}C NMR (67.8 MHz) δ 12.69 (q), 20.02 (q), 28.14 (q), 30.15 (t), 32.70 (d), 35.04 (t), 51.39 (q), 80.11 (s), 121.11 (d), 128.55 (s), 145.59 (d), 149.07 (d), 167.04 (s), 167.62 (s). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.80; H, 9.02.

(1*R*,2*R*,3*S*)-2-[(1*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-3-methylcyclohexane-1-carboxylic Acid, Methyl Ester (56). A 1.0 M THF solution of L-Selectride (4.0 mL) was stirred under Ar at −90 °C, and a cooled (−80 °C) solution of **53** (1.107 g, 3.93 mmol) in THF (2.1 mL) was added over 20 min using a double-ended needle (an additional 0.5 mL of the solvent was used for rinsing the transfer vessel). The solution was allowed to warm to −25 °C for 1 h and then kept at the same temperature for 5 h. The reaction mixture was quenched with MeOH (2 mL) at −20 °C before addition of AcOEt (6 mL). A pH 7 phosphate buffer (2.5 mL) and 30% H_2O_2 (3.5 mL) were added, and the mixture was stirred at room temperature for 5 h before partition between AcOEt (20 mL) and water (5 mL). The aqueous layer was extracted with AcOEt (15 mL × 3). The combined extracts were washed with brine (2 mL × 3), dried, and concentrated. The residual oil was chromatographed (silica gel, 50 g, 1:19 AcOEt/hexane) to give **56** (621 mg, 56%), R_f = 0.43 (1:6 AcOEt/hexane). Further elution with AcOEt afforded *tert*-butyl 9-hydroxy-2,4-dimethyl-2-nonenoate (ca. 10%) and intermolecular reaction products (unidentified). An analytical sample of **56** was obtained by distillation (Kugelrohr): bp 88–90 °C (0.01 Torr) (ot); $[\alpha]^{24}_D$ +22.4° (*c* 4.57); IR (film) 1732 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (3 H, d, J = 6.6 Hz), 1.04 (3 H, d, J = 7.2 Hz), 1.45 (9 H, s), 1.90 (1 H, dm, J = 12.6 Hz, H_{eq}-6), 2.08 (1 H, td, J = 11.3, 1.9 Hz, H-2), 2.25 (1 H, qd, J = 7.2, 1.9 Hz, H-1′), 2.33 (1 H, td, J = 11.3, 3.7 Hz, H-1), 3.67 (3 H, s); MS m/e 285 (M^+ + 1), 228, 55 (base peak). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.58; H, 10.19.

(1*R*,2*R*,3*S*)-2-[(1*S*)-1-(*tert*-Butoxycarbonyl)ethyl]-3-methylcyclohexane-1-methanol (57). To a stirred and ice-cooled solution of **56** (445 mg, 1.57 mmol) in dry THF (5.7 mL) was added a 3.5 M toluene solution of Red-Al (1.34 mL, 4.70 mmol). After continued stirring at 0 °C for 1 h and then at room temperature for 1 h, the pale yellow solution was treated with saturated NH_4Cl (2 mL) before extraction with AcOEt (10 mL × 3). The combined extracts were washed with brine (2 mL ×

3), dried, and concentrated to leave an oil (636 mg). It was purified by chromatography (silica gel, 50 g, 1:5 AcOEt/hexane) to give **57** (355 mg, 89%) as a colorless oil: bp 86–8 °C (0.02 Torr) (ot); R_f = 0.25 (1:3 AcOEt/hexane); $[\alpha]^{26}_D$ +22.1° (*c* 3.05); IR (film) 3429, 1722 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.84 (3 H, d, *J* = 6.4 Hz), 1.05 (3 H, d, *J* = 7.3 Hz), 1.45 (9 H, s), 2.71 (1 H, qd, *J* = 7.3, 1.5 Hz), 3.60 (1 H, dd, *J* = 11.2, 2.9 Hz), 3.71 (1 H, dd, *J* = 11.2, 4.4 Hz). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.25; H, 11.25.

(4*S*,4a*R*,5*S*,8a*R*)-4,5-Dimethyl-3-oxoperhydroisochroman (58). Trifluoroacetic acid (0.21 mL, 2.7 mmol) was added to an ice-cooled solution of **57** (70 mg, 0.27 mmol) in CH_2Cl_2 (2 mL), and then the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with AcOEt (20 mL), washed with saturated naHCO$_3$ (1 mL × 2), and dried. A yellow oil obtained by evaporation of the solvent was purified by chromatography (silica gel, 7 g, 1:4 AcOEt/hexane) to give **58** (37 mg, 74%) as an oil: bp 65–8 °C (0.02 Torr); R_f = 0.32 (1:3 AcOEt/hexane); $[\alpha]^{24}_D$ +9.61° (*c* 1.09); IR (film) 1734 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.81–1.11 (2 H, m, H-6 and H-7), 0.96 (3 H, d, *J* = 6.7 Hz, Me-5), 1.19–1.34 (1 H, m, H-8), 1.41 (1 H, td, *J* = 10.8, 7.4 Hz, H-4a), 1.42 (3 H, d, *J* = 7.4 Hz, Me-4), 1.52 (1 H, tqd, *J* = 10.8, 6.7, 3.3 Hz, h-5), 1.79 (1 H, dtdd, *J* = 11.0, 10.8, 5.6, 4.0 Hz, H-8a), 2.49 (1 H, quint, *J* = 7.4 Hz, H-4), 3.92 (1 H, t, *J* = 11.0 Hz, H-1), 4l16 (1 H, dd, *J* = 11.0, 4.0 Hz, H-1). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.37; H, 10.23.

(1*R*,2*R*,3*S*)-2-[(*R*)-1-Cyanoethyl]-1-(hydroxymethyl)-3-methylcyclohexane (59). To a solution of **49** (Scheme IX) (46 mg, 0.25 mmol) in dry xylene (4 mL) under Ar was added 4.0 mL (4 equiv) of a stock solution of Me_2AlNH_2 which was prepared by reacting liquid NH_3 (0.5 mL) with Me_3Al (1.0 M in hexane, 5 mL) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 1 h, and then the bulk of the low-boiling solvents was distilled off by slow heating to 95 °C. The remaining solution was heated at 95–100 °C for 24 h. The reaction mixture was quenched with water (2 mL) after cooling, and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL × 4). The combined organic layers were washed with brine, dried, and concentrated. Flash chromatography of the residue (silica gel, 10 g, 1:4 AcOEt/hexane) afforded starting material (ca. 10%) and **59** (34 mg, 74%) as an oil: R_f = 0.22 (1:2 AcOEt/hexane); $[\alpha]^{28}_D$ −1.63° (*c* 1.82); IR (film) 3446, 2236 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.98 (3 H, d, *J* = 5.9 Hz), 1.29 (3 H, d, *J* = 7.4 Hz), 1.44 (1 H, br s, OH), 3.14 (1 H, q, *J* = 7.4 Hz), 3.70 (1 H, dd, *J* = 11.7, 2.2 Hz), 3.91 (1 H, dd, *J* = 11.7, 3.5 Hz). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.79; H, 10.57; N, 8.10. The optical purity of this sample was found to be 95% ee by GC and ^{19}F NMR analysis of the corresponding Mosher's ester.

Aldol Condensation of 5 and 6 ((*E*)/(*Z*)-61). To a stirred and cooled (−100 °C) solution of **6** (796 mg, 2.3 mmol) in THF (25 mL) was added via a cannula a cooled (−100 °C) LDA solution which was prepared from *i*-Pr$_2$NH (0.90 mL, 2.8 mmol) and a 1.64 M hexane solution of BuLi (1.6 mL, 2.7 mmol) in THF (10 mL). After an additional stirring for 20 min at the same temperature, a cooled (−100 °C) solution of freshly prepared **5** (440 mg, 2.5 mmol) in THF (3 mL) was added via a cannula. Two portions of 2 mL of THF were used for rinsing the vessel. After the addition was completed, the reaction mixture was stirred for 35 min at −100 °C and then quenched with saturated NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with AcOEt (20 mL × 4). The combined organic layers were successively washed with water (20 mL) and brine (20 mL × 2), dried, and concentrated. Flash chromatography (silica gel, 58 g, 1:2 AcOEt/hexane) afforded **60** (1.23 g) consisting of two major diastereomers: R_f = 0.36 and 0.17 (1:2 AcOEt/hexane). A solution of this aldol product (22.3 mmol) and DMAP (270 mg, 2.3 mmol) in pyridine (20 mL) was ice-cooled and MsCl (0.92 mL, 12 mmol) was added. The mixture was stirred at room temperature for 2 d and then poured into ice–water (100 mL). The whole was extracted with AcOEt (30 mL × 5), and the combined extracts were successively washed with 10% HCl (20 mL × 5), water, saturated NaHCO$_3$, and brine. Evaporation of the solvent after drying afforded an oil, which was purified by chromatography (silica gel, 58 g, 1:2 AcOEt/hexane) to yield the *O*-mesylate (1.17 g), R_f = 0.25 (1:2 AcOEt/hexane). This material was dissolved in DBU (9 mL), and the solution was stirred at room temperature for 2 d before being poured into ice–water (100 mL) followed by extraction with AcOEt (30 mL × 2). The combined extracts were successively washed with 10% HCl (20 mL), water (20 mL), saturated NaHCO$_3$ (30 mL), and brine (30 mL × 2). The solvent was evaporated after drying, and the residue was subjected to chromatography (silica gel, 58 g, 1:3 AcOEt/hexane) to provide a 17:1 mixture of (*E*)-**61** and (*Z*)-**61** (1.05 g, 91% overall yield) as an oil: R_f = 0.28 (1:3 AcOEt/hexane).

A solution of the *E*/*Z* mixture (60 mg) in degassed acetone (24 mL) was placed in a test tube (17-mm i.d.) and irradiated under ice cooling with a low-pressure Hg lamp (an immersion type, 20 W) for 25 min. The same procedure was repeated twice, and the combined acetone solution was evaporated. The residue was subjected to flash chromatography (silica gel, 10 g, 1:3 AcOEt/hexane) to give an *E*/*Z* = 58:42 mixture (by ^{1}H NMR analysis). The diastereomers were separated by MPLC (1:6 AcOEt/benzene) to yield, in the order of elution, (*Z*)-**61** (45 mg, 25%) and (*E*)-**61** (95 mg, 52%), along with intermediate fractions (14 mg).

(*E*)-61: oil; R_f = 0.28 (1:3 AcOEt/hexane); IR (film) 1714 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.76 (3 H, d, *J* = 6.6 Hz, Me-16), 1.08 (3 H, d, *J* = 6.3 Hz, Me-8), 1.11 (3 H, d, *J* = 6.3 Hz, Me-27), 1.31 (3 H, d, *J* = 7.6 Hz, Me-6), 2.17 (1 H, dt, *J* = 13.9, 6.6 Hz, H-22), 2.35 (1 H, dt, *J* = 13.9, 6.6 Hz, H-22), 2.84–2.98 (2 H, m, H-6 and H-12), 3.33 (1 H, qd, *J* = 6.3, 4.7 Hz, H-27), 3.37 (3 H, s, OMe-27), 3.73 (3 H, s, COOMe), 3.81 (1 H, m, H-19), 3.88 (1 H, ddd, *J* = 7.6, 6.6, 4.7 Hz, H-26), 3.99 (1 H, m, H-23), 4.20 (1 H, d, *J* = 10.3 Hz, H-15), 5.62 (1 H, dt, *J* = 15.6, 6.6 Hz, H-21), 5.73 (1 H, dd, *J* = 15.6, 7.0 Hz, H-20), 6.66 (1 H, d, *J* = 10.8 Hz, H-13); ^{13}C NMR (100 MHz) δ 15.66, 17.41, 19.15, 21.63, 24.88, 27.02, 28.03, 31.17, 32.39, 32.57, 33.04, 35.18, 35.52, 35.74, 38.38, 41.92, 51.79, 51.99, 57.07, 78.91, 79.03, 80.08, 80.16, 81.87, 122.16, 128.11, 132.77, 134.00, 149.51, 167.77; MS *m*/*e* 501 (M$^+$), 442, 410, 129 (base peak).

(*Z*)-61: oil; R_f = 0.30 (1:6 AcOEt/benzene); $[\alpha]^{27}_D$ −14.3° (*c* 0.84); IR (film) 1716 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.77 (3 H, d, *J* = 6.6 Hz, Me-16), 1.06 (3 H, d, *J* = 6.6 Hz, Me-8), 1.12 (3 H, d, *J* = 6.1 Hz, Me-27), 1.33 (3 H, d, *J* = 7.5 Hz, Me-6), 2.14 (1 H, dt, *J* = 13.5, 6.7 Hz, H-22), 2.35 (1 H, dt, *J* = 13.5, 5.7 Hz, H-22), 2.78 (1 H, qd, *J* = 10.9, 3.2 Hz, H-12), 3.07 (1 H, q, *J* = 7.5 Hz, H-6), 3.33 (1 H, qd, *J* = 6.1, 4.7 Hz, H-27), 3.37 (3 H, s, OMe-27), 3.77–4.06 (3 H, m, H-15, H-19 and H-23), 3.79 (3 H, s, COOMe), 3.89 (1 H, ddd, *J* = 7.6, 6.7, 4.7 Hz, H-26), 5.55 (1 H, dd, *J* = 15.6, 4.7 Hz, H-20), 5.60 (1 H, ddd, *J* = 15.6, 6.7, 5.7 Hz, H-21), 5.87 (1 H, d, *J* = 10.9 Hz, H-13); ^{13}C NMR (100 MHz) δ 15.62, 17.54, 17.62, 21.54, 25.03, 27.08, 27.20, 31.34, 32.40, 32.84, 33.31, 34.94, 35.79, 35.86, 38.69, 41.95, 51.27, 51.58, 57.05, 78.29, 78.93, 78.97, 81.96, 83.83, 122.42, 126.79, 133.57, 134.50, 143.36, 167.88; MS *m*/*e* 501 (M$^+$), 442, 149, 129 (base peak). Anal. Calcd for $C_{30}H_{47}O_5N$: C, 71.82; H, 9.44; N, 2.79. Found: C, 71.68; H, 9.36; N, 2.72.

ABC-Ring Aldehyde 63. To a stirred and cooled (−85 °C) solution of (*Z*)-**61** (68 mg, 0.136 mol) in dry toluene (3 mL) was added a 0.93 M hexane solution of DIBALH (0.51 mL, 0.475 mol). After being stirred at −80 to −70 °C for 35 min, the reaction mixture was poured into ice and AcOH (0.14 mL). $CHCl_3$ (10 mL) was used to transfer the residual mixture. The two-phase mixture was vigorously stirred at room temperature after addition of 1 M HCl (0.33 mL). After 1 h, the layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 mL × 3). The combined organic layers were successively washed with saturated NaHCO$_3$ (5 mL) and brine (5 mL), dried, and concentrated. The residual oil (**62**, 50 mg) showed a single spot on TLC, R_f = 0.28 (1:2 AcOEt/hexane). This material was dissolved in CH_2Cl_2 (3 mL), and the solution was treated at room temperature with imidazole (46 mg, 0.68 mmol) and a 1:1 mixture of Et_3SiCl and Et_3N (0.09 mL). After 35 min, the mixture was diluted with AcOEt (20 mL), washed with water (5 mL × 2) and brine (5 mL), dried, and concentrated. Chromatography of the residue (silica gel, 10 g, 1:4 AcOEt/hexane) afforded **63** (44 mg, 55%) as an oil: R_f = 0.36 (1:4 AcOEt/hexane); $[\alpha]^{25}_D$ +23.1° (*c* 2.35); IR (film) 1718 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.60 (6 H, qd, *J* = 8.1, 1.0 Hz), 0.71 (3 H, d, *J* = 6.6 Hz), 0.92 (3 H, d, *J* = 6.1 Hz), 0.96 (9 H, t, *J* = 8.1 Hz), 1.08 (3 H, d, *J* = 7.1 Hz), 1.19 (3 H, d, *J* = 6.2 Hz), 3.29 (1 H, d, *J* = 10.3 Hz), 3.34 (1 H, qd, *J* = 6.2, 4.7 Hz), 3.37 (3 H, s), 3.74 (1 H, m), 3.89 (1 H, ddd, *J* = 7.6, 6.7, 4.7 Hz), 3.98 (1 H, m), 4.15 (2 H, s), 5.05 (1 H, d, *J* = 10.3 Hz), 5.48–5.64 (2 H, m), 9.68 (1 H, s); HRMS calcd for $C_{35}H_{62}O_5Si$ 590.4363, found

590.4376.

Tetronomycin Na Salt. To a stirred and cooled (-100 °C) solution of **4** (40 mg, 0.32 mmol) in THF (4 mL) was added via cannula a cooled (-100 °C) LDA solution prepared from *i*-Pr_2NH (49 μL, 0.34 mmol) and BuLi (1.48 M in hexane, 0.22 mL, 0.33 mmol) in THF (1.5 mL). After 8 min, dry DMPU (77 μL, 0.64 mmol) was introduced, and to the mixture was added a solution of **63** (63 mg, 0.107 mmol) in THF (1.5 mL) over a 2-min period. Additional 1- and 0.5-mL portions of THF were used to transfer all of the aldehyde **63**. After being stirred at -100 to -95 °C for 20 min, the reaction mixture was quenched with saturated NH_4Cl (3 mL) and then allowed to warm to room temperature before addition of AcOEt (10 mL). The layers were separated, and the aqueous layer was extracted with AcOEt (5 mL × 3). The combined organic extracts were washed with water (5 mL × 2) and brine (5 mL), dried, and concentrated. The residue was subjected to chromatography (silica gel, 11 g, 1:3 AcOEt/hexane) to give an aldol adduct (44 mg, 58%), R_f = 0.25 (1:4 AcOEt/hexane), along with recovered aldehyde **63** (5 mg). A solution of the carbinol product in CH_2Cl_2 (3 mL) was added to a stirred suspension of PCC (45 mg) and powdered 4-Å molecular sieves (150 mg) in CH_2Cl_2 (1 mL). After 20 min, Et_2O (10 mL) was added, and the whole was filtered through a Florisil column (1 g). Evaporation of the filtrate followed by chromatography of the residue (silica gel, 6 g, 1:4 AcOEt/hexane) gave **64** (18.1 mg, 26% from **63**) as an oil: R_f = 0.35 (1:4 AcOEt/hexane). Since this compound is unstable, it was used for the subsequent reaction immediately after ^1H NMR measurement: ^1H NMR (270 MHz) δ 0.58 (6 H, q, *J* = 8.0 Hz), 0.70 (3 H, d, *J* = 6.6 Hz), 0.95 (9 H, t, *J* = 8.0 Hz), 1.00 (3 H, d, *J* = 6.6 Hz), 1.11 (3 H, d, *J* = 6.3 Hz), 1.13 (3 H, d, *J* = 7.6 Hz), 3.05 (1 H, d, *J* = 9.8 Hz), 3.32 (1 H, qd, *J* = 6.3, 4.8 Hz), 3.36 (3 H, s), 3.57 (1 H, m), 3.66 (1 H, q, *J* = 7.6 Hz), 3.90 (3 H, s), 4.08 (2 H, s), 5.14 and 5.15 (each 1 H, d, *J* = 2.7 Hz), 5.43 (1 H, d, *J* = 10.3 Hz).

Treatment of **64** (18 mg, 0.025 mmol) in MeCN (3 mL) with 5% HF (0.15 mL) for 5 min followed by extractive workup with AcOEt (saturated $NaHCO_3$ washing) gave the desilylation product (12.7 mg): R_f = 0.15 (1:4 AcOEt/hexane). It was dissolved in dry DMSO (2 mL) containing LiCl (13 mg, 0.3 mmol), and the solution was stirred at room temperature for 3 d. The mixture was treated with saturated $NaHCO_3$ (5 mL) with stirring for 30 min before extraction with CH_2Cl_2 (5 mL × 4). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residual oil was subjected to chromatography (silica gel, 4 g, 2:3 AcOEt/hexane) to give tetronomycin Na salt (5.5 mg, 36% from **64**) as an oil: R_f = 0.32 (2:3 AcOEt/hexane); $[\alpha]^{25}_D$ +140° (*c* 0.648, MeOH). This material was crystallized from *i*-Pr_2O/Et_2O as fine needles: mp 187-189 °C. Natural tetronomycin Na salt recrystallized from the same solvent showed mp 187-189 °C (lit.[1] mp 107-110 °C): $[\alpha]^{28}_D$ +147° (*c* 0.696, MeOH) [lit.[1] $[\alpha]^{28}_D$ +122.5° (*c* 0.8, MeOH)]; IR (KBr) 3328, 1745, 1605, 1438, 966 cm^{-1}; ^1H NMR (270 MHz) δ 0.53 (3 H, d, *J* = 6.6 Hz, Me-16), 0.93 (3 H, d, *J* = 6.4 Hz, Me-27), 1.00 (3 H, d, *J* = 7.1 Hz, Me-6), 2.34 (1 H, m, H-22), 2.50 (1 H, qd, *J* = 10.6, 4.5 Hz, H-12), 3.26 (1 H, d, *J* = 9.8 Hz, H-15), 3.33 (1 H, qd, *J* = 6.4, 2.2 Hz, H-27), 3.38 (3 H, s, OMe), 3.76-3.98 (3 H, m, H-6, CH-14 and H-19), 4.10-4.21 (2 H, m, H-23 and H-26), 4.28 (1 H, d, *J* = 11.2 Hz, CH-14), 4.39 (1 H, br, OH), 4.74 (1 H, d, *J* = 1.5 Hz, CH-4), 5.15 (1 H, d, *J* = 10.6 Hz, H-13), 5.22 (1 H, d, *J* = 1.5 Hz, CH-4), 5.48 (1 H, dd, *J* = 15.2, 9.4 Hz, H-20), 6.15 (1 H, ddd, *J* = 15.2, 11.0, 4.1 Hz, H-21); MS *m/e* 608 (M^+), 470, 469, 442, 441 (base peak); HRMS calcd for $C_{34}H_{49}O_8Na$ 608.3324, found 608,3307.

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Supplementary Material Available: ^1H NMR spectra of all title compounds (57 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Structure and Reactivity of 1,2,3,3-Tetrakis(4-(dimethylamino)pyridinium-1-yl)cyclopropene

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The X-ray single crystal structure of 1,2,3,3-tetrakis(4-(dimethylamino)pyridinium-1-yl)cyclopropene, **1**, is presented together with some reactions of **1**. Both triphenylphosphine and 1-methylimidazole react with **1** to form the ring-opened products, (*Z*)-1-(triphenylphosphonio)-1,2,3,3-tetrakis(4-(dimethylamino)pyridinium-1-yl)allylide (**6**), and the isomeric (*E*)- and (*Z*)-1-(3-methylimidazolium-1-yl)-1,2,3,3-tetrakis(4-(dimethylamino)-pyridinium-1-yl)allylides (**7**), respectively. Cyclic voltammetry shows that **6** oxidizes to its corresponding allyl radical at 1.3 V vs SCE; the isomers of **7** oxidize at 0.48 and 0.61 V. The pK_a's of the conjugate acids of **6** and **7** are -1 and 3.0, respectively. Reaction of **1** with potassium nitrite gave an unexpected product, 1,1,2-tris(4-(dimethylamino)pyridinium-1-yl)ethylene. The reactivity of **1** was compared to some analogous systems, 2-phenyl-1,3,3-tris(4-(dimethylamino)pyridinium-1-yl)cyclopropene (**12**) and 2-phenyl-1,3,3-tris(3-methylimidazolium-1-yl)cyclopropene (**13**). The phenyl substituent significantly alters the reactivity of **12** and **13**, such that both compounds do not form ring-opened products when treated with strong nucleophiles.

In earlier papers,[1,2] we reported the reaction of tetrachlorocyclopropene with 4-(dimethylamino)pyridine (DMAP) to give 1,2,3,3-tetrakis(4-(dimethylamino)-pyridinium-1-yl)cyclopropene tetrachloride (**1**) and the further reaction with DMAP to give the highly stabilized allylic anion, 1,1,2,3,3-pentakis(4-(dimethylamino)-pyridinium-1-yl)allylide tetrachloride, **3** (Scheme I). In this paper we report the X-ray single-crystal structure of **1** and the preparation and properties of new compounds formed from **1** with other nucleophiles. The general reactivity of **1** was explored further by comparing it with similar highly charged cyclopropenyl systems.

Structure of 1. The structure of **1** (PF_6^- salt) has been determined by X-ray crystallography. An ORTEP diagram not including the four PF_6^- gegenions is shown in Figure

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