Total Synthesis of Tautomycin

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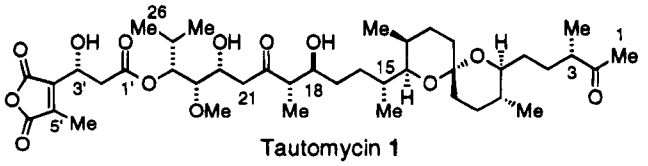
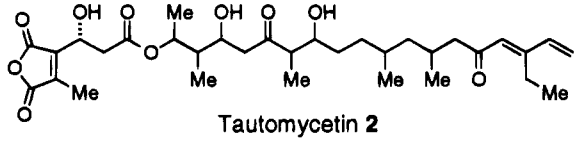
A convergent stereocontrolled synthesis of the antifungal antibiotic tautomycin, a potent protein phosphatases inhibitor, has been achieved first *via* key aldol coupling of two large subunits, a right-hand C_1–C_{21} ketone and a left-hand aldehyde (left from C_{22}). The C_1–C_{10} segment was synthesized through a remote stereochemical control process using a spiroketal template. After joining with the C_{11}–C_{18} segment, the spiroketal moiety was selectively constructed. Then the right-hand C_1–C_{21} ketone was synthesized *via* Roush asymmetric crotylboration. The left-hand aldehyde was prepared from a C_{21}–C_{26} segment and a dialkylmaleic anhydride segment. Completely stereoselective assemblage of the two subunits, the right-hand and the left-hand, was achieved by employing the Mukaiyama aldol reaction. Further functional group manipulations including desilylation, oxidation at C_2, and deprotection of *tert*-butyl ester with concomitant anhydride formation provided tautomycin which was identical with the natural product. As a preliminary study, derivatizations and degradation of the natural product were also examined to support the total synthesis.

Tautomycin (**1**) was isolated by Isono and co-workers in 1987 from a culture of *Streptomyces spiroverticillatus*, which had been collected from Chinese soil.[1] Tautomycin exhibits antifungal activity against *Sclerotinia sclerotiorum*, and also it induces a morphological change (bleb formation) in human leukemia cells K562. Furthermore, it was found afterwards that tautomycin inhibited protein–serine/threonine phosphatases (PP) type 1 and 2A specifically (IC_{50} = 22 and 32 nM, respectively), whereas this antibiotic inhibits PP2B only at high concentration (IC_{50} = >10 μM) and does not inhibit PP2C.[2] Thus tautomycin is expected to be a useful probe for elucidating intracellular events because reversible phosphorylation of proteins has been recognized to be a major mechanism for the intracellular transductions in eukaryotic cells.[3] Tautomycin is similar to okadaic acid, a well-known tumor promotor, in its PP inhibitory activity and molecular size and is thus considered a member of the okadaic acid class of tumor promotors along with other members such as calyculin A, microcystin-LR, and nodularin. Isono's research group also isolated tautomycetin (**2**) from *Streptomyces griseochromogenes* as a related compound,[4] but the absolute structure and the PP inhibitory activity of **2** are still unknown.



Tautomycin **1**



Tautomycetin **2**

Because of its noncrystalline nature, the absolute structure of tautomycin was determined on the basis of spectroscopic analysis of chemical degradation products and their derivatives.[5] For determination of the C_{15} chiral center, conformational calculation was also used. We have intended to establish the correctness of the published structure by a total synthesis, and the project was recently completed. Here, we describe a highly convergent first total synthesis of tautomycin.[6,7]

Tautomycin is biosynthetically constructed from two components, the dialkylmaleic anhydride and the polyketide carbon chain, which are united by ester linking. In aqueous methanol at pH 7.3, 60% of the dialkylmaleic anhydride opens affording dicarboxylic acid which may mimic the phosphate moiety of the phosphoprotein on the serine or threonine part.[1,5d] Besides cleavage of the ester linkage and dehydration (C_{21}–C_{22}) occurring at pH9 (aqueous Cs_2CO_3, methanol, room temperature), retro-aldol reaction (C_{18}–C_{19}) and epimerization (C_3) are

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(1) Cheng, X.-C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R.-P.; Ni, Z.-F.; Shen, Y.-C.; Ko, K.; Yamaguchi, I.; Isono, K. *J. Antibiot.* **1987**, *40*, 907–909.

(2) (a) Magae, J.; Osada, H.; Fujiki, H.; Saido, T. C.; Suzuki, K.; Nagai, K.; Yamazaki, M.; Isono, K. *Proc. Jpn. Acad. Ser. B* **1990**, *66*, 209–212. (b) MacKintosh, C.; Klumpp, S. *FEBS Lett.* **1990**, *277*, 137–140. (c) Hori, M.; Magae, J.; Han, Y.-G.; Hartshorne, D. J.; Karaki, H. *FEBS Lett.* **1991**, *285*, 145–148. (d) Magae, J.; Hino, A.; Isono, K.; Nagai, K. *J. Antibiot.* **1992**, *45*, 246–251. (f) Kurisaki, T.; Magae, J.; Isono, K.; Nagai, K.; Yamasaki, M. *J. Antibiot.* **1992**, *45*, 252–257.

(3) Cohen, P. *Annu. Rev. Biochem.* **1989**, *58*, 453–508.

(4) (a) Cheng, X.-C.; Kihara, T.; Ying, X.; Uramoto, M.; Osada, H.; Kusakabe, H.; Wang, B.-N.; Kobayashi, Y.; Ko, K.; Yamaguchi, I.; Shen, Y.-C.; Isono, K. *J. Antibiot.* **1989**, *40*, 141–144. (b) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 890–896.

(5) (a) Ubukata, M.; Cheng, X.-C.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1990**, 244–246. (b) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809–819. (c) Ubukata, M.; Cheng, X.-C.; Isono, K. *Symposium Papers of 33rd Symposium on the Chemistry of Natural Products*; Osaka, Japan, 1991; pp 643–650. (d) Ubukata, M.; Cheng, X.-C.; Isobe, M.; Isono, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 617–624.

(6) For preliminary accounts from this laboratory on this subject, see: (a) Oikawa, M.; Oikawa, H.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 4797–4800. (b) Oikawa, H.; Oikawa, M.; Ueno, T.; Ichihara, A. *Tetrahedron Lett.* **1994**, *35*, 4809–4812. (c) Oikawa, H.; Oikawa, M.; Ichihara, A.; Ubukata, M.; Isono, K. *Biosci. Biotech. Biochem.* **1994**, *58*, 1933–1935.

(7) For other efforts directed toward the synthesis of tautomycin, see: (a) Ichikawa, Y.; Isobe, M.; Ubukata, M.; Isono, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 1382–1383. (b) Ichikawa, Y.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 737–738. (c) Ichikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 907–908. (d) Naganawa, A.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1994**, *50*, 8969–8982. (e) Nakamura, S.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 4145–4148.

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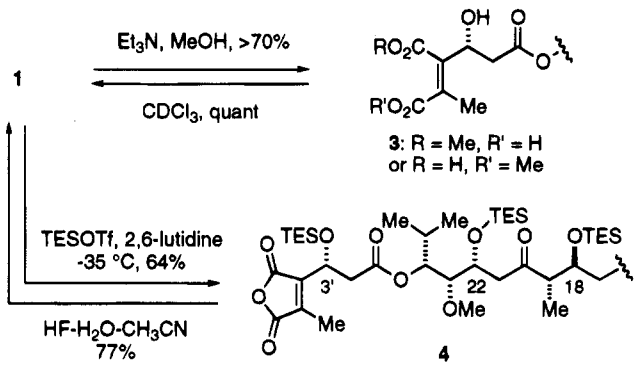
Scheme 1



simultaneously induced under slightly more basic conditions (aqueous Cs_2CO_3, methanol, pH 10).[5b,d] Thus, neutral or mild acidic reactions were preferred for the last stages of the total synthesis.

Derivatizations and Degradation of Tautomycin as Preliminary Studies

Protective group chemistry plays an important role in the synthesis of natural products. Appropriate protections of the anhydride, the hydroxyl groups ($C_{3'}$ and C_{18}), and the carbonyl group (C_2) are involved in the case of tautomycin and are a serious problem in achieving total synthesis with good success. We took a shortcut to obtain information on effective protecting groups for these functionalities, which were to be protected until the end of total synthesis, by examination of the natural product. Upon treatment with triethylamine in methanol, tautomycin was converted to half-ester **3** in a nonselective manner (Scheme 1). Half-ester **3** was unstable and easily released 1 mol of methanol to regenerate tautomycin in chloroform-*d* within 12 h.

Meanwhile, tris(triethylsilyl) (TES)-protected tautomycin **4**, which was prepared in 64% yield (TESOTf, 2,6-lutidine, −35 °C), was desilylated by the action of dilute HF in acetonitrile at 3 °C. When desilylation was attempted at 25 °C, decomposition was observed due to the lability of the anhydride moiety. It was also found that the $C_{3'}$ *tert*-butyldimethylsilyl (TBDMS) ether of tris-TBDMS-protected tautomycin resisted desilylation caused by dilute HF in acetonitrile or HF·pyridine in THF at 0 → 25 °C. Therefore, a silyl protecting group that is more sensitive toward acidic hydrolysis than TBDMS was preferred especially for the $C_{3'}$ hydroxyl group in the total synthesis.

Degradation of tautomycin was efficiently performed as illustrated in Scheme 2. Methanolysis at the ester linkage with a modification of a literature procedure[5b] afforded trimethyl ester **5** and anhydrodeacyltautomycin (**6**). To avoid epimerization at C_3, deoxygenation at C_2 had to be carried out before the retro-aldol reaction. Thus, the two hydroxyls of **6** were protected by TES groups followed by selective enol triflate formation (lithium bis(trimethylsilyl)amide, Tf_2NPh),[8] and a subsequent Stille reaction (*n*-Bu_3SnH, $Pd(PPh_3)_4$, LiCl)[9] yielded terminal olefin **9** without any epimerization at C_3. The TES groups were then removed by dilute HF in acetonitrile, and **10** was subjected to a thermal retro-aldol reaction.[10] For this substrate, the thermal condition (170 °C in a sealed tube) was superior to the basic treatment (aqueous Cs_2CO_3, methanol, pH 9−10) in which fragment **11** was not obtained. As discussed later, **12** is a key intermediate in our synthesis of tautomycin. Therefore, aldehyde **12** can be utilized not only for confirmation of the partial structure of tautomycin by comparison with our synthetic sample (*vide infra*) but also for the syntheses of various analogues of this antibiotic.

Synthetic Plan

Our retrosynthesis of tautomycin is shown in Scheme 3. Disconnection at the base sensitive $C_{21}-C_{22}$ bond divided the target into two large subunits, a right-hand C_1-C_{21} ketone and a left-hand aldehyde (left from C_{22}). The transform of this coupling is an aldol reaction controlled by chelation of the C_{23} methyl ether.

The plan for functional group protection is as follows. Considering its lability, the anhydride moiety was intended to construct at the latest stage in the synthesis. A nonsymmetrical diester containing *tert*-butyl ester was employed as a protecting group for this functionality, and the generation of the anhydride was anticipated *via* the half-ester (e.g., **3**) in one acid treatment step. For the two hydroxyls ($C_{3'}$ and C_{18}) which would be protected until near the end of the synthesis, a silicon group such as triethylsilyl was guaranteed, according to the results of the natural product examination, to be removed under mild acidity. Silicon, acyl, acetal, and benzyl groups were used for temporary protection of other hydroxyls *en route*. The C_1-C_2 vinyl group was adopted for the latent methyl ketone group, of which the C_2 carbonyl function tended to induce epimerization of C_3 under moderately basic conditions and was expected to be converted to methyl ketone by regioselective oxidation of the olefin.

Stereocontrolled syntheses of the right-hand ketone and the left-hand aldehyde and highly selective aldol coupling of these subunits to attain the total synthesis are described in the following discussions.

Synthesis of Right-Hand C_1-C_{21} Ketone

The right-hand ketone could be synthesized by enantioselective addition of a $C_{19}-C_{21}$ segment to a C_1-C_{18} segment in a reagent-controlled manner (Scheme 4). On our synthetic way to the right-hand ketone, the C_1-C_{18} absolute structure would be confirmed by comparison of natural C_1-C_{18} degradation products such as **12** with our synthetic samples. The C_1-C_{18} segment was further divided into two segments, C_1-C_{10} and $C_{11}-C_{18}$, using a transform of the sulfone carbanion method. Thermodynamically controlled C_6-C_{14} spiroketal formation was anticipated to proceed successfully affording only one isomer on the basis of a precedent example, Isobe's okadaic acid synthesis.[11]

Stereoselective Synthesis of C_1-C_{10} Segment Using the Strategy of Selective Reduction of Spiroketal. We have already reported the development of a remote stereochemical control process using a spiroketal template directed toward the synthesis of the C_1-C_{10}

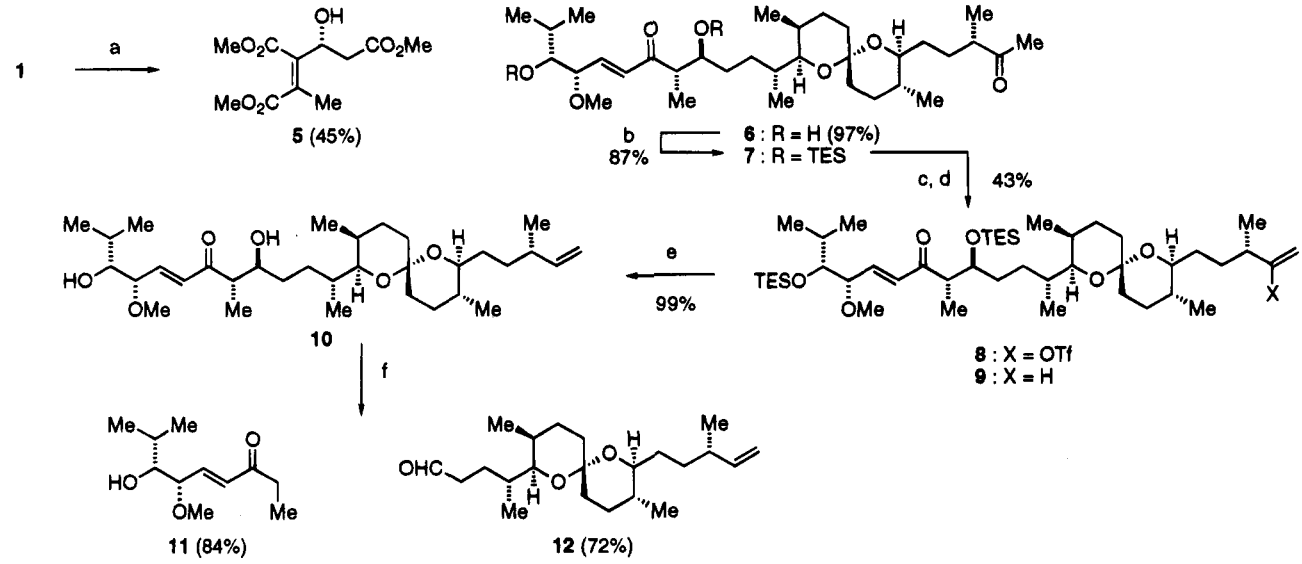
(8) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.

(9) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

(10) For an example of thermal retro-aldol reaction, see: Westley, J. W.; Evans, R. H., Jr.; Williams, T.; Stempel, A. *J. Org. Chem.* **1973**, *38*, 3431–3433.

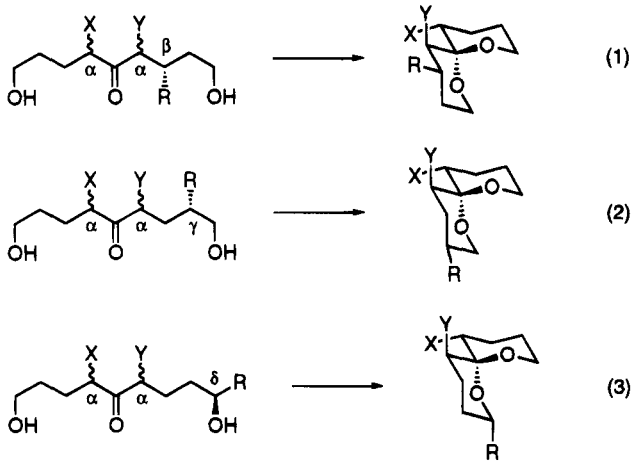
(11) Relative stereochemistries of tautomycin spiroketal including C_7, C_{10}, C_{13}, and C_{14} chiral centers are identical with the FG ring of okadaic acid. For okadaic acid synthesis, see: Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759–4766.

Scheme 2[a]



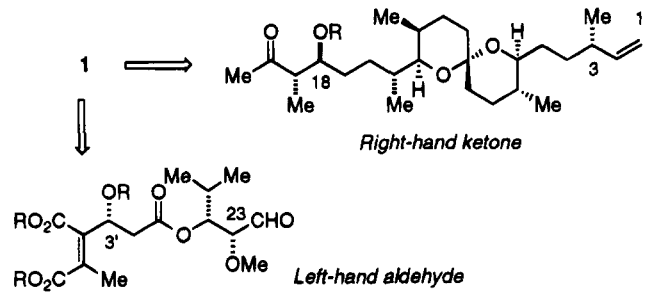
[a] Key: (a) 0.3 M K_2CO_3, methanol, 3 °C; CH_2N_2; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −45 → 3 °C; (c) LiHMDS, Tf_2NPh, THF, −78 → 0 °C; (d) *n*-Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF, reflux; (e) aqueous HF, CH_3CN–THF, 15 °C; (f) toluene, 170 °C in a sealed tube.

segment.[12] This process features two key points, the selective spiroketal formation (chiral transfer) and subsequent acetal reduction. Generally, the stereogenic centers of the acetal and the α position chiral centers can be controlled by other established β, γ, or δ asymmetric carbons through thermodynamic spiroketalization (eq 1, 2, or 3, respectively).[13] These stereochemistries could be

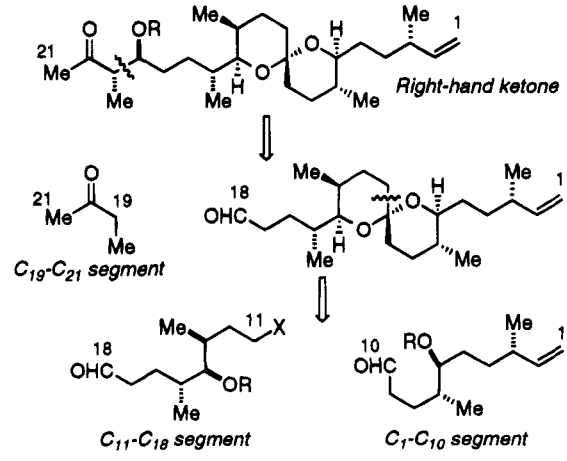


easily predicted by consideration of anomeric effect stabilization and the steric interactions of substituents.[14]

Scheme 3



Scheme 4



On the other hand, although there have been some reports concerning nucleophilic acetal cleavage induced by a silane–Lewis acid combination,[15] the reduction outcome of the spiroketal using this system could not be estimated beforehand.[16,17]

Nevertheless, in this study we observed opposite regioselectivities for the reduction cases (Et_3SiH, $SnCl_4$, CH_2Cl_2) of **13** and **15**, both of which have been prepared

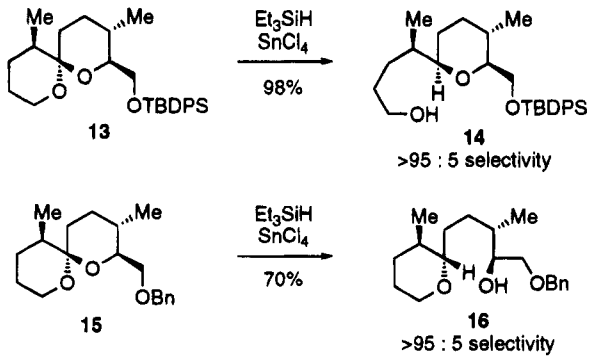
(12) Oikawa, H.; Oikawa, M.; Ichihara, A.; Kobayashi, K.; Uramoto, M. *Tetrahedron Lett.* **1993**, *34*, 5303–5306.

(13) For chirality control using the spiroketal template toward natural product synthesis, see: (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–6791. (b) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303–1312. (c) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312–1325. (d) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810–2814. (e) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2814–2818. (f) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818–2820. (g) Totah, N. I.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 6255–6256. (h) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5305. (i) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.

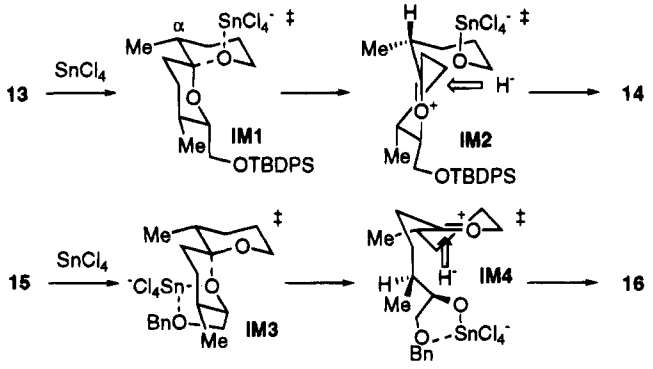
(14) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; Vol. 1, pp 4–53.

(15) (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107–6115. (b) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595–4612. (c) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089–8110.

Scheme 5



Scheme 6



stereoselectively (Scheme 5). On the basis of other experiments in this study, we considered that the selectivity of **13** → **14** could be attributed to the steric effect of the α-methyl substituent (Scheme 6). Namely, the acetal oxygen which occupies the *anti* position *vs* the α-methyl substituent would be activated by the Lewis acid (**IM1**), followed by oxocarbenium ion formation (**IM2**) and subsequent hydride attack from the completely axial side to afford **14** in >95:5 selectivity. On the other hand, by switching the TBDPS protective group to benzyl (Bn), spiroketal **15** was reduced producing **16** in high selectivity (>95:5) as well. Such a dramatic change in regioselectivity could be explained by chelation of the Lewis acid with the benzyl ether oxygen. In this case, the neighboring acetal oxygen of benzyl ether was activated by the Lewis acid in a bidentate manner, causing **IM3** to open, and an exclusive hydride attack on **IM4** from the axial side followed, yielding **16**. Both reactions proceeded regio- and stereoselectively, and both products seemed to be very suitable for the intermediate of the C_1-C_{10} segment. At a glance, **16** was attractive because of its three stereogenic centers identical to those of C_3, C_6, and C_7 of tautomycin. However, oxidative functionalization induced by RuO_4 at C_{10} (tautomycin numbering) rather than the benzyl position in **16** was estimated to be difficult, and furthermore the RuO_4 oxidation of the cyclic ether sometimes causes overoxidation, providing a ring-opened product.[18] So we attempted to synthesize the C_1-C_{10} segment *via* **14**, which had the requisite carbon chain and the correct stereochemistry except for the C_6 position.

As illustrated in Scheme 7, aldehyde **17**[19] was subjected to Brown's asymmetric crotylboration protocol ((−)-(*E*)-crotyldiisopinocampheylborane, and then aqueous NaOOH)[20] to afford adduct **18** in high diastereo- and enantioselectivity (100% de and 92% ee). Diastereomeric excess (de) was determined chromatographically and spectroscopically (^{1}H-NMR), and enantiomeric excess (ee) was also examined by the ^{1}H-NMR spectrum of the corresponding Mosher's α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA)[21] ester. After the free hydroxyl was protected as a methoxymethyl (MOM) ether, the vinyl group was converted to phenyl sulfone in a three-step sequence; hydroboration (9-BBN, 15 °C; H_2O_2, NaOH), substitution by a phenylthio group (PhSSPh, *n*-Bu_3P),[22] and oxidation to the sulfone (*m*-CPBA). Sulfone **22** was then lithiated by *n*-BuLi and coupled with 2-methyl-δ-valerolactone[23] to yield **23** as a four component mixture. Lewis acid-promoted MOM deprotection and spiroketalization were successfully achieved by bromotrimethylsilane (TMSBr)[24] in CH_2Cl_2 producing crystalline product **24**, whose structure was confirmed by X-ray diffraction,[25] as a single isomer. In this transacetalization, MOM deprotection and spiroketalization occurred at −30 °C, and thermodynamic spiroketal isomerization then followed between −30 and 3 °C. As we expected from steric interaction of the substituents and the anomeric effect stabilization, the structure of **24** was thermodynamically the most stable one among the other isomers. Desulfurization using Raney nickel (W-2) and subsequent acetal reduction induced by triethylsilane−$SnCl_4$, followed by acid treatment to deprotect the resulting triethylsilyl (TES) ether, provided **14** in 86% overall yield with high regio- and stereoselection. The C_{10} hydroxyl group was then protected as the acetate ester (Ac_2O, pyridine, 4-(dimethylamino)pyridine).

For the synthesis of the C_1-C_{10} segment, ring-opening of the tetrahydropyran moiety and successive inversion of C_6 stereochemistry were examined next. The C_1 siloxy group was converted to bromide **28** in three steps (tetra-*n*-butylammonium fluoride; MsCl, pyridine, DMAP; LiBr) and, following zinc metal treatment, proceeded smoothly, attaining ring-opening to give **29** in 77% overall yield. The stereochemistry of the C_6 hydroxyl was then inverted by the Mitsunobu reaction using *p*-nitrobenzoic acid (PNBzOH),[26] and selective deacetylation by sodium methoxide and Swern oxidation[27] of the C_{10} hydroxyl then provided the C_1-C_{10} segment **32**. Our remote stereo-

(16) Only a few examples using other reductants have been reported. Alane reduction of sapogenin spiroketal: (a) Pettit, G. R.; Bowyer, W. J. *J. Org. Chem.* **1960**, *25*, 84−86. (b) Pettit, G. R.; Albert, A. H.; Brown, P. *J. Am. Chem. Soc.* **1972**, *94*, 8095−8099. Intramolecular oxido reduction and $NaBH_3CN$ reduction of spiroketal: (c) Deslongchamps, P.; Rowan, D. D.; Pothier, N. *Can. J. Chem.* **1981**, *59*, 2787−2791.

(17) Recently, spiroketal opening by a silane−Lewis acid system was reported; see: Zhao, Y.-b.; Albizati, K. F. *Tetrahedron Lett.* **1993**, *34*, 575−578.

(18) Cere, V.; Mazzini, C.; Paolucci, C.; Pollicino, S.; Fava, A. *J. Org. Chem.* **1993**, *58*, 4567−4571.

(19) Aldehyde **17** was synthesized from *cis*-2-butene-1,4-diol through bis-silylation (TBDPSCl, imidazole) and ozone treatment (ozone, −80 °C; PPh_3) in 98% overall yield.

(20) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576.

(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(22) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *17*, 1409−1412.

(23) Synthesized from δ-valerolactone by alkylation in 70% yield (LDA, iodomethane, HMPA, THF, −70 °C).

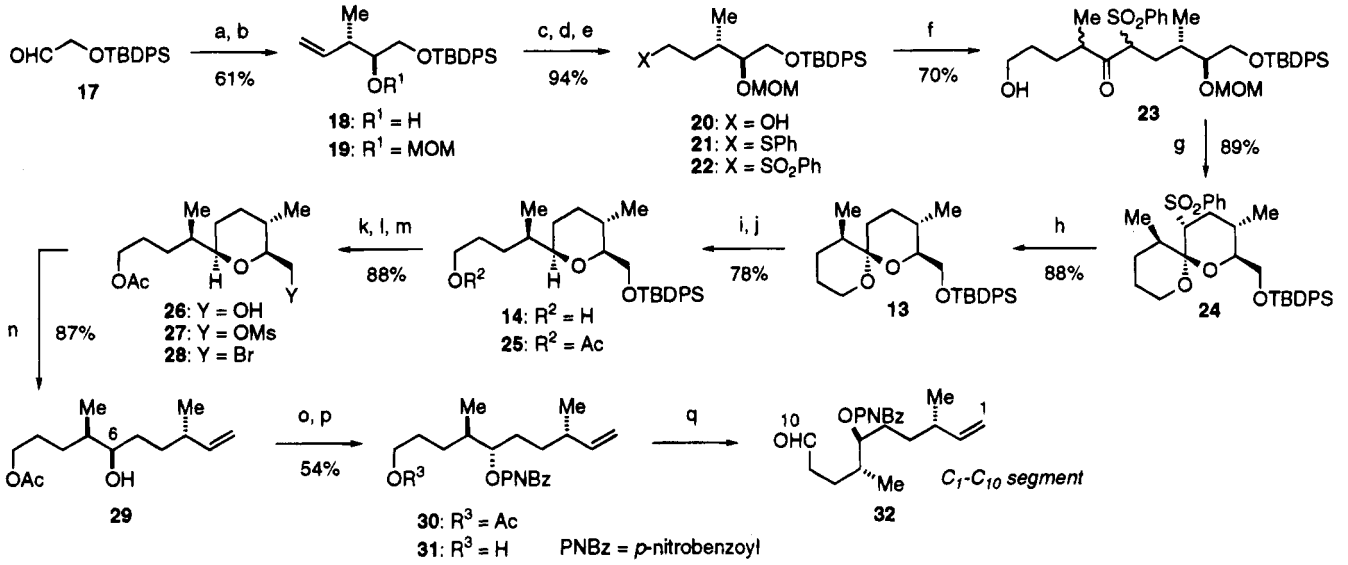
(24) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515−2518.

(25) The X-ray crystallographic data have been deposited to the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. They are also included in supplementary material.

(26) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656. (c) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234−236.

(27) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

Scheme 7[a]

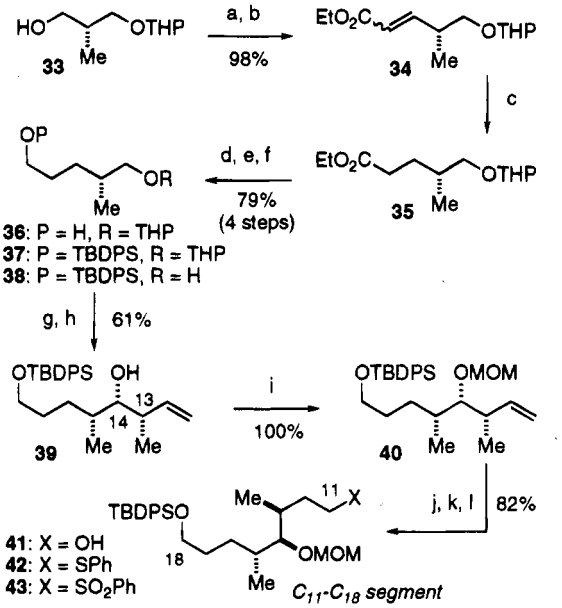


[a] Key: (a) (−)-(*E*)-crotyldiisopinocampheylborane, Et_2O–THF, −78 °C; 3N NaOH, H_2O_2, reflux; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C; (c) 9-BBN, THF, 15 °C; 3 N NaOH, H_2O_2, 4 → 25 °C; (d) PhSSPh, *n*-Bu_3P, pyridine, 25 °C; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 5 → 25 °C; (f) *n*-BuLi, 2-methyl-δ-valerolactone, Et_2O–hexane, −65 → 25 °C; (g) TMSBr, CH_2Cl_2, −30 → 3 °C; (h) Raney-Ni (W-2), ethanol, reflux; (i) Et_3SiH, $SnCl_4$, CH_2Cl_2, −78 → −60 °C; AcOH, THF–H_2O, 25 °C; (j) Ac_2O, pyridine, DMAP, CH_2Cl_2, 25 °C; (k) TBAF, THF, 25 °C; (l) MsCl, pyridine, DMAP, CH_2Cl_2, 25 °C; (m) LiBr, DMF, 70 °C; (n) Zn, EtOH–H_2O, reflux; (o) *p*-nitrobenzoic acid, PPh_3, DEAD, benzene, 25 °C; (p) NaH, methanol, 5 °C; (q) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 0 °C.

chemical control process using a spiroketal template, thus successfully demonstrated in the synthesis of C_1–C_{10} segment, would be well suited for short carbon chain synthesis in some special cases. This process is also a convenient means of providing **32** whose *exo*-olefin is synthetically equivalent to methyl ketone at C_1–C_2.

Synthesis of C_{11}–C_{18} Segment. We planned to synthesize the segment corresponding to C_{11}–C_{18} directly through incorporation of C_{13} and C_{14} stereogenic centers by *erythro*-selective crotyl addition to α-methyl-substituted C_{14}–C_{18} aldehyde. As shown in Scheme 8, the synthesis was begun using known alcohol **33**.[28] The aldehyde derived from **33** by Swern oxidation[27] was found to be easy to racemize, so it was immediately subjected to Horner–Wadsworth–Emmons reaction conditions, affording ene ester **34** as an isomeric mixture (*E*:*Z* = 85:15). Ene ester **34** was hydrogenated (H_2, Pd/C), reduced by lithium aluminum hydride, and submitted to subsequent protective group manipulations (*tert*-butylchlorodiphenylsilane, imidazole; *p*-TsOH, high dilution in methanol) to yield C_{14}–C_{18} alcohol **38** in 79% overall yield. After **38** was oxidized, elongation of the four carbon unit was attained by employing Yamamoto's crotylstannane addition (tri-*n*-butylcrotylstannane, BF_3·OEt_2).[29] This reaction gave the desired Cram *erythro* adduct **39** in 61% yield while 20% of the anti-Cram *erythro* adduct was produced as determined by HPLC analysis. The C_{14} hydroxyl was then protected by methoxymethyl (MOM) ether for the purpose of smooth spiroketal formation at C_6–C_{14} (*vide infra*) as in the case of **23** → **24**. A further routine sequence including hydroboration, phenylthio substitution, and oxidation afforded C_{11}–C_{18} phenyl sulfone **43** in 82% overall yield.

Scheme 8[a]



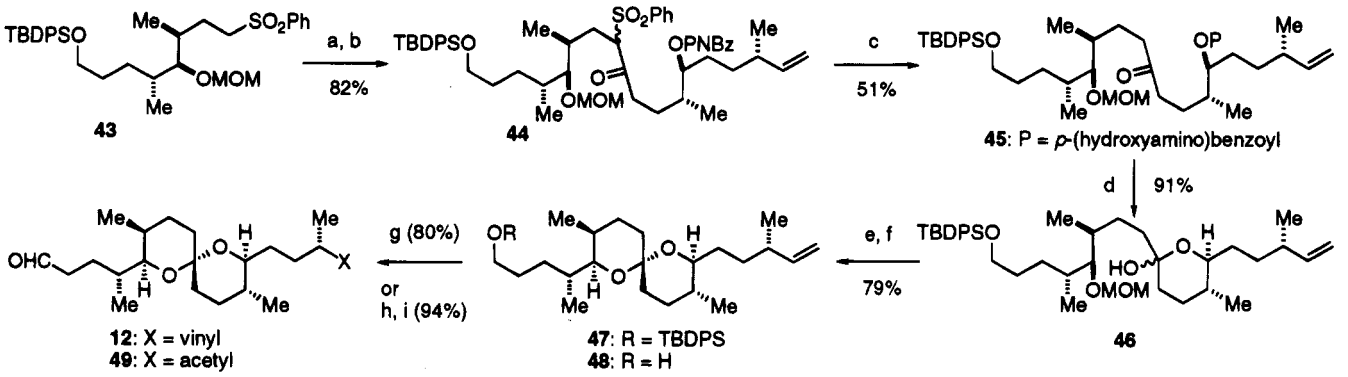
[a] Key: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −70 °C; Et_3N, −70 → 25 °C; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 → 25 °C; (c) H_2, Pd/C, EtOAc, 25 °C; (d) $LiAlH_4$, Et_2O, 3 → 25 °C; (e) TBDPSCl, imidazole, DMF, 25 °C; (f) TsOH, methanol, 25 °C; (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 25 °C; (h) tri-*n*-butylcrotylstannane, BF_3·OEt_2, CH_2Cl_2, −86 → 0 °C; (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C; (j) 9-BBN, THF, 3 → 25 °C; 3 N NaOH, H_2O_2, 3 → 25 °C; (k) PhSSPh, *n*-Bu_3P, pyridine, 25 °C; (l) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 3 → 25 °C.

Segment Coupling toward Right-Hand C_1–C_{21} Ketone. The lithium salt of **43** generated by *n*-butyllithium was coupled with **32**, and the resultant alcohol was successively oxidized (Swern oxidation)[27] to give two isomeric β-keto sulfone **44** in 82% overall yield (Scheme 9). Although desulfurization from **44** appeared to be troublesome due to the instability of the *p*-nitrobenzoyl (PNBz) group toward reductive materials such as Al(Hg)

(28) Mori, K. *Tetrahedron* **1983**, *39*, 3107–3109.

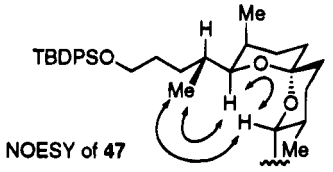
(29) (a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109. (b) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239–2246. For preparation of tri-*n*-butylcrotylstannane, see: (c) Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237–239.

Scheme 9[a]



[a] Key: (a) *n*-BuLi, **32**, Et_2O–hexane, −78 → 25 °C; (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 5 °C; (c) SmI_2, THF–methanol, −78 °C; (d) K_2CO_3, methanol, 60 °C; (e) TMSBr, CH_2Cl_2, −30 → 3 °C; (f) TBAF, THF, 25 °C; (g) Dess–Martin periodinane, CH_2Cl_2, 25 °C; (h) O_2, $PdCl_2$, CuCl, DMF–H_2O, 25 °C; (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 → 5 °C.

or *n*-Bu_3SnH, the phenylsulfonyl group was effectively removed by SmI_2[30] which also caused the reduction of the nitro functionality to a hydroxyamino group at −78 °C. Because the rate of desulfurization and reduction of the nitro group was close at −78 °C, at least 6 equiv of SmI_2 was required to complete the reaction (2 equiv for desulfurization and 4 equiv for reduction of the nitro group).[31] Additionally, it should be noted that the hydroxyamino moiety of **45** was unstable toward air and underwent self-condensation, generating the dimeric azoxy derivative, which occurred in thin layer chromatography of **45** or during the next deacylation as a reaction intermediate. The spiroketal moiety was then stereoselectively constructed by the deprotection sequence of acyl (K_2CO_3, methanol, 60 °C) and acetal groups (bromotrimethylsilane, CH_2Cl_2) in 72% overall yield. As we expected, the Lewis acid-promoted spiroketalization proceeded smoothly, constructing spiroketal **47** whose structure was unambiguously confirmed by NOESY experiment as depicted. These observed NOEs were identical with those of the natural degradation product as reported by Ubukata *et al.*[5d]



After desilylation using tetra-*n*-butylammonium fluoride, **48** was further converted independently to **12** by Dess–Martin oxidation[32] in 80% or to **49**[5b] by Wacker oxidation (O_2, $PdCl_2$, CuCl)[33] followed by Swern oxidation[27] in 94% yield. Both **12** and **49** were identical with the natural degradation products in chromatographic and spectroscopic properties. Thus, the absolute structure of the C_1–C_{18} fragment was synthetically confirmed as initially indicated.

The right-hand C_1–C_{21} ketone was then synthesized from aldehyde **12**, as illustrated in Scheme 10. The C_{18} and C_{19} chiral centers were successfully introduced by enantioselective crotyl addition protocol ((*S,S*)-diisopropyl tartrate (*E*)-crotyl boronate, molecular sieves 4 Å) developed by Roush,[34] affording (18*S*,19*R*)-adduct **50** in 86% yield with 11% of another (18*R*,19*S*)-adduct. The observed diastereoselectivity was close to the case of enantioselective addition to an achiral aldehyde such as *n*-decanal reported by Roush. When Brown's (+)-(*E*)-crotyldiisopinocampheylborane was used,[20] only **50** was produced but the yield was about 50%. Roush's crotyl boronate reagent could be stored as a toluene solution in a freezer, and no oxidative workup was needed after the addition was complete. Accordingly, in micromolar scale work for aldehyde **12**, crotylboronate addition seemed to be preferable for its yield[35] and ease of operation. Next, the homoallylic alcohol was epoxidized (*t*-BuOOH, $VO(acac)_2$), and the C_{18} hydroxyl was protected as the triethylsilyl ether (TESCl, Et_3N, DMAP) in 78% overall yield. Subsequent $LiEt_3BH$ reduction at 3 °C caused completely regioselective oxirane opening which could not be attained by either $LiAlH_4$ (TES deprotection) or *i*-Bu_2AlH (production of **53** and primary alcohol in ca. 1:1 ratio). This was followed by PDC (pyridinium dichromate) oxidation in the presence of molecular sieves 3 Å[36] to yield the right-hand segment **54** in 95% yield.

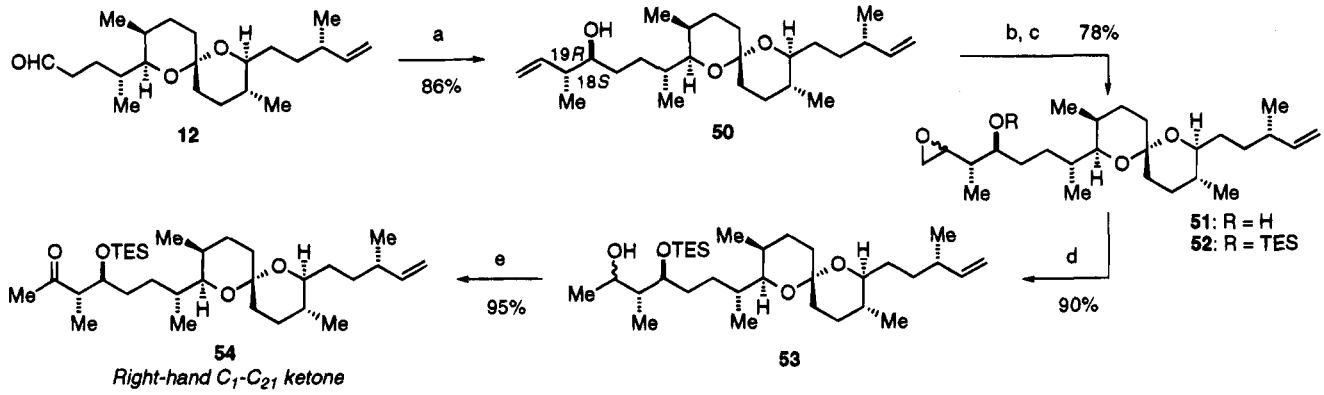
Synthesis of Left-Hand Aldehyde

The left-hand aldehyde is a polyoxygenated segment and has three stereogenic centers at the C_{23}, C_{24}, and $C_{3'}$ oxymethines. We planned that these stereogenic centers would be introduced by asymmetric oxidation of olefins. Our retrosynthesis of the left-hand aldehyde is shown in Scheme 11. By disconnection at the ester linkage, the C_{22}–C_{26} segment and dialkylmaleic anhydride (DMA) segment were produced retrosynthetically. Stereocontrolled syntheses of each segment and the synthesis of the left-hand aldehyde are described in the following sections.

Synthesis of the C_{22}–C_{26} Segment. Optically active epoxy alcohol **55**, which has been obtained by Sharpless

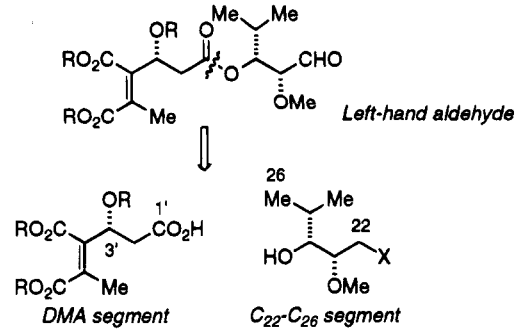
(30) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135–1138.
(31) Aliphatic nitro group suffers reduction by SmI_2 at room temperature; see: Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699–1702.
(32) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. For preparation of Dess–Martin periodinane, see: (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(33) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9–13.
(34) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348.
(35) A related example has been shown; see: Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405–3408.
(36) (a) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402. (b) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561–562.

Scheme 10[a]

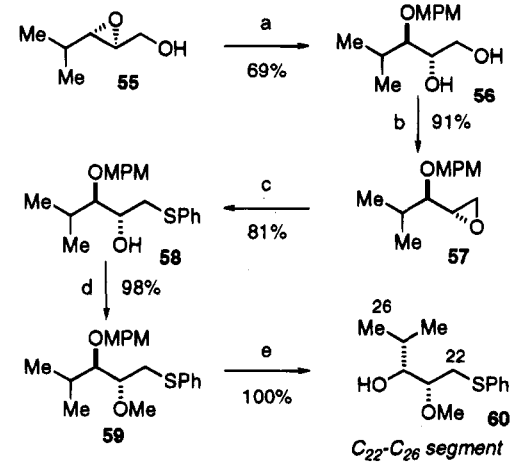


[a] Key: (a) (*S,S*)-diisopropyl tartrate (*E*)-crotylboronate, 4-Å molecular sieves, toluene, −78 °C; (b) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 3 → 25 °C; (c) TESCl, Et_3N, DMAP, CH_2Cl_2, 3 °C; (d) $LiEt_3BH$, THF, 3 °C; (e) PDC, 3-Å molecular sieves, CH_2Cl_2, 25 °C.

Scheme 11



Scheme 12[a]



[a] Key: (a) $Ti(OMPM)_4$, toluene, 85 °C; (b) TsCl, KH, THF, 50 °C; (c) PhSH, NaOMe, methanol, 50 °C; (d) MeI, NaH, THF−DMF, 3 → 25 °C; (e) DDQ, CH_2Cl_2−H_2O, 25 °C.

asymmetric epoxidation in 90% ee, was employed as the starting material.[37] Epoxy alcohol **55** was subjected to a titanium(IV)-mediated oxirane opening reaction ($Ti(OMPM)_4$, 85 °C)[38] to produce 1,2-diol **56** and a 1,3-diol derivative in a ratio of 9.5:1 (Scheme 12). Because chromatographic separation of these isomers proved to be difficult even if the primary alcohol was derivatized as trityl ether, pivaloyl ester, or TBDMS ether, the mixture was treated with *p*-toluenesulfonyl chloride (*p*-TsCl) in the presence of excess potassium hydride for selective oxirane formation to afford pure **57** in 91% yield. Regioselective opening of **57** was achieved by sodium thiophenoxide at 50 °C followed by methylation (MeI, NaH) of the resulting alcohol to yield **59** in 79% overall yield. Incorporation of phenyl sulfide at C_{22} was more effective than alkoxyl introduction with respect to functional group differentiation, and conversion of C_{22}-phenyl sulfide to the aldehyde *via* phenyl sulfoxide was smoothly achieved using the Pummerer reaction as will be discussed later. Subsequent oxidative deprotection induced by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2−H_2O[39] provided C_{22}−C_{26} segment **60**.

Synthesis of Dialkylmaleic Anhydride (DMA) Segment. Sharpless asymmetric dihydroxylation for $C_{3'}$ chiral center introduction and a diastereoselective Horner−Wadsworth−Emmons reaction for tetrasubstituted olefin construction were adopted as the key reactions. The synthesis began with mono(3,4-dimethoxy)benzyl (DMPM) ether **61**[40] (Scheme 13). Alcohol **61** was oxidized under Parikh−Doering conditions (DMSO, SO_3·pyridine)[41] and olefinated to afford *trans*-olefin **62** in 90% yield. Subsequent asymmetric dihydroxylation using AD-mix-β[42] in the presence of methanesulfonamide successfully developed by Sharpless functioned with high enantioselectivity to provide diol **63** in quantitative yield. The enantiomeric excess of **63** was measured as the bis-MTPA derivative by ^{1}H-NMR analysis to be 96.2% ee. Oxidative acetalization by DDQ in nonaqueous media (molecular sieves 4 Å, CH_2Cl_2)[39b,43] achieved effective protection of the $C_{1'}$ and $C_{3'}$ hydroxyl groups as 3,4-dimethoxybenzylidene acetal regio- and stereoselectively. The remaining free hydroxyl in **64** was then oxidized by Dess−Martin periodinane.[32] For the next homologation, we considered the report of Sutherland *et al.* They showed that the

(37) Epoxy alcohol **55** was prepared from isobutylaldehyde in a three-step sequence of Wittig olefination, reduction by *i*-Bu_2AlH, and Sharpless asymmetric epoxidation according to literature procedures; see: (a) Baker, R.; Head, J. C.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 85−97. (b) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34−36.

(38) Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1557−1560.

(39) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888. (b) Yonemitsu, O. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 691−702. (c) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021−3028.

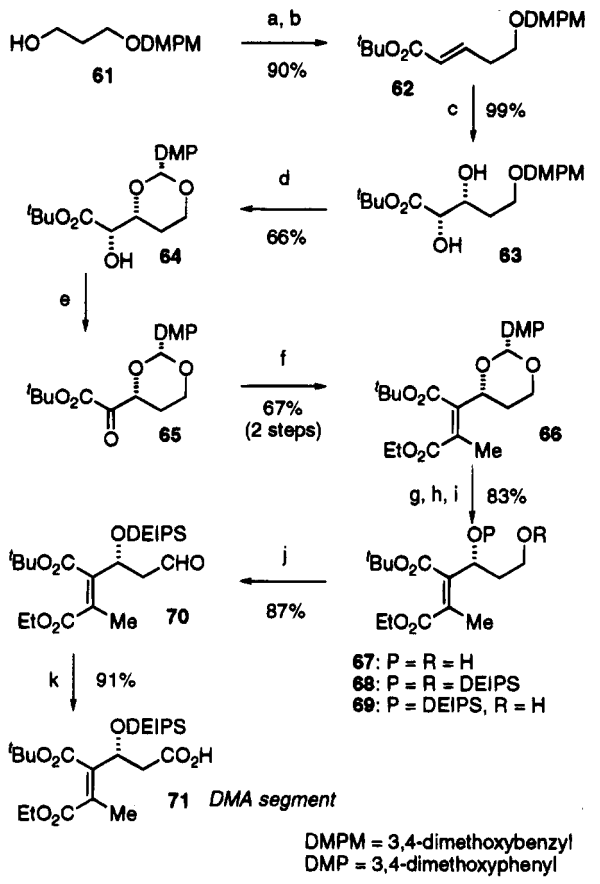
(40) Synthesized from 1,3-propanediol through acetalization (3,4-dimethoxybenzaldehyde dimethyl acetal, camphorsulfonic acid) followed by acetal reduction ($LiAlH_4$, $AlCl_3$) in 52% yield.

(41) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(42) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispinio, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

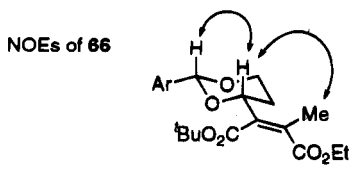
(43) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−892.

Scheme 13[a]



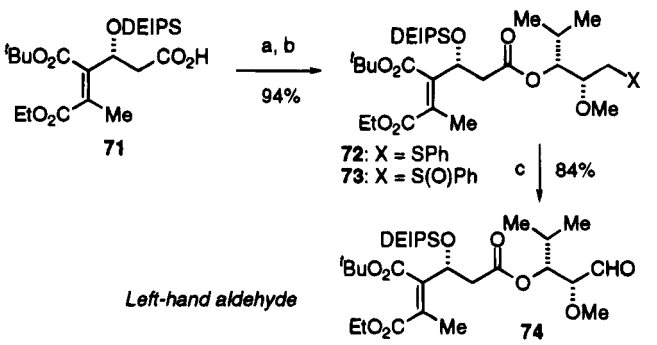
[a] Key: (a) DMSO, SO_3·pyridine, CH_2Cl_2, 0 °C; (b) $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, 25 °C; (c) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0 °C; (d) DDQ, pyridine, 4-Å molecular sieves, CH_2Cl_2, 5 °C; (e) Dess–Martin periodinane, pyridine, CH_2Cl_2, 25 °C; (f) $(EtO)_2P(O)CH(Me)CO_2Et$, KO-*t*-Bu, THF, −60 → −20 °C; (g) PPTS, methanol, 25 °C; (h) DEIPSCl, imidazole, CH_2Cl_2, 3 → 25 °C; (i) AcOH, THF–H_2O, 0 → 25 °C; (j) Dess–Martin periodinane, CH_2Cl_2, 25 °C; (k) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O, 25 °C.

Horner–Wadsworth–Emmons reaction between ethyl α-ketohexanoate and the triethyl phosphonopropionate carbanion effected the selective construction of the dialkylmaleate ester in greater than 95:5 selectivity.[44] On the basis of their findings, keto ester **65** was subjected to the Horner–Wadsworth–Emmons reaction (triethyl phosphonopropionate, KO-*t*-Bu, THF) producing the desired dialkyl maleate **66** in 67% yield accompanied by 28% of the dialkyl fumarate isomer from alcohol **64**. In this case, the use of 3,4-dimethoxybenzylidene acetal protection of the $C_{1'}$ and $C_{3'}$ hydroxyls held the key to maleate ester construction because the 4-methoxybenzylidene acetal was labile toward the olefination conditions and caused epimerization at $C_{3'}$. The structure of **66** was established by NOE experiment as depicted.



Next, the acetal protecting group was removed by the action of pyridinium *p*-toluenesulfonate (PPTS) in methanol with 98% yield. The diethylisopropylsilyl (DEIPS) group,[45] a slightly more acid-sensitive protecting group than TBDMS, was employed for final protection of the $C_{3'}$ hydroxyl, and thus the diol **67** was bis-silylated (chlorodiethylisopropylsilane, imidazole). Selective primary silyl ether deprotection (AcOH/H_2O/THF 4:1:4) yielded $C_{3'}$ diethylisopropylsilyl (DEIPS) ether **69**, which was successively converted to DMA segment **71** *via* aldehyde **70** (Dess–Martin periodinane followed by $NaClO_2$[46] oxidation) in 75% overall yield.

Scheme 14[a]



[a] Key: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, 25 °C; **60**, DMAP, 60 °C; (b) $NaIO_4$, methanol–H_2O, 35 °C; (c) TFAA, pyridine, CH_2Cl_2, 3 → 25 °C; $NaHCO_3$, methanol, 3 °C.

Segment Coupling toward Left-Hand Aldehyde. Esterification of the C_{22}–C_{26} segment and the DMA segment did not proceed *via* the acid chloride of **71** (oxalyl chloride, DMF, benzene; pyridine, DMAP, CH_2Cl_2) probably due to steric repulsion of both segments. Although dicyclohexylcarbodiimide-mediated esterification in the presence of DMAP proceeded to ca. 60% yield, the Yamaguchi method[47] produced **72** in 94% yield (Scheme 14). Phenyl sulfide **72** was oxidized to sulfoxide **73** by $NaIO_4$, and **73** was further subjected to the Pummerer reaction promoted by trifluoroacetic acid anhydride (TFAA) and pyridine in CH_2Cl_2.[48] The resultant α-(trifluoroacetoxy)sulfide was finally treated with sodium bicarbonate in methanol to furnish left-hand aldehyde **74** without any epimerization at the C_{23} position in 75% yield from sulfide **72**.

Aldol Coupling of Right-Hand Ketone and Left-Hand Aldehyde

Aldol coupling of the two large subunits, the right-hand and the left-hand, should be controlled by metal cation chelation (Cram-chelated model) to the methyl ether oxygen located at α (α-chelation) on the aldehyde functionality of **74**, providing an anti-Felkin aldol.[49,50] Because the left-hand aldehyde was a heavily oxygenated segment, we investigated effective aldol conditions to achieve high stereoselection (Table 1). When the lithium

(44) Huff, R. K.; Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc. C* **1968**, 2725–2726.

(45) (a) Toshima, K.; Mukaiyama, S.; Kinoshita, M.; Tatsuta, K. *Tetrahedron Lett.* **1989**, *30*, 6413–6416. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369–2381.

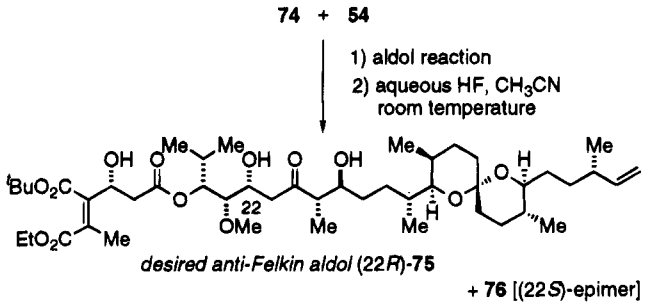
(46) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1776. For experimental procedures, see: (b) Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767–4776.

(47) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(48) (a) Lucchi, O. D.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157–405. (b) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807–4815.

(49) Anti-Felkin aldol refers to the diastereomer that does not arise through the Felkin–Anh model mechanistically, describing 22,23-*syn* aldol in this case. For the definition of Felkin and anti-Felkin aldol, see: Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.

Table 1. Aldol Coupling of Right-Hand Ketone and Left-Hand Aldehyde



aldol condns	% yield (22*R*)-**75**[a]	% yield **76**[a]
LiHMDS, THF, −78 °C, 30 min[b]	7.5	30
$TiCl_4$, *i*-Pr_2NEt, CH_2Cl, −78 → −50 °C	15	48
TMSOTf, Et_3N, CH_2Cl_2, 3 °C, then $TiCl_4$, CH_2Cl_2, −78 → −15 °C	54	0

[a] Based on isolated yields. [b] Yields calculated before silyl deprotection.

enolate from **54** (LiHMDS, THF, −78 °C, 30 min) was coupled with **74**, the undesired Felkin (22*S*)-*epi*-aldol was preferencially produced in 30% yield with 4:1 stereoselectivity. Heathcock *et al.* have reported that the addition of lithium enolates to an α-alkoxy aldehyde proceeded through the Felkin–Anh model, in that the alkoxy group was assumed to be a large group, and not through the Cram-chelated model.[51] Our observation obviously followed Heathcock's result whether or not it really was *via* the Felkin–Anh or the dipolar model.[52] Using Evans' chlorotitanium enolate method ($TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 → −50 °C),[53] the desired anti-Felkin adduct **75** was obtained in only 15% yield, although 48% of **76** was produced after silyl group deprotection.[54] In this methyl ketone case, the Felkin–Anh path seemed to have advantages over the usual Evans' hypothesis, which explained that aldol stereoselectivity was controlled by the stereochemistry at the α asymmetric carbon of the enolate. Although these two triols **75** and **76** could be easily separated by silica gel flash chromatography, we explored more efficient conditions by which the desired (22*R*)-aldol would be supplied in high stereoselection. After many trials,[55] we attained highly selective subunit coupling using Mukaiyama aldol reaction.[56] That is, right-hand ketone **54** was first converted to the enol silane (TMSOTf, Et_3N, CH_2Cl_2, 3 °C). The enol silane was then treated with left-hand aldehyde **74** in the presence of $TiCl_4$ providing the desired anti-Felkin adduct **75** in 54% yield after deprotection of the silyl groups, and none of the Felkin adduct **76** was detected. In order to achieve such a high stereoselection in the Mukaiyama reaction, chelation of the Lewis acid with the C_{23} methyl ether oxygen (α-chelation),[57] most likely not with the C_{24} acyl oxygen (β-chelation), would play a definitive role.[58]

In this way, we have achieved highly anti-Felkin selective coupling between the two key subunits, the right-hand ketone and the left-hand aldehyde, employing the Mukaiyama aldol reaction. By use of these two subunits, an unnatural (22*S*)-*epi* isomer can be also synthesized in 4:1 selectivity *via* lithium enolate mediated aldol coupling.

Completion of Total Synthesis

As illustrated in Scheme 15, palladium-assisted oxidation (O_2, $PdCl_2$, CuCl)[33] of the terminal olefin in **75** afforded methyl ketone **77** in 72% yield as a single product. Model studies of anhydride formation from nonsymmetrical diester containing *tert*-butyl ester on simple substrates showed that the reaction proceeded by both the protic (HF, CH_3CN, or TFA, CH_2Cl_2) and the Lewis-acidic (TMSOTf, 2,6-lutidine)[59] conditions, probably *via* the half ester analogous to **3**, in moderate yields (>50%). However, anhydride formation by a protic acid such as HF or TFA on **77** was unsuccessful probably due to the lability of the generated anhydride itself. Instead of the protic conditions, the reaction proceeded smoothly using Lewis acid conditions (17.4 equiv of TESOTf, 6.8 equiv of 2,6-lutidine, 3 → 25 °C) without any silylation of the three hydroxyl groups. For **77**, the use of more acidic and reactive TMSOTf failed, resulting only in decomposition which was then avoided by employing TESOTf. There was no epimerization at C_3 under these reaction conditions, and our synthetic material was indistinguishable from the natural product[5b] chromatographically (TLC, HPLC) and spectroscopically (IR, ^{1}H-NMR, HR-MS). The value of the optical rotation, $[\alpha]^{23}_D$ +3.3° (*c* 0.60, $CHCl_3$), was also identical with that of the natural product [$[\alpha]^{25}_D$ +3.4° (*c* 1, $CHCl_3$)]. Thus, our synthesis confirmed the relative and the absolute structure of tautomycin reported by Ubukata *et al.*[5d] Further, (22*S*)-*epi*-tautomycin was synthesized from **76** ((22*S*)-epimer), which had been derived from lithium enolate-mediated aldol coupling in 30% yield, using the same synthetic operations in 82% overall yield.

Conclusion

The first total synthesis of tautomycin, a specific protein phosphatase (PP) inhibitor, and its C_{22}-epimer have been achieved. Our synthesis specifically features

(50) For chelation-controlled aldol reaction *via* metal enolate, see: (a) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118–2120. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568–1571. (c) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526–5528.

(51) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846–3856.

(52) A similar observation has been reported; see: Martin, S. F.; Lee, W.-C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674–4688.

(53) (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049.

(54) For Lewis acid mediated aldol reaction, diastereoselectivity was determined on desilylated adducts because Lewis acid caused partial decomposition of triethylsilyl ether.

(55) Model studies on C_{18} protecting group (TES, benzyloxymethyl) using several metal countercations (lithium, titanium, boron, magnesium, and zinc) were unsuccessful, providing undesired Felkin aldol preferencially.

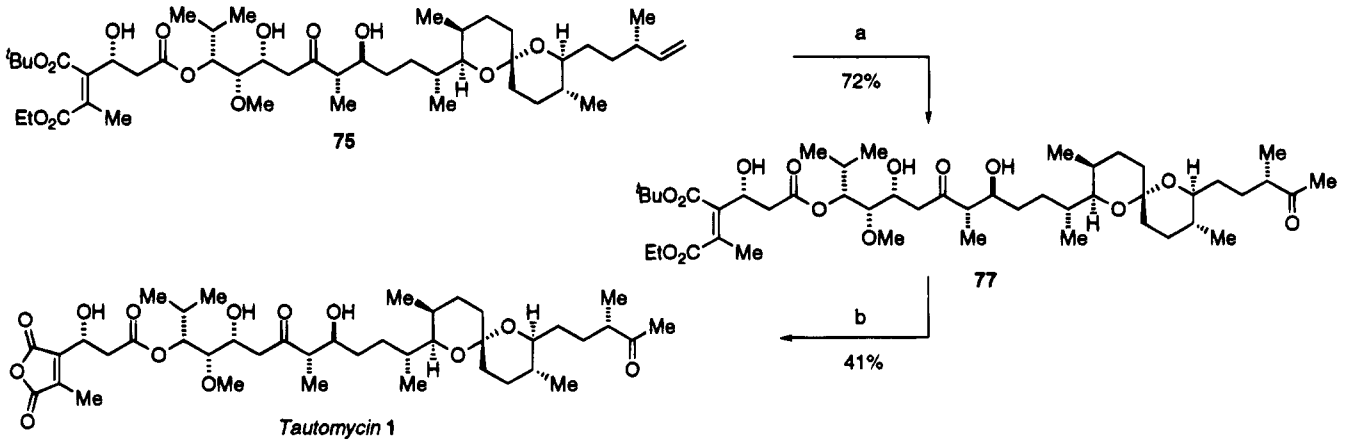
(56) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331.

(57) (a) Reetz, M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5434–5436. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569. (c) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: West Berlin, 1986. (d) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893–909.

(58) Mukaiyama aldol reaction exhibits also high Felkin stereocontrol, see: (a) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513. (c) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441–444. (d) Reference 35.

(59) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459.

Scheme 15[a]



[a] Key: (a) O_2, $PdCl_2$, CuCl, DMF–H_2O, 25 °C; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 3 → 25 °C.

stereoselective preparation of the C_1–C_{10} segment using a spiroketal template. An exceptionally stereoselective Mukaiyama aldol reaction was developed for the final subunit coupling, and opposite stereoselectivity was also obtained using an aldol reaction mediated by lithium enolate. Our synthetic pathway will provide valuable tautomycin analogues to elucidate the relationships between reversible phosphorylation and tumor promotion.

Experimental Section

General Methods. Unless otherwise noted, nonaqueous reactions were carried out under argon atmosphere. Diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were distilled from sodium metal/benzophenone ketyl. Benzene (PhH), CH_2Cl_2, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide, and triethylamine were distilled from calcium hydride and were stored under argon atmosphere. Hexane was distilled from *n*-butyllithium, and methanol was from magnesium methoxide. Powdered molecular sieves (3 and 4 Å) were activated at 140 °C for 10 h *in vacuo*. Dess–Martin periodinane,[32b] tri-*n*-butylcrotylstannane,[29c] anhydrous *tert*-BuOOH in CH_2Cl_2,[60] chlorodiethylisopropylsilane,[45b] and AD-mix-β[42] were all prepared according to literature procedures. All other commercially obtained reagents were used as received.

Methanolysis of Tautomycin and Regeneration of Tautomycin. To a solution of 8.8 mg (ca. 50%) of tautomycin[61] in 0.5 mL of methanol at −30 °C was added 20 μL of triethylamine. After the mixture was stirred at 0 °C for 1 h, 2 mL of 1 N hydrochloric acid was added and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Crude half ester **3** (8.0 mg) thus obtained regenerated tautomycin with releasing 1 mol of methanol in chloroform-*d* at ambient temperature in 12 h. Data for **3**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.24–5.04 (m, 2H), 4.40–4.25 (m, 1H), 3.79, 3.76 (singlets, 3H), 3.75–3.65 (m, 1H), 3.45 (s, 3H), 3.31–3.12 (m, 3H), 3.05–2.89 (m, 2H), 2.83–2.50 (m, 4H), 2.18 (s, 3H), 2.18–1.92 (m, 2H), 2.04, 2.03 (singlets, 3H), 1.84 (m, 1H), 1.75–1.20 (m, 17H), 1.13–0.80 (m, 21H); FAB-HR-MS (glycerine matrix) calcd for $C_{42}H_{71}O_{14}$ (M^+ + H) *m/z* 799.4844, found 799.4835.

18,22,3′-Tris-*O*-(triethylsilyl)tautomycin (4) and Its Conversion to Tautomycin. To a solution of 53 mg (ca. 50% purity, 35 μmol) of tautomycin in 1 mL of CH_2Cl_2 at −35 °C was added 48 μL (0.41 mmol) of 2,6-lutidine and 63 μL (0.28 mmol) of triethylsilyl trifluoromethanesulfonate. The mixture was stirred for 1 h and then quenched by the addition of 5 mL of 1 N hydrochloric acid. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (EtOAc/hexane/AcOH, 19:80:1) gave 25 mg (64%) of TES-protected tautomycin **4** as a colorless oil: $[\alpha]^{22}_D$ = +21.7° (*c* 2.50, $CHCl_3$); IR (thin film) 2940, 1840, 1765, 1735, 1720, 1095 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.17 (t, *J* = 6.3 Hz, 1H), 4.94 (dd, *J* = 7.3, 4.0 Hz, 1H), 4.45 (m, 1H), 3.97 (m, 1H), 3.36 (s, 3H), 3.28–3.14 (m, 3H), 2.83 (dd, *J* = 15.8, 6.8 Hz, 1H), 2.73–2.65 (m, 4H), 2.57 (m, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 2.15–1.95 (m, 2H), 1.87 (m, 1H), 1.70–1.20 (m, 17H), 1.10 (d, *J* = 7.3 Hz, 3H), 1.00–0.89 (m, 42H), 0.80 (d, *J* = 5.9 Hz, 3H), 0.65–0.52 (m, 18H); FAB-HR-MS (glycerine matrix) calcd for $C_{59}H_{109}O_{13}Si_3$ (M^+ + H) *m/z* 1109.7176, found 1109.7152.

To TES-protected tautomycin **4** (3.8 mg, 3.4 μmol) at 3 °C was added 0.4 mL of HF solution freshly prepared from 0.5 mL of 47% hydrofluoric acid, 8.6 mL of CH_3CN, and 0.9 mL of water. After being stirred for 1 h, the mixture was directly purified by preparative thin layer chromatography (methanol/$CHCl_3$/AcOH, 9:90:1) to give 2.0 mg (77%) of tautomycin as a white amorphous solid.

[2*S*,2(7*E*,1*R*,4*S*,5*S*,9*S*,10*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[4,10-Bis[(triethylsilyl)oxy]-9-methoxy-1,5,11-trimethyl-6-oxo-7-dodecenyl]-3,9-dimethyl-8-(3-methyl-4-oxopentyl)-1,7-dioxaspiro[5.5]undecane (Bis(triethylsilyl)-Protected Anhydrodeacyltautomycin) (7). To a solution of 16.6 g (ca. 60% purity, 13.0 mmol) of tautomycin in 230 mL of methanol at 3 °C was added 8.90 g (64.4 mmol) of K_2CO_3. After being stirred for 40 min, 170 mL of water was added, and methanol was removed at 30 °C *in vacuo*. The residual water layer was extracted with EtOAc (3 × 150 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (acetone/$CHCl_3$, 10:90 → 15:85) gave 7.12 g (97%) of anhydrodeacyltautomycin (**6**) as a colorless oil. The water layer was acidfied by the addition of 200 mL of 2 N hydrochloric acid and further extracted with EtOAc (3 × 100 mL). To the combined extracts were added diazomethane in Et_2O until the solution turned yellow, and the solution was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (acetone/$CHCl_3$, 10:90 → 15:85) to give 1.52 g (45%) of trimethyl ester **5** as a colorless oil. The chromatographic and spectroscopic properties of both trimethyl ester **5** and anhydrodeacyltautomycin (**6**) were identical with those reported by Isono *et al.*[5b]

To a solution of 382 mg (0.674 mmol) of anhydrodeacyltautomycin (**6**) in 8 mL of CH_2Cl_2 at −45 °C was added 0.471 mL (4.04 mmol) of 2,6-lutidine and 0.457 mL (2.02 mmol) of triethylsilyl trifluoromethanesulfonate. The temperature was gradually raised up to 3 °C over 1.5 h, and then the mixture

(60) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

(61) Crude tautomycin was purified to be 50–60% purity using literature procedure. See ref 5b.

was quenched by the addition of 15 mL of 1 N hydrochloric acid. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/PhH, 7:93) gave 468 mg (87%) of TES ether **7** as a colorless oil: $[\alpha]^{24}_D$ = +14.2° (*c* 2.46, $CHCl_3$); IR (thin film) 2900, 1710, 1675, 1625, 1095 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.32 (d, *J* = 15.8 Hz, 1H), 4.02 (m, 1H), 3.71 (dd, *J* = 6.6, 4.6 Hz, 1H), 3.52 (dd, *J* = 5.9, 4.6 Hz, 1H), 3.28 (s, 3H), 3.26 (br d, *J* = 9.6 Hz, 1H), 3.17 (br t, *J* = 9.0 Hz, 1H), 3.02 (m, 1H), 2.56 (m, 1H), 2.15 (s, 3H), 2.03 (m, 1H), 1.84 (m, 1H), 1.77−1.17 (m, 18H), 1.09 (d, *J* = 7.3 Hz, 3H), 1.04−0.88 (m, 33H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.67−0.53 (m, 12H); EI-HR-MS calcd for $C_{45}H_{86}O_7Si_2$ (M^+) *m*/*z* 794.5911, found 794.5919.

[2*S*,2(7*E*,1*R*,4*S*,5*S*,9*S*,10*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[4,10-Bis[(triethylsilyl)oxy]-9-methoxy-1,5,11-trimethyl-6-oxo-7-dodecenyl]-8-[4-[[(trifluoromethyl)sulfonyl]oxy]-3-methyl-4-pentenyl]-3,9-dimethyl-1,7-dioxaspiro[5.5]undecane (8). To a solution of 5.05 g (6.35 mmol) of **7** in 90 mL of THF at −78 °C was added 7.60 mL (7.60 mmol) of 1 M lithium bis(trimethylsilyl)amide in THF. After being stirred for 1 h, 3.40 g (9.52 mmol) of *N*-phenyltrifluoromethanesulfonimide in 11 mL of THF was added, and the solution was stirred for 30 min. The mixture was further stirred at 0 °C for 2 h, and then quenched by the addition of 1 mL of methanol and 50 mL of EtOAc. The solution was filtered through a plug of silica gel (75 g) and concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (Et_2O/hexane, 7:93 → 9:91) to give 2.52 g (43%) of enol triflate **8** as a colorless oil: $[\alpha]^{23}_D$ = +11.2° (*c* 0.50, $CHCl_3$); IR (thin film) 2920, 2870, 1665, 1625, 1200, 1080 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 15.8, 6.6 Hz, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 5.10 (d, *J* = 3.3 Hz, 1H), 4.93 (d, *J* = 3.3 Hz, 1H), 4.01 (m, 1H), 3.70 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.52 (dd, *J* = 5.9, 4.0 Hz, 1H), 3.27 (s, 3H), 3.27−3.16 (m, 2H), 3.02 (m, 1H), 2.46 (m, 1H), 2.02 (m, 1H), 1.84 (m, 1H), 1.80−1.20 (m, 18H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.03−0.88 (m, 33H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.65−0.52 (m, 12H); EI-HR-MS calcd for $C_{46}H_{85}O_9F_3Si_2S$ (M^+) *m*/*z* 926.5400, found 926.5367.

[2*S*,2(7*E*,1*R*,4*S*,5*S*,9*S*,10*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[4,10-Bis[(triethylsilyl)oxy]-9-methoxy-1,5,11-trimethyl-6-oxo-7-dodecenyl]-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (9). To a solution of 2.44 g (2.63 mmol) of **8** in 53 mL of THF was added 335 mg (7.90 mmol) of lithium chloride, 61 mg (53 μmol) of tetrakis(triphenylphosphine)palladium(0), and 0.848 mL (3.16 mmol) of tri-*n*-butyltin hydride. This was stirred at reflux for 3 h and then concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 8:92) gave 2.03 g (100%) of reduction product **9** as a colorless oil: $[\alpha]^{24}_D$ = +6.0° (*c* 0.86, $CHCl_3$); IR (thin film) 2920, 2870, 1670, 1630, 1100 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 15.8, 6.6 Hz, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 5.72 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 4.96 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.91 (d, *J* = 9.9 Hz, 1H), 4.03 (m, 1H), 3.71 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.52 (dd, *J* = 5.9, 4.0 Hz, 1H), 3.29 (d, *J* = 8.6 Hz, 1H), 3.27 (s, 3H), 3.16 (m, 1H), 3.03 (m, 1H), 2.19−1.98 (m, 2H), 1.84 (m, 1H), 1.76−1.20 (m, 18H), 1.03−0.88 (m, 36H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.65−0.53 (m, 12H); EI-HR-MS calcd for $C_{45}H_{85}O_6Si_2$ (M^+) *m*/*z* 778.5962, found 778.5984.

[2*S*,2(7*E*,1*R*,4*S*,5*S*,9*S*,10*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-(4,10-Dihydroxy-9-methoxy-1,5,11-trimethyl-6-oxo-7-dodecenyl)-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (10). To a solution of 2.03 g (2.60 mmol) of **9** in 4 mL of THF at 15 °C was added 20 mL of HF solution freshly prepared from 0.5 mL of 47% hydrofluoric acid, 8.6 mL of CH_3CN, and 0.9 mL of water. The mixture was stirred for 2 h, and then 20 mL of 1 N hydrochloric acid was added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 10 mL of saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 25:75) gave 1.43 g (99%) of diol **10** as a colorless oil: $[\alpha]^{24}_D$ = −24.7° (*c* 1.10, $CHCl_3$); IR (thin film) 3400 (br), 2920, 1660, 1620, 1095 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 15.8, 6.6 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 5.72 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 9.9 Hz, 1H), 3.83 (m, 1H), 3.70 (m, 1H), 3.49 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.34 (s, 3H), 3.29 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.15 (br t, *J* = 8.6 Hz, 1H), 2.94 (m, 1H), 2.20−1.96 (m, 2H), 1.85 (m, 1H), 1.75−1.20 (m, 18H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{33}H_{57}O_5$ (M^+ − OH) *m*/*z* 533.4203, found 533.4196.

(4*E*,6*S*,7*R*)-7-Hydroxy-6-methoxy-8-methyl-4-nonen-3-one (11) and [γ*R*,2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]-γ,3,9-Trimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane-2-butanal (12). A solution of 147 mg (0.267 mmol) of **10** in 13 mL of toluene was heated at 170 °C for 3 h in a sealed tube. The reaction mixture was directly purified by silica gel flash chromatography (EtOAc/PhH, 5:95 → 20:80) to give, in order, 67 mg (72%) of C_1−C_{18} ene aldehyde **12** and 45 mg (84%) of C_{19}−C_{26} ethyl ketone **11** as colorless oils. Data for **11**:[62] $[\alpha]^{26}_D$ = +25.3° (*c* 1.40, $CHCl_3$); IR (thin film) 3450 (br), 2930, 1695, 1645 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.28 (d, *J* = 15.8 Hz, 1H), 3.80 (dd, *J* = 7.3, 3.3 Hz, 1H), 3.49 (m, 1H), 3.33 (s, 3H), 2.64 (q, *J* = 7.3 Hz, 2H), 2.22 (br s, 1H), 1.66 (m, 1H), 1.12 (t, *J* = 7.3 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); TLC R_f = 0.23 (MeOH/$CHCl_3$ = 1:50); EI-HR-MS calcd for $C_{11}H_{18}O_2$ (M^+ − H_2O) *m*/*z* 182.1307, found 182.1339.

Data for **12**: $[\alpha]^{25}_D$ = −58.3° (*c* 3.00, $CHCl_3$); IR (thin film) 2930, 1730, 1640, 1095 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.80 (t, *J* = 1.6 Hz, 1H), 5.72 (ddd, *J* = 17.2, 10.6, 7.3 Hz, 1H), 4.96 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.92 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.25 (dd, *J* = 9.9, 2.0 Hz, 1H), 3.14 (dt, *J* = 2.0, 8.6 Hz, 1H), 2.57−2.35 (m, 2H), 2.17−1.97 (m, 2H), 1.90−1.73 (m, 2H), 1.70−1.20 (m, 14H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{22}H_{39}O_3$ (M^+ + H) *m*/*z* 351.2900, found 351.2893.

(2*S*,3*S*)-3-Methyl-1-[[(1,1-dimethylethyl)diphenylsilyl]-oxy]-4-penten-2-ol (18). To a solution of 7.39 g (65.9 mmol) of potassium *tert*-butoxide and 7.56 mL (84.0 mmol) of *trans*-2-butene in 66 mL of THF at −78 °C was added 41.1 mL (65.8 mmol) of 1.6 M *n*-butyllithium in hexane. This was stirred at −45 °C for 15 min, cooled to −78 °C, and then 25.0 g (79.0 mmol) of (−)-*B*-methoxydiisopinocampheylborane in 80 mL of Et_2O, 10.7 mL (87.0 mmol) of boron trifluoride etherate, and 16.1 g (53.8 mmol) of **17** in 35 mL of THF were added successively. After being stirred for 20 h, 70 mL of 3 N aqueous NaOH and 22 mL of 30% aqueous H_2O_2 were added, and the mixture was refluxed for 1 h. Three hundred milliliters of water was then added. The aqueous layer was separated and extracted with Et_2O (2 × 300 mL). The combined organic extracts were washed with 150 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 5:95) gave 12.6 g (66%) of crotyl adduct **18** as a colorless oil: $[\alpha]^{23}_D$ = −3.3° (*c* 1.75, $CHCl_3$); IR (thin film) 3460 (br), 3075, 2950, 2880, 1115 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.45−7.36 (m, 6H), 5.82 (ddd, *J* = 17.8, 9.9, 7.9 Hz, 1H), 5.03 (d, *J* = 9.9 Hz, 1H), 5.03 (d, *J* = 17.8 Hz, 1H), 3.73−3.52 (m, 3H), 2.33 (m, 1H), 1.06 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H). Anal. Calcd for $C_{22}H_{30}O_2Si$: C, 74.53; H, 8.53. Found: C, 74.09; H, 8.48.

(2*S*,3*S*)-[[2-(Methoxymethoxy)-3-methyl-4-pentenyl]-oxy](1,1-dimethylethyl)diphenylsilane (19). To a solution of 13.4 g (37.9 mmol) of **18** in 126 mL of CH_2Cl_2 was added 19.8 mL (0.114 mol) of *N*,*N*-diisopropylethylamine and 5.76 mL (75.8 mmol) of chloromethyl methyl ether. After being stirred at ambient temperature for 1 day, 120 mL of 10% aqueous citric acid was added to the mixture. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica

(62) Only the data of **11** was erroneously reported in ref 5b. See refs 6c and 7c.

gel flash chromatography (Et_2O/hexane, 5:95) gave 13.9 g (92%) of MOM ether **19** as a colorless oil: $[\alpha]^{24}_D = -17.8°$ (*c* 2.90, $CHCl_3$); IR (thin film) 3070, 2935, 2880, 1115 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.46–7.31 (m, 6H), 5.77 (ddd, J = 17.5, 9.9, 7.3 Hz, 1H), 5.01 (dd, J = 17.5, 2 Hz, 1H), 4.99 (dd, J = 9.9, 2 Hz, 1H), 4.76 (d, J = 6.6 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 3.72–3.55 (m, 3H), 3.34 (s, 3H), 2.55 (m, 1H), 1.05 (d, J = 7.3 Hz, 3H), 1.04 (s, 9H). Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.39; H, 8.57.

(3*S*,4*S*)-4-(Methoxymethoxy)-3-methyl-5-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-pentanol (20). To a solution of 13.9 g (34.8 mmol) of **19** in 35 mL of THF at 15 °C was added 8.50 g (34.8 mmol) of 9-borabicyclo[3.3.1]nonane dimer in 140 mL of THF over 1 h. The mixture was stirred for 3 h, and then 35 mL of 3 N aqueous NaOH and 35 mL of 30% aqueous H_2O_2 were added. After being stirred at ambient temperature for 18 h, 50 mL of water was added. The aqueous layer was separated and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90 → 20:80) gave 14.5 g (100%) of alcohol **20** as a colorless oil: $[\alpha]^{24}_D = -22.5°$ (*c* 2.00, $CHCl_3$); IR (thin film) 3400 (br), 3050, 2940, 2870, 1105 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.68–7.35 (m, 4H), 7.45–7.36 (m, 6H), 4.78 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 3.78–3.52 (m, 5H), 3.35 (s, 3H), 1.97 (m, 1H), 1.87 (br s, 1H), 1.65 (m, 1H), 1.47 (m, 1H), 1.05 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 68.98; H, 8.90.

(2*S*,3*S*)-[[2-(Methoxymethoxy)-3-methyl-5-(phenylthio)-1-pentyl]oxy](1,1-dimethylethyl)diphenylsilane (21). Alcohol **20** (14.5 g, 34.8 mmol), 11.4 g (52.2 mmol) of diphenyl disulfide, 28.0 mL (0.346 mol) of pyridine, and 13.0 mL (52.2 mmol) of tri-*n*-butylphosphine were mixed and stirred at ambient temperature for 2.5 h. The mixture was concentrated *in vacuo* and purified by silica gel flash chromatography (Et_2O/hexane, 5:95 → 10:90) to give 16.6 g (94%) of sulfide **21** as a colorless oil: $[\alpha]^{24}_D = -20.9°$ (*c* 1.06, $CHCl_3$); IR (thin film) 3050, 2925, 2860, 1110 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H), 7.45–7.11 (m, 11H), 4.73 (d, J = 6.6 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 3.72–3.61 (m, 2H), 3.49 (dt, J = 5.9, 4.6 Hz, 1H), 3.31 (s, 3H), 3.00 (ddd, J = 12.5, 5.3, 4.6 Hz, 1H), 2.83 (ddd, J = 12.5, 9.9, 6.6 Hz, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.47 (m, 1H), 1.04 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{30}H_{40}O_3SiS$: C, 70.82; H, 7.92; S, 6.30. Found: C, 70.62; H, 7.89; S, 6.43.

(2*S*,3*S*)-[[2-(Methoxymethoxy)-3-methyl-5-(phenylsulfonyl)-1-pentyl]oxy](1,1-dimethylethyl)diphenylsilane (22). To a solution of 10.6 g (20.8 mmol) of **21** in 208 mL of CH_2Cl_2 at 5 °C was added 7.34 g (83.4 mmol) of $NaHCO_3$ and 9.42 g (43.7 mmol) of 80% *m*-chloroperoxybenzoic acid. After the mixture was stirred at ambient temperature for 1 h, 220 mL of 10% aqueous $Na_2S_2O_3$ was added and the resulting mixture stirred for 20 min. The aqueous layer was separated and extracted with $CHCl_3$ (2 × 100 mL). The combined organic extracts were washed with 400 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90) gave 11.2 g (100%) of sulfone **22** as a colorless oil: $[\alpha]^{25}_D = -21.1°$ (*c* 2.13, $CHCl_3$); IR (thin film) 3075, 2955, 2900, 1120 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H), 7.66–7.34 (m, 13H), 4.65 (d, J = 7.3 Hz, 1H), 4.50 (d, J = 7.3 Hz, 1H), 3.67–3.57 (m, 2H), 3.38 (q, J = 5.3 Hz, 1H), 3.26 (s, 3H), 3.23–3.00 (m, 2H), 1.97–1.81 (m, 2H), 1.61 (m, 1H), 1.02 (s, 9H), 0.87 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{30}H_{40}O_5SiS$: C, 66.63; H, 7.46; S, 5.93. Found: C, 66.21; H, 7.49; S, 5.87.

(8*S*,9*S*)-1-Hydroxy-9-(methoxymethoxy)-4,8-dimethyl-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6-(phenylsulfonyl)-5-decanone (23). To a solution of 2.85 g (5.27 mmol) of **22** in 13 mL of Et_2O and 13 mL of hexane at −65 °C was added 3.62 mL (5.79 mmol) of 1.6 M *n*-butyllithium in hexane. After being stirred for 50 min, 721 mg (6.32 mmol) of 2-methyl-δ-valerolactone in 4 mL of Et_2O was added and the resulting mixture further stirred at ambient temperature for 5 h. To the mixture was added 0.330 mL (5.80 mmol) of acetic acid and 30 mL of brine. The aqueous layer was separated and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 5:95 → 50:50) gave 664 mg (23%) of unreacted **22** and then 2.41 g (70%) of four (1:1:1:1) β-keto sulfones **23** as a colorless oil: $[\alpha]^{25}_D = -12.9°$ (*c* 1.12, $CHCl_3$); IR (thin film) 3430 (br), 3050, 2925, 1720 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.77–7.33 (m, 15H), 4.77–4.40 (m, 3H), 3.70–3.56 (m, 4H), 3.37–3.02 (m, 4H), 2.20–1.20 (m, 8H), 1.17–0.82 (m, 15H); FI-HR-MS calcd for $C_{36}H_{51}O_7SiS$ ($M^+ + H$) *m/z* 655.3125, found 655.3115.

(2*S*,3*S*,5*R*,6*S*,11*R*)-3,11-Dimethyl-2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-5-(phenylsulfonyl)-1,7-dioxaspiro[5.5]undecane (24). To a solution of 426 mg (0.650 mmol) of **23** in 9.3 mL of CH_2Cl_2 at −30 °C was added 0.686 mL (5.20 mmol) of bromotrimethylsilane. The mixture was allowed to warm to 3 °C over 2 h and further stirred at that temperature for 7 h. It was poured into 20 mL of saturated aqueous $NaHCO_3$, and then the aqueous layer was separated and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 5:95) followed by recrystallization from hexane gave 343 mg (89%) of spiroketal **24** as white crystals: mp 176–177 °C; $[\alpha]^{23}_D = +38.0°$ (*c* 1.52, $CHCl_3$); IR (KBr pellet) 2960, 2890, 1085 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.91–7.34 (m, 15H), 3.74 (dd, J = 11.2, 2.6 Hz, 1H), 3.66 (dd, J = 11.2, 5.3 Hz, 1H), 3.55–3.36 (m, 2H), 3.26 (ddd, J = 9.9, 5.3, 2.6 Hz, 1H), 2.93–2.85 (m, 1H), 1.97 (m, 1H), 1.83–1.00 (m, 7H), 1.11 (d, J = 7.3 Hz, 3H), 1.01 (s, 9H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 139.1, 135.6, 135.5, 133.5, 133.4, 133.2, 129.8, 129.6, 128.3, 127.6, 98.2, 75.0, 65.0, 63.9, 60.5, 35.5, 31.2, 30.2, 26.9, 26.6, 25.8, 19.1, 17.1, 16.3; EI-HR-MS calcd for $C_{34}H_{44}O_5SiS$ (M^+) *m/z* 592.2676, found 592.2665.

(2*S*,3*S*,6*R*,11*R*)-3,11-Dimethyl-2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-1,7-dioxaspiro[5.5]undecane (13). To a solution of 2.83 g (4.77 mmol) of **24** in 100 mL of ethanol was added a suspension of 42.0 g of Raney-Nickel (W-2) in 100 mL of ethanol. After the mixture was heated to reflux with vigorous stirring for 22 h, 100 mL of Et_2O was added and the mixture refluxed again for 30 min. Insoluble material was removed by filtration through a pad of Celite, and the bed was washed with 200 mL of Et_2O. The combined filtrate was concentrated *in vacuo*, and then the residue was purified by silica gel flash chromatography (benzene as eluent) and subsequent recrystallization from acetonitrile to give 1.90 g (88%) of desulfurized spiroketal **13** as colorless needles: mp 82–84 °C; $[\alpha]^{22}_D = +40.9°$ (*c* 1.80, $CHCl_3$); IR (KBr pellet) 2925, 2870, 1105 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.80–7.35 (m, 10H), 3.81 (dd, J = 10.6, 2.5 Hz, 1H), 3.73 (dd, J = 10.6, 5.3 Hz, 1H), 3.68 (dt, J = 2.3, 11.3 Hz, 1H), 3.53 (ddd, J = 11.3, 3.1, 1.6 Hz, 1H), 3.37 (ddd, J = 9.0, 5.3, 2.5 Hz, 1H), 1.89–1.00 (m, 10H), 1.04 (s, 9H), 0.99 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 5.8 Hz, 3H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 135.7, 135.7, 134.0, 133.8, 129.5, 127.7, 97.9, 75.9, 64.9, 59.8, 38.8, 31.8, 30.6, 27.8, 27.5, 26.6, 26.4, 19.2, 17.6, 16.8; EI-HR-MS calcd for $C_{28}H_{40}O_3Si$ (M^+) *m/z* 452.2747, found 452.2729.

(δ*R*,2*R*,5*S*,6*S*)-δ,5-Dimethyl-6-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]tetrahydro-2-pyranylbutanol (14). To a solution of 1.12 g (2.47 mmol) of **13** in 24 mL of CH_2Cl_2 at −78 °C was added 0.474 mL (2.97 mmol) of triethylsilane and 0.347 mL (2.97 mmol) of tin(IV) chloride. The mixture was allowed to warm to −60 °C over 2 h, and then 20 mL of 1 N hydrochloric acid was added and the mixture warmed to ambient temperature. The aqueous layer was separated and extracted with $CHCl_3$ (2 × 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 8 mL of THF, followed by the addition of 8 mL of acetic acid and 1 mL of water. After being stirred at ambient temperature for 1 h, 80 mL of 3 N aqueous NaOH and 50 mL of Et_2O at 0 °C were added. The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined organic

extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/PhH, 5:95) gave 1.10 g (98%) of pyran alcohol **14** as a colorless oil: $[\alpha]^{27}_D = +11.4°$ (*c* 1.25, $CHCl_3$); IR (thin film) 3350 (br), 2925, 2870, 1110 cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6) δ 7.95–7.86 (m, 4H), 7.34–7.23 (m, 6H), 3.89 (dd, J = 11.2, 2.0 Hz, 1H), 3.79 (dd, J = 11.2, 4.6 Hz, 1H), 3.42 (t, J = 6.6 Hz, 2H), 3.05 (dt, J = 9.9, 4.6 Hz, 1H), 2.90 (ddd, J = 9.2, 4.6, 2.0 Hz, 1H), 1.68–0.90 (m, 10H), 1.21 (s, 9H), 1.03 (d, J = 7.3 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{28}H_{43}O_3Si$ (M^+ + H) *m/z* 455.2981, found 455.2972.

(δ*R*,2*R*,5*S*,6*S*)-δ,5-Dimethyl-6-[[[(1,1-dimethylethyl)-diphenylsilyl]oxy]methyl]tetrahydro-2-pyranylbutyl Acetate (25). To a solution of 864 mg (1.90 mmol) of **14** in 9.5 mL of CH_2Cl_2 at ambient temperature was added 0.215 mL (2.28 mmol) of acetic anhydride, 0.231 mL (2.86 mmol) of pyridine, and 11 mg (90 μmol) of 4-(dimethylamino)pyridine. After being stirred for 2 h, the mixture was concentrated *in vacuo* and purified by silica gel flash chromatography (Et_2O/hexane, 10:90 → 20:80) to give 754 mg (80%) of acetate **25** as a colorless oil: $[\alpha]^{24}_D = +9.6°$ (*c* 1.23, $CHCl_3$); IR (thin film) 3060, 2950, 2870, 1745 cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6) δ 7.95–7.86 (m, 4H), 7.33–7.24 (m, 6H), 4.05 (t, J = 6.3 Hz, 2H), 3.89 (dd, J = 11.2, 2.0 Hz, 1H), 3.79 (dd, J = 11.2, 4.6 Hz, 1H), 3.01 (dt, J = 9.9, 4.0 Hz, 1H), 2.88 (ddd, J = 9.2, 4.6, 2.0 Hz, 1H), 1.70 (s, 3H), 1.70–0.90 (m, 10H), 1.21 (s, 9H), 0.99 (d, J = 7.3 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{30}H_{45}O_4Si$ (M^+ + H) *m/z* 497.3087, found 497.3093.

(δ*R*,2*R*,5*S*,6*S*)-δ,5-Dimethyl-6-(hydroxylmethyl)tetrahydro-2-pyranylbutyl Acetate (26). To a solution of 341 mg (0.686 mmol) of **25** in 3.5 mL of THF at ambient temperature was added 2.0 mL (2.0 mmol) of 1.0 M tetra-*n*-butylammonium fluoride in THF. After the mixture was stirred for 15 h, it was concentrated *in vacuo* and purified by silica gel flash chromatography (EtOAc/PhH, 5:95 → 20:80) to give 177 mg (100%) of alcohol **26** as a colorless oil: $[\alpha]^{24}_D = +15.9°$ (*c* 4.78 $CHCl_3$); IR (thin film) 3470 (br), 2950, 2870, 1735, 1235 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.05 (t, J = 6.6 Hz, 2H), 3.74 (ddd, J = 11.2, 8.6, 3.0 Hz, 1H), 3.50 (ddd, J = 11.2, 7.3, 4.0 Hz, 1H), 3.16 (ddd, J = 10.9, 5.0, 2.3 Hz, 1H), 3.05 (ddd, J = 9.6, 7.3, 3.0 Hz, 1H), 2.22 (dd, J = 8.6, 4.0 Hz, 1H), 2.05 (s, 3H), 1.85–1.10 (m, 10H), 0.92 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.79; H, 9.95.

(δ*R*,2*R*,5*S*,6*S*)-δ,5-Dimethyl-6-[[(methylsulfonyl)oxy]-methyl]tetrahydro-2-pyranylbutyl Acetate (27). To a solution of 385 mg (1.49 mmol) of **26** in 5 mL of CH_2Cl_2 at ambient temperature was added 0.362 mL (4.48 mmol) of pyridine, 0.231 mL (2.98 mmol) of methanesulfonyl chloride, and 9.0 mg (74 μmol) of 4-(dimethylamino)pyridine. After the mixture was stirred for 13 h, 20 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90) gave 499 mg (100%) of mesylate **27** as a colorless oil: $[\alpha]^{25}_D = +9.7°$ (*c* 2.36, $CHCl_3$); IR (thin film) 2960, 2880, 1740, 1355 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.39 (dd, J = 11.2, 2.0 Hz, 1H), 4.25 (dd, J = 11.2, 5.6 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 3.23–3.11 (m, 2H), 3.05 (s, 3H), 2.05 (s, 3H), 1.92–1.08 (m, 10H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{15}H_{28}O_6S$ (M^+) *m/z* 336.1607, found 336.1598.

(δ*R*,2*R*,5*S*,6*S*)-6-(Bromomethyl)-δ,5-dimethyltetrahydro-2-pyranylbutyl Acetate (28). To a solution of 376 mg (1.12 mmol) of **27** in 3.7 mL of DMF was added 586 mg (5.59 mmol) of lithium bromide monohydrate. The mixture was stirred at 70 °C for 7.5 h, and then 35 mL of water and 35 mL of Et_2O was added. The aqueous layer was separated and extracted with Et_2O (2 × 35 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 10:90) gave 316 mg (88%) of bromide **28** as a colorless oil: $[\alpha]^{21}_D = +23.9°$ (*c* 1.99, $CHCl_3$); IR (thin film) 2940, 2880, 1735, 1230 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.05 (t, J = 6.6 Hz, 2H), 3.61 (dd, J = 10.9, 2.3 Hz, 1H), 3.40 (dd, J = 10.9, 6.6 Hz, 1H), 3.17–3.05 (m, 2H), 2.05 (s, 3H), 1.88–1.12 (m, 10H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{14}H_{25}O_3{}^{79}Br$ (M^+) *m/z* 320.0985, found 320.0972.

(4*R*,5*R*,8*S*)-5-Hydroxy-4,8-dimethyl-9-decenyl Acetate (29). To a solution of 1.10 g (3.42 mmol) of **28** in 18 mL of ethanol and 2 mL of water was added 1.79 g (27.0 mmol) of zinc dust. The mixture was heated to reflux with vigorous stirring for 22 h, and then the insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (EtOAc/PhH, 5:95 → 10:90) to give 724 mg (87%) of alcohol **29** as a colorless oil: $[\alpha]^{23}_D = +21.4°$ (*c* 2.17, $CHCl_3$); IR (thin film) 3450 (br), 2950, 2875, 1730, 1240 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.68 (ddd, J = 17.2, 10.2, 7.6 Hz, 1H), 4.96 (ddd, J = 17.2, 2.0, 1.2 Hz, 1H), 4.93 (ddd, J = 10.2, 2.0, 0.7 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.49 (m, 1H), 2.13 (m, 1H), 2.05 (s, 3H), 1.80–1.16 (m, 9H), 1.01 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); EI-HR-MS calcd for $C_{14}H_{26}O_3$ (M^+) *m/z* 242.1879, found 242.1871.

(4*R*,5*S*,8*S*)-1-Acetoxy-4,8-dimethyl-9-decen-5-yl 4-Nitrobenzoate (30). To a solution of 101 mg (0.417 mmol) of **29** in 8.4 mL of benzene at ambient temperature was added 547 mg (2.09 mmol) of triphenylphosphine, 307 mg (1.84 mmol) of *p*-nitrobenzoic acid, and 0.328 mL (2.08 mmol) of diethyl azodicarboxylate. After the mixture was stirred for 15 h, the volatile material was removed *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 10:90 → 20:80) gave 110 mg (67%) of *p*-nitrobenzoate **30** as a colorless oil: $[\alpha]^{20}_D = +5.2°$ (*c* 2.13, $CHCl_3$); IR (thin film) 2960, 2860, 1735, 1725, 1270 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.32–8.19 (m, 4H), 5.65 (ddd, J = 17.2, 9.9, 7.9 Hz, 1H), 5.08 (q, J = 5.9 Hz, 1H), 4.96 (br d, J = 17.2 Hz, 1H), 4.93 (br d, J = 9.9 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 2.11 (m, 1H), 1.95–1.15 (m, 9H), 0.98 (d, J = 6.6 Hz, 6H); FI-HR-MS calcd for $C_{21}H_{30}O_6N$ (M^+ + H) *m/z* 392.2073, found 392.2085.

(4*R*,5*S*,8*S*)-1-Hydroxy-4,8-dimethyl-9-decen-5-yl 4-Nitrobenzoate (31). To a solution of 102 mg (0.259 mmol) of **30** in 6.5 mL of methanol at 5 °C was added 22.0 mg (0.548 mmol) of 60% sodium hydride. After the mixture was stirred for 2 h, 0.3 mL of acetic acid was added and the resulting mixture concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90) gave 72 mg (80%) of alcohol **31** as a colorless oil: $[\alpha]^{20}_D = +3.1°$ (*c* 2.32, $CHCl_3$); IR (thin film) 3370 (br), 2930, 2860, 1720, 1270 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.32–8.19 (m, 4H), 5.65 (ddd, J = 17.2, 9.9, 7.9 Hz, 1H), 5.09 (q, J = 5.9 Hz, 1H), 4.96 (dd, J = 17.2, 2.0 Hz, 1H), 4.93 (br d, J = 9.9 Hz, 1H), 3.66 (t, J = 5.9 Hz, 2H), 2.11 (m, 1H), 1.88 (m, 1H), 1.80–1.20 (m, 8H), 0.98 (d, J = 6.6 Hz, 6H); FI-HR-MS calcd for $C_{19}H_{28}O_5N$ (M^+ + H) *m/z* 350.1967, found 350.1950.

(3*R*,4*S*,7*S*)-1-Formyl-3,7-dimethyl-8-nonen-4-yl 4-Nitrobenzoate (32). To a solution of 30 μL (0.34 mmol) of oxalyl chloride in 1.3 mL of CH_2Cl_2 at −78 °C was added 32 μL (0.45 mmol) of dimethyl sulfoxide in 0.5 mL of CH_2Cl_2. After the mixture was stirred for 10 min, 59.0 mg (0.169 mmol) of **31** in 1.3 mL of CH_2Cl_2 was introduced and the resulting mixture stirred for 30 min. To this was added 0.172 mL (1.23 mmol) of triethylamine. The mixture was further stirred at 0 °C for 10 min and quenched with 20 mL of saturated aqueous NH_4Cl. This mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The labile aldehyde **32** thus produced was used immediately without further purification. Data for **32**: $[\alpha]^{24}_D = +4.8°$ (*c* 1.33, $CHCl_3$); IR (thin film) 2925, 2870, 1725, 1270 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.80 (t, J = 1.3 Hz, 1H), 8.32–8.18 (m, 4H), 5.65 (ddd, J = 17.2, 9.9, 7.9 Hz, 1H), 5.08 (q, J = 5.7 Hz, 1H), 4.96 (dd, J = 17.2, 1.3 Hz, 1H), 4.93 (br d, J = 9.9 Hz, 1H), 2.65–2.40 (m, 2H), 2.11 (m, 1H), 1.95–1.80 (m, 2H), 1.73–1.63 (m, 2H), 1.50 (m, 1H), 1.40–1.20 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{19}H_{25}O_5N$ (M^+) *m/z* 347.1733, found 347.1745.

Ethyl (4*R*)-5-(Tetrahydropyran-2-yloxy)-4-methyl-2-pentenoate (34). To a solution of 5.00 mL (57.3 mmol) of oxalyl chloride in 300 mL of CH_2Cl_2 at −70 °C was added 5.10

mL (71.9 mmol) of dimethyl sulfoxide in 18 mL of CH_2Cl_2. After the mixture was stirred for 10 min, 5.00 g (28.7 mmol) of **33** in 100 mL of CH_2Cl_2 was introduced and the resulting mixture stirred for 30 min. To this was added 28.0 mL (0.201 mol) of triethylamine. The mixture was further stirred at ambient temperature for 30 min and quenched with 500 mL of 5% aqueous $NaHSO_4$. The aqueous layer was separated and extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with 200 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde thus obtained was used without further purification.

Sodium hydride (60% in mineral oil, 1.38 g, 34.5 mmol) was washed with THF (3 × 5 mL) and suspended in 44 mL of THF. To this at 0 °C was added 8.36 g (37.3 mmol) of triethyl phosphonoacetate in 44 mL of THF, and the solution was stirred at ambient temperature for 20 min. The mixture was cooled to −78 °C, followed by the addition of the above freshly prepared aldehyde in 37 mL of THF. After being stirred for 30 min, this was allowed to warm to ambient temperature. The mixture was stirred for another 1 h and was then quenched by the addition of 200 mL of water. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with 50 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 15:85 → 20:80) gave 6.82 g (98%) of four (concerning olefin geometry (*E*:*Z* = 85:15) and THP diastereomer (1:1)) esters **34** as a colorless oil: $[\alpha]^{25}_D = +14.2°$ (*c* 3.30, $CHCl_3$); IR (thin film) 2930, 2860, 1715 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 6,97, 6.12 (multiplets, 85:15 ratio, 1H), 5.86, 5.77 (multiplets, 85:15 ratio, 1H), 4.59 (m, 1H), 4.18 (m, 2H), 3.84 (m, 1H), 3.68 (m, 1H), 3.50 (m, 1H), 3.33 (m, 1H), 2.64 (m, 1H), 1.83−1.54 (m, 6H), 1.29 (m, 3H), 1.10 (m, 3H). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.40; H, 9.18.

Ethyl (4*R*)-5-(Tetrahydropyran-2-yloxy)-4-methylpentanoate (35) and (4*R*)-5-(Tetrahydropyran-2-yloxy)-4-methyl-1-pentanol (36). To a solution of 3.85 g (15.9 mmol) of **34** in 53 mL of EtOAc was added 0.39 g of 10% palladium on carbon, and the mixture was stirred vigorously at ambient temperature under hydrogen atmosphere for 6 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated *in vacuo* to give saturated ester **35** which was used without further purification. Data for **35**: $[\alpha]^{24}_D = +4.2°$ (*c* 3.76, $CHCl_3$); IR (thin film) 2940, 2870, 1735 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 4.57 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.85 (m, 1H), 3.63−3.48 (m, 2H), 3.21 (m, 1H), 2.35 (m, 2H), 1.88−1.43 (m, 9H), 1.26 (t, *J* = 7.3 Hz, 3H), 0.95, 0.94 (doublets, *J* = 6.6 Hz, ca. 1:1 ratio, 3H). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.85; H, 9.90. Found: C, 63.45; H, 9.88.

To a suspension of 415 mg (10.9 mmol) of lithium aluminum hydride in 28 mL of Et_2O at 3 °C was added the above ester **35** in 14 mL of Et_2O. After it was stirred at ambient temperature for 30 min, saturated aqueous potassium sodium tartrate (Rochelle's salt) was added with stirring until a clear supernatant appeared. The mixture was further stirred for 30 min, and the precipitate was removed by filtration through a pad of Celite. The filtrate was concentrated *in vacuo* and was then purified by silica gel flash chromatography (EtOAc/PhH, 10:90 → 50:50) to give 3.22 g (100%) of two (1:1, concerning THP diastereomer) alcohols **36** as a colorless oil: $[\alpha]^{24}_D = +4.7°$ (*c* 7.19, $CHCl_3$); IR (thin film) 3350 (br), 2920, 2850, 1015 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 4.56 (m, 1H), 3.86 (m, 1H), 3.68−3.46 (m, 4H), 3.21 (m, 1H), 1.87−1.44 (m, 10H), 1.38 (br s, 1H), 1.21 (m, 1H), 0.95, 0.94 (doublets, *J* = 6.6 Hz, ca. 1:1 ratio, 3H). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 64.96; H, 10.95.

(4*R*)-[[5-(Tetrahydropyran-2-yloxy)-4-methyl-1-pentyl]oxy](1,1-dimethylethyl)diphenylsilane (37). To a solution of 2.18 g (10.8 mmol) of **36** in 22 mL of DMF at ambient temperature was added 3.36 mL (12.9 mmol) of *tert*-butylchlorodiphenylsilane and 1.84 g (27.0 mmol) of imidazole. After the mixture was stirred for 18 h, 30 mL of water and 30 mL of hexane were added. The aqueous layer was separated and extracted with hexane (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 5:95 → 8:92) gave 4.71 g (99%) of two (1:1, concerning THP diastereomer) TBDPS ethers **37** as a colorless oil: $[\alpha]^{27}_D = +1.2°$ (*c* 3.22, $CHCl_3$); IR (thin film) 2910, 2840, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.45−7.34 (m, 6H), 4.56 (m, 1H), 3.85 (m, 1H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.61−3.47 (m, 2H), 3.18 (m, 1H), 1.83−1.45 (m, 10H), 1.27−1.10 (m, 1H), 1.04 (s, 9H), 0.92, 0.90 (doublets, *J* = 6.6 Hz, ca. 1:1 ratio, 3H); FI-HR-MS calcd for $C_{27}H_{41}O_3Si$ ($M^+ + H$) *m*/*z* 441.2824, found 441.2832.

(2*R*)-2-Methyl-5-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-pentanol (38). To a solution of 3.45 g (7.83 mmol) of **37** in 391 mL of methanol at ambient temperature was added 447 mg (2.35 mmol) of *p*-toluenesulfonic acid monohydrate. This was stirred for 50 min, and then 0.655 mL (4.70 mmol) of triethylamine was added. The mixture was concentrated *in vacuo* and partitioned between 50 mL of water and 50 mL of $CHCl_3$. The aqueous layer was separated and extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 10:90 → 50:50) gave 2.23 g (80%) of alcohol **38** as a colorless oil: $[\alpha]^{26}_D = +4.8°$ (*c* 4.30, $CHCl_3$) (lit.[63] $[\alpha]_D$ +4.71°); IR (thin film) 3330 (br), 2900, 2830, 1095 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.45−7.34 (m, 6H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.48 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.39 (dd, *J* = 10.6, 5.9 Hz, 1H), 1.66−1.37 (m, 4H), 1.16 (m, 1H), 1.05 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H). Anal. Calcd for $C_{22}H_{32}O_2Si$: C, 74.10; H, 9.05. Found: C, 73.74; H, 9.06.

(2*R*)-2-Methyl-5-[[(1,1-dimethylethyl)diphenylsilyl]oxy]pentanal and (3*S*,4*S*,5*R*)-3,5-Dimethyl-8-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-octen-4-ol (39). To a solution of 1.31 mL (15.0 mmol) of oxalyl chloride in 78 mL of CH_2Cl_2 at −78 °C was added 1.33 mL (19.0 mmol) of dimethyl sulfoxide in 5.2 mL of CH_2Cl_2. After the mixture was stirred for 10 min, 2.67 g (7.49 mmol) of **38** in 26 mL of CH_2Cl_2 was introduced and stirred for 30 min. To this was added 7.31 mL (52.0 mmol) of triethylamine. The mixture was further stirred at ambient temperature for 30 min and quenched with 200 mL of 5% aqueous $NaHSO_4$. The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with 100 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The aldehyde thus produced was used immediately without further purification. Data for **the aldehyde**: $[\alpha]^{24}_D = -10.0°$ (*c* 4.46, $CHCl_3$); IR (thin film) 2930, 2860, 1710, 1105 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.0 Hz, 1H), 7.67−7.64 (m, 4H), 7.46−7.34 (m, 6H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.33 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.45 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H); FI-HR-MS calcd for $C_{22}H_{31}O_2Si$ ($M^+ + H$) *m*/*z* 355.2093, found 355.2107.

To a solution of the above aldehyde in 37 mL of CH_2Cl_2 at −86 °C was added 1.84 mL (15.0 mmol) of boron trifluoride etherate and 3.00 mL (7.50 mmol) of tri-*n*-butylcrotylstannane. After the mixture was stirred for 15 min, it was allowed to warm to −70 °C over 45 min and finally stirred at 0 °C for 1 h. Then 100 mL of water was added and the resulting mixture extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with 100 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 5:95 → 10:90) gave 2.83 g (92%) of a mixture of crotyl adducts as a colorless oil. The ratio of these isomers was determined by high-performance liquid chromatography (Wakosil 5sil, 6.0 × 250 mm, 5 μm; EtOAc/hexane, 8:92) to be 66 (**39**, Cram *erythro*):22 (anti-Cram *erythro*):12 (other isomers). The mixture was further purified by medium-pressure liquid chromatography (Merck LiChroprep Si 60; EtOAc/hexane, 20:80) to give 1.32 g (43%) of completely pure Cram *erythro* adduct **39** as a colorless oil: $[\alpha]^{23}_D = -1.2°$ (*c* 1.31, $CHCl_3$); IR (thin film) 3450 (br), 2940, 2875, 1105 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.45−7.34 (m, 6H), 5.69 (ddd, *J* = 17.2, 10.3, 7.9 Hz, 1H), 5.05 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.01 (dd, *J*

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= 10.3, 1.3 Hz, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.24 (dd, J = 7.3, 4.6 Hz, 1H), 2.34 (m, 1H), 1.68−1.38 (m, 4H), 1.40 (br s, 1H), 1.24 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 1.05 (s, 9H), 0.87 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{26}H_{39}O_2Si$ ($M^+ + H$) m/z 411.2719, found 411.2723.

(4*R*,5*S*,6*S*)-[[5-(Methoxymethoxy)-4,6-dimethyl-7-octen-1-yl]oxy](1,1-dimethylethyl)diphenylsilane (40). To a solution of 491 mg (1.20 mmol) of **39** in 6 mL of CH_2Cl_2 was added 0.625 mL (3.59 mmol) of *N,N*-diisopropylethylamine and 0.182 mL (2.40 mmol) of chloromethyl methyl ether. After being stirred at ambient temperature for 18 h, 20 mL of 10% aqueous citric acid was added. The aqueous layer was separated and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 5:95) gave 543 mg (100%) of MOM ether **40** as a colorless oil: $[\alpha]^{23}_D$ = −5.7° (*c* 1.19, $CHCl_3$); IR (thin film) 2935, 2875, 1110 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.45−7.34 (m, 6H), 5.72 (ddd, J = 17.2, 9.9, 7.9 Hz, 1H), 5.00 (dd, J = 17.2, 1.3 Hz, 1H), 4.95 (dd, J = 9.9, 1.3 Hz, 1H), 4.63 (s, 2H), 3.64 (t, J = 6.6 Hz, 2H), 3.37 (s, 3H), 3.18 (dd, J = 7.3, 4.0 Hz, 1H), 2.41 (m, 1H), 1.69−1.41 (m, 4H), 1.27 (m, 1H), 1.04 (s, 9H), 1.03 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{28}H_{42}O_3Si$: C, 73.96; H, 9.31. Found: C, 73.74; H, 9.21.

(3*S*,4*S*,5*R*)-4-(Methoxymethoxy)-3,5-dimethyl-8-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-octanol (41). To a solution of 718 mg (1.58 mmol) of **40** in 9.5 mL of THF at 3 °C was added 6.30 mL (3.15 mmol) of 0.5 M 9-borabicyclo[3.3.1]-nonane in THF. The mixture was stirred at ambient temperature for 17 h, and then 1.6 mL of 3 N aqueous NaOH and 1.6 mL of 31% aqueous H_2O_2 were added. After being stirred at ambient temperature for 7 h, 20 mL of water was added to the mixture. The aqueous layer was separated and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90 → 15:85) gave 703 mg (94%) of alcohol **41** as a colorless oil: $[\alpha]^{27}_D$ = +8.5° (*c* 3.87, $CHCl_3$); IR (thin film) 3460 (br), 2960, 2890, 1125 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.44−7.35 (m, 6H), 4.65 (s, 2H), 3.72 (m, 1H), 3.66 (m, 1H), 3.65 (t, J = 6.3 Hz, 2H), 3.39 (s, 3H), 3.20 (t, J = 5.3 Hz, 1H), 1.87−1.38 (m, 7H), 1.20 (m, 1H), 1.05 (s, 9H), 0.92 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{28}H_{44}O_4Si$: C, 71.14; H, 9.38. Found: C, 70.78; H, 9.43.

(4*R*,5*S*,6*S*)-[[5-(Methoxymethoxy)-4,6-dimethyl-8-(phenylthio)-1-octyl]oxy](1,1-dimethylethyl)diphenylsilane (42). Alcohol **41** (703 mg, 1.49 mmol), 487 mg (2.23 mmol) of diphenyl disulfide, 1.20 mL (14.8 mmol) of pyridine, and 0.556 mL (2.23 mmol) of tri-*n*-butylphosphine were mixed and stirred at ambient temperature for 45 h. The mixture was concentrated *in vacuo* and purified by silica gel flash chromatography (Et_2O/hexane, 10:90) to give 732 mg (87%) of sulfide **42** as a colorless oil: $[\alpha]^{25}_D$ = +0.76° (*c* 5.24, $CHCl_3$); IR (thin film) 2955, 1100 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.44−7.12 (m, 11H), 4.60 (s, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.34 (s, 3H), 3.11 (t, J = 5.0 Hz, 1H), 2.99 (ddd, J = 12.5, 9.2, 5.9 Hz, 1H), 2.89 (ddd, J = 12.5, 9.2, 6.6 Hz, 1H), 1.90−1.42 (m, 7H), 1.19 (m, 1H), 1.05 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); FI-HR-MS calcd for $C_{34}H_{48}O_3SiS$ (M^+) m/z 564.3093, found 564.3077.

(4*R*,5*S*,6*S*)-[[5-(Methoxymethoxy)-4,6-dimethyl-8-(phenylsulfonyl)-1-octyl]oxy](1,1-dimethylethyl)diphenylsilane (43). To a solution of 730 mg (1.29 mmol) of **42** in 13 mL of CH_2Cl_2 at 3 °C was added 478 mg (5.69 mmol) of $NaHCO_3$ and 613 mg (2.84 mmol) of 80% *m*-chloroperoxybenzoic acid. After the mixture was stirred at ambient temperature for 1.5 h, 15 mL of 10% aqueous $Na_2S_2O_3$ was added. The aqueous layer was separated and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 15:85 → 20:80) gave 775 mg (100%) of sulfone **43** as a colorless oil: $[\alpha]^{24}_D$ = +16.5° (*c* 0.52, $CHCl_3$); IR (thin film) 2955, 1305, 1150, 1095 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.67−7.53 (m, 7H), 7.45−7.34 (m, 6H), 4.55 (s, 2H), 3.62 (t, J = 6.3 Hz, 2H), 3.28−3.02 (m, 3H), 3.25 (s, 3H), 1.87−1.36 (m, 7H), 1.12 (m, 1H), 1.04 (s, 9H), 0.85 (d, J = 5.9 Hz, 6H). Anal. Calcd for $C_{34}H_{48}O_5SiS$: C, 68.42; H, 8.11; S, 5.37. Found: C, 68.26; H, 7.95; S, 5.56.

(3*S*,6*S*,7*R*,13*S*,14*S*,15*R*)-14-(Methoxymethoxy)-3,7,13,15-tetramethyl-18-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-10-oxo-11-(phenylsulfonyl)-1-octadecen-6-yl 4-Nitrobenzoate (44). To a solution of 101 mg (0.169 mmol) of **43** in 0.5 mL of Et_2O and 0.38 mL of hexane at −78 °C was added 0.118 mL (0.186 mmol) of 1.58 M *n*-butyllithium in hexane. After the mixture was stirred for 30 min, ca. 0.169 mmol of **32** in 2.4 mL of 1:1 Et_2O/hexane was added, and the mixture was further stirred at ambient temperature for 4.5 h. To the mixture was added 5 mL of saturated aqueous NH_4Cl and 20 mL of Et_2O, and then the aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The adduct thus obtained was used without further purification.

To a solution of 30 μL (0.35 mmol) of oxalyl chloride in 0.75 mL of CH_2Cl_2 at −78 °C was added 32 μL (0.45 mmol) of dimethyl sulfoxide in 0.5 mL of CH_2Cl_2. After the solution was stirred for 10 min, the above adduct in 1.25 mL of CH_2Cl_2 was introduced and the resulting mixture stirred for 30 min. To this was added 0.172 mL (1.23 mmol) of triethylamine. The mixture was further stirred at 5 °C for 30 min and quenched with 20 mL of saturated aqueous NH_4Cl. This was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 15:85 → 20:80) gave 130 mg (82% in three steps from **31**) of two (1:1) β-keto sulfones **44** as a colorless oil: $[\alpha]^{24}_D$ = +10.1° (*c* 1.89, $CHCl_3$); IR (thin film) 2925, 2860, 1715, 1270, 1100 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 8.31−8.19 (m, 4H), 7.79−7.73 (m, 2H), 7.66−7.60 (m, 5H), 7.56−7.47 (m, 2H), 7.44−7.34 (m, 6H), 5.72−5.58 (m, 1H), 5.07−4.90 (m, 3H), 4.56−4.49 (m, 2H), 4.33−4.19 (m, 1H), 3.61 (m, 2H), 3.28, 3.26 (singlets, ca. 1:1 ratio, 3H), 3.02 (m, 1H), 3.18−2.90 (m, 1H), 2.75−2.48 (m, 1H), 2.20−1.20 (m, 16H), 1.05, 1.03 (singlets, ca. 1:1 ratio, 9H), 1.00−0.75 (m, 12H); FI-HR-MS calcd for $C_{53}H_{71}O_{10}NSiS$ (M^+) m/z 941.4568, found 941.4552.

(3*S*,6*S*,7*R*,13*S*,14*S*,15*R*)-14-(Methoxymethoxy)-3,7,13,-15-tetramethyl-18-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-10-oxo-1-octadecen-6-yl 4-(Hydroxyamino)benzoate (45). To a well-degassed solution of 139 mg (0.148 mmol) of **44** in 0.75 mL of 4:1 THF/methanol at −78 °C was added 9 mL (0.9 mmol) of 0.1 M samarium(II) iodide in THF. After the mixture was stirred for 20 min, 3 mL of water was added and the mixture allowed to warm to ambient temperature. To this was added 20 mL of saturated aqueous K_2CO_3 and the mixture extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/PhH, 7:93 → 20:80) gave 60 mg (51%) of desulfurized ketone **45** as a colorless oil: $[\alpha]^{23}_D$ = +8.8° (*c* 0.25, $CHCl_3$); IR (thin film) 3306 (br), 2960, 1706, 1607, 1275, 1111 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.98−7.94 (m, 2H), 7.68−7.65 (m, 4H), 7.45−7.26 (m, 6H), 7.00−6.97 (m, 2H), 5.65 (ddd, J = 17.2, 9.9, 3.3 Hz, 1H), 5.03−4.88 (m, 3H), 4.61 (m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.37 (s, 3H), 3.08 (t, J = 4.6 Hz, 1H), 2.57−2.32 (m, 4H), 2.09 (m, 1H), 1.85−1.15 (m, 15H), 1.05 (s, 9H), 0.98−0.85 (m, 12H); FI-HR-MS calcd for $C_{47}H_{70}O_7NSi$ (M^+ + H) m/z 788.4922, found 788.4898.

[2(3*S*,4*S*,5*R*),5*R*,6*S*,6(3*S*)]-2-Hydroxy-2-[4-(methoxymethoxy)-3,5-dimethyl-8-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]octyl]-5-methyl-6-(3-methyl-4-pentenyl)-tetrahydropyran (46). To a solution of 53 mg (67 μmol) of **45** in 2 mL of methanol was added 138 mg (1.00 mmol) of K_2CO_3. After the mixture was stirred at 60 °C for 2.5 h, 10 mL of water was added, and the resultant solution was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/

hexane, 10:90) gave 40 mg (91%) of considerable component mixture of hemiacetal **46** as a colorless oil: $[\alpha]^{24}_D = -8.9°$ (*c* 3.20, $CHCl_3$); IR (thin film) 3450 (br), 2940, 1720, 1110 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.44–7.34 (m, 6H), 5.70 (ddd, J = 17.2, 9.9, 7.3 Hz, 1H), 4.95 (br d, J = 17.2 Hz, 1H), 4.90 (dd, J = 9.9, 2.6 Hz, 1H), 4.63 (m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 3.45 (m, 1H), 3.37 (s, 3H), 3.13 (m, 1H), 2.10 (m, 1H), 2.10–1.10 (m, 19H), 1.04 (s, 9H), 1.00–0.82 (m, 12H); EI-HR-MS calcd for $C_{40}H_{62}O_4Si$ ($M^+ - H_2O$) *m/z* 634.4416, found 634.4432.

[2*S*,2(1*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-3,9-Dimethyl-2-[1-methyl-4-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butyl]-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (47). To a solution of 320 mg (0.490 mmol) of **46** in 15 mL of CH_2Cl_2 at −30 °C was added 0.510 mL (3.90 mmol) of bromotrimethylsilane. After the mixture was stirred for 5 min, the temperature was allowed to rise to 3 °C and the solution was stirred for 30 min. Then 30 mL of saturated aqueous $NaHCO_3$ was added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 6:94) gave 230 mg (79%) of spiroketal **47** as a colorless oil: $[\alpha]^{22}_D = -35.4°$ (*c* 2.03, $CHCl_3$); IR (thin film) 2940, 2870, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.45–7.34 (m, 6H), 5.71 (ddd, J = 17.2, 10.6, 7.3 Hz, 1H), 4.95 (dt, J = 17.2, 1.6 Hz, 1H), 4.90 (dd, J = 10.6, 1.6 Hz, 1H), 3.65 (t, J = 6.3 Hz, 2H), 3.28 (dd, J = 9.9, 2.0 Hz, 1H), 3.16 (br t, J = 8.7 Hz, 1H), 2.17–1.97 (m, 2H), 1.81 (m, 1H), 1.68–1.20 (m, 17H), 1.05 (s, 9H), 1.00 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 5.9 Hz, 3H), 0.87 (d, J = 7.3 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{38}H_{58}O_3Si$ (M^+) *m/z* 590.4152, found 590.4137.

[2*S*,2(1*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-(4-Hydroxy-1-methylbutyl)-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (48). To a solution of 160 mg (0.270 mmol) of **47** in 10 mL of THF at ambient temperature was added 0.80 mL (0.80 mmol) of 1.0 M tetra-*n*-butylammonium fluoride in THF. After the mixture was stirred for 5.5 h, it was concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 5:95 → 10:90) gave 97 mg (100%) of alcohol **48** as a colorless oil: $[\alpha]^{24}_D = -59.6°$ (*c* 1.10, $CHCl_3$); IR (thin film) 3330 (br), 2930, 2860, 1450 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.73 (ddd, J = 17.2, 9.9, 7.3 Hz, 1H), 4.96 (dt, J = 17.2, 1.6 Hz, 1H), 4.92 (dd, J = 9.9, 1.6 Hz, 1H), 3.65 (dt, J = 2.6, 6.6 Hz, 2H), 3.30 (dd, J = 10.3, 2.3 Hz, 1H), 3.16 (dt, J = 1.6, 9.9 Hz, 1H), 2.17–1.97 (m, 2H), 1.85 (m, 1H), 1.73–1.20 (m, 17H), 1.02 (d, J = 5.9 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{22}H_{40}O_3$ (M^+) *m/z* 352.2978, found 352.3002.

[γ*R*,2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]-γ,3,9-Trimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane-2-butanal (12). To a solution of 163 mg (0.462 mmol) of **48** in 5 mL of CH_2Cl_2 at ambient temperature was added 260 mg (0.691 mmol) of Dess–Martin periodinane. After being stirred for 2 h, 5 mL of saturated aqueous Na_2SO_3 and 5 mL of saturated aqueous $NaHCO_3$ were added. The mixture was stirred for 1 h, and then the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 10:90) gave 130 mg (80%) of aldehyde **12** as a colorless oil. The spectroscopic properties including IR, HR-MS, and ^1H-NMR of **12** were identical with those of natural degradation product. Optical rotation for synthetic **12**: $[\alpha]^{25}_D = -63.1°$ (*c* 1.22, $CHCl_3$).

[2*S*,2(1*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-(4-Hydroxy-1-methylbutyl)-3,9-dimethyl-8-(3-methyl-4-oxopentyl)-1,7-dioxaspiro[5.5]undecane (Wacker Oxidation Product) and [γ*R*,2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]-γ,3,9-Trimethyl-8-(3-methyl-4-oxopentyl)-1,7-dioxaspiro[5.5]undecane-2-butanal (49). Palladium(II) chloride (3.0 mg, 17 μmol) and 8.4 mg (89 μmol) of copper(I) chloride were dissolved in 0.2 mL of 7:1 DMF/water. This was stirred under oxygen atmosphere for 1 h. Then a solution of 0.80 mg (2.3 μmol) of **48** in 0.5 mL of 7:1 DMF/water was added, and the mixture was stirred vigorously for 1 day. The reaction was quenched by the addition of 1 mL of 1 N hydrochloric acid and extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (EtOAc/PhH, 20:80) gave 0.80 mg (94%) of methyl ketone as a colorless oil. Data for **Wacker oxidation product**: $[\alpha]^{25}_D = -25.0°$ (*c* 0.60, $CHCl_3$); IR (thin film) 3425 (br), 2940, 1710 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 3.64 (br t, J = 6.6 Hz, 2H), 3.30 (dd, J = 9.9, 2.0 Hz, 1H), 3.18 (dt, J = 2.0, 9.9 Hz, 1H), 2.54 (m, 1H), 2.15 (s, 3H), 2.02 (m, 1H), 1.84 (m, 1H), 1.75–1.18 (m, 17H), 1.10 (d, J = 7.3 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{22}H_{40}O_4$ (M^+) *m/z* 368.2926, found 368.2913.

To a solution of 2.4 μL (28 μmol) of oxalyl chloride in 0.3 mL of CH_2Cl_2 at −78 °C was added 3.8 μL (54 μmol) of dimethyl sulfoxide in 0.2 mL of CH_2Cl_2. After the mixture was stirred for 15 min, 2.0 mg (5.4 μmol) of the above keto alcohol in 0.8 mL of CH_2Cl_2 was introduced, and the solution was stirred for 30 min. To this was added 12 μL (86 μmol) of triethylamine. The mixture was further stirred at 5 °C for 2 h and quenched with 2 mL of saturated aqueous NH_4Cl. This was extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (EtOAc/PhH, 20:80) gave 2.0 mg (100%) of keto aldehyde **49** as a colorless oil. Keto aldehyde **49** thus produced was identical in spectroscopic respects with those of natural degradation product.[5b] Data for **49**: $[\alpha]^{25}_D = -42.2°$ (*c* 0.45, $CHCl_3$) (lit.[5b] $[\alpha]^{25}_D = -45.8°$, *c* 1.35, $CHCl_3$); IR (thin film) 2910, 2850, 1730, 1705 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 9.80 (t, J = 2.0 Hz, 1H), 3.27 (dd, J = 9.9, 2.0 Hz, 1H), 3.15 (dt, J = 2.0, 9.9 Hz, 1H), 2.61–2.35 (m, 3H), 2.15 (s, 3H), 2.02 (m, 1H), 1.90–1.18 (m, 16H), 1.10 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{22}H_{38}O_4$ (M^+) *m/z* 366.2770, found 366.2809.

[2*S*,2(1*R*,4*S*,5*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-(4-Hydroxy-1,5-dimethyl-6-heptenyl)-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (50). A solution of 0.540 mL (0.243 mmol) of 0.45 M (*S*,*S*)-diisopropyl tartrate (*E*)-crotylboronate in toluene and 30 mg of powdered 4-Å molecular sieves was stirred at ambient temperature for 10 min. The resultant slurry was cooled to −78 °C, and 57.0 mg (0.163 mmol) of **12** in 1 mL of toluene was added. After being stirred for 2 h, the mixture was allowed to warm to ambient temperature and directly purified by silica gel flash chromatography (Et_2O/hexane, 10:90 → 20:80) to give 7.0 mg (11%) of undesired crotyl adduct and then 57.0 mg (86%) of desired adduct **50** as a colorless oil: $[\alpha]^{24}_D = -54.1°$ (*c* 0.34, $CHCl_3$); IR (thin film) 3470 (br), 2940, 2860, 1445 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.83–5.66 (m, 2H), 5.13 (dd, J = 10.6, 1.6 Hz, 1H), 5.12 (dt, J = 17.8, 1.6 Hz, 1H), 4.96 (dt, J = 17.2, 1.6 Hz, 1H), 4.92 (dd, J = 9.2, 1.6 Hz, 1H), 3.35 (m, 1H), 3.30 (dd, J = 9.9, 2.0 Hz, 1H), 3.16 (dt, J = 2.6, 7.9 Hz, 1H), 2.3–1.97 (m, 3H), 1.85 (m, 1H), 1.70–1.17 (m, 17H), 1.05 (d, J = 7.3 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{26}H_{46}O_3$ (M^+) *m/z* 406.3447, found 406.3453.

[2*S*,2(1*R*,4*S*,5*S*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-(6,7-Epoxy-4-hydroxy-1,5-dimethylheptyl)-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (51). To a solution of 24.0 mg (59.0 μmol) of **50** in 1 mL of CH_2Cl_2 at 3 °C was added 0.3 mg (1.1 μmol) of vanadyl acetylacetonate and 20 μL (90 μmol) of 4.5 M *tert*-butyl hydroperoxide in CH_2Cl_2. After the mixture was stirred at ambient temperature for 7 h, 2 mL of 10% aqueous $Na_2S_2O_3$ was added and the resulting mixture extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with 2 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90 → 15:85) gave 21.2 mg (85%) of two (ca. 3:1) oxiranes **51** as a colorless oil: $[\alpha]^{25}_D = -57.8°$ (*c* 2.67, $CHCl_3$); IR (thin film) 3450 (br), 2920 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.2, 10.6, 7.3 Hz, 1H), 4.96 (dt, J = 17.2, 1.6 Hz, 1H), 4.91 (dd, J = 10.6, 1.6 Hz, 1H), 3.64, 3.49 (multiplets, ca. 3:1 ratio, 1H),

3.31 (dd, J = 9.9, 2.0 Hz, 1H), 3.16 (dt, J = 2.0, 6.6 Hz, 1H), 3.00, 2.92 (multiplets, ca. 1:3 ratio, 1H), 2.82, 2.76 (triplets, J = 4.6 Hz, ca. 1:3 ratio, 1H), 2.70, 2.47 (multiplets, ca. 1:3 ratio, 1H), 2.17–1.98 (m, 3H), 1.87 (m, 1H), 1.80–1.20 (m, 18H), 1.09, 1.02 (doublets, J = 6.6 Hz, ca. 3:1 ratio, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{26}H_{46}O_4$ (M^+) m/z 422.3396, found 422.3400.

[2*S*,2(1*R*,4*S*,5*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[6,7-Epoxy-4-[(triethylsilyl)oxy]-1,5-dimethylheptyl]-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (52). To a solution of 105 mg (0.248 mmol) of **51** in 2.5 mL of CH_2Cl_2 at 3 °C was added 70 μL (0.50 mmol) of triethylamine, 62 μL (0.37 mmol) of chlorotriethylsilane, and 1.5 mg (12 μmol) of 4-(dimethylamino)pyridine. After the reaction mixture was stirred for 2.5 h, 20 mL of brine was added and the resulting mixture extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 10:90) gave 123 mg (92%) of two (ca. 3:1) TES ethers **52** as a colorless oil: $[\alpha]^{26}_D$ = −35.1° (*c* 4.39, $CHCl_3$); IR (thin film) 2950, 2875, 1450 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.2, 9.9, 7.3 Hz, 1H), 4.96 (dt, J = 17.2, 1.6 Hz, 1H), 4.92 (dd, J = 9.9, 1.6 Hz, 1H), 3.74–3.65 (m, 1H), 3.28 (dd, J = 9.9, 2.0 Hz, 1H), 3.17 (br t, J = 8.3 Hz, 1H), 2.95, 2.85 (multiplets, ca. 3:1 ratio, 1H), 2.80, 2.71 (triplets, J = 4.6 Hz, ca. 1:3 ratio, 1H), 2.58, 2.43 (multiplets, ca. 1:3 ratio, 1H), 2.17–2.00 (m, 2H), 1.84 (m, 1H), 1.77–1.22 (m, 18H), 1.03–0.80 (m, 24H), 0.65–0.47 (m, 6H); FI-HR-MS calcd for $C_{32}H_{60}O_4Si$ (M^+) m/z 536.4261, found 536.4250.

[2*S*,2(1*R*,4*S*,5*R*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[4-[(Triethylsilyl)oxy]-6-hydroxy-1,5-dimethylheptyl]-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (53). To a solution of 121 mg (0.225 mmol) of **52** in 1.7 mL of THF at 3 °C was added 0.560 mL (0.560 mmol) of 1 M lithium triethylborohydride (Super-Hydride) in THF. After the mixture was stirred for 1 h, 5 mL of aqueous pH 7 phosphate buffer was added. This was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to remove solvent and triethylborane absolutely. Purification by silica gel flash chromatography (Et_2O/hexane, 10:90 → 15:85) gave 109 mg (90%) of two (ca. 3:1) alcohols **53** as a colorless oil: $[\alpha]^{25}_D$ = −32.1° (*c* 5.76, $CHCl_3$); IR (thin film) 3450 (br), 2920, 1445 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.2, 10.6, 7.9 Hz, 1H), 4.96 (br d, J = 17.2 Hz, 1H), 4.91 (dd, J = 7.9, 2.0 Hz, 1H), 4.24, 3.64 (multiplets, ca. 1:3 ratio, 1H), 3.64 (m, 1H), 3.32–3.25 (m, 1H), 3.18–3.13 (m, 1H), 2.17–2.01 (m, 2H), 1.85 (m, 1H), 1.66–1.21 (m, 18H), 1.16, 1.13 (doublets, J = 6.6 Hz, ca. 3:1 ratio, 3H), 1.02–0.78 (m, 24H), 0.68–0.59 (m, 6H); FI-HR-MS calcd for $C_{32}H_{63}O_4Si$ (M^+ + H) m/z 539.4496, found 539.4475.

[2*S*,2(1*R*,4*S*,5*S*),3*S*,6*R*,8*S*,8(3*S*),9*R*]-2-[4-[(Triethylsilyl)oxy]-1,5-dimethyl-6-oxoheptyl]-3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undecane (54). To a solution of 109 mg (0.202 mmol) of **53** in 10 mL of CH_2Cl_2 at ambient temperature were added 2.5 g of powdered 3-Å molecular sieves and 273 mg (0.726 mmol) of pyridinium dichromate. The mixture was stirred for 1 h and was then diluted with 10 mL of Et_2O. The insoluble material was removed by filtration through a plug of Celite, and the bed was washed with 50 mL of Et_2O. The combined filtrate was concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (Et_2O/hexane, 10:90) to give 103 mg (95%) of right-hand ketone **54** as a colorless oil: $[\alpha]^{25}_D$ = −17.9° (*c* 1.23, $CHCl_3$); IR (thin film) 2940, 1720 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.2, 10.6, 7.3 Hz, 1H), 4.96 (dt, J = 17.2, 1.6 Hz, 1H), 4.92 (br d, J = 10.6 Hz, 1H), 3.93 (m, 1H), 3.29 (dd, J = 9.9, 2.0 Hz, 1H), 3.15 (br t, J = 8.6 Hz, 1H), 2.73 (quintet, J = 7.3 Hz, 1H), 2.17 (s, 3H), 2.17–2.01 (m, 2H), 1.85 (m, 1H), 1.66–1.21 (m, 17H), 1.02–0.98 (m, 9H), 0.95 (t, J = 7.9 Hz, 9H), 0.89 (d, J = 7.3 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.58 (q, J = 7.9 Hz, 6H). Anal. Calcd for $C_{32}H_{60}O_4Si$: C, 71.59; H, 11.26. Found: C, 71.68; H, 11.17.

(2*S*,3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1,2-pentanediol (56). Titanium(IV) isopropoxide (1.77 g, 6.23 mmol) and 4.66 mL (37.4 mmol) of *p*-methoxybenzyl alcohol were stirred at 100 °C for 30 min. Then 2-propanol was azeotropically removed with toluene *in vacuo*. To titanium(IV) *p*-methoxybenzyl oxide thus obtained was added a solution of 482 mg (4.15 mmol) of **55** in 3 mL of toluene at 85 °C. This was stirred for 1 h and allowed to cool to ambient temperature, and then 16 mL of 5% sulfuric acid was added. The mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with 20 mL of saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 50:50) gave 732 mg (69%) of an inseparable 9.5:1 mixture of the desired 1,2-diol **56** and 1,3-diol derivative as a colorless oil. Data for the 9.5:1 mixture of **56** and 1,3-diol isomer: $[\alpha]^{24}_D$ = −14.0° (*c* 1.19, $CHCl_3$); IR (thin film) 3350 (br), 2930, 1600 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$, for **56**) δ 7.29–7.25 (m, 2H), 6.91–6.86 (m, 2H), 4.63 (d, J = 10.6 Hz, 1H), 4.55 (d, J = 10.6 Hz, 1H), 3.81 (s, 3H), 3.77 (m, 3H), 3.34 (dd, J = 6.6, 4.6 Hz, 1H), 2.40 (br s, 1H), 2.29 (br s, 1H), 1.91 (octet, J = 6.6 Hz, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{14}H_{22}O_4$ (M^+) m/z 254.1518, found 254.1510.

[2*S*,2(1*R*)]-2-[[1-[(4-Methoxyphenyl)methoxy]-2-methyl]propyl]oxirane (57). To a suspension of 853 mg (7.44 mmol) of potassium hydride (35% in mineral oil) in 6 mL of THF was added 473 mg (1.68 mmol) of **56**, being contaminated by ca. 10% of 1,3-diol isomer, in 3.3 mL of THF. After the mixture was stirred at 50 °C for 10 min, 390 mg (2.05 mmol) of *p*-toluenesulfonyl chloride was added, and the resultant solution was stirred for 10 h. The reaction mixture was allowed to cool to 0 °C and diluted with 20 mL of Et_2O. To this was added 50 μL of methanol and 50 mL of saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 10:90) gave 362 mg (91%) of oxirane **57** as a colorless oil: $[\alpha]^{23}_D$ = +6.9° (*c* 2.65, $CHCl_3$); IR (thin film) 2960, 2880, 1245 cm^{-1}; ^{1}H-NMR (270 MHz270 MHz, $CDCl_3$) δ 7.30–7.22 (m, 2H), 6.89–6.84 (m, 2H), 4.59 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.05 (t, J = 5.0 Hz, 1H), 2.97 (ddd, J = 5.3, 4.0, 2.6 Hz, 1H), 2.77 (dd, J = 5.3, 4.0 Hz, 1H), 2.71 (dd, J = 5.3, 2.6 Hz, 1H), 1.94 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{14}H_{20}O_3$ (M^+) m/z 236.1412, found 236.1405.

(2*R*,3*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-1-(phenylthio)-2-pentanol (58). Sodium hydride (60% in mineral oil, 508 mg, 12.7 mmol) was added to 3 mL of methanol at 3 °C and allowed to warm to ambient temperature. To this were added 0.143 mL (1.39 mmol) of thiophenol and a solution of 300 mg (1.27 mmol) of **57** in 3 mL of methanol. After the mixture was stirred at 50 °C for 11 h, 20 mL of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 18:82 → 20:80) gave 356 mg (81%) of sulfide **58** as a colorless oil: $[\alpha]^{23}_D$ = −14.9° (*c* 5.26, $CHCl_3$); IR (thin film) 3460 (br), 2960, 1240 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.40–7.17 (m, 7H), 6.90–6.86 (m, 2H), 4.62 (d, J = 10.6 Hz, 1H), 4.57 (d, J = 10.6 Hz, 1H), 3.81 (s, 3H), 3.79 (m, 1H), 3.30 (dd, J = 13.9, 3.3 Hz, 1H), 3.28 (t, J = 5.3 Hz, 1H), 3.00 (dd, J = 13.9, 9.2 Hz, 1H), 2.49 (d, J = 4.6 Hz, 1H), 1.91 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H); EI-HR-MS calcd for $C_{20}H_{26}O_3S$ (M^+) m/z 346.1602, found 346.1582.

(2*R*,3*R*)-2-Methoxy-3-[(4-methoxyphenyl)methoxy]-4-methyl-1-(phenylthio)pentane (59). To a solution of 239 mg (0.690 mmol) of **58** in 3.5 mL of THF and 1.3 mL of DMF at 3 °C was added 0.430 mL (6.91 mmol) of iodomethane and 69 mg (1.7 mmol) of sodium hydride (60% in mineral oil). After the mixture was stirred at ambient temperature for 2 h, 20 mL of brine was added and the resulting mixture extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/

hexane, 10:90) gave 243 mg (98%) of methyl ether **59** as a colorless oil: $[\alpha]^{23}_D = +5.4°$ (*c* 6.43, $CHCl_3$); IR (thin film) 3050, 2950, 1240, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.38–7.13 (m, 7H), 6.87–6.82 (m, 2H), 4.66 (d, J = 10.6 Hz, 1H), 4.51 (d, J = 10.6 Hz, 1H), 3.79 (s, 3H), 3.47 (m, 1H), 3.41 (s, 3H), 3.36 (dd, J = 5.9, 4.6 Hz, 1H), 3.27 (dd, J = 13.2, 3.3 Hz, 1H), 3.18 (dd, J = 13.2, 7.3 Hz, 1H), 1.88 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H); EI-HR-MS calcd for $C_{21}H_{28}O_3S$ (M^+) m/z 360.1759, found 360.1794.

(2*R*,3*R*)-2-Methoxy-4-methyl-1-(phenylthio)-3-pentanol (60). To a solution of 233 mg (0.646 mmol) of **59** in 3.2 mL of CH_2Cl_2 and 0.16 mL of water at ambient temperature was added 162 mg (0.711 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After the mixture was stirred vigorously for 45 min, it was poured into 15 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 5 mL of Et_2O, and 18 mg (0.474 mmol) of lithium aluminum hydride was added at 5 °C to reduce *p*-methoxybenzaldehyde which was inseparable chromatographically from **60**. After the mixture was stirred for 30 min, it was quenched by the addition of 50 μL of methanol. To this was added $Na_2SO_4 \cdot 10H_2O$ with stirring until clear supernatant appeared. The insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated *in vacuo* and then purified by silica gel flash chromatography (Et_2O/hexane, 13:87 → 15:85) to give 156 mg (100%) of alcohol **60** as a colorless oil: $[\alpha]^{25}_D = -10.4°$ (*c* 2.18, $CHCl_3$); IR (thin film) 3480 (br), 2970, 2840, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.42–7.15 (m, 5H), 3.51 (m, 1H), 3.42 (s, 3H), 3.40 (m, 1H), 3.18–3.15 (m, 2H), 2.10 (d, J = 3.3 Hz, 1H), 1.78 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); EI-HR-MS calcd for $C_{13}H_{20}O_2S$ (M^+) m/z 240.1184, found 240.1206.

3-[(3,4-Dimethoxyphenyl)methoxy]propanal and 1,1-Dimethylethyl (2*E*)-5-[(3,4-Dimethoxyphenyl)methoxy]-2-pentenoate (62). To a solution of 1.14 g (5.02 mmol) of **61** in 20 mL of CH_2Cl_2 at 0 °C was added 2.10 mL (15.1 mmol) of triethylamine, 5.30 mL (74.7 mmol) of dimethyl sulfoxide, and 2.40 g (15.1 mmol) of sulfur trioxide–pyridine complex in sequence. After the mixture was stirred for 1 h, 100 mL of saturated aqueous NH_4Cl was added, and the solution was extracted with 80 mL of EtOAc. The organic extract was washed successively with 10 mL of saturated aqueous $NaHCO_3$, 10 mL of water, and 20 mL of brine. Then it was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a brownish oil. The aldehyde thus obtained was used without further purification. Data for **the aldehyde**: IR (thin film) 2930, 2840, 1720 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 9.80 (t, J = 1.3 Hz, 1H), 6.88–6.84 (m, 3H), 4.47 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.80 (t, J = 5.9 Hz, 2H), 2.70 (dt, J = 1.3, 5.9 Hz, 2H); EI-HR-MS calcd for $C_{12}H_{16}O_4$ (M^+) m/z 224.1048, found 224.1036.

To a solution of above aldehyde in 25 mL of CH_2Cl_2 at ambient temperature was added 2.40 g (6.38 mmol) of [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane. After being stirred for 1.5 h, it was concentrated *in vacuo* to remove the solvent. Purification of the residue by silica gel flash chromatography (EtOAc/hexane, 15:85) gave 1.46 g (90%) of *tert*-butyl ester **62** as a colorless oil: IR (thin film) 2930, 2840, 1710, 1685, 1265 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 6.92–6.81 (m, 4H), 5.82 (dt, J = 15.8, 1.3 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.56 (t, J = 6.6 Hz, 2H), 2.48 (dq, J = 1.3, 6.6 Hz, 2H), 1.47 (s, 9H); EI-HR-MS calcd for $C_{18}H_{26}O_5$ (M^+) m/z 322.1770, found 322.1749.

1,1-Dimethylethyl (2*S*,3*R*)-2,3-Dihydroxy-5-[(3,4-dimethoxyphenyl)methoxy]pentanoate (63). Potassium ferricyanide(III) (8.94 g, 27.2 mmol), 3.74 g (27.1 mmol) of K_2CO_3, 71.7 mg (92.5 μmol) of hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$], and 0.10 mL (19 μmol) of 0.19 M aqueous osmium tetraoxide were stirred in 90 mL of 1:1 2-methyl-2-propanol/water at ambient temperature for 15 min. To this was added 844 mg (8.87 mmol) of methanesulfonamide, and the solution was cooled to 0 °C. Then 2.06 g (6.39 mmol) of **62** in 10 mL of 1:1 2-methyl-2-propanol/water was introduced, and the mixture was stirred at 0 °C for 20 h. The reaction was quenched by the addition of 13.7 g (109 mmol) of Na_2SO_3, stirred at ambient temperature for another 1 h, and subsequently extracted with EtOAc (100 mL, then 3 × 40 mL). The combined organic extracts were washed with 50 mL of 2 N aqueous KOH, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 30:70) gave 2.27 g (99%) of diol **63** as a colorless oil: $[\alpha]^{25}_D = +1.6°$ (*c* 1.00, $CHCl_3$); IR (thin film) 3840 (br), 2940, 2860, 1730, 1250, 1155 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 6.89–6.81 (m, 3H), 4.47 (s, 2H), 4.11 (m, 1H), 3.95 (dd, J = 5.9, 2.0 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.68 (m, 2H), 3.11 (d, J = 5.9 Hz, 1H), 2.63 (d, J = 7.3 Hz, 1H), 1.98 (m, 1H), 1.84 (m, 1H), 1.50 (s, 9H); EI-HR-MS calcd for $C_{18}H_{28}O_7$ (M^+) m/z 356.1835, found 356.1841.

1,1-Dimethylethyl (α*S*,2*R*,4*R*)-α-Hydroxy-2-(3,4-dimethoxyphenyl)-1,3-dioxane-4-acetate (64). To a solution of 4.59 g (12.9 mmol) of **63** in 25 mL of CH_2Cl_2 at ambient temperature was added 1.56 mL (19.4 mmol) of pyridine and 2 g of powdered 4-Å molecular sieves. After being stirred for 30 min, it was cooled to 5 °C. To the mixture was added 4.39 g (19.4 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and the resulting mixture was stirred for 6 h. Then, 0.30 mL (3.9 mmol) of pyridine and 878 mg (3.86 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were supplemented, and the suspension was further stirred for 18 h. The insoluble material was removed by filtration through a pad of Celite, and the bed was washed with 50 mL of CH_2Cl_2. The combined organic filtrate was washed with a mixture of 350 mL of saturated aqueous $NaHCO_3$ and 50 mL of 10% aqueous $CuSO_4$. The aqueous layer was further extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (acetone/PhH, 10:90) gave 3.00 g (66%) of acetal **64** as a colorless oil: $[\alpha]^{26}_D = -26.6°$ (*c* 1.02, $CHCl_3$); IR (thin film) 3500 (br), 2970, 2930, 2870, 2840, 1735, 1260, 1165 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 6.99–6.97 (m, 2H), 6.84–6.81 (m, 1H), 5.48 (s, 1H), 4.34 (ddd, J = 11.2, 5.3, 1.3 Hz, 1H), 4.20 (dt, J = 11.2, 2.6 Hz, 1H), 4.05 (dd, J = 7.9, 2.6 Hz, 1H), 3.98 (dt, J = 2.6, 11.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.97 (d, J = 7.9 Hz, 1H), 2.31 (dq, J = 5.3, 11.2 Hz, 1H), 1.50 (m, 1H), 1.49 (s, 9H); EI-HR-MS calcd for $C_{18}H_{26}O_7$ (M^+) m/z 354.1678, found 354.1663.

1,1-Dimethylethyl (2*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-α-oxo-1,3-dioxane-4-acetate (65) and Ethyl (α*Z*,2*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-α-methyl-β-[(1,1-dimethylethoxy)carbonyl]-1,3-dioxane-4-prop-α-enoate (66). To a solution of 1.78 g (5.02 mmol) of **64** in 50 mL of CH_2Cl_2 at ambient temperature were added 2.03 mL (25.1 mmol) of pyridine and 2.79 g (7.42 mmol) of Dess–Martin periodinane. The mixture was stirred for 2 h, and then 10 mL of saturated aqueous Na_2SO_3 and 10 mL of saturated aqueous $NaHCO_3$ were added. After the mixture was stirred for 1 h, the aqueous layer was separated and was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were shaken again with 10 mL of saturated aqueous Na_2SO_3 and 10 mL of saturated aqueous $NaHCO_3$ for 10 min. The aqueous layer was separated and was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.71 g of a brownish oil. The ketone **65** thus obtained was used immediately without further purification. Data for **65**: $[\alpha]^{25}_D = +4.9°$ (*c* 1.75, $CHCl_3$); IR (thin film) 2960, 2940, 2840, 1740, 1730, 1275, 1165 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.04–6.99 (m, 2H), 6.86–6.82 (m, 1H), 5.57 (s, 1H), 4.90 (dd, J = 11.9, 2.6 Hz, 1H), 4.36 (ddd, J = 11.9, 5.3, 1.3 Hz, 1H), 4.04 (dt, J = 2.6, 11.9 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.11 (dq, J = 5.3, 11.9 Hz, 1H), 1.89 (ddt, J = 11.9, 1.3, 2.6 Hz, 1H), 1.52 (s, 9H); EI-HR-MS calcd for $C_{18}H_{24}O_7$ (M^+) m/z 352.1522, found 352.1516.

To a solution of 1.71 g (15.2 mmol) of potassium *tert*-butoxide in 30 mL of THF at 0 °C was added a cold solution of 3.80 g (15.9 mmol) of triethyl 2-phosphonopropionate in 30 mL of THF. After being stirred at ambient temperature for 40 min, it was cooled to −60 °C. Freshly prepared **65** in 15 mL of THF was then introduced to the mixture. The temperature was gradually raised to −40 °C over 1 h, maintained between −42 and −32 °C for the next 2.5 h, and was finally allowed to raise

to −20 °C over 30 min. Then the reaction was quenched by the addition 50 mL of brine and 15 mL of saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90 → 15:85) gave 1.47 g (67%) of maleate **66** and 623 mg (28%) of the fumarate isomer as colorless oils. Data for **66**: $[\alpha]^{26}_D = -8.9°$ (*c* 1.02, $CHCl_3$); IR (thin film) 2950, 2860, 1730, 1265, 1160 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.03−6.99 (m, 2H), 6.83−6.80 (m, 1H), 5.51 (s, 1H), 4.86 (dd, J = 11.2, 2.6 Hz, 1H), 4.32 (ddd, J = 11.2, 4.0, 1.3 Hz, 1H), 4.22 (m, 2H), 3.98 (dt, J = 2.6, 11.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.44 (dq, J = 4.0, 11.2 Hz, 1H), 2.02 (s, 3H), 1.58 (ddt, J = 11.2, 1.3, 2.6 Hz, 1H), 1.47 (s, 9H), 1.29 (t, J = 7.3 Hz, 3H); EI-HR-MS calcd for $C_{23}H_{32}O_8$ (M^+) m/z 436.2098, found 436.2075.

Ethyl (2*Z*,4*R*)-4,6-Dihydroxy-2-methyl-3-[(1,1-dimethylethoxy)carbonyl]-2-hexenoate (67). To a solution of 1.47 g (3.37 mmol) of **66** in 34 mL of methanol at ambient temperature was added 482 mg (1.92 mmol) of pyridinium *p*-toluenesulfonate. After the solution was stirred for 2.5 h, 30 mL of methanol was supplemented, and the solution was further stirred for 1 h. To the mixture was then added 60 mL of saturated aqueous $NaHCO_3$, and the solution was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 10:90 → 50:50) gave 945 mg (98%) of diol **67** as a colorless oil: $[\alpha]^{25}_D = -4.7°$ (*c* 1.35, $CHCl_3$); IR (thin film) 3420 (br), 2980, 2930, 1710 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 4.82 (ddd, J = 14.5, 7.3, 4.0 Hz, 1H), 4.23 (q, J = 7.3 Hz, 2H), 3.86 (m, 2H), 3.07 (d, J = 7.3 Hz, 1H), 2.19 (dd, J = 6.6, 4.0 Hz, 1H), 2.09 (m, 1H), 1.96 (s, 3H), 1.80 (ddt, J = 14.5, 6.6, 4.0 Hz, 1H), 1.52 (s, 9H), 1.30 (t, J = 7.3 Hz, 3H). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.30; H, 8.36.

Ethyl (2*Z*,4*R*)-4,6-Bis[[diethyl(1-methylethyl)silyl]oxy]-2-methyl-3-[(1,1-dimethylethoxy)carbonyl]-2-hexenoate (68). To a solution of 865 mg (3.00 mmol) of **67** and 627 mg (9.22 mmol) of imidazole in 30 mL of CH_2Cl_2 at 3 °C was added 1.23 g (7.50 mmol) of chlorodiethylisopropylsilane in a dropwise manner. The mixture was allowed to warm to ambient temperature and was stirred for 18 h before the reaction was quenched by the addition of 50 mL of water. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 10:90) gave 1.46 g (89%) of bis DEIPS ether **68** as a colorless oil: $[\alpha]^{25}_D = -6.0°$ (*c* 0.94, $CHCl_3$); IR (thin film) 2960, 2880, 1730 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 4.89 (dd, J = 7.6, 5.6 Hz, 1H), 4.20 (m, 2H), 3.68 (m, 2H), 1.99 (m, 2H), 1.94 (s, 3H), 1.49 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H), 1.04−0.85 (m, 26H), 0.70−0.56 (m, 8H). Anal. Calcd for $C_{28}H_{56}O_6Si$: C, 61.72; H, 10.36. Found: C, 61.50; H, 10.41.

Ethyl (2*Z*,4*R*)-4-[[Diethyl(1-methylethyl)silyl]oxy]-6-hydroxy-2-methyl-3-[(1,1-dimethylethoxy)carbonyl]-2-hexenoate (69). The bis-DEIPS ether **68** (1.46 g, 2.68 mmol) was added a precooled solution of 22.5 mL of 4:1:4 acetic acid/water/THF at 0 °C. After being stirred at ambient temperature for 4 h, the solution was poured into 250 mL of saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with 100 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 15:85) gave 1.05 g (95%) of alcohol **69** as a colorless oil: $[\alpha]^{25}_D = -5.5°$ (*c* 1.24, $CHCl_3$); IR (thin film) 3520, 2940, 2880, 1725 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 4.84 (t, J = 6.6 Hz, 1H), 4.20 (m, 2H), 3.74 (m, 2H), 2.25 (dd, J = 5.9, 5.3 Hz, 1H), 2.11 (m, 1H), 1.99 (s, 3H), 1.95 (m, 1H), 1.50 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H), 1.03−0.91 (m, 13H), 0.71−0.59 (m, 4H). Anal. Calcd for $C_{21}H_{40}O_6Si$: C, 60.54; H, 9.68. Found: C, 60.32; H, 9.67.

Ethyl (2*Z*,4*R*)-4-[[Diethyl(1-methylethyl)silyl]oxy]-5-formyl-2-methyl-3-[(1,1-dimethylethoxy)carbonyl]-2-pentenoate (70). To a solution of 506 mg (1.22 mmol) of **69** in 12 mL of CH_2Cl_2 at ambient temperature was added 637 mg (1.79 mmol) of Dess−Martin periodinane. After the mixture was stirred for 25 min, 10 mL of saturated aqueous Na_2SO_3 and 10 mL of saturated aqueous $NaHCO_3$ were added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 10:90) gave 436 mg (87%) of aldehyde **70** as a colorless oil: $[\alpha]^{25}_D = -6.6°$ (*c* 0.91, $CHCl_3$); IR (thin film) 2930, 2880, 1730 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 9.79 (t, J = 2.0 Hz, 1H), 5.18 (dd, J = 7.9, 5.3 Hz, 1H), 4.20 (m, 2H), 3.05 (ddd, J = 16.5, 7.9, 2.0 Hz, 1H), 2.84 (ddd, J = 16.5, 5.3, 2.0 Hz, 1H), 1.98 (s, 3H), 1.51 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H), 0.99−0.85 (m, 13H), 0.69−0.57 (m, 4H); FI-HR-MS calcd for $C_{21}H_{38}O_6Si$ (M^+) m/z 414.2438, found 414.2419.

(4*Z*,3*R*)-5-(Ethoxycarbonyl)-3-[[diethyl(1-methylethyl)silyl]oxy]-4-[(1,1-dimethylethoxy)carbonyl]-4-hexenoic Acid (71). To a solution of 218 mg (0.507 mmol) of **70** in 4.6 mL of 18:5 2-methyl-2-propanol/water at ambient temperature was added 80 mg (0.52 mmol) of $NaH_2PO_4 \cdot H_2O$, 151 mg (2.16 mmol) of 2-methyl-2-butene, and 138 mg (1.53 mmol) of sodium chlorite. After the mixture was stirred for 40 min, 10 mL of brine was added, and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (acetone/$CHCl_3$, 5:95 → 20:80) gave 199 mg (91%) of carboxylic acid **71** as a colorless oil: $[\alpha]^{24}_D = -0.83°$ (*c* 0.96, $CHCl_3$); IR (thin film) 3500−2300 (br), 2930, 2870, 1730 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.12 (dd, J = 7.9, 5.3 Hz, 1H), 4.20 (m, 2H), 2.96 (dd, J = 15.2, 7.9 Hz, 1H), 2.78 (dd, J = 15.2, 5.3 Hz, 1H), 1.99 (s, 3H), 1.51 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H), 0.99−0.89 (m, 13H), 0.69−0.59 (m, 4H); FI-HR-MS calcd for $C_{21}H_{39}O_7Si$ ($M^+ + H$) m/z 431.2464, found 431.2474.

(2*R*,3*R*)-2-Methoxy-4-methyl-1-(phenylthio)-3-pentyl (4*Z*,3*R*)-5-(Ethoxycarbonyl)-3-[[diethyl(1-methylethyl)silyl]oxy]-4-[(1,1-dimethylethoxy)carbonyl]-4-hexenoate (72). To a solution of 28 mg (65 μmol) of **71** in 0.5 mL of toluene at ambient temperature was added 12 μL (86 μmol) of triethylamine and 12 μL (77 μmol) of 2,4,6-trichlorobenzoyl chloride. After being stirred for 2 h, the mixture was warmed to 60 °C followed by the successive addition of 18 mg (75 μmol) of **60** in 0.5 mL of toluene and 10 mg (82 μmol) of 4-(dimethylamino)pyridine. The mixture was stirred for 3 h and then concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 10:90) gave 40 mg (94%) of triester **72** as a colorless oil: $[\alpha]^{25}_D = +3.6°$ (*c* 1.12, $CHCl_3$); IR (thin film) 2950, 1730 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.39−7.15 (m, 5H), 5.16 (dd, J = 7.3, 5.3 Hz, 1H), 4.96 (dd, J = 7.3, 4.6 Hz, 1H), 4.18 (m, 2H), 3.43 (m, 1H), 3.35 (s, 3H), 3.10 (dd, J = 13.9, 3.3 Hz, 1H), 3.00 (dd, J = 13.9, 7.9 Hz, 1H), 2.94 (dd, J = 16.5, 7.3 Hz, 1H), 2.83 (dd, J = 16.5, 5.3 Hz, 1H), 1.97 (s, 3H), 1.93 (m, 1H), 1.50 (s, 9H), 1.27 (t, J = 7.3 Hz, 3H), 0.99−0.82 (m, 13H), 0.91 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 7.3 Hz, 3H), 0.70−0.59 (m, 4H). Anal. Calcd for $C_{34}H_{56}O_8SiS$: C, 62.54; H, 8.64; S, 4.91. Found: C, 62.52; H, 8.58; S, 4.82.

(2*R*,3*R*)-2-Methoxy-4-methyl-1-(phenylsulfoxy)-3-pentyl (4*Z*,3*R*)-5-(Ethoxycarbonyl)-3-[[diethyl(1-methylethyl)silyl]oxy]-4-[(1,1-dimethylethoxy)carbonyl]-4-hexenoate (73). To a solution of 125 mg (0.191 mmol) of **72** in 4 mL of methanol was added 409 mg (1.91 mmol) of sodium periodate in 2 mL of water. After the mixture was stirred at 35 °C for 2.5 h, 10 mL of water was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 20:80) gave 114 mg (89%) of two (ca. 2:1) sulfoxides **73** as a colorless oil: $[\alpha]^{25}_D = -24.5°$ (*c* 1.65, $CHCl_3$); IR (thin film) 2950, 1725 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 7.76−7.48 (m, 5H), 5.16 (m, 1H), 5.05, 4.90 (multiplets, ca. 2:1 ratio, 1H), 4.21 (q, J = 7.3 Hz, 2H), 4.20, 3.93 (multiplets, ca. 1:2 ratio, 1H), 3.46, 3.07 (singlets, ca. 2:1 ratio, 3H), 3.42, 3.18 (multi-

plets, ca. 2:1 ratio, 1H), 3.10–2.69 (m, 3H), 1.96, 1.93 (singlets, ca. 1:2 ratio, 3H), 1.70 (m, 1H), 1.50, 1.47 (singlets, ca. 1:2 ratio, 9H), 1.29 (m, 3H), 0.99–0.61 (m, 23H); EI-HR-MS calcd for $C_{34}H_{56}O_9SSi$ (M^+) m/z 668.3414, found 668.3436.

(1*R*,2*R*)-1-Formyl-1-methoxy-3-methyl-2-butyl (4*Z*,3*R*)-5-(Ethoxycarbonyl)-3-[[diethyl(1-methylethyl)silyl]oxy]-4-[(1,1-dimethylethoxy)carbonyl]-4-hexenoate (74). To a solution of 39.0 mg (58.3 μmol) of **73** in 1.2 mL of CH_2Cl_2 at 3 °C was added 47 μL (0.58 mmol) of pyridine and 41 μL (0.29 mmol) of trifluoroacetic anhydride. After being stirred at ambient temperature for 1 h, the mixture was cooled to 3 °C. Methanol (0.5 mL) and 50 mg (0.60 mmol) of $NaHCO_3$ were then added to the solution. The mixture was stirred for 1 h before the addition of 2 mL of brine and was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/hexane, 20:80 → 30:70) gave 27.3 mg (84%) of left-hand aldehyde **74** as a colorless oil: $[\alpha]^{25}_D = +27.4°$ (*c* 0.87, $CHCl_3$); IR (thin film) 2950, 1730 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.3 Hz, 1H), 5.14 (dd, *J* = 7.3, 5.9 Hz, 1H), 5.02 (dd, *J* = 7.6, 4.3 Hz, 1H), 4.19 (m, 2H), 3.62 (dd, *J* = 4.3, 2.3 Hz, 1H), 3.43 (s, 3H), 2.93 (dd, *J* = 16.2, 7.3 Hz, 1H), 2.83 (dd, *J* = 16.2, 5.9 Hz, 1H), 2.06 (m, 1H), 1.98 (s, 3H), 1.49 (s, 9H), 1.27 (t, *J* = 7.3 Hz, 3H), 0.99–0.86 (m, 19H), 0.72–0.58 (m, 4H); FI-HR-MS calcd for $C_{28}H_{51}O_9Si$ (M^+ + H) m/z 559.3302, found 559.3300.

Ethyl [2*Z*,4*R*,8*R*,9*S*,10*R*,13*S*,14*S*,17*R*,17[2*S*,3*S*,6*R*,8*S*,8-(3*S*),9*R*]]-4,10,14-Trihydroxy-9-methoxy-2,13,17-trimethyl-3-[(1,1-dimethylethoxy)carbonyl]-8-(1-methylethyl)-17-[3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undec-2-yl]-6,12-dioxo-7-oxa-2-heptadecenoate (75) [Mukaiyama Aldol Reaction]. To a solution of 11.4 mg (21.2 μmol) of **54** in 1 mL of CH_2Cl_2 at 3 °C was added 5.0 μL (36 μmol) of triethylamine and 6.0 μL (31 μmol) of trimethylsilyl trifluoromethanesulfonate. After the mixture was stirred for 1 h, 2 mL of saturated aqueous $NaHCO_3$ was added and the resulting mixture extracted with 1:4 CH_2Cl_2/hexane (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The enol silane thus produced was immediately used without further purification.

To a solution of 11.9 mg (21.3 μmol) of **74** and 7 μL (64 μmol) of titanium(IV) chloride in 1 mL of CH_2Cl_2 at −78 °C was added the above enol silane in 1 mL of CH_2Cl_2. The reaction mixture was allowed to warm to −15 °C over 3 h and then was poured into 4 mL of aqueous pH 7 phosphate buffer with vigorous stirring. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The triethylsilyl group of the aldol thus obtained was found to be decomposed partially, so complete deprotection of silyl protecting groups was performed without purification at this stage.

To the above crude aldol at ambient temperature was added 2 mL of HF solution freshly prepared from 0.5 mL of 47% hydrofluoric acid, 8.6 mL of CH_3CN, and 0.9 mL of water. The mixture was stirred for 2 h, and then 2 mL of 1 N hydrochloric acid was added. The mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 30:70) gave 9.8 mg (54%) of triol **75** as a colorless oil: $[\alpha]^{23}_D = -34.0°$ (*c* 0.1, $CHCl_3$); IR (thin film) 3430 (br), 2930, 1730, 1715, 1445, 1260, 1150, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 5.08 (m, 1H), 5.06 (t, *J* = 5.9 Hz, 1H), 4.97 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 9.9 Hz, 1H), 4.26 (m, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 3.69 (m, 1H), 3.54 (d, *J* = 5.9 Hz, 1H), 3.46 (s, 3H), 3.29 (dd, *J* = ~10, ~2 Hz, 1H), 3.28 (dd, *J* = 5.9, 2.6 Hz, 1H), 3.15 (br t, *J* = 9 Hz, 1H), 3.05–2.91 (m, 2H), 2.67–2.57 (m, 3H), 2.21–2.0 (m, 3H), 1.99 (s, 3H), 1.84 (m, 1H), 1.70–1.20 (m, 17H), 1.51 (s, 9H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.11 (d, *J* = 7.3 Hz, 3H), 1.02–0.96 (m, 12H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{47}H_{80}O_{13}Na$ (M^+ + Na) m/z 875.5497, found 875.5513.

Ethyl [2*Z*,4*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*,17[2*S*,3*S*,6*R*,8*S*,8-(3*S*),9*R*]]-4-[[Diethyl(1-methylethyl)silyl]oxy]-14-[(triethylsilyl)oxy]-10-hydroxy-9-methoxy-2,13,17-trimethyl-3-[(1,1-dimethylethoxy)carbonyl]-8-(1-methylethyl)-17-[3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undec-2-yl]-6,12-dioxo-7-oxa-2-heptadecenoate and Ethyl [2*Z*,4*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*,17[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-4,10,14-Trihydroxy-9-methoxy-2,13,17-trimethyl-3-[(1,1-dimethylethoxy)carbonyl]-8-(1-methylethyl)-17-[3,9-dimethyl-8-(3-methyl-4-pentenyl)-1,7-dioxaspiro[5.5]undec-2-yl]-6,12-dioxo-7-oxa-2-heptadecenoate (76) [Lithium Enolate-Mediated Aldol Reaction]. To a solution of 6.9 mg (13 μmol) of **54** in 0.3 mL of THF at −78 °C was added 39 μL (39 μmol) of 1 M lithium bis(trimethylsilyl)amide in THF. After the mixture was stirred for 30 min, 6.7 mg (12 μmol) of **74** in 0.6 mL of THF was introduced, and the mixture was further stirred for 30 min. Then it was poured into the vigorously stirred solution of 4 mL of aqueous pH 7 phosphate buffer and 5 mL of Et_2O. The aqueous layer was separated and extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 13:87 → 20:80) gave 4.0 mg (30%) of (*S*)-*epi*-aldol followed by the mixture of 0.99 mg (7.5%) of (*R*)-aldol and unreacted **74**, as colorless oils. Data for **(*S*)-*epi*-aldol**: $[\alpha]^{25}_D = -15.8°$ (*c* 0.91, $CHCl_3$); IR (thin film) 3500 (br), 2950, 1730, 1450, 1365, 1255, 1160, 1090 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 5.14 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.96 (dd, *J* = 17.2, ~1 Hz, 1H), 4.92 (dd, *J* = 9.9, ~1 Hz, 1H), 4.86 (t, *J* = 5.9 Hz, 1H), 4.20 (m, 2H), 4.00 (m, 2H), 3.48 (d, *J* = ~4 Hz, 1H), 3.46 (s, 3H), 3.34 (dd, *J* = 5.9, 4.6 Hz, 1H), 3.29 (dd, *J* = 9.9, ~1 Hz, 1H), 3.16 (br t, *J* = ~9 Hz, 1H), 2.98–2.62 (m, 5H), 2.17–2.00 (m, 3H), 1.97 (s, 3H), 1.85 (m, 1H), 1.66–1.20 (m, 17H), 1.49 (s, 9H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.18–0.87 (m, 40H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.69–0.54 (m, 10H); EI-HR-MS calcd for $C_{60}H_{110}O_{13}Si_2$ (M^+) m/z 1094.7482, found 1094.7481.

To a solution of 8.9 mg (8.1 μmol) of (*S*)-*epi*-aldol at ambient temperature was added 0.5 mL of HF solution freshly prepared from 0.5 mL of 47% hydrofluoric acid, 8.6 mL of CH_3CN, and 0.9 mL of water. The mixture was stirred for 1.5 h, and then 0.5 mL of 1 N hydrochloric acid was added. This was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 20:80 → 25:75) gave 6.9 mg (100%) of triol **76** as a colorless oil: $[\alpha]^{23}_D = -56.7°$ (*c* 0.24, $CHCl_3$); IR (thin film) 3430 (br), 2940, 1730, 1460, 1370, 1260, 1160, 1105 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 10.6, 7.3 Hz, 1H), 5.04–4.86 (m, 4H), 4.22 (q, *J* = 7.3 Hz, 2H), 4.11 (m, 1H), 3.66 (m, 1H), 3.57 (d, *J* = 4.0 Hz, 1H), 3.50 (s, 3H), 3.45 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.29 (dd, *J* = 10.6, 2.5 Hz, 1H), 3.24 (d, *J* = 6.6 Hz, 1H), 3.15 (br t, *J* = 9 Hz, 1H), 2.97–2.54 (m, 5H), 2.20–2.00 (m, 3H), 1.99 (s, 3H), 1.84 (m, 1H), 1.65–1.20 (m, 17H), 1.51 (s, 9H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.11 (d, *J* = 7.3 Hz, 3H), 1.02–0.93 (m, 12H), 0.89 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{47}H_{80}O_{13}Na$ (M^+ + Na) m/z 875.5496, found 875.5482.

Ethyl [2*Z*,4*R*,8*R*,9*S*,10*R*,13*S*,14*S*,17*R*,17[2*S*,3*S*,6*R*,8*S*,8-(3*S*),9*R*]]-4,10,14-Trihydroxy-9-methoxy-2,13,17-trimethyl-3-[(1,1-dimethylethoxy)carbonyl]-8-(1-methylethyl)-17-[3,9-dimethyl-8-(3-methyl-4-oxopentyl)-1,7-dioxaspiro[5.5]undec-2-yl]-6,12-dioxo-7-oxa-2-heptadecenoate (77). Palladium(II) chloride (3.0 mg, 17 μmol) and 8.4 mg (89 μmol) of copper(I) chloride were dissolved in 0.2 mL of 7:1 DMF/water. This was stirred under oxygen atmosphere for 1 h. Then a solution of 7.0 mg (8.2 μmol) of **75** in 1 mL of 7:1 DMF/water was added, and the mixture was stirred vigorously for 15 h. The reaction was quenched by the addition of 10 mL of 1 N hydrochloric acid, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 50:50) gave 5.1 mg (72%) of methyl ketone **77** as a colorless oil: $[\alpha]^{25}_D = -21.5°$ (*c* 0.65, $CHCl_3$);

IR (thin film) 3450 (br), 2930, 1735, 1720, 1710, 1450, 1365, 1250, 1150, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.09 (dd, J = 5.9, 3.3 Hz, 1H), 5.06 (t, J = 5.6 Hz, 1H), 4.26 (m, 1H), 4.22 (q, J = 7.3 Hz, 2H), 3.69 (m, 1H), 3.55 (d, J = 5.9 Hz, 1H), 3.46 (s, 3H), 3.29–3.25 (m, 2H), 3.17 (t, J = 9.9 Hz, 1H), 3.03–2.91 (m, 2H), 2.67–2.51 (m, 4H), 2.15 (s, 3H), 2.11 (m, 1H), 2.00 (m, 1H), 1.99 (s, 3H), 1.86 (m, 1H), 1.67–1.20 (m, 17H), 1.51 (s, 9H), 1.29 (t, J = 7.3 Hz, 3H), 1.12 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.01–0.96 (m, 9H), 0.89 (d, J = 7.3 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{47}H_{80}O_{14}Na$ (M^+ + Na) m/z 891.5446, found 891.5444.

Tautomycin. To diester **77** (3.3 mg, 3.8 μmol) at ambient temperature was added a premixed and cooled (3 °C) solution of 3.0 μL (26 μmol) of 2,6-lutidine and 15 μL (66 μmol) of triethylsilyl trifluoromethanesulfonate in 0.5 mL of CH_2Cl_2. The reaction mixture was stirred at ambient temperature for 4 h and was then quenched by the addition of 2 mL of 1 N hydrochloric acid. This was extracted with $CHCl_3$ (3 × 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by high-performance liquid chromatography (GL SCIENCE Inertsil PREP-ODS, 6.0 × 250 mm, 5 μm; methanol/water, 80:20) gave 1.2 mg (41%) of tautomycin as a white amorphous solid: mp 42–43 °C; $[\alpha]^{23}_D$ = +3.3° (*c* 0.60, $CHCl_3$); IR (KBr pellet) 3320 (br), 2910, 1820, 1760, 1725, 1700, 1610, 1350, 1240, 1160, 1070 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.22 (dd, J = 10.2, 2.8 Hz, 1H), 5.10 (t, J = 5.1 Hz, 1H), 4.36 (m, 1H), 3.71 (m, 1H), 3.45 (s, 3H), 3.28 (m, 2H), 3.17 (br t, J = 9.0 Hz, 1H), 3.01 (dd, J = 16.2, 7.7 Hz, 1H), 2.94 (dd, J = 16.2, 3.0 Hz, 1H), 2.77 (dd, J = 16.2, 9.8 Hz, 1H), 2.73–2.62 (m, 2H), 2.53 (m, 1H), 2.27 (s, 3H), 2.15 (s, 3H), 2.00 (m, 2H), 1.84 (m, 1H), 1.75–1.20 (m, 17H), 1.12 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{44}H_{75}O_{16}$ (M^+ + H + glycerine) m/z 859.5055, found 859.5044.

Ethyl [2*Z*,4*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*,17[2*S*,3*S*,6*R*,8*S*,8-(3*S*),9*R*]]-4,10,14-Trihydroxy-9-methoxy-2,13,17-trimethyl-3-[(1,1-dimethylethoxy)carbonyl]-8-(1-methylethyl)-17-[3,9-dimethyl-8-(3-methyl-4-oxopentyl)-1,7-dioxaspiro[5.5]undec-2-yl]-6,12-dioxo-7-oxa-2-heptadecenoate and (22*S*)-*epi*-Tautomycin. The experimental procedure was followed as described for **77** from **75** and **1** from **77**. The yields were 100% for the (*S*)-epimer of **77** and 82% for (22*S*)-*epi*-tautomycin. Data for **(*S*)-epimer of 77**: $[\alpha]^{25}_D$ = −39.3° (*c* 0.57, $CHCl_3$); IR (thin film) 3450 (br), 2930, 1735, 1715, 1450, 1365, 1255, 1150, 1100 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.02 (ddd, J = 9.9, 6.6, 4.0 Hz, 1H), 4.89 (dd, J = 6.9, 5.0 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 4.12 (m, 1H), 3.66 (m, 1H), 3.59 (d, J = 4.0 Hz, 1H), 3.50 (s, 3H), 3.45 (dd, J = 6.9, 3.6 Hz, 1H), 3.28 (d, J = 6.6 Hz, 1H), 3.27 (dd, J = 9.6, 2.3 Hz, 1H), 3.17 (br t, J = 9.6 Hz, 1H), 2.97–2.51 (m, 6H), 2.17–1.97 (m, 2H), 2.15 (s, 3H), 1.86 (m, 1H), 1.66–1.20 (m, 17H), 1.51 (s, 9H), 1.30 (t, J = 7.3 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.9 Hz, 6H), 0.89 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{47}H_{80}O_{14}Na$ (M^+ + Na) m/z 891.5446, found 891.5458.

Data for **(22*S*)-*epi*-tautomycin**: mp 42–45 °C; $[\alpha]^{19}_D$ = −10.0° (*c* 0.20, $CHCl_3$); IR (KBr pellet) 3430 (br), 2930, 1820, 1760, 1735, 1695, 1500, 1450, 1360, 1080 cm^{-1}; ^1H-NMR (270 MHz, $CDCl_3$) δ 5.14 (m, 1H), 4.94 (t, J = 5.9 Hz, 1H), 4.16 (m, 1H), 3.65 (m, 1H), 3.46 (s, 3H), 3.45 (m, 1H), 3.27 (dd, J = 9.9, 2.0 Hz, 1H), 3.17 (br t, J = 9.3 Hz, 1H), 2.94 (dd, J = 16.5, 4.6 Hz, 1H), 2.78 (m, 2H), 2.73 (dd, J = 16.5, 8.6 Hz, 1H), 2.68 (m, 1H), 2.53 (m, 1H), 2.27 (s, 3H), 2.15 (s, 3H), 2.10 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.80–1.10 (m, 17H), 1.12 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 7.3 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); FAB-HR-MS (glycerine matrix) calcd for $C_{44}H_{75}O_{16}$ (M^+ + H + glycerine) m/z 859.5055, found 859.5037.

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Supporting Information Available: Spectroscopic data for compounds **16**, X-ray crystal structure of **24**, and ^1H-NMR spectra of those compounds lacking combustion analysis (57 pages). This material is contained in 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.

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