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Synthetic Studies on Tautomycin Synthesis of Segment B

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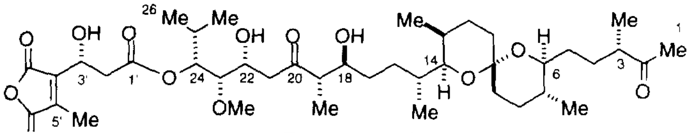
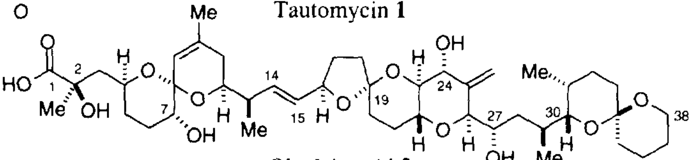
Abstract: The synthesis of Segment B corresponding to the C26-C17 portion of tautomycin was accomplished by coupling reaction between the epoxide (Sub-segment B-1) and the dithiane (Sub-segment B-2). The degradation product of tautomycin corresponding to the C26-C19 portion was also synthesized from Sub-segment B-1. © 1997 Elsevier Science Ltd.

Tautomycin **1** was isolated from *Streptomyces spiroverticillatus* in 1987 by Isono and co-workers as a new antibiotic with strong antifungal activity against *Sclerotinia sclerotiorum*.[1] This antibiotic was also found to induce a morphological exchange in human leukemia cells K562.[2] Moreover, tautomycin was recognized as an inhibitor of protein phosphatases type 1 and type 2A.[3] While all the other inhibitors, okadaic acid,[4] calyculin A,[5] microcystin-LR[6] and nodularin,[7] have been isolated from marine sponge and similar sources, tautomycin is the first such inhibitor that has been found from non-marine sources. The structure of **1** containing 13 chiral centers was determined on the basis of chemical degradation and conformational calculations.[8] Its important biological activities as well as its unique structure encouraged synthetic efforts,[9] and the first total synthesis was achieved by Ichihara's group in 1994.[10] We have reported the total synthesis of okadaic acid **2** in 1986[11] and continued our research on the molecular mechanism of protein phosphatase inhibition.[12] Structural similarity between **1** and **2** led us to start our research on the inhibitory mechanisms with special reference to the molecular-shape and activity relationship.[13] During this study, we achieved the total synthesis of **1** in 1995.[14,15] In the following three papers, we report the full detail of our total synthesis.

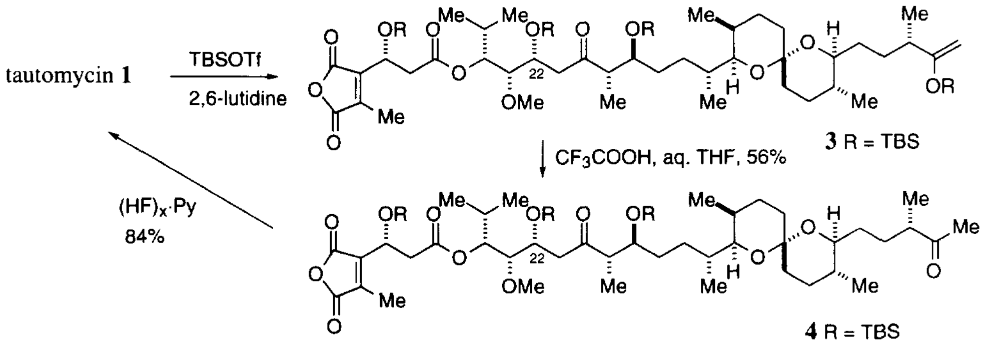


Tautomycin **1**

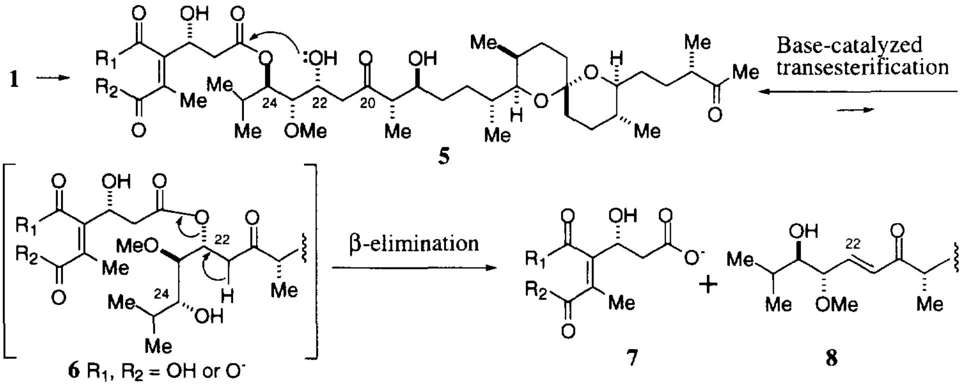


Okadaic acid **2**

Preliminary Studies At the beginning of our synthesis, we examined the stability of tautomycin to confirm the deprotection conditions at the final stage of the synthesis. Basic conditions for the removal of protecting groups seemed to constitute a serious problem, because Ubukata et al. observed base-catalyzed elimination of C22 hydroxy group under weakly basic conditions (MeOH, 20% Cs_2CO_3, pH 9).[8] Therefore, the silyl protecting group was considered most acceptable, because the silyl group could be removed under weakly acidic conditions.[16] Tris(*t*-butyldimethylsilyl)tautomycin **4** was prepared from natural tautomycin as shown in Scheme 1. Reaction of tautomycin with *t*-butyldimethylsilyl trifluoromethanesulfonate (*t*-$BuMe_2SiOTf$) and 2,6-lutidine gave the silyl vinyl ether **3** which was successively treated with trifluoroacetic acid (TFA) in aqueous tetrahydrofuran (THF) providing **4** in 56% yield. The resulting tris(*t*-butyldimethylsilyl)tautomycin **4** was subjected to the conditions for the removal of the silyl group and we found that **4** was reconverted into tautomycin **1** with poly(hydrogen fluoride) pyridine complex in 84% yield without C22 hydroxy group elimination.[17]



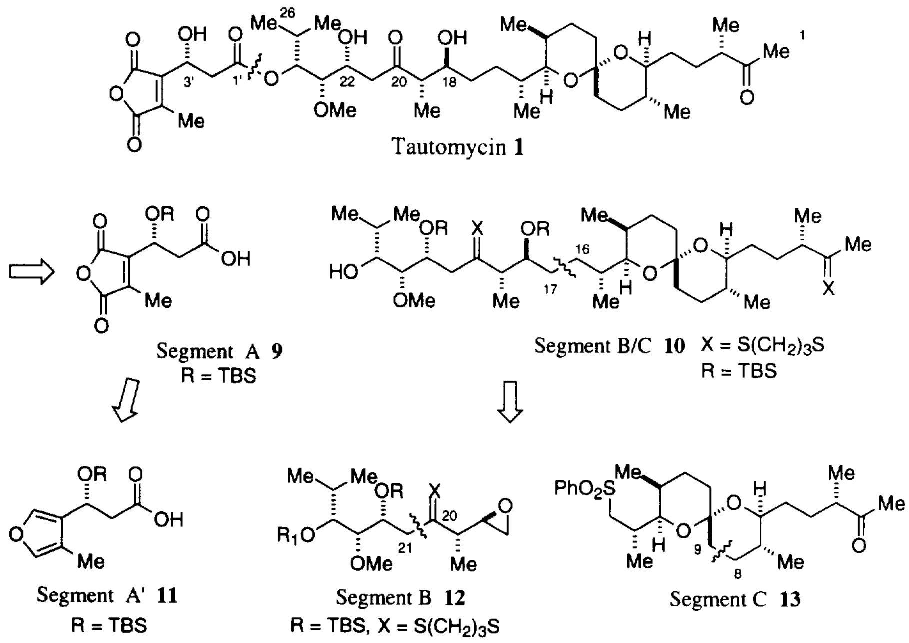
Scheme 1



Scheme 2

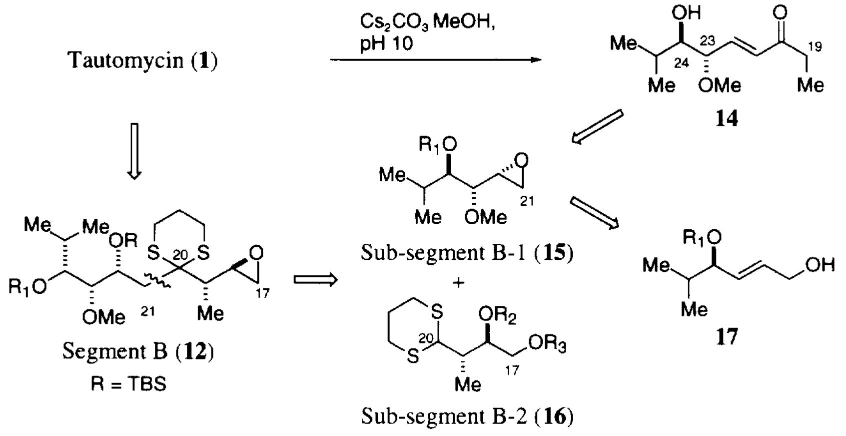
In addition, we have recognized an interesting behavior of tris(*t*-butyldimethylsilyl)tautomycin **4**. Many attempts failed to hydrolyze the ester moiety of tris(*t*-butyldimethylsilyl)tautomycin under basic conditions, and no elimination of C22 *t*-butyldimethylsiloxy group was observed. From this observation, we envisioned that treatment of tautomycin **1** with base resulted in the equilibration shifting the ester moiety from C24 to C22 hydroxy group, and the resulting **6** underwent β-elimination to provide the enone **8** as shown in Scheme 2. These observations suggested that protection of the C22 hydroxy group and/or C20 carbonyl group may prevent the β-elimination. Based on these assumption, our synthetic strategy was designed as illustrated in Scheme 3.

Retrosynthetic Analysis Disconnection of the C1' ester bond in **1** afforded Segment A (**9** or **11**) and Segment B/C **10** which was further disconnected into Segment B **12** and Segment C **13**. The most interesting feature of our disconnection analysis is based on the construction of carbon backbone employing the epoxide opening reaction with carbanions. In fact, carbon-carbon bond formation between C21 and C20 as well as C8 and C9 were considered along this strategy. In this context, we planned to construct Segment B/C **10** by the reaction of Segment B **12** (epoxide) with Segment C **13** (sulfone carbanion). After the union of these segments, maleic anhydride moiety would be introduced either by direct esterification of **9** with Segment B/C **10** or via oxidation of furan ring **11** after connection with Segment B/C **10**. Three hydroxyls at the C3', C22 and C18 were protected with *t*-butyldimethylsilyl group as described before. Two carbonyl groups were also planned to protect as 1,3-dithiane to avoid epimerization at the C3 and C19 stereogenic centers and elimination of the C22 hydroxy group during synthesis.



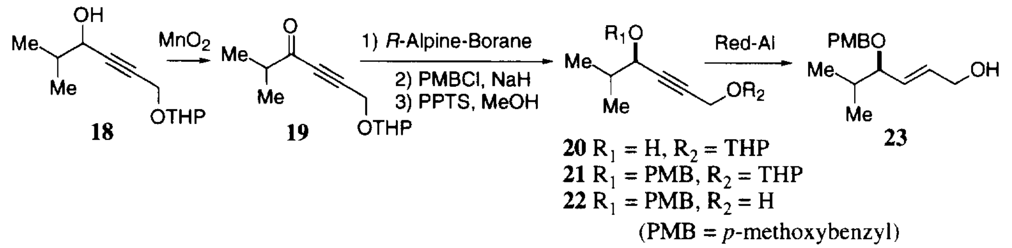
Scheme 3

Synthetic plan of Segment B In the degradation studies, the enone **14** corresponding to the C26-C19 portion was isolated by retro-aldol reaction (tautomycin numbering) as shown in Scheme 4.[8] The relative stereochemistry at the C23 and C24 positions was confirmed by the synthesis of the corresponding racemic enone **14**.[18] We had the plan to synthesize Segment B (in the form of **12**) and the chiral enone **14** from a common intermediate, therefore, disconnection of Segment B between the C21 and the C20 positions resulted in Sub-segment B-1 (**15**) and Sub-segment B-2 (**16**). Sub-segment B-1 was planned to prepare from the chiral allyl alcohol **17**. In this manuscript, we described the full detail of the synthesis of Segment B and the chiral enone **14**.[14(b)]



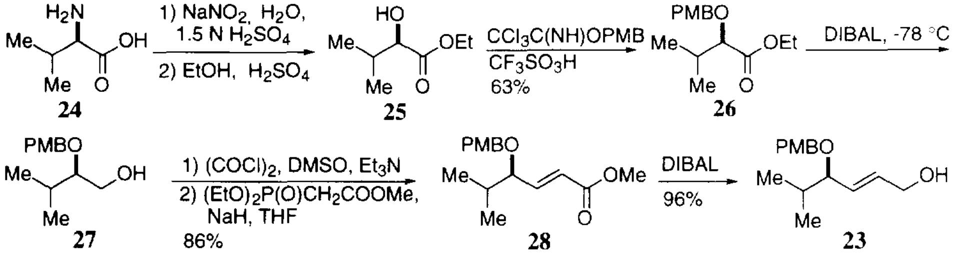
Scheme 4

Synthesis of Sub-segment B-1. We examined two methods for the synthesis of the chiral allyl alcohol **17** wherein the first synthetic route involves the asymmetric reduction developed by Midland[19] as depicted in Scheme 5. Activated manganese (IV) oxide oxidation of the racemic allyl alcohol **18**[18] furnished the ynone **19** which was treated with *R*-Alpine-Borane. Since many products arising from the *R*-Alpine-Borane reagent were observed after the work-up, we could not purify **20** at this stage. Therefore, a portion of **20** was converted into the corresponding MTPA ester,[20] and the optical purity was confirmed to be more than 95% after hydrolysis of tetrahydropyranyl moiety. Protection of **20** with *p*-methoxybenzyl chloride and sodium hydride provided **21** in 67% overall yield from **19**. It should be noted that use of excess sodium hydride suffered from a substantial amount of racemization. Hydrolysis of **21** with pyridinium *p*-toluenesulfonate in methanol followed by reduction using sodium bis(2-methoxyethoxy)aluminum hydride furnished **23** in 57% overall yield from **21**.



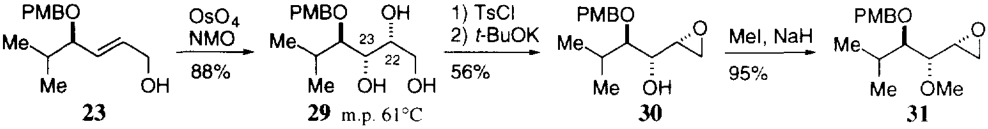
Scheme 5

Although the first route provided the chiral allyl alcohol **23** with high enantioselectivity, we further examined derivation from enantiomerically pure precursor as shown in Scheme 6. The second route started from the α-hydroxy ester **25** which was easily prepared by deamination of D-valine **24**.[21] Protection of the hydroxy group of **25** with *p*-methoxybenzyl 2,2,2-trichloroacetimidate in the presence of trifluoromethanesulfonic acid gave the *p*-methoxybenzyl ether **26** in 63% yield.[22] Reduction of **26** with diisobutylaluminum hydride (DIBAL) provided **27** which was transformed into the unsaturated ester **28** by the Swern oxidation and the Horner-Emmons olefination using methyl diethylphosphonoacetate in 86% overall yield from **26** with high selectivity (*E*:*Z* = 97:3). Treatment of **28** with DIBAL at -78 °C furnished the chiral allyl alcohol **23** in 96% yield.



Scheme 6

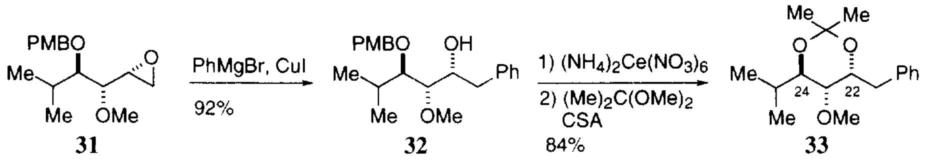
Introduction of the two hydroxy groups to the allyl alcohol **23** at the C22 and C23 was achieved by osmium-catalyzed dihydroxylation which established both the stereogenic centers in a single step. Thus, diastereoselective dihydroxylation of the allyl alcohol **23** using a catalytic amount of osmium tetroxide with *N*-methylmorpholine *N*-oxide (NMO) as oxidants proceeded at -20 °C for 48 h to provide a 12:1 mixture of the triol **29** and its diastereoisomer in 88% yield (Scheme 7). The stereochemistry of **29** was tentatively assigned based on the empirical rule reported by Kishi.[23] Recrystallization of the mixture of the triols furnished the pure **29** as crystals (m.p. 61°C, from ether/hexane). Selective tosylation of the primary hydroxy group of **29** with *p*-toluenesulfonyl chloride provided the corresponding β-hydroxy sulfonate which was treated with potassium *t*-butoxide in tetrahydrofuran at -78 °C to yield the epoxy alcohol **30**. Finally, the epoxy alcohol **30** was converted with sodium hydride and methyl iodide into Sub-segment B-1 (**31**) in 95% yield without Payne rearrangement.



Scheme 7

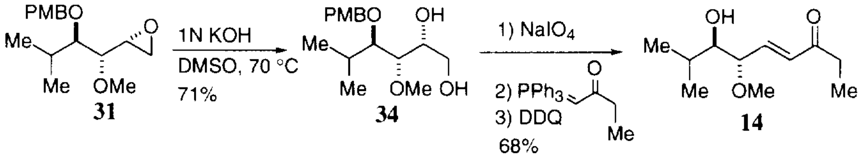
Confirmation of the Stereochemistry of the triol 29. Rychnovsky reported that *syn*- and *anti*-1,3-diol acetonides could be assigned from the ^{13}C NMR chemical shifts of the acetal methyl groups.[24] In general, the *syn*-1,3-diol acetonides have acetal methyl signals appearing at 19 and 30 ppm, while the *anti*-acetonides have methyl signals in the range of 24-25 ppm. The stereochemistry of **29** was supported by using his generalization. Thus, Sub-segment B-1 (**31**) was transformed into the 1,3-diol acetonide **33** as shown in Scheme 8. Epoxide opening of **31** with phenylmagnesium bromide gave **32**. Removal of *p*-methoxybenzyl ether of **32** by ceric ammonium nitrate (CAN)[25] provided the diol which was treated with 2,2-

dimethoxypropane in the presence of a catalytic amount of camphorsulfonic acid to afford the acetonide **33**. The ^{13}C NMR spectra of the acetonide **33** showed two methyl groups at 23.6 and 25.1 ppm, which confirmed the stereochemistry of **29**.

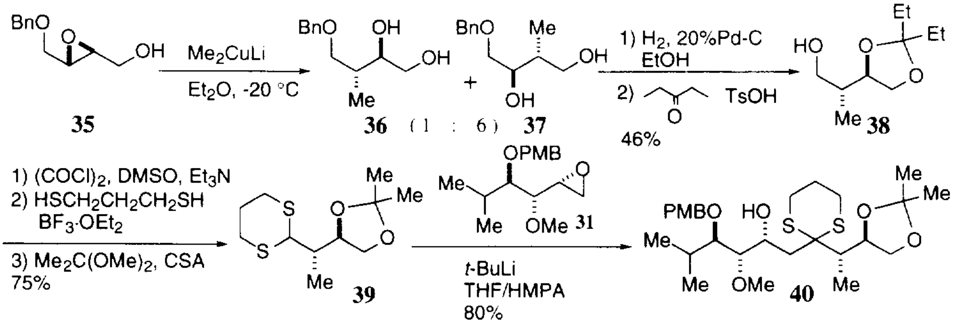


Scheme 8

Synthesis of the Enone 14. Scheme 9 illustrated the synthesis of the enone **14** starting from Sub-segment B-1 **31**. Cleavage of the epoxide **31** with aqueous potassium hydroxide in dimethyl sulfoxide provided the diol **34**. Oxidative cleavage of the diol **34** with sodium periodate provided the aldehyde which was subjected to the Wittig olefination by 2-oxo-1-triphenylphosphoranyllidenebutane (*E*:*Z* = 5:1). Finally, deprotection with DDQ furnished the enone **14** in 68% overall yield from **34**. The spectroscopic data (IR, NMR, $[\alpha]_D$) of our synthetic material proved to be identical with those derived from natural tautomycin.[26]



Scheme 9

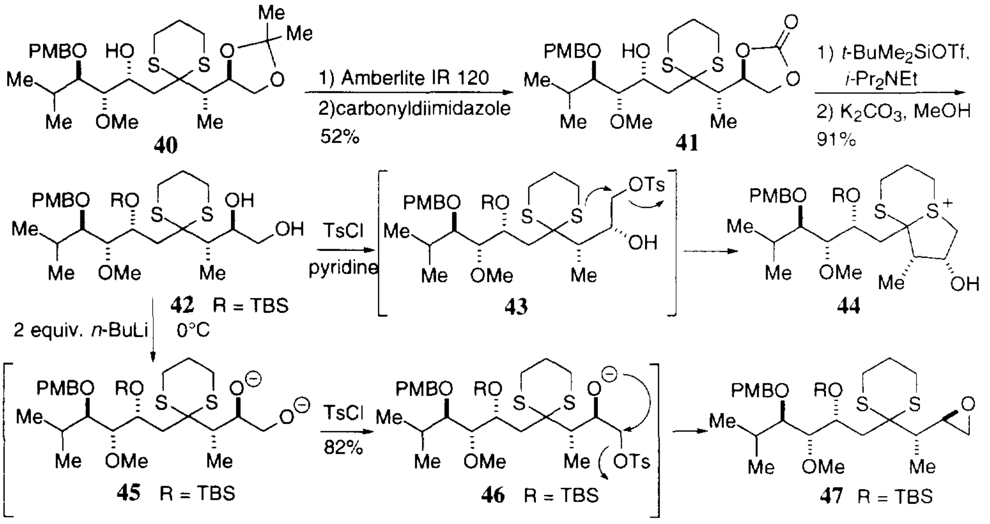


Scheme 10

Synthesis of Sub-segment B-2 and Coupling Reaction with Sub-segment B-1. Synthesis of Sub-segment B-2 began with chiral epoxide **35**[27] as depicted in Scheme 10. Treatment of **35** with dimethyl cuprate in ether at -20 °C afforded a mixture of **36** and **37**.[28] Removal of the benzyl group of this mixture by hydrogenolysis[29] and selective 1,2-diol protection with 3-pentanone provided **38** in 46% overall yield.[30] The resulting alcohol **38** was oxidized by Swern oxidation to afford the aldehyde, which was subsequently treated with 1,3-propanedithiol and 2,2-dimethoxypropane in the presence of acid catalysts (boron trifluoride etherate and CSA) to yield Sub-segment B-2 (**39**) in 75% yield. Treatment of Sub-segment B-2 dithiane (**39**) with *t*-

butyllithium in a mixture of tetrahydrofuran and HMPA provided the corresponding dithiane anion which was coupled with Sub-segment B-1 epoxide (**39**) at -20 °C for 2 h to furnish the coupling product **40** in 80% yield.[31]

The final stage for the synthesis of Segment B was shown in Scheme 11. Protecting group manipulation of **40** [i) Amberlite IR 120, ii) carbonyldiimidazole, iii) *t*-BuMe$_2$SiOTf, *i*-Pr$_2$NEt, iv) K$_2$CO$_3$, MeOH] provided the diol **42** in 47% overall yield. Treatment of **42** with *p*-toluenesulfonyl chloride in pyridine gave no isolable tosylate **43** which may be the result of the neighboring group participation of the sulfur in dithiane to form the bicyclic sulfonium compound **44**. We speculated that the reaction of the alkoxide such as **45** with *p*-toluenesulfonyl chloride afforded the tosylate **46** which would effect more rapid epoxide formation than sulfonium ion formation due to the high nucleophilicity of the alkoxide at the β-position of the sulfonate. In fact, the alkoxide **45** prepared by the reaction of **42** with two equivalents of *n*-butyllithium was treated with *p*-toluenesulfonyl chloride at 0 °C to furnish Segment B (**47**) in 82% yield. The resulting Segment B was stable enough to purify by rapid silica gel chromatography and could be stored at -20 °C for a few weeks.



Scheme 11

A convergent synthesis of Segment B of tautomycin has been accomplished through the coupling reaction of the two sub-segments. The chiral enone **14** was also synthesized from Sub-segment B-1. Synthesis of Segment C and further coupling reaction of each segment for the total synthesis of tautomycin is reported in the following manuscripts.

Experimental Section

General: Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Infrared spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance

(^{13}C NMR) spectra were recorded on a JEOL EX-270, a Varian Gemini-2000, a BRUKER ARX-400 or an AMX-600 spectrometers. Tautomycin numbering corresponding to the front page is employed for assignment of ^{1}H NMR. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Low-resolution mass spectra (EI, FAB) were recorded on a JEOL JMS-D 100 spectrometer or a JEOL DX-705L spectrometer. High-resolution mass spectra (HRMS) were recorded on a JEOL DX-705L spectrometer and reported in *m/z*. Elemental analysis were performed by Mr. S. Kitamura in Analytical Laboratory at School of Agricultural Sciences, Nagoya University to whom the authors gratefully acknowledge. All organic solutions from work-ups were dried by brief exposure to anhydrous sodium sulfate.

Protection of tautomycin (1) with *t*-butyldimethylsilyl ether.

To a solution of **1** (284 mg, 0.37 mmol) dissolved in dichloromethane (6 ml) were added 2,6-lutidine (0.85 ml, 7.3 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.85 ml, 3.7 mmol) at 0 °C. After being stirred for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was poured into saturated aqueous ammonium chloride and extracted with dichloromethane. The combined organic phase was dried and then concentrated. The residue (0.93 g) was diluted with ether and hexane (1/5) and then filtered. The filtrate was dried and concentrated to give the crude silyl vinyl ether **3** (369 mg).

The crude silyl vinyl ether **3** (74 mg) dissolved in tetrahydrofuran (1 ml) was treated with trifluoroacetic acid (13 µl) at room temperature overnight. The reaction mixture was concentrated, and the residue was purified by an ODS column and eluted with a mixture of acetonitrile and water (v/v 70%, 90% and 100%). The acetonitrile fraction was evaporated to afford the tris(*t*-butyldimethylsilyl)tautomycin **4** (30 mg, 56%). IR (KBr) ν_{max} 2930, 1772, 1739, 1715, 1464, 1386, 1255, 1180, 1098, 1005, 987, 915, 837, 780, 731 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) δ -0.02 (3H, s, SiC*H*$_3$), 0.02 (6H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.80 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.82 (9H, s, Si*t-Bu*), 0.85 (9H, s, Si*t-Bu*), 0.86 (9H, s, Si*t-Bu*), 0.88 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.90 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.91 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.95 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.97 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.09 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.20-2.14 (20H, m), 2.14 (3H, s, H-1), 2.22 (3H, d, *J* = 1 Hz, Ar-C*H*$_3$), 2.56 (1H, sext, *J* = 7 Hz, H-3), 2.65-2.72 (3H, m, H-21, H-19), 2.72 (1H, dd, *J* = 16, 6 Hz, one of H-2'), 2.86 (1H, dd, *J* = 16, 7 Hz, one of H-2'), 3.17 (1H, td, *J* = 10, 2 Hz, H-6), 3.23 (1H, dd, *J* = 7, 4 Hz, H-23), 3.26 (1H, dd, *J* = 10, 2 Hz, H-14), 3.35 (3H, s, OC*H*$_3$), 3.96 (1H, m, H-18), 4.46 (1H, dt, *J* = 7, 4 Hz, H-22), 4.92 (1H, dd, *J* = 7, 4 Hz, H-24), 5.16 (1H, dd, *J* = 7, 6 Hz, H-3'). ^{13}C NMR (CDCl$_3$, 100.6 MHz) δ -5.2, -4.9, -4.9, -4.7, -4.5, -4.3, 10.1, 10.9, 11.5, 16.0, 16.6, 16.8, 18.0, 18.1, 20.0, 25.6, 25.8, 25.9, 26.7, 27.6, 28.0, 28.1, 28.6, 29.1, 30.2, 30.4, 30.5, 34.8, 35.0, 36.1, 41.2, 46.8, 47.3, 52.0, 58.8, 63.0, 67.0, 73.1, 74.3, 75.1, 81.7, 95.6, 142.2, 143.5, 163.9, 165.8, 169.0, 210.9, 212.7. $[\alpha]_D^{27}$ +16.1° (*c* 0.21, CHCl$_3$).

Deprotection of tris(*t*-butyldimethylsilyl)tautomycin (4).

A solution of tri-*t*-butyldimethylsilyl-tautomycin **4** (8.0 mg, 7.2 µmol) dissolved in tetrahydrofuran (0.5ml) was transferred into a teflon vial. Pyridinium poly(hydrogen fluoride) (three drops) was added at 0 °C and the reaction mixture was stirred overnight. After careful addition of saturated aqueous sodium hydrogen carbonate, the aqueous layer at pH 4 was extracted with ethyl acetate. The combined organic phase was dried and then concentrated to afford the residue which was purified by a short column of silica gel (1g, ethyl acetate/hexane, 1:1) to provide tautomycin **1** (4.7 mg, 84%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.80 (3H, d, *J* = 7 Hz, CHCH_3), 0.89 (3H, d, *J* = 7 Hz, CHCH_3), 0.96 (3H, d, *J* = 7 Hz, CHCH_3), 0.98 (3H, d, *J* = 7 Hz, CHCH_3), 0.99 (1H, m), 1.00 (3H, d, *J* = 7 Hz, CHCH_3), 1.10 (3H, d, *J* = 7 Hz, CHCH_3), 1.11 (3H, d, *J* = 7 Hz, CHCH_3), 1.20-2.12 (19H, m), 2.11 (1H, m, H-25), 2.15 (3H, s, H-1), 2.27 (3H, d, *J* = 1 Hz, 5'-CH_3), 2.53 (1H, sext, *J* = 7 Hz, H-3), 2.67 (1H, m, H-19), 2.67 (1H, dd, *J* = 17, 4 Hz, one of H-21), 2.77 (1H, dd, *J* = 16, 10 Hz, one of H-2'), 2.93 (1H, dd, *J* = 16, 3 Hz, one of H-2'), 3.00 (1H, dd, *J* = 17, 9 Hz, one of H-21), 3.16 (1H, td, *J* = 10, 2 Hz, H-6), 3.27 (1H, dd, *J* = 6, 2 Hz, H-23), 3.27 (1H, dd, *J* = 10, 2 Hz, H-14), 3.44 (3H, s, OCH_3), 3.70 (1H, td, J = 8, 3 Hz, H-18), 4.36 (1H, m, H-22), 5.10 (1H, t, *J* = 6 Hz, H-24), 5.21 (1H, m, H-3').

5-Methyl-4-oxo-1-(tetrahydropyran-2-yloxy)-2-hexyne (19).

A solution of **18** (2.0 g, 9.4 mmol) and manganese (IV) oxide (12.0 g, ~140 mmol) in dichloromethane was vigorously stirred at room temperature for 4 h, and the mixture was diluted with ether, filtered through Celite and then concentrated. Purification by silica gel chromatography (60 g, ether/hexane, 1:3) afforded the ynone **19** (0.92 g, 46%). IR (KBr) ν_{max} 2946, 2214, 1678, 1467, 1387, 1344, 1243, 1190, 1123, 1080, 1059, 1032, 951, 903, 871, 817 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ 1.20 (6H, d, *J* = 7 Hz, H-26), 1.50-1.92 (6H, m, THP), 2.66 (1H, m, H-25), 3.50-3.61 (1H, m, THP), 3.78-3.91 (1H, m, THP), 4.44 (2H, s, CH_2OTHP), 4.83 (1H, t, *J* = 3 Hz, THP). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 17.7, 18.8, 25.2, 30.0, 42.8, 53.7, 61.9, 83.7, 88.7, 97.0, 191.4.

(4*R*)-4-(4-Methoxybenzyl)oxy-5-methyl-2-hexyne-1-ol (22).

A dry two necked flask was charged with *R*-Alpine-Borane (0.5M solution in tetrahydrofuran, 1.92 ml 0.96 mmol) and **19** (100 mg, 0.48 mmol). Tetrahydrofuran was removed under reduced pressure, and the resulting mixture was stirred at room temperature overnight. Propionaldehyde (0.08 ml, 1.11 mmol) was added. After stirring for 1 h, liberated α-pinene was removed in vacuum. The mixture was diluted with tetrahydrofuran (0.4 ml) and 3N aqueous sodium hydroxide. Hydrogen peroxide (30%; 0.3 ml) was added dropwise. After being stirred at room temperature for 3 h, the mixture was diluted with ether, and the resulting aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by silica gel chromatography (15 g, ether/hexane, 1:2) to provide the crude **20** (108 mg).

A suspension of sodium hydride (60% dispersion in mineral oil, 7.4 mg, 0.18 mmol, washed with hexane before use) in dimethyl sulfoxide (0.7 ml) was heated at 60°C for 30 min. The mixture was cooled to room temperature, and the crude **20** (38 mg, 0.18 mmol) and *p*-methoxybenzyl chloride (0.025 ml, 0.28 mmol) was added. After being stirred for 40 min, the mixture was poured into ice. The solution was extracted with ether, and the combined organic phase was washed with water and brine and then dried. Concentration of the solution under reduced pressure and subsequent preparative thin layer chromatography (ether/hexane, 1:5) gave **21** (32 mg, 67%, 2 steps).

A mixture of **21** (27 mg, 0.081 mmol) and pyridinium *p*-toluenesulfonate (6 mg, 0.024 mmol) dissolved in methanol (1.5 ml) was heated at 55 °C for 90 min. The reaction mixture was poured into saturated sodium hydrogen carbonate, and the separated aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by silica gel chromatography (2 g, ether/hexane, 1:2) to afford **22** (19 mg, 94%). IR (KBr) ν_{max} 3416, 2963, 2871, 2326, 1613, 1515, 1466, 1303, 1250, 1175, 1111, 1071, 1036, 823 cm^{-1}. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.97 (3H, d, *J* = 7 Hz, H-26), 1.00 (3H, d, *J* = 7 Hz, H-26), 1.65 (1H, br, OH), 1.94 (1H, m, H-25), 3.80 (3H, s, Ar-OC*H*$_3$), 3.86 (1H, dt, *J* = 6, 1 Hz, H-24), 4.34 (2H, br, C*H*$_2$OH), 4.44 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 4.72 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.28 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR (CDCl$_3$, 100 MHz) δ 18.0, 18.5, 33.0, 51.2, 55.3, 70.3, 74.0, 83.9, 84.6, 129.5, 130.2, 159.2. EI-MS m/z 248 (M$^+$). HRMS (EI) calcd for $C_{15}H_{20}O_4$ 248.1412, found 248.1398. $[\alpha]_D^{26}$ +124.2° (*c* 0.19, CHCl$_3$).

(2*E*,4*R*)-4-(4-Methoxybenzyl)oxy-5-methyl-2-hexene-1-ol (23). (From asymmetric reduction)

Sodium bis(2-methoxyethoxy)aluminum hydride (70% in toluene; 0.08 ml, 0.29 mmol) was added to a cold solution of **22** (18 mg, 0.073 mmol) in ether (1 ml) at -20 °C. After stirring for 8 h, methanol was added cautiously, and the mixture was poured into aqueous potassium sodium tartrate (1 g). The separated aqueous phase was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated. Purification of the resulting residue by preparative thin layer chromatography (ether/hexane, 3:2) afforded **23** (11 mg, 61%). $[\alpha]_D^{26}$ +36.0° (*c* 0.53, CHCl$_3$).

(2*R*)-Ethyl 2-(4-methoxybenzyl)oxy-3-methylbutanoate (26).

Trifluoromethane-sulfonic acid (60 μl, 0.68 mmol) was added dropwise to a solution of **25** (10 g, 68 mmol) and *p*-methoxybenzyl trichloroacetimidate (34 g, 122 mmol) in ether (350 ml) at 0 °C. After stirring for 30 min, saturated aqueous sodium hydrogen carbonate was added and the resulting mixture was extracted with ether (3 times). The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure. The resulting residue was dissolved in hexane, and the precipitated trichloroacetamide was removed by filtration. The filtrate was concentrated and then purified by silica gel chromatography (300 g, ethyl acetate-hexane 1:10) to afford **26** (11.5 g, 63%). IR (KBr) ν_{max} 2964, 1745, 1613, 1514, 1465, 1250, 1182, 1142, 1034 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.93 (3H, d, *J* = 7 Hz, H-26), 0.96 (3H, d, *J* = 7 Hz, H-26), 1.29 (3H, t, *J* = 7 Hz, OCH$_2$C*H*$_3$), 2.07 (1H, m, H-25), 3.64 (1H, d, *J* = 6 Hz, H-24), 3.80 (3H, s, Ar-OC*H*$_3$), 4.21 (1H, q, *J* = 7 Hz, one of OC*H*$_2$CH$_3$), 4.22 (1H, q, *J* = 7 Hz, one of OC*H*$_2$CH$_3$), 4.31 (1H, d, *J* = 12 Hz, one of C*H*$_2$Ar), 4.63 (1H, d, *J* = 12 Hz, one of C*H*$_2$Ar), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.27 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 14.3, 17.8, 18.7, 31.5, 55.2, 60.5, 82.9, 113.6, 129.6, 129.8, 159.2, 172.5. EI-MS m/z 266 (M$^+$). HRMS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1513. $[\alpha]_D^{27}$ +81.3° (*c* 0.51, CHCl$_3$).

(2*R*)-2-(4-Methoxybenzyl)oxy-3-methyl-1-butanol (27).

A three-necked round-bottomed flask (500 ml) equipped with a nitrogen inlet, a dropping funnel and a magnetic stirring bar were charged with **26** (11 g, 41 mmol) and dichloromethane (100 ml) and then was cooled to -78 °C. Diisobutylaluminum hydride (1 M solution in hexane; 95 ml, 95 mmol) was added through a dropping funnel over 25 min. After being stirred at -78 °C for 20 min, the reaction mixture was allowed to warm to 0 °C over 2 h. Methanol was added to the mixture until the evolution of gas ceased, and the reaction mixture was poured into ice-cooled aqueous potassium sodium tartrate (40 g). The separated aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried and then concentrated to give the residue which was purified by silica gel chromatography (300 g, ether-hexane 1:1) to afford **27** (8.5 g, 92%). IR (KBr) ν_{max} 3423, 2959, 1613, 1514, 1466, 1302, 1249, 1174, 1078, 1037, 824 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, *J* = 7 Hz, H-26), 0.97 (3H, d, *J* = 7 Hz, H-26), 1.95 (1H, m, H-25), 2.04 (1H, br, OH), 3.21 (1H, ddd, *J* = 7, 7, 3 Hz, H-24), 3.57 (1H, dd, *J* = 11, 7 Hz, one of CH_2OH), 3.68 (1H, dd, *J* = 11, 3 Hz, one of CH_2OH), 3.79 (3H, s, Ar-OCH_3), 4.48 (1H, d, *J* = 11 Hz, one of CH_2Ar), 4.55 (1H, d, *J* = 11 Hz, one of CH_2Ar), 6.88 (2H, d, *J* = 8 Hz, ArH), 7.28 (2H, d, *J* = 8 Hz, ArH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.2, 18.7, 29.0, 55.2, 61.7, 72.1, 84.6, 113.8, 129.3, 130.6, 159.2. EI-MS m/z 224 (M^+). HRMS (EI) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1400. $[\alpha]_D^{26}$ -10.9° (*c* 1.23, $CHCl_3$).

(2*E*,4*R*)-Methyl 4-(4-methoxybenzyl)oxy-5-methyl-2-hexanoate (28).

Dimethyl sulfoxide (6.55 ml, 93 mmol) was added dropwise to a solution of oxalyl chloride (4.84 ml, 56 mmol) in dichloromethane (100 ml) at -78 °C over 5 min. After stirring for 10 min, a solution of **27** prepared above (8.25 g, 37 mmol) in dichloromethane (40 ml) was added over 10 min. After stirring at -78 °C for 20 min, triethylamine (24.5 ml, 185 mmol) was added, and stirring was continued for 30 min. The reaction mixture was allowed to warm to 0 °C over 1 h, and the resulting mixture was poured into a mixture of ether and saturated aqueous ammonium chloride. The aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to afford the crude aldehyde (9.39 g).

Methyl diethylphosphonoacetate (10.2 ml, 56 mmol) in tetrahydrofuran (50 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 2.1 g, 53 mmol, washed with hexane before use) in tetrahydrofuran (50 ml) under nitrogen atmosphere at 0 °C over 5 min. After stirring at room temperature for 30 min, the resulting homogeneous solution was cooled to -78 °C. A solution of the crude aldehyde (9.39 g) dissolved in tetrahydrofuran (100 ml) was added, and the reaction mixture was stirred at -78 °C for 15 min . The cooling bath was removed, and stirring was continued at room temperature for 1.5 h. Water was added to the mixture and the resulting aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give the residue which was purified by silica gel chromatography (300 g, ether-hexane 1:5) to afford **28** (9.60 g, 94%, 2 steps). IR (KBr) ν_{max} 2961, 1727, 1613, 1514, 1466, 1437, 1302, 1249, 1172, 1071, 1036, 987, 821 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.88 (3H, d, *J* = 7 Hz, H-26), 0.94 (3H, d, *J* = 7 Hz, H-26), 1.86 (1H, m, H-25), 3.64 (1H, td, *J* = 7, 1 Hz, H-24), 3.76 (3H, s, COOCH_3), 3.80 (3H, s, Ar-OCH_3), 4.27 (1H, d, *J* = 11 Hz, one of CH_2Ar), 4.52 (1H, d, *J* = 11 Hz, one of CH_2Ar), 6.00 (1H, dd, *J* = 16, 1 Hz, H-22), 6.87 (1H, dd, *J* = 16, 7 Hz, H-23), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.24 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.2, 18.3, 32.6, 51.5, 55.2, 70.8, 82.8, 113.7, 122.5, 129.2, 130.3, 147.5, 159.1, 166.5. EI-MS m/z 278 (M^+). $[\alpha]_D^{25}$ +60.4° (*c* 0.80, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.00; H, 8.05.

(2*E*,4*R*)-4-(4-Methoxybenzyl)oxy-5-methyl-2-hexene-1-ol (23). (From D-valine)

A three-necked round-bottomed flask (500 ml) equipped with a nitrogen inlet, a dropping funnel and a magnetic stirring bar were charged with the ester **28** (8.62 g, 31 mmol) and dichloromethane (100 ml). To this solution was added diisobutylaluminum hydride (1 M solution in hexane; 78 ml, 78 mmol) at -78°C *via* a dropping funnel over 25 min and then stirring was continued for 20 min. The reaction mixture was allowed to warm to 0 °C over 2 h and methanol was added to the mixture until the evolution of gas ceased. The reaction mixture was poured into ice-cooled aqueous potassium sodium tartrate (40 g). The separated aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried and then concentrated under reduced pressure to give the residue which was purified by silica gel chromatography (250 g, ether-hexane 1:1) to afford **23** (7.45 g, 96%). IR (KBr) ν_{max} 3403, 2959, 2870, 1612, 1514, 1466, 1384, 1302, 1248, 1173, 1079, 1037, 977, 820 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.86 (3H, d, *J* = 7 Hz, H-26), 0.94 (3H, d, *J* = 7 Hz, H-26), 1.78 (1H, m, H-25), 1.97 (1H, br, OH), 3.43 (1H, dd, *J* = 8, 7 Hz, H-24), 3.79 (3H, s, Ar-OCH_3), 4.17 (2H, dd, *J* = 5, 1 Hz, CH_2OH), 4.27 (1H, d, *J* = 11 Hz, one of CH_2Ar), 4.51 (1H, d, *J* = 11 Hz, one of CH_2Ar), 5.59 (1H, ddq, *J* = 16, 8, 1 Hz, H-23), 5.78 (1H, dt, *J* = 16, 5 Hz, H-22), 6.86 (2H, d, *J* = 9 Hz, ArH), 7.25 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.4, 18.7, 32.6, 55.2, 62.9, 69.8, 84.4, 113.6, 129.2, 130.4, 130.9, 132.9, 158.9. EI-MS m/z 250 (M^+). $[\alpha]_D^{27}$ +41.8° (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.97; H, 9.10.

(2*R*,3*R*,4*R*)-2,3-Dihydroxy-4-(4-methoxybenzyl)oxy-5-methyl-1-hexanol (29).

A solution of **23** (7.36 g, 29 mmol), 4-methylmorpholine *N*-oxide (5.87 g, 44 mmol) and osmium tetroxide (4% in water; 15 ml, 2.4 mmol) dissolved in a mixture of acetone and water (250 ml, 8:1) was stirred at -20 °C for 48 h. Saturated aqueous sodium hydrogen sulfite was added, and the mixture was filtered through Celite. The filtrate was acidified with 1N HCl and then acetone was evaporated under reduced pressure. The resulting aqueous layer was extracted with chloroform, and the combined organic layer was dried, concentrated and then purified by silica gel chromatography (250 g, ethyl acetate-hexane 2:1) to afford the triol **29** (7.38 g, 88%). Further purification by recrystallization from a mixture of ether and hexane afforded the pure **29** as crystals (5.19 g, 62%). Mp 61 °C. IR (KBr) ν_{max} 3463, 3345, 3222, 2908, 1616, 1515, 1461, 1405, 1299, 1251, 1181, 1109, 1058, 1004, 826 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.97 (3H, d, *J* = 7 Hz, H-26), 1.01 (3H, d, *J* = 7 Hz, H-26), 1.95 (1H, m, H-25), 3.21 (1H, br, OH), 3.32 (1H, br, OH), 3.38 (1H, t, *J* = 6 Hz, H-24), 3.68-3.76 (4H, m, H-22, H-23, CH_2OH), 3.78 (3H, s, Ar-OCH_3), 3.92 (1H, br, OH), 4.57 (1H, d, *J* = 11 Hz, one of CH_2Ar), 4.64 (1H, d, *J* = 11 Hz, one of CH_2Ar), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.27 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 17.9, 19.7, 29.8, 55.2, 65.5, 69.4, 71.8, 75.2, 86.5, 113.8, 129.5, 130.4, 159.3. EI-MS m/z 284 (M^+). $[\alpha]_D^{22}$ -14.3° (*c* 0.48, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.30; H, 8.50.

(2*R*,3*R*,4*R*)-1,2-Epoxy-3-hydroxy-4-(4-methoxybenzyl)oxy-5-methylhexane (30).

p-Toluenesulfonyl chloride (3.84 g, 20.1 mmol) was added at 0 °C to a solution of the triol **29** (5.19 g, 18.3 mmol) and triethylamine (3.64 ml, 27.5 mmol) in dichloromethane (200 ml) . After stirring overnight, ice was added to the reaction mixture. The aqueous layer was extracted with dichloromethane and the combined organic layer was dried and concentrated. The resulting crude tosylate was dissolved in tetrahydrofuran (250 ml). To this solution was added potassium *t*-butoxide (0.95M in *t*-butanol; 22.4 ml, 21.3 mmol) at -78 °C. After being stirred for 15 min, the mixture was allowed to warm to 0 °C. After being stirred for 30 min, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride. The aqueous layer was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give the residue which was purified by silica gel chromatography (250 g, ether-hexane 1:1) to afford the epoxy alcohol **30** (2.73 g, 56%, 2 steps). IR (KBr) ν_{max} 3463, 2961, 2874, 1614, 1515, 1466, 1303, 1249, 1176, 1065, 1036, 920, 819 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.99 (3H, d, *J* = 7 Hz, H-26), 1.02 (3H, d, *J* = 7 Hz, H-26), 2.05 (1H, m, H-25), 2.20 (1H, brd, *J* = 7 Hz, OH), 2.77 (1H, dd, *J* = 5, 3 Hz, one of H-21), 2.82 (1H, dd, *J* = 5, 4 Hz, one of H-21), 3.25 (1H, td, *J* = 4, 3 Hz, H-22), 3.29 (1H, dd, *J* = 7, 5 Hz, H-24), 3.54 (1H, m, H-23), 3.80 (3H, s, Ar-OC*H*$_3$), 4.61 (2H, s, C*H*$_2$Ar), 6.88 (2H, d, *J* = 9 Hz, ArH), 7.28 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 17.1, 19.8, 29.6, 45.3, 52.9, 55.2, 71.3, 74.5, 85.3, 113.7, 129.2, 130.7, 159.1. EI-MS m/z 266 (M$^+$). $[\alpha]_D^{23}$ -22.7° (*c* 0.49, CHCl$_3$). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.66; H, 8.40.

(2*R*,3*R*,4*R*)-1,2-Epoxy-3-methoxy-4-(4-methoxybenzyl)oxy-5-methylhexane (31) (Sub-segment B1).

To a suspension of sodium hydride (60% dispersion in mineral oil; 775 mg, 19.4 mmol) in a mixture of methyl iodide (8.00 ml, 129 mmol), tetrahydrofuran (30 ml) and DMF (30 ml) cooled to 0 °C was added a solution of the epoxy alcohol **30** (3.44 g, 12.9 mmol) in a mixture of tetrahydrofuran (30 ml) and DMF (30 ml). After being stirred for 30 min, the mixture was allowed to warm to room temperature and stirring was continued for 1.5 h. Saturated aqueous ammonium chloride was added and the aqueous layer was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated. Purification by silica gel chromatography (180 g, ether-hexane 1:3) afforded the methyl ether **31** (3.43 g, 95%). IR (KBr) ν_{max} 2960, 1614, 1515, 1466, 1302, 1249, 1174, 1094, 1037, 911, 821 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.95 (3H, d, *J* = 7 Hz, H-26), 0.98 (3H, d, *J* = 7 Hz, H-26), 1.97 (1H, m, H-25), 2.59 (1H, dd, *J* = 5, 3 Hz, one of H-21), 2.78 (1H, dd, *J* = 5, 4 Hz, one of H-21), 2.94 (1H, t, *J* = 6 Hz, H-23), 3.14 (1H, ddd, *J* = 6, 4, 3 Hz, H-22), 3.30 (1H, dd, *J* = 6, 5 Hz, H-24), 3.48 (3H, s, OC*H*$_3$), 3.79 (3H, s, Ar-OC*H*$_3$), 4.51 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 4.64 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.27 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 17.3, 20.0, 29.6, 43.8, 53.0, 55.2, 58.3, 74.4, 83.1, 84.2, 113.7, 129.3, 130.8, 159.1. $[\alpha]_D^{26}$ +17.6° (*c* 0.53, CHCl$_3$). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.86.

(2*R*,3*S*,4*R*)-2-Hydroxy-3-methoxy-4-(4-methoxybenzyl)oxy-5-methyl-1-phenylhexane (32).

Phenylmagnesium bromide (2 M solution in tetrahydrofuran; 0.16 ml, 0.32 mmol) was added to a suspension of copper (I) iodide (3.1 mg, 0.016 mmol) in tetrahydrofuran (1 ml) at -20 °C. After stirring for 15 min, a solution of **31** (29 mg, 0.11 mmol) in tetrahydrofuran (0.7 ml) was added, and stirring was continued for 30 min. The reaction mixture was allowed to warm to 0 °C and stirred for 40 min. Saturated aqueous ammonium chloride was added and the aqueous layer was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated. Purification by preparative thin layer chromatography (ether/hexane 1:1) afforded **32** (34 mg, 92%). IR (KBr) ν_{max} 3476, 2932, 1614, 1515, 1455, 1303, 1249, 1175, 1104, 1067, 1035, 822, 701 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.74 (3H, d, *J* = 7 Hz, H-26), 0.99 (3H, d, *J* = 7 Hz, H-26), 1.86 (1H, m, H-25), 2.88 (1H, dd, *J* = 14, 7 Hz, one of C*H*$_2$Ph), 2.96 (1H, dd, *J* = 14, 7 Hz, one of C*H*$_2$Ph), 3.07 (1H, dd, *J* = 4, 1 Hz, H-23), 3.45 (1H, dd, *J* = 7, 4 Hz, H-24), 3.48 (3H, s, OC*H*$_3$), 3.62 (1H, brd, *J* = 3 Hz, OH), 3.78 (3H, s, Ar-OC*H*$_3$), 4.12 (1H, m, H-22), 4.51 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 4.74 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 6.86 (2H, d, *J* = 9 Hz, ArH), 7.17-7.33 (7H, m, ArH). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 18.8, 19.5, 30.0, 40.2, 55.2, 58.5, 72.3, 74.9, 80.8, 84.3, 113.9, 126.3, 128.5, 129.4, 129.7, 130.5, 139.0, 159.4. EI-MS m/z 358 (M^+). HRMS (EI) calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2127. $[\alpha]_D^{23}$ +10.6° (*c* 0.34, $CHCl_3$).

(2*R*,3*S*,4*R*)-2,4-Isopropyridenedioxy-3-methoxy-5-methyl-1-phenylhexane (33).

Ceric ammonium nitrate (70 mg, 0.13 mmol) was added to a solution of **32** (12 mg, 0.036 mmol) in acetonitrile and water (1 ml, 9:1) at room temperature. After stirring for 4 h, ice was added. The mixture was diluted with dichloromethane and the aqueous layer was extracted with dichloromethane. The combined organic phase was dried and then concentrated. Purification by preparative thin layer chromatography (ether/hexane 3:1) afforded the diol (7.0 mg, 88%). A portion of the diol (4.5 mg, 0.019 mmol) was dissolved in dichloromethane (0.5 ml), and 2,2-dimethoxypropane (0.017 ml, 0.19 mmol) and (*dl*)-camphorsulfonic acid (1.3 mg, 5.7 μmol) were added at room temperature. After being stirred at room temperature overnight, the mixture was poured into aqueous sodium hydrogen carbonate and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried and then concentrated under reduced pressure to give the residue which was purified by preparative thin layer chromatography (ether-hexane 1:2) to afford **33** (5.0 mg, 95%). IR (KBr) ν_{max} 2962, 2932, 1456, 1379, 1228, 1171, 1101, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (3H, d, *J* = 7 Hz, H-26), 0.97 (3H, d, *J* = 7 Hz, H-26), 1.13 (3H, s, CH_3 of acetonide), 1.35 (3H, s, CH_3 of acetonide), 1.78 (1H, m, H-25), 2.84 (1H, dd, *J* = 14, 6 Hz, one of CH_2Ar), 2.95 (1H, dd, *J* = 14, 9 Hz, one of CH_2Ar), 3.17 (1H, dd, *J* = 6, 3 Hz, H-23), 3.40 (3H, s, OCH_3), 3.44 (1H, dd, *J* = 6, 5 Hz, H-24), 3.96 (1H, ddd, *J* = 9, 6, 3 Hz, H-22), 7.15-7.35 (5H, m, ArH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 17.1, 18.8, 23.6, 25.1, 31.4, 35.7, 59.2, 72.3, 77.3, 81.7, 100.4, 126.0, 128.1, 129.2, 139.0. EI-MS m/z 278 (M^+). HRMS (EI) calcd for $C_{17}H_{26}O_3$ 278.1881, found 278.1880. $[\alpha]_D^{23}$ +7.4° (*c* 0.25, $CHCl_3$).

(2*R*,3*R*,4*R*)-2-Hydroxy-3-methoxy-4-(4-methoxybenzyl)oxy-5-methyl-1-hexanol (34).

A solution of **31** (250 mg, 0.93 mmol) dissolved in a mixture of dimethyl sulfoxide (9 ml) and 1N KOH (3 ml) was heated at 70 °C overnight. The reaction mixture was cooled and then extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried and then concentrated to give the residue which was purified by silica gel chromatography (15g, ether) to afford the diol **34** (190 mg, 71%). IR (KBr) ν_{max} 3460, 2958, 1614, 1515, 1465, 1302, 1249, 1175, 1064, 824 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (3H, d, *J* = 7 Hz, H-26), 1.02 (3H, d, *J* = 7 Hz, H-26), 1.93 (1H, m, H-25), 2.38 (1H, br, OH), 3.30 (1H, dd, *J* = 5, 2 Hz, H-23), 3.39-3.48 (2H, m), 3.45 (3H, s, OCH_3), 3.60-3.80 (2H, m), 3.80 (3H, s, Ar-OCH_3), 3.96 (1H, m, H-22), 4.53 (1H, d, *J* = 11 Hz, one of CH_2Ar), 4.70 (1H, d, *J* = 11 Hz, one of CH_2Ar), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.28 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.4, 20.0, 29.8, 55.2, 58.8, 64.3, 71.2, 74.7, 80.8, 84.2, 113.9, 129.6, 130.4, 159.4. $[\alpha]_D^{23}$ -8.9° (*c* 0.41, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.39; H, 8.79. Found: C, 64.30; H, 8.92.

(3*R*,4*S*,5*E*)-3-Hydroxy-4-methoxy-2-methyl-7-oxo-5-nonene (14).

Two solutions of the diol **34** (125 mg, 0.419 mmol) in ether (3 ml) and sodium metaperiodate (135 mg, 0.629 mmol) in water (1.5 ml) were vigorously stirred at room temperature for 2 h. The organic layer was separated, washed with brine, dried and concentrated to give the aldehyde. This aldehyde was dissolved in dichloromethane (8 ml), and mixed with 2-oxo-1-triphenylphosphoranylidenebutane (696 mg, 2.10 mmol).

The resulting solution was heated at 70 °C overnight. Concentration of the resulting mixture and subsequent TLC purification (ether/hexane 1:1) provided *E*-enone (96 mg, 71%) and its *Z*-enone isomer (20 mg, 15%) from **34**.

The major *E*-enone (59 mg, 0.18 mmol) was dissolved in a mixture of dichloromethane (2 ml) and water (0.2 ml) and treated with DDQ (61 mg, 0.27 mmol) at room temperature for 20 min. The resulting mixture was diluted with ether, washed with saturated aqueous sodium hydrogen carbonate and brine and dried. Concentration under reduced pressure and subsequent TLC purification (ether/hexane 1:1) of the crude product afforded the enone **14** (35 mg, 95%). IR (KBr) ν_{max} 3449, 2964, 2939, 1676, 1636, 1465, 1366, 1195, 1121, 988 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (3H, d, *J* = 7 Hz, H-26), 0.98 (3H, d, *J* = 7 Hz, H-26), 1.10 (3H, t, *J* = 7 Hz, C_{19}-CH_3), 1.65 (1H, m, H-25), 2.63 (2H, q, *J* = 7 Hz, H-19), 3.32 (3H, s, OCH_3), 3.47 (1H, dd, *J* = 8, 4 Hz, H-24), 3.78 (1H, ddd, *J* = 7, 4, 1 Hz, H-23), 6.27 (1H, dd, *J* = 16, 1 Hz, H-21), 6.73 (1H, dd, *J* = 16, 7 Hz, H-22). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.9, 18.4, 18.8, 29.7, 33.3, 57.0, 77.9, 82.1, 132.8, 140.8, 200.6. $[\alpha]_D^{26}$ +28.2° (*c* 0.7, $CHCl_3$).[8(b),26] Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 65.90; H, 10.23.

(2*R*,3*R*)-3,4-Diethylmethylenedioxy-2-methyl-1-butanol (38).

Methyllithium with lithium bromide (1.5 M in ether; 103 ml, 155 mmol) was added to a suspension of copper (I) iodide (14.7 g, 77.4 mmol) in ether (70 ml) at -20 °C. After stirring at -20 °C for 40 min, a solution of **35** (4.8 g, 24.7 mmol) in ether (10 ml) was added to the mixture, and stirring was continued for 3 h. The mixture was poured into saturated aqueous ammonium chloride, and aqueous phase was extracted with ether. The combined organic phase was washed with saturated aqueous ammonium chloride, water and brine, dried and then concentrated under reduced pressure to give a mixture of **36** and **37** (4.78 g).

This mixture of **36** and **37** (4.78 g) dissolved in ethanol (120 ml) was stirred with palladium on carbon (20%, 0.8 g) under hydrogen atmosphere overnight. The mixture was filtered through Celite and then concentrated under reduced pressure to afford the crude triol (2.53 g).

p-Toluenesulfonic acid monohydrate (100 mg, 0.53 mmol) was added to a solution of the triol (2.53 g) dissolved in 3-pentanone (50 ml) at room temperature. After being stirred for 48 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give the residue which was purified by silica gel chromatography (150 g, ether-hexane 1:3) to afford **38** (2.14 g, 46%, 3 steps). IR (KBr) ν_{max} 3453, 2977, 2882, 1465, 1356, 1200, 1172, 1078, 921, 767 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.82 (3H, d, *J* = 9 Hz, C_{19}-CH_3), 0.90 (3H, t, *J* = 9 Hz, one of CH_2CH_3), 0.91 (3H, t, *J* = 9 Hz, one of CH_2CH_3), 1.63 (2H, q, *J* = 9 Hz, one of CH_2CH_3), 1.65 (2H, q, *J* = 9 Hz, one of CH_2CH_3), 1.85 (1H, m, H-19), 2.83 (1H, br, OH), 3.60 (1H, t, *J* = 10 Hz, one of H-17), 3.60 (1H, dd, *J* = 14, 6 Hz, one of CH_2OH), 3.68 (1H, dd, *J* = 14, 10 Hz, one of CH_2OH), 3.93 (1H, td, *J* = 10, 8 Hz, H-18), 4,11 (1H, dd, *J* = 10, 8 Hz, one of H-17). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 7.9, 8.1, 12.8, 29.4, 29.8, 39.1, 67.5, 69.4, 81.0, 113.3. $[\alpha]_D^{25}$ -15.3° (*c* 1.12, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}O_3$: C, 63.78; H, 10.71. Found: C, 63.70; H, 10.69.

(2*R*,3*S*)-1,2-Isopropyridenedioxy-4-methyl-3-(1,3-dithian-2-yl)-butane (39) (Sub-segment B-2).

Dimethyl sulfoxide (1.17 ml, 16.5 mmol) was added to a solution of oxalyl chloride (1.07 ml, 12.2 mmol) in dichloromethane (30 ml) at -78 °C over 5 min. After stirring for 10 min, a solution of **38** (1.15 g, 6.12 mmol) in dichloromethane (8 ml) was added over 10 min. After 20 min at -78 °C, triethylamine (5.92 ml, 44.7 mmol) was introduced and stirring was continued for 30 min. The reaction mixture was allowed to warm to 0 °C for 1 h, and the resulting mixture was poured into a mixture of ether and saturated aqueous ammonium chloride. The aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to afford the crude aldehyde.

This aldehyde was dissolved in dichloromethane (40 ml) and mixed with 1,3-propanedithiol (1.84 ml, 18.4 mmol) and $BF_3 \cdot Et_2O$ (0.08 ml, 0.61 mmol) at room temperature. After stirring for 2 h, 2,2-dimethoxypropane (7.5 ml) and (*dl*)-camphorsulfonic acid (71 mg, 0.31 mmol) were added. The stirring was continued overnight, and the mixture was poured into saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated. Purification by silica gel chromatography (200 g, ether-hexane 1:5) afforded **39** (1.14 g, 75%, 2 steps). IR (KBr) ν_{max} 2984, 2935, 2898, 1457, 1423, 1381, 1370, 1248, 1216, 1156, 1070, 907, 861, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.01 (3H, d, J = 9 Hz, C_{19}-$C\mathit{H}_3$), 1.37 (3H, s, acetonide), 1.41 (3H, s, acetonide), 1.74-2.20 (3H, m, H-19, $SCH_2C\mathit{H}_2CH_2S$), 2.78-3.09 (4H, m, $SC\mathit{H}_2CH_2C\mathit{H}_2S$), 3.62 (1H, dd, J = 8, 7 Hz, one of H-17), 4.04 (1H, dd, J = 8, 6 Hz, one of H-17), 4.16 (1H, ddd, J = 9, 7, 6 Hz, H-18), 4.54 (1H, d, J = 3 Hz, $SC\mathit{H}S$). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 12.0, 25.6, 26.3, 26.8, 30.4, 31.2, 42.8, 51.5, 67.8, 76.5, 109.0. $[\alpha]_D^{26}$ -8.8° (*c* 0.45, $CHCl_3$). Anal. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.19; H, 8.12. Found: C, 53.19; H, 8.38.

(2*R*,3*S*,6*R*,7*S*,8*R*)-6-Hydroxy-1,2-isopropyridenedioxy-7-methoxy-8-(4-methoxybenzyl)oxy-3,9-dimethyl-4-(1,3-dithian-2-yl)-decane (40).

t-Butyllithium (2 M in pentane; 4.69 ml, 9.38 mmol) was added to a solution of **39** (2.35 g, 9.48 mmol) dissolved in a mixture of hexamethylphosphoramide (4.1 ml, 23.7 mmol) and tetrahydrofuran (40 ml) at -50 °C . The bath temperature was gradually changed to -20°C in 30 min and maintained for 2 h to result a deep red solution. To this solution was introduced a solution of **31** (1.0 g, 3.57 mmol) in tetrahydrofuran (15 ml) at -50 °C. The reaction mixture was allowed to warm to -20 °C. After stirring for 1 h, saturated aqueous ammonium chloride was added and the aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give the residue which was purified by silica gel chromatography (150 g, ether-hexane 1:2) to afford **40** (1.51 g, 80%) and recovered **39** (1.19 g). IR (KBr) ν_{max} 3490, 2936, 1613, 1515, 1458, 1370, 1249, 1174, 1102, 1058, 866, 823 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (3H, d, J = 7 Hz, H-26), 1.05 (3H, d, J = 7 Hz, H-26), 1.14 (3H, d, J = 7 Hz, C_{19}-$C\mathit{H}_3$), 1.35 (3H, s, acetonide), 1.43 (3H, s, acetonide), 1.79-2.07 (3H, m, $SCH_2C\mathit{H}_2CH_2S$, H-25), 2.32 (1H, dd, J = 15, 3 Hz, one of H-21), 2.44 (1H, dd, J = 15, 8 Hz, one of H-21), 2.63-3.04 (5H, m, $SC\mathit{H}_2CH_2C\mathit{H}_2S$, H-19), 3.12 (1H, dd, J = 7, 2 Hz, H-23), 3.50 (3H, s, $OC\mathit{H}_3$), 3.51 (1H, dd, J = 7, 4 Hz, H-24), 3.68-3.70 (2H, m, one of H-17, OH), 3.80 (3H, s, Ar-$OC\mathit{H}_3$), 4.01 (1H, dd, J = 8, 6 Hz, one of H-17), 4.38 (1H, m, H-22), 4.54 (1H, d, J = 11 Hz, one of $C\mathit{H}_2$Ar), 4.65 (1H, d, J = 11 Hz, one of $C\mathit{H}_2$Ar), 4.66 (1H, m, H-18), 6.85 (2H, d, J = 9 Hz, ArH), 7.28 (2H, d, J = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.1, 17.5, 20.6, 24.9, 25.4, 25.7, 26.1, 26.6, 29.5, 40.0, 42.2, 55.3, 56.6, 59.6, 66.5, 68.4, 74.7, 75.9, 83.3, 84.3, 107.8, 113.8, 129.7, 130.8, 159.2. EI-MS m/z 528 (M^+). $[\alpha]_D^{24}$ +10.3° (*c* 1.37, $CHCl_3$). Anal. Calcd for $C_{27}H_{44}O_6S_2$: C, 61.33; H, 8.39. Found: C, 61.11; H, 8.39.

(2*R*,3*S*,6*R*,7*S*,8*R*)-1,2-Carbonyldioxy-6-hydroxy-7-methoxy-8-(4-methoxybenzyl)oxy-3,9-dimethyl-4-(1,3-dithian-2-yl)-decane (41).

Amberlite IR 120 (1 g) was added to a solution of **40** (526 mg, 1.00 mmol) in methanol (17 ml) at 50 °C. After being stirred for 4.5 h, the mixture was filtered and then concentrated. The resulting triol was dissolved in dichloromethane (16 ml), and 1,1'-carbonyldiimidazole (424 mg, 2.62 mmol) was added to this solution at room temperature. After being stirred for 30 min, the mixture was poured into saturated aqueous ammonium chloride and then extracted with dichloromethane. The combined organic phase was dried and concentrated to give the residue which was purified by silica gel chromatography (30 g, ether-hexane 2:1) to afford the carbonate **41** (267 mg, 52%, 2 steps) and **40** (61 mg, 12%). IR (KBr) ν_{max} 2936, 1801, 1613, 1515, 1250, 1175, 1056 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (3H, d, *J* = 7 Hz, H-26), 1.04 (3H, d, *J* = 7 Hz, H-26), 1.18 (3H, d, *J* = 7 Hz, C_{19}-C*H*$_3$), 1.82 (1H, m, H-25), 1.95-2.08 (2H, m, SCH_2-C*H*$_2$$CH_2S$), 2.18 (1H, dd, *J* = 15, 8 Hz, one of H-21), 2.40 (1H, dd, *J* = 15, 2 Hz, one of H-21), 2.63-3.05 (5H, m, SC*H*$_2$$CH_2$C*H*$_2$S, H-19), 3.18 (1H, dd, *J* = 6, 2 Hz, H-23), 3.47 (3H, s, OC*H*$_3$), 3.51 (1H, t, *J* = 6 Hz, H-24), 3.72 (1H, d, *J* = 5 Hz, OH), 3.80 (3H, s, Ar-OC*H*$_3$), 4.19 (1H, m, H-22), 4.36 (1H, t, *J* = 8 Hz, one of H-17), 4.42 (1H, t, *J* = 8 Hz, one of H-17), 4.57 (1H, d, *J* = 10 Hz, one of C*H*$_2$Ar), 4.62 (1H, d, *J* = 10 Hz, one of C*H*$_2$Ar), 5.30 (1H, td, *J* = 8, 3 Hz, H-18), 6.88 (2H, d, *J* = 9 Hz, ArH), 7.26 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.4, 18.1, 19.9, 24.4, 25.4, 25.9, 29.8, 40.0, 41.5, 55.2, 55.2, 58.6, 66.1, 68.1, 74.5, 77.4, 83.3, 84.2, 113.9, 129.5, 130.0, 154.8, 159.4. $[\alpha]_D^{29}$ +9.0° (*c* 0.42, $CHCl_3$). Anal. Calcd for $C_{25}H_{38}O_7S_2$: C, 58.34; H, 7.45. Found: C, 58.21; H, 7.51.

(2*R*,3*S*,6*R*,7*S*,8*R*)-6-(*t*-Butyldimethylsiloxy)-1,2-dihydroxy-7-methoxy-8-(4-methoxybenzyl)oxy-3,9-dimethyl-4-(1,3-dithian-2-yl)-decane (42).

t-Butyldimethylsilyl trifluoromethanesulfonate (0.38 ml, 1.7 mmol) was added to a solution of the carbonate **41** (226 mg, 0.440 mmol) and *N*,*N*-diisopropylethylamine (0.50 ml, 2.88 mmol) in dichloromethane (8.3 ml) at 0 °C. After being stirred for 1.5 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated. The resulting residue was dissolved in methanol (14 ml). To this solution was added potassium carbonate (132 mg, 0.96 mmol). After being stirred at 50 °C for 2.5 h, the reaction mixture was concentrated and the resulting residue was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated. Purification by silica gel chromatography (20 g, ether-hexane 3:1) afforded **42** (242 mg, 91%, 2 steps). IR (KBr) ν_{max} 3432, 2959, 1614, 1515, 1464, 1250, 1174, 1096, 836, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.15 (3H, s, SiC*H*$_3$), 0.19 (3H, s, SiC*H*$_3$), 0.90 (9H, s, Si*t*-*Bu*), 1.00 (3H, d, *J* = 7 Hz, H-26), 1.06 (3H, d, *J* = 7 Hz, H-26), 1.15 (3H, d, *J* = 7 Hz, C_{19}-C*H*$_3$), 1.82-1.94 (2H, m, SCH_2C*H*$_2$$CH_2S$), 2.06 (1H, m, H-25), 2.31 (1H, dd, *J* = 15, 7 Hz, one of H-21), 2.45 (1H, dd, *J* = 15, 4 Hz, one of H-21), 2.48 (1H, br, OH), 2.54 (1H, *J* = 7 Hz, H-19), 2.74-2.86 (4H, m, SC*H*$_2$$CH_2$C*H*$_2$S), 3.36 (1H, dd, *J* = 7, 3 Hz, H-23), 3.43 (1H, t, *J* = 3 Hz, H-24), 3.45 (3H, s, OC*H*$_3$), 3.51 (1H, brd, one of H-17), 3.70 (1H, brd, one of H-17), 3.79 (3H, s, Ar-OC*H*$_3$), 3.88 (1H, m, H-18), 4.51 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 4.59 (1H, td, *J* = 7, 4 Hz, H-22), 4.69 (1H, d, *J* = 11 Hz, one of C*H*$_2$Ar), 4.76 (1H, brd, J = 3 Hz, OH), 6.85 (2H, d, J = 9 Hz, ArH), 7.34 (2H, d, J = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ -3.1, -2.6, 12.8, 17.1, 18.4, 21.0, 24.5, 25.8, 25.9, 26.3, 29.7, 38.1, 41.5, 56.2, 57.8, 58.9, 65.4, 71.1, 71.8, 73.6, 83.1, 84.2, 113.4, 129.1, 131.4, 158.9. $[\alpha]_D^{27}$ +16.1° (c 0.36, $CHCl_3$). Anal. Calcd for $C_{30}H_{54}O_5S_2Si$: C, 59.77; H, 9.04. Found: C, 59.66; H, 9.20.

(2*R*,3*S*,6*R*,7*S*,8*R*)-6-(*t*-Butyldimethylsiloxy)-1,2-epoxy-7-methoxy-8-(4-methoxybenzyl)oxy-3,9-dimethyl-4-(1,3-dithian-2-yl)-decane (47) (Segment B).

n-Butyllithium (1.5 M in hexane; 0.17 ml, 0.26 mmol) was added to a solution of **42** (70 mg, 0.12 mmol) in tetrahydrofuran (2 ml) at 0 °C. After stirring for 10 min, a solution of *p*-toluenesulfonyl chloride (49 mg, 0.26 mmol) in tetrahydrofuran (1 ml) was added. The stirring was continued at 0 °C for 20 min, and the reaction mixture was quenched by the addition of pH 7 phosphate buffer. The aqueous phase was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated. Purification by silica gel chromatography (10 g, dichloromethane) provided **47** (56 mg, 82%). IR (KBr) ν_{max} 2932, 1515, 1364, 1302, 1249, 1178, 1097, 1038, 968, 833, 774, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.13 (3H, s, SiCH_3), 0.16 (3H, s, SiCH_3), 0.88 (9H, s, Si*t*-*Bu*), 1.00 (3H, d, J = 7 Hz, H-26), 1.03 (3H, d, J = 7 Hz, H-26), 1.16 (3H, d, J = 7 Hz, C_{19}-CH_3), 1.84-1.93 (2H, m, $SCH_2CH_2CH_2S$), 2.08 (1H, m, H-25), 2.17 (1H, dd, J = 15, 6 Hz, one of H-21), 2.49 (1H, dd, J = 15, 4 Hz, one of H-21), 2.49-2.56 (2H, m, H-19, one of H-17), 2.68 (1H, dd, J = 5, 4 Hz, one of H-17), 2.72-2.86 (4H, m, $SCH_2CH_2CH_2S$), 3.35 (1H, m, H-18), 3.44-3.46 (2H, m, H-23, H-24), 3.47 (3H, s, OCH_3), 3.80 (3H, s, Ar-OCH_3), 4.52 (1H, d, J = 11 Hz, one of CH_2Ar), 4.55 (1H, m, H-22), 4.69 (1H, d, J = 11 Hz, one of CH_2Ar), 6.85 (2H, d, J = 9 Hz, ArH), 7.34 (2H, d, J = 9 Hz, ArH). EI-MS m/z 584 (M^+). HRMS (EI) calcd for $C_{30}H_{52}O_5S_2Si$ 584.3025, found 584.3010. $[\alpha]_D^{23}$ +1.2° (c 0.66, $CHCl_3$).

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