A Stereoselective Total Synthesis of (9*S*)-9-Dihydroerythronolide A *via* Coupling between the Right-Half (C1—C6) Aldehyde and the Left-Half (C7—C15) Sulfoxide[1,2)]

Hitoshi TONE, Takao NISHI, Yuji OIKAWA, Masataka HIKOTA and Osamu YONEMITSU*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kitaku, Sapporo 060, Japan. *Received August 26, 1988*

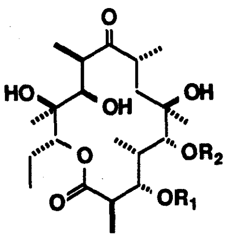
As part of a study directed at the total synthesis of (9*S*)-9-dihydroerythronolide A, the C7—C15 sulfoxide, (2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-1-phenylsulfinyl-2,4,6-trimethylnonane, was coupled with the C1—C6 aldehyde, (2*R*,3*S*,4*S*,5*R*)-6-*tert*-butyldiphenylsilyloxy-3,5-dimethyl-2,4-isopropylidenedioxyhexanal, to give the C1—C15 hydroxysulfoxide, which was converted to the seco-acid *via* a stereocontrolled methylation at the C6 position. Macrocyclization of the seco-acid by Yamaguchi's method gave the 14-membered lactone, which was converted to (9*S*)-9-dihydroerythronolide A.

Keywords macrolide antibiotic; erythromycin A; aglycone; erythronolide A; stereoselective synthesis; sulfone coupling; protecting group; seco-acid; macrolactonization; high dilution

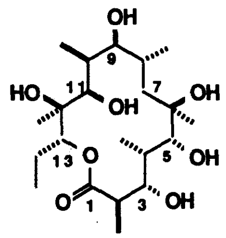
As part of our continuing study directed toward the stereoselective synthesis of the well-known macrolide antibiotic erythromycin A (1),[2,3)] in the preceding paper[1)] we reported the synthesis of the enone (4) having the whole carbon skeleton of (9*S*)-9-dihydroerythronolide A (3) by the Wittig–Horner coupling[4)] between the aldehyde (5) and the β-ketophosphonate (6). However, the yield of 4 was too low to complete the synthesis of 3, although improvements are now in progress. In the present paper,[2)] we report another approach *via* coupling between a C7—C15 sulfoxide (7) and a C1—C6 carbonyl compound (8),[5)] leading to completion of the stereoselective total synthesis of 3. Actually, coupling of 9 and 10 followed by introduction of the final methyl group at C6 and Yamaguchi's macrolactonization[6)] gave 3.

Results and Discussion

Synthesis of the C7—C15 Sulfoxide (9), the C1—C6 Aldehyde (10), and the C1—C6 Methyl Ketone (11) Conversion of the C7-alcohol (12)[1,7)] into the sulfide (14) was readily carried out *via* the tosylate (13).[5,8)] Treatment of 12 with *p*-toluenesulfonyl chloride followed by sodium thiophenoxide gave 14 in high yield. Another method involving treatment of 12 with diphenyl disulfide and tributylphosphine[9)] gave only poor results. Periodate oxidation of 14 gave the expected C7—C15 sulfoxide (9) as a



1 : R_1 = L-cladinosyl
R_2 = D-desosaminyl
2 : R_1,R_2 = H



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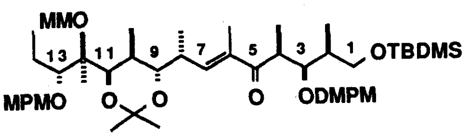

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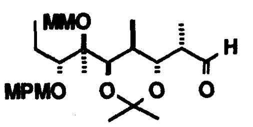

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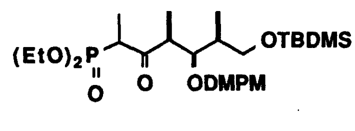

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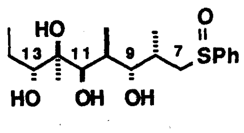

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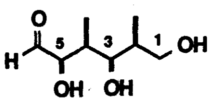

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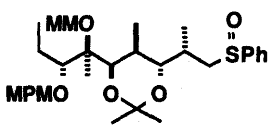

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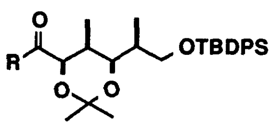
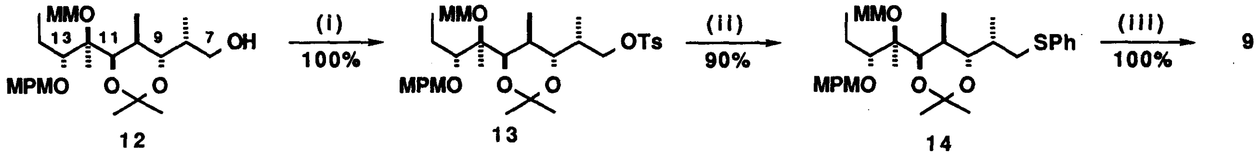


10 : R=H
11 : R=Me

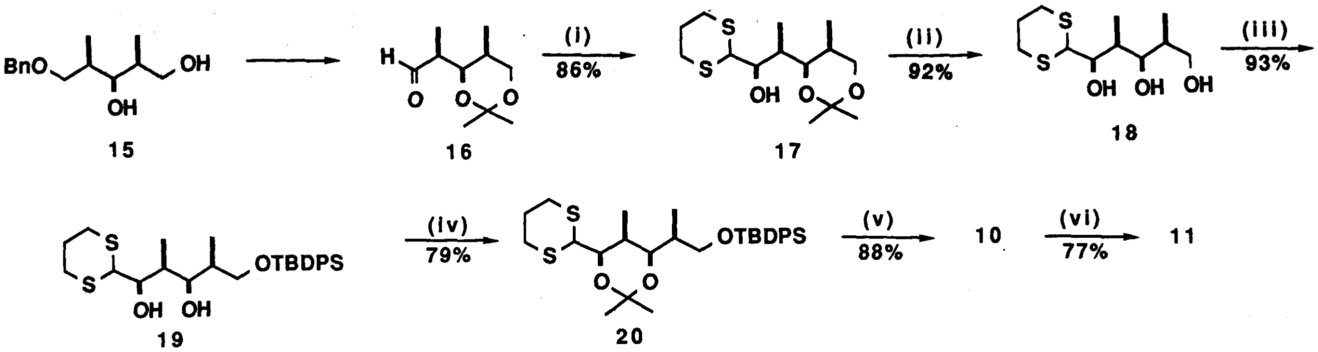
MPM = 4-$MeOC_6H_4CH_2$; MM = $MeOCH_2$; DMPM = 3,4-$(MeO)_2C_6H_3CH_2$; TBDMS = *tert*-$BuMe_2Si$; TBDPS = *tert*-$BuPh_2Si$.

Chart 1



(i) TsCl, Et_3N, DMAP, CH_2Cl_2, reflux, 23 h; (ii) PhSNa, EtOH–DME (1 : 1), reflux, 2 h; (iii) $NaIO_4$, MeOH–H_2O, room temperature, 8.5 h.

Chart 2



(i) 1,3-Dithiane, *n*-BuLi, THF, −80 °C, 40 min; (ii) 4 N HCl, THF, room temperature, 11 h; (iii) TBDPSCl, imidazole, CH_2Cl_2, room temperature, 2 h; (iv) CH_2=CMe(OMe), PPTS, CH_2Cl_2, room temperature, 2.5 h; (v) MeI, $NaHCO_3$, 90%MeCN, 70 °C, 1.5 h or NBS, 2,6-lutidine, 80%MeCN, room temperature, 1 h (71%); (vi) a) MeMgI, Et_2O, −15 °C, 1 h (89%), b) $(COCl)_2$, DMSO, Et_3N (86%).

Chart 3

1 : 1 stereoisomeric mixture with regard to the sulfoxide position.

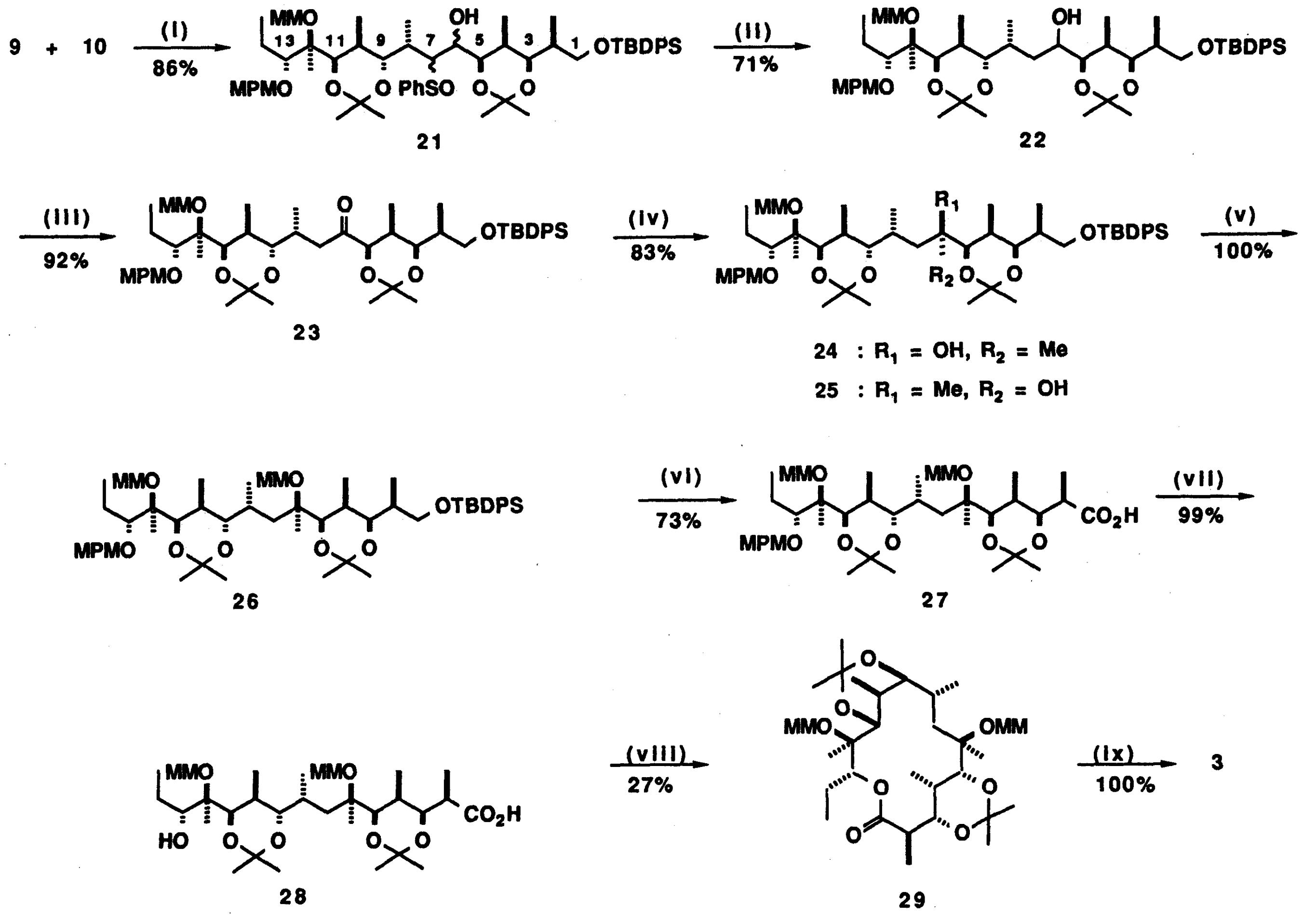
The diol (**15**), derived from D-glucose[10] or methallyl alcohol,[11] was readily converted to the aldehyde (**16**),[10] which was treated with the carbanion of 1,3-dithiane to give a 4.9 : 1 diastereoisomeric mixture of adducts mainly consisting of the non-chelation-controlled Cram adduct (**17**) in high yield. After purification of **17** by recrystallization, the isopropylidene protection of **17** was removed by treatment with 4 N hydrochloric acid in tetrahydrofuran (THF) to give the triol (**18**), and selective protection of the primary alcohol of **18** with a *tert*-butyldiphenylsilyl (TBDPS) group gave **19**, the remaining diol of which was then protected as an acetonide to give **20**. Removal of the 1,3-dithiane protection of **20** proceeded rather smoothly by treatment with *N*-bromosuccinimide (NBS) in the presence of 2,6-lutidine,[12] but the yield of the expected C1—C6 aldehyde (**10**) was not so good. Treatment with methyl iodide in the presence of sodium hydrogencarbonate[13] gave a better result.

The C1—C6 methyl ketone (**11**)[5] was easily obtained from **10** by Grignard reaction followed by Swern oxidation.

Coupling between 9 and 10, and Total Synthesis of 3 Coupling between the sulfoxide (**9**) and the ketone (**11**) in the presence of lithium diisopropylamide (LDA)[5] under several conditions was first examined, but the yield was always less than 20%. Therefore, the ketone (**11**) was replaced by the more reactive aldehyde (**10**), and the coupling product (**21**) was obtained in high yield as a mixture of four stereoisomers. Desulfurization with Raney nickel gave the alcohol (**22**) as a stereoisomeric mixture, which was subjected to Swern oxidation to give the ketone (**23**) as a single product.

Introduction of the final methyl group at the C6 position was achieved as follows. No reaction of **23** occurred with methylmagnesium iodide in ether, but when **23** was treated with a large excess of methyllithium (MeLi) in ether at −85—−65 °C, a chelation-controlled reaction proceeded quite smoothly to give a 4.9 : 1 stereoisomeric mixture in quantitative yield mainly consisting of the unexpected isomer (**25**; 83%), with the desired isomer (**24**) as the minor product (17%). However, when hexamethylphosphoramide (HMPA: 40 eq) was added to the above reaction system, the reaction changed clearly to a non-chelation-controlled reaction, and a 5.6 : 1 mixture of the desired Cram adduct (**24**: 73%) and its isomer (**25**: 13%) together with the recovered starting material (**23**: 9%) was isolated. The reaction of **23** with MeLi in THF gave a better result, that is, a 7.2 : 1 mixture mainly consisting of **24** (83%) was obtained. After purification by thin-layer chromatography (TLC), **24** was treated with methoxymethyl (MM) chloride to give quantitatively **26**, which was treated with fluoride anion and then oxidized at the resulting primary alcohol with Jones reagent to give the carboxylic acid (**27**). The *p*-methoxybenzyl (MPM) protective group of **27** was removed by catalytic hydrogenation over palladium charcoal or by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[14] and the seco-acid (**28**) required for macrolactonization was isolated in quantitative yield.

We were now ready to try macrolactonization. Two of Corey's methods using 4-*tert*-butyl-*N*-isopropyl-2-imidazolyl disulfide[3a,15] and 2-pyridyl disulfide[3b,16] were first applied, but unfortunately all attempts were unsuccessful. However, macrolactonization of **28** was achieved by Yamaguchi's method[6] in the presence of a rather high concentration of 4-dimethylaminopyridine (DMAP). When 2 mM toluene solution of a mixed anhydride, prepared from **28** and 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine in THF, was added very slowly to an equal volume of 50 mM toluene solution of 25 eq of DMAP under reflux over a period of 39 h, in spite of the fact that an axial methyl group of the 9,11-isopropylidene group hinders this



(i) LDA, THF, $-80\,°C$, 1 h; (ii) Raney Ni (W-2), EtOH, room temperature, 30 min; (iii) $(COCl)_2$, DMSO, Et_3N; (iv) MeLi, THF, $-85\,°C$, 1 h; (v) MMCl, iso-Pr_2EtN, CH_2Cl_2, 55 °C, 11 h; (vi) a) n-Bu_4NF, THF, 60 °C, 2 h (94%), b) 2.67 M Jones reagent, Me_2CO, $-17\,°C$, 2 h (78%); (vii) 10% Pd–C, H_2, EtOH, 55 °C, 13 h; (viii) a) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, room temperature, 2 h, b) DMAP, toluene, reflux, 50 h; (ix) 67% AcOH, 55 °C, 2 h.

Chart 4

lactonization as pointed out by Stork and Rychnovsky,[3e)] the macrolactonization proceeded gradually to give the expected lactone (**29**), though the yield was only 27%. In this high dilution macrolactonization, the yield of **29** was decisively dependent on the concentration of DMAP. When the final concentration of DMAP was 3 mM, no **29** was obtained. However, the yield increased with increasing concentration of DMAP, that is, yields of **29** at various final concentrations of DMAP were as follows: 0% at 3 mM, 13% at 6 mM, 14% at 9.5 mM, and 27% at 25 mM. All the protecting groups of **29** were removed with 50% acetic acid, and the title compound (**3**) was isolated in excellent yield. Compounds **3**, **28**, and **29** were identical with the respective authentic samples derived from natural erythromycin A in terms of infrared (IR), nuclear magnetic resonance (NMR) and mass spectra, and chromatographic mobilities.

Experimental

Physical data were measured as described in the previous paper.[11)]

(2S,3R,4S,5R,6R,7R)-3,5-Isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-1-(4-toluenesulfonyloxy)-2,4,6-trimethylnonane (13) A solution of the alcohol (**12**) (327 mg, 0.721 mmol), Et_3N (0.90 ml, 6.48 mmol), DMAP (27 mg, 0.22 mmol), and p-toluenesulfonyl chloride (413 mg, 2.16 mmol) in CH_2Cl_2 (30 ml) was stirred under reflux for 23 h. It was then cooled, H_2O was added, and the mixture was stirred at room temperature for 3 h. The CH_2Cl_2 layer was washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave the tosylate (**13**) as a colorless solid (448 mg, 100%). Recrystallization from n-hexane gave pure **13** as colorless needles, mp 97—99 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.07 (3H, t, J=7.5 Hz), 1.21 (6H, s), 1.29 (3H, s), 1.62 (1H, quintet, J=7.5 Hz), 1.72—1.96 (3H, m), 2.45 (3H, s), 3.33 (1H, dd, J=7.5, 2.0 Hz), 3.35 (3H, s), 3.45 (1H, dd, J=8.0, 2.5 Hz), 3.80 (3H, s), 3.85 (1H, d, J=4.5 Hz), 3.88 (1H, dd, J=8.0, 2.5 Hz), 3.97 (1H, dd, J=9.0, 8.0 Hz), 4.48, 4.61 (1H each, ABq, J=11.0 Hz), 4.76, 4.98 (1H each, ABq, J=7.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.24 (2H, d, J=9.0 Hz), 7.34 (2H, d, J=8.0 Hz), 7.79 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 505 (M^+-103, 0.1), 429 (0.7), 371 (7.9), 166 (13), 121 (100). $[\alpha]_D^{17}$ $-15.1°$ (c=1.11, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{48}O_9S$: C, 63.13; H, 7.95. Found: C, 62.94; H, 8.00.

(2S,3S,4S,5R,6R,7R)-3,5-Isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-1-phenylthio-2,4,6-trimethylnonane (14) NaH (60%, 80 mg, 2.0 mmol) was dissolved in EtOH (10 ml). After evolution of H_2 had ceased, thiophenol (206 μl, 2.0 mmol) was added, and the solution was stirred at room temperature for 10 min. A solution of **13** (304 mg, 0.5 mmol) in 1,2-dimethoxyethane (DME) (10 ml) was added, and the solution was refluxed under argon for 2 h, then cooled, Et_2O and H_2O were added. The Et_2O layer was washed with 1 N NaOH and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with n-hexane–EtOAc (16 : 1) as the eluent to give **14** as a colorless oil (246 mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=7.0 Hz), 1.01 (3H, d, J=7.0 Hz), 1.07 (3H, t, J=7.5 Hz), 1.28 (3H, s), 1.31 (3H, s), 1.34 (3H, s), 1.67 (1H, quintet, J=7.5 Hz), 1.68—1.90 (3H, m), 2.85 (1H, dd, J=13.0, 6.5 Hz), 2.99 (1H, dd, J=13.0, 7.5 Hz), 3.46 (1H, dd, J=8.5, 2.5 Hz), 3.79 (3H, s), 3.90 (1H, d, J=4.0 Hz), 4.50, 4.61 (1H each, ABq, J=11.0 Hz), 4.79, 5.00 (1H each, ABq, J=7.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.14—7.35 (5H, m). MS m/z (relative intensity): 547 (M^+ + 1, 0.02), 546 (0.05), 457 (0.06), 443 (0.4), 368 (0.5), 348 (0.6), 309 (5.7), 221 (4.7), 121 (100). $[\alpha]_D^{11}$ −24.6° (*c*=2.95, $CHCl_3$). Exact MS *m*/*z* Calcd for $C_{26}H_{35}O_4S$ (M^+ − 103): 443.2256. Found: 443.2263.

(2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,5-Isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-1-phenylsulfinyl-2,4,6-trimethylnonane (9) A solution of $NaIO_4$ (290 mg, 1.35 mmol) in H_2O (3 ml) was added to a stirred solution of **14** (246 mg, 0.451 mmol) in MeOH (20 ml) at room temperature. After 8.5 h, CH_2Cl_2 and H_2O were added, and the CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2 as the eluent to give a 1 : 1 diastereoisomeric mixture of the sulfoxide (**9**) as a pale yellow oil (250 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J*=7.0 Hz), 1.08 (3H, t, *J*=6.5 Hz), 1.08 (1.5H, d, *J*=6.5 Hz), 1.17 (1.5H, d, *J*=6.5 Hz), 1.24 (1.5H, s), 1.25 (1.5H, s), 1.29 (1.5H, s), 1.30 (1.5H, s), 1.32 (1.5H, s), 1.39 (1.5H, s), 1.50—1.75 (1H, m), 1.74—1.96 (2H, m), 2.10—2.34 (1H, m), 2.64—2.91 (2H, m), 3.19 (0.5H, dd, *J*=7.0, 2.0 Hz), 3.35 (1.5H, s), 3.36 (1.5H, s), 3.46 (0.5H, t, *J*=7.5 Hz), 3.47 (0.5H, t, *J*=7.5 Hz), 3.60 (0.5H, dd, *J*=7.0, 2.0 Hz), 3.79 (1.5H, s), 3.81 (1.5H, s), 3.89 (1H, dd, *J*=5.5, 4.5 Hz), 4.76, 4.98 (0.5H each, ABq, *J*=6.5 Hz), 4.79, 5.01 (0.5H each, ABq, *J*=6.5 Hz), 6.86 (2H, d, *J*=9.0 Hz), 7.25 (2H, d, *J*=9.0 Hz), 7.47—7.70 (5H, m). MS *m*/*z* (relative intensity): 547 (M^+ − 15, 0.1), 545 (0.1), 487 (0.4), 477 (1.1), 383 (5.2), 325 (8.4), 121 (100). $[\alpha]_D^{13}$ −12.2° (*c*=3.53, $CHCl_3$). *Anal.* Calcd for $C_{31}H_{46}O_7S$: C, 66.16; H, 8.23; S, 5.69. Found: C, 65.99; H, 8.18; S, 5.45. Exact MS *m*/*z* Calcd for $C_{30}H_{43}O_7S$ (M^+ − 15): 547.2729. Found: 547.2723.

(2*R*,3*S*,4*S*,5*S*)-3,5-Dimethyl-2-hydroxy-4,6-isopropylidenedioxyhexanal Trimethylene Dithioacetal (17) A 1.5 M solution of *n*-BuLi in hexane (2.21 ml, 3.32 mmol) was added dropwise to a stirred solution of 1,3-dithiane (399 mg, 3.32 mmol) in THF (5 ml) at −50 °C under argon. The solution was stirred at −23—−20 °C for 2.5 h and then cooled to −80 °C. A solution of the aldehyde (**16**) (308 mg, 1.66 mmol) in THF was added dropwise at −80—−70 °C. After 40 min, aqueous NH_4Cl was added, and the mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with CH_2Cl_2 as the eluent to give a 4.9 : 1 mixture of **17** and its C-2 isomer as a colorless oil (435 mg, 86%), which was solidified with MeOH. Recrystallization from MeOH gave pure **17** as colorless needles, mp 108—109 °C. IR ν_{max}^{KBr} cm^{-1}: 3410. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, *J*=6.5 Hz), 1.14 (3H, d, *J*=7.0 Hz), 1.41 (3H, s), 1.44 (3H, s), 1.60—1.84 (1H, m), 1.90—2.20 (3H, m), 2.58 (1H, t, *J*=1.5 Hz), 2.64—3.16 (4H, m), 3.61 (1H, dd, *J*=11.5, 1.5 Hz), 3.84 (1H, d, *J*=11.0 Hz), 3.91 (2H, dd, *J*=10.0, 2.0 Hz), 4.14 (1H, dd, *J*=11.5, 2.5 Hz). MS *m*/*z* (relative intensity): 307 (M^+ + 1, 0.2), 306 (1.1), 291 (9.5), 129 (94), 119 (100). $[\alpha]_D^{16}$ +6.6° (*c*=1.46, $CHCl_3$). Exact MS *m*/*z* Calcd for $C_{14}H_{26}O_3S_2$ (M^+): 306.1323. Found: 306.1317.

(2*R*,3*S*,4*R*,5*S*)-3,5-Dimethyl-2,4,6-trihydroxyhexanal Trimethylene Dithioacetal (18) A 4 N HCl solution (7.2 ml) was added to a stirred solution of the mixture of **17** and its C-2 isomer (435 mg, 1.43 mmol) in THF (15 ml) at room temperature. After 11 h, the solution was poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2–MeOH (40 : 1) as the eluent to give a mixture of the triol (**18**) and its C-2 isomer as a colorless oil (350 mg, 92%), which was solidified with CH_2Cl_2. Recrystallization from CH_2Cl_2 gave pure **18** as colorless needles, mp 140—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, *J*=7.0 Hz), 1.05 (3H, d, *J*=7.0 Hz), 1.90—2.20 (4H, m), 2.20—2.50 (1H, m), 2.50—3.20 (5H, m), 3.23 (1H, s), 3.67 (2H, d, *J*=5.0 Hz), 3.80 (1H, d, *J*=10.0 Hz), 3.89 (1H, dd, *J*=9.0, 5.0 Hz), 4.02 (1H, dd, *J*=10.0, 2.5 Hz). MS *m*/*z* (relative intensity): 266 (M^+, 0.2), 250 (0.3), 248 (3.8), 207 (2.1), 160 (11), 129 (15), 119 (100). $[\alpha]_D^{17}$ +2.2° (*c*=1.06, EtOH). *Anal.* Calcd for $C_{11}H_{22}O_3S_2$: C, 49.59; H, 8.32. Found: C, 49.05; H, 8.41. Exact MS *m*/*z* Calcd for $C_{11}H_{22}O_3S_2$ (M^+): 266.1010. Found: 266.1012.

(2*R*,3*S*,4*S*,5*R*)-6-*tert*-Butyldiphenylsilyloxy-2,4-dihydroxy-3,5-dimethylhexanal Trimethylene Dithioacetal (19) Imidazole (269 mg, 3.96 mmol) and *tert*-butyldiphenylsilyl chloride (688 μl, 2.64 mmol) were added to a stirred solution of the mixture of **18** and its C-2 isomer (350 mg, 1.32 mmol) in CH_2Cl_2 (30 ml) at room temperature. After 2 h, MeOH was added and the stirring was continued for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2 as the eluent to give a mixture of the diol (**19**) and its C-2 isomer as a colorless oil (620 mg, 93%). IR ν_{max}^{neat} cm^{-1}: 3410. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, *J*=7.0 Hz), 1.06 (9H, s), 1.09 (3H, d, *J*=7.0 Hz), 1.64—2.20 (3H, m), 2.30—3.05 (5H, m), 3.14 (1H, s), 3.27 (1H, s), 3.64—4.00 (2H, m), 3.58 (1H, dd, *J*=10.5, 4.0 Hz), 3.74 (1H, dd, *J*=10.5, 4.0 Hz), 4.03 (1H, d, *J*=10.5 Hz), 7.30—7.50 (6H, m), 7.54—7.76 (4H, m). $[\alpha]_D^{18}$ +4.2° (*c*=2.08, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*)-6-*tert*-Butyldiphenylsilyloxy-3,5-dimethyl-2,4-isopropylidenedioxyhexanal Trimethylene Dithioacetal (20) 2-Methoxypropene (1.18 ml, 12.3 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (31.2 mg, 0.123 mmol) were added to a stirred solution of the mixture of **19** and its C-2 isomer (620 mg, 1.23 mmol) in CH_2Cl_2 (60 ml). After 2.5 h, the solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (32 : 1) as the eluent to give **20** (528 mg, 79%) and its C-2 isomer (108 mg, 16%) as colorless oils.

Compound **20**: ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, *J*=6.5 Hz), 1.05 (3H, d, *J*=6.5 Hz), 1.05 (9H, s), 1.44 (6H, s), 1.70—2.01 (3H, m), 2.05—2.20 (1H, m), 2.75—2.90 (4H, m), 3.51 (1H, dd, *J*=10.5, 4.0 Hz), 3.57 (1H, dd, *J*=10.5, 5.0 Hz), 3.76 (1H, dd, *J*=9.5, 2.0 Hz), 3.96 (1H, dd, *J*=10.5, 2.0 Hz), 4.15 (1H, d, *J*=10.5 Hz), 7.34—7.47 (6H, m), 7.62—7.70 (4H, m). MS *m*/*z* (relative intensity): 545 (M^+ + 1, 1.5), 544 (3.8), 487 (0.8), 469 (3.1), 425 (26), 367 (69), 269 (100). $[\alpha]_D^{13}$ +4.5° (*c*=1.12, $CHCl_3$). Exact MS *m*/*z* Calcd for $C_{30}H_{44}O_3S_2Si$: (M^+): 544.2501. Found: 544.2526.

(2*R*,3*S*,4*S*,5*R*)-6-*tert*-Butyldiphenylsilyloxy-3,5-dimethyl-2,4-isopropylidenedioxyhexanal (10) $NaHCO_3$ (1.29 g, 15.3 mmol) and MeI (477 μl, 7.62 mmol) were added to a solution of **20** (207 mg, 0.381 mmol) in 90% MeCN (10 ml), and the mixture was stirred at 70 °C for 1.5 h, then cooled, CH_2Cl_2 and H_2O were added. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (8 : 1) as the eluent to give the aldehyde (**10**) as a colorless oil (153 mg, 88%). IR ν_{max}^{neat} cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, d, *J*=6.5 Hz), 1.04 (3H, d, *J*=5.0 Hz), 1.06 (9H, s), 1.43 (3H, s), 1.50 (3H, s), 1.60—2.10 (2H, m), 3.55 (1H, dd, *J*=4.5, 2.0 Hz), 3.74 (1H, dd, *J*=9.5, 2.0 Hz), 4.22 (1H, d, *J*=2.5 Hz), 7.30—7.50 (6H, m), 7.54—7.76 (4H, m), 9.48 (1H, s). MS *m*/*z* (relative intensity): 441 (M^+ − 13, 0.3), 440 (0.9), 439 (2.7), 397 (4.7), 367 (3.6), 339 (42), 309 (30), 269 (100). Exact MS *m*/*z* Calcd for $C_{26}H_{35}O_4Si$ (M^+ − 15): 439.2304. Found: 439.2295.

(2*R*,3*S*,4*S*,5*R*)-1-*tert*-Butyldiphenylsilyloxy-2,4-dimethyl-3,5-isopropylidenedioxyheptan-6-one (11) A 1.0 M solution of MeMgI in Et_2O (0.65 ml) was added dropwise to a stirred solution of **10** (58.5 mg, 0.129 mmol) in Et_2O (5 ml) at −15 °C. After 1 h, the reaction mixture was poured into ice-cooled aqueous NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (16 : 1) as the eluant to give (2*R*,3*S*,4*S*,5*R*)-1-*tert*-butyldiphenylsilyloxy-2,4-dimethyl-6-hydroxy-3,5-isopropylidenedioxyheptane as a colorless oil (54.1 mg, 89%). MS *m*/*z* (relative intensity): 456 (M^+ − 14, 0.1), 455 (0.4), 425 (0.2), 355 (19), 269 (16), 199 (58), 43 (100). Exact MS *m*/*z* Calcd for $C_{27}H_{39}O_4Si$ (M^+ − 15): 455.2618. Found: 455.2619.

Dimethyl sulfoxide (DMSO) (48 μl, 0.68 mmol) was added dropwise to a stirred solution of oxalyl chloride (30 μl, 0.34 mmol) in CH_2Cl_2 (3 ml) at −60 °C, and the solution was stirred at −60—−55 °C for 30 min. A solution of the above alcohol (54.1 mg, 0.113 mmol) in CH_2Cl_2 (3 ml) was added dropwise at −70 °C, and the mixture was stirred at −65—−55 °C for 1 h. Et_3N (141 μl, 1.02 mmol) was added dropwise at −70 °C. The reaction mixture was allowed to warm to room temperature, washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (16 : 1) as the eluent to give the recovered alcohol (4.7 mg, 8.7%) and the ketone (**11**) as a colorless oil (45.4 mg, 86%). IR ν_{max}^{neat} cm^{-1}: 1715. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, d, *J*=7.0 Hz), 1.04 (3H, d, *J*=6.5 Hz), 1.06 (9H, s), 1.41 (3H, s), 1.48 (3H, s), 1.60—2.08 (2H, m), 2.12 (3H, s), 3.53 (2H, dd, *J*=5.0, 2.0 Hz), 3.74 (1H, dd, *J*=10.0, 2.0 Hz), 4.23 (1H, d, *J*=2.5 Hz), 7.30—7.50 (6H, m), 7.54—7.76 (4H, m). MS *m*/*z* (relative intensity): 455 (M^+ − 13, 0.3), 454 (0.7), 453 (2.0), 425 (1.4), 412 (2.0), 411 (6.0), 353 (34), 281 (34), 269 (100). $[\alpha]_D^{25}$ +19.3° (*c*=1.45, $CHCl_3$). Exact MS *m*/*z* Calcd for $C_{27}H_{37}O_4Si$ (M^+ − 15): 453.2461. Found: 453.2474.

(2*R*,3*S*,4*S*,5*R*,6*RS*,7*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5 : 9,11-Bis(isopropylidenedioxy)-1-*tert*-butyldiphenylsilyloxy-13-(4-methoxybenzyloxy)-12-methoxymethoxy-2,4,8,10,12-pentamethyl-7-phenylsulfinylpentadecan-6-ol (21) A 1.5 M solution of *n*-BuLi in hexane (0.34 ml, 0.52 mmol) was added dropwise to a stirred solution of diisopropylamine (80 μl, 0.57 mmol) in THF (2 ml) at 0 °C under argon. After 20 min, a solution of **9** (282 mg, 0.502 mmol) in THF (2 ml) was added dropwise at −15 °C. After 30 min, the solution was cooled at −80 °C, and a solution of **10** (117 mg, 0.258 mmol) in THF (1.2 ml) was added dropwise at −81—−77 °C. The reaction mixture was stirred at −80 °C for 1 h, then treated with aqueous NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (8:1—4:1) to give recovered **10** (11 mg, 10%), recovered **9** (138 mg, 49%), and a mixture of four diastereoisomers of **21** as a colorless oil (225 mg, 86%).

(2*R*,3*S*,4*S*,5*R*,6*RS*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-Bis(isopropylidenedioxy)-1-*tert*-butyldiphenylsilyloxy-13-(4-methoxybenzyloxy)-12-methoxymethoxy-2,4,8,10,12-pentamethylpentadecan-6-ol (22) A solution of **21** (72.3 mg, 0.072 mmol) in EtOH (20 ml) was stirred in the presence of Raney Ni (W-2) (*ca.* 20 ml) at room temperature for 30 min. The catalyst was removed by filtration and washed with EtOH and CH_2Cl_2. The filtrates were evaporated *in vacuo* to leave an oil, which was subjected to preparative TLC on silica gel. Development with *n*-hexane–EtOAc (4:1) gave the alcohol (**22**) as a colorless oil (45.6 mg, 71%). IR ν_{max}^{neat} cm^{-1}: 3420. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.5 Hz), 0.96 (3H, d, J=6.0 Hz), 1.03 (3H, d, J=7.0 Hz), 1.04 (9H, s), 1.06 (3H, d, J=8.0 Hz), 1.07 (3H, t, J=7.5 Hz), 1.30 (3H, s), 1.34 (3H, s), 1.35 (3H, s), 1.37 (3H, s), 1.38 (3H, s), 1.63 (1H, quint, J=7.5 Hz), 1.72—2.00 (7H, m), 2.92 (1H, d, J=3.0 Hz), 3.35 (3H, s), 3.37—3.51 (3H, m), 3.54—3.68 (3H, m), 3.80 (3H, s), 3.88 (1H, d, J=4.0 Hz), 4.51, 4.60 (1H each, ABq, J=10.5 Hz), 4.79, 4.98 (1H each, ABq, J=7.0 Hz, 6.86 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.32—7.45 (6H, m), 7.60—7.70 (4H, m). MS *m/z* (relative intensity): 877 (M^+ − 15, 0.1), 835 (0.3), 623 (0.2), 597 (0.3), 579 (0.6), 565 (0.6), 535 (0.8), 367 (1.6), 121 (100). $[\alpha]_D^{15}$ −3.4° (c=1.66, $CHCl_3$). Exact MS *m/z* Calcd for $C_{31}H_{49}O_9$ (M^+ −327): 565.3376. Found: 565.3365.

(2*R*,3*S*,4*S*,5*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-Bis(isopropylidenedioxy)-1-*tert*-butyldiphenylsilyloxy-13-(4-methoxybenzyloxy)-12-methoxymethoxy-2,4,8,10,12-pentamethylpentadecan-6-one (23) The alcohol (**22**) (98.5 mg, 0.111 mmol) was oxidized with oxalyl chloride (40 μl, 0.45 mmol), DMSO (64 μl, 0.90 mmol), and Et_3N (188 μl, 0.135 mmol) as indicated for the preparation of **11**. The crude product was chromatographed on a silica gel column with *n*-hexane–EtOAc (16:1) as the eluent to give the ketone (**23**) as a colorless oil (90.2 mg, 92%). IR ν_{max}^{neat} cm^{-1}: 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, d, J=7.0 Hz), 0.91 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=4.5 Hz), 1.05 (3H, d, J=4.5 Hz), 1.06 (9H, s), 1.07 (3H, t, J=7.5 Hz), 1.26 (3H, s), 1.27 (3H, s), 1.33 (3H, s), 1.40 (3H, s), 1.47 (3H, s), 1.55—1.90 (6H, m), 2.42 (1H, dd, J=18.0, 6.0 Hz), 2.56 (1H, dd, J=18.0, 7.5 Hz), 3.15 (1H, dd, J=7.0, 2.0 Hz), 3.36 (3H, s), 3.44 (1H, dd, J=8.5, 2.5 Hz), 3.48 (1H, dd, J=10.5, 5.5 Hz), 3.56 (1H, dd, J=10.5, 4.0 Hz), 3.73 (1H, dd, J=9.5, 2.0 Hz), 3.80 (3H, s), 3.87 (1H, d, J=4.0 Hz), 4.21 (1H, d, J=2.0 Hz), 4.52, 4.61 (1H each, ABq, J=10.5 Hz), 4.78, 4.99 (1H each ABq, J=7.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.34—7.48 (6H, m), 7.60—7.80 (4H, m). MS *m/z* (relative intensity): 833 (M^+ −57, 0.3), 800 (0.2), 782 (0.3), 742 (0.4), 653 (0.5), 621 (0.5), 595 (0.7), 563 (0.9), 269 (10), 121 (100). $[\alpha]_D^{18}$ +3.4° (c=3.37, $CHCl_3$). Exact MS *m/z* Calcd for $C_{35}H_{57}O_9$ (M^+ −269): 621.4002. Found: 621.3954.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-Bis(isopropylidenedioxy)-1-*tert*-butyldiphenylsilyloxy-2,4,6,8,10,12-hexamethyl-13-(4-methoxybenzyloxy)-12-methoxymethoxypentadecan-6-ol (24) A 1.40 M solution of MeLi in Et_2O (0.36 ml, 0.51 mmol) was added dropwise to a stirred solution of **23** (45.0 mg, 0.056 mmol) in THF (8 ml) at −85 °C under argon. After 1 h, aqueous NH_4Cl was added, and the mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was subjected to preparative TLC on silica gel. Development with CH_2Cl_2–MeOH (80:1) gave **24** (38.0 mg, 82.9%) and its C-6 isomer (**25**) (5.3 mg, 11.6%) as colorless oils.

Compound **24**: IR ν_{max}^{neat} cm^{-1}: 3550. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=6.5 Hz), 0.95 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.5 Hz), 1.05 (9H, s), 1.06 (3H, d, J=6.5 Hz), 1.07 (3H, t, J=6.0 Hz), 1.25 (3H, s), 1.28 (3H, s), 1.33 (3H, s), 1.34 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.50—2.00 (8H, m), 2.40 (1H, s), 3.28 (1H, dd, J=6.5, 2.5 Hz), 3.35 (3H, s), 3.41 (1H, dd, J=6.0, 2.5 Hz), 3.43 (1H, s), 3.54 (2H, d, J=5.0 Hz), 3.67 (1H, d, J=9.0 Hz), 3.80 (3H, s), 3.87 (1H, d, J=4.0 Hz), 4.52, 4.60 (1H each, ABq, J=11.0 Hz), 4.80, 4.99 (1H each, ABq, J=7.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.32—7.50 (6H, m), 7.58—7.70 (4H, m). MS *m/z* (relative intensity): 849 (M^+ −57, 0.1), 621 (0.2), 549 (1.2), 425 (0.5), 411 (1.3), 367 (2.5), 269 (5.8), 121 (100). $[\alpha]_D^{23}$ +14.1° (c=1.24, $CHCl_3$). Exact MS *m/z* Calcd for $C_{31}H_{49}O_8$ (M^+ −357): 549.3426. Found: 549.3414.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-Bis(isopropylidenedioxy)-6,12-bis(methoxymethoxy)-1-*tert*-butyldiphenylsilyloxy-2,4,6,8,10,12-hexamethyl-13-(4-methoxybenzyloxy)pentadecane (26) Diisopropylethylamine (0.60 ml, 3.4 mmol) and then chloromethyl methyl ether (0.13 ml, 1.7 mmol) were added dropwise to a stirred solution of **24** (61.8 mg, 0.0682 mmol) in CH_2Cl_2 (2 ml) at room temperature. The solution was stirred at 50—55 °C for 11 h. MeOH was added, and the stirring was continued at room temperature for 30 min. The reaction mixture was diluted with Et_2O, washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave **26** as a pale yellow oil (66.0 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.5 Hz), 1.01 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=6.0 Hz), 1.04 (9H, s), 1.05 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=7.5 Hz), 1.25 (6H, s), 1.28 (3H, s), 1.32 (3H, s), 1.40 (6H, s), 1.54 (1H, s), 1.60—1.92 (7H, m), 3.27 (1H, dd, J=6.5, 2.0 Hz), 3.34 (3H, s), 3.36 (3H, s), 3.45 (1H, dd, J=8.5, 2.0 Hz), 3.50 (2H, d, J=3.5 Hz), 3.68 (1H, dd, J=9.5, 1.0 Hz), 3.74 (1H, d, J=1.0 Hz), 3.80 (3H, s), 3.89 (1H, d, J=4.0 Hz), 4.52, 4.61 (1H each, ABq, J=10.5 Hz), 4.75, 4.84 (1H each, ABq, J=6.5 Hz), 4.78, 5.00 (1H each, ABq, J=7.0 Hz), 6.87 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.30—7.50 (6H, m), 7.58—7.70 (4H, m). MS *m/z* (relative intensity): 637 (M^+ −313, 0.2), 607 (0.5), 593 (0.6), 579 (0.7), 549 (1.5), 425 (1.1), 367 (5.1), 269 (7.5), 121 (100). FD MS *m/z*: 951 (M^+ +1). $[\alpha]_D^{22}$ +11.4° (c=1.18, $CHCl_3$).

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-Bis(isopropylidenedioxy)-6,12-bis(methoxymethoxy)-2,4,6,8,10,12-hexamethyl-13-(4-methoxybenzyloxy)pentadecanoic Acid (27) A 1.0 M solution of *n*-Bu_4NF in THF (0.40 ml, 0.40 mmol) was added to a stirred solution of **26** (63.1 mg, 0.0664 mmol) in THF (4 ml) at room temperature. The solution was stirred at 55—60 °C for 2 h, then diluted with Et_2O, washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2–MeOH (80:1) as the eluent to give (2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-3,5:9,11-bis(isopropylidenedioxy)-6,12-bis(methoxymethoxy)-2,4,6,8,10,12-hexamethyl-13-(4-methoxybenzyloxy)pentadecan-1-ol as a colorless oil (44.4 mg, 94%). IR ν_{max}^{neat} cm^{-1}: 3480. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.5 Hz), 1.00 (3H, d, J=6.5 Hz), 1.03 (3H, d, J=6.5 Hz), 1.05 (3H, d, J=5.5 Hz), 1.07 (3H, t, J=7.5 Hz), 1.27 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 1.35 (3H, s), 1.39 (3H, s), 1.40 (3H, s), 1.52 (1H, s), 1.60—2.00 (7H, m), 3.27 (1H, dd, J=6.5, 2.0 Hz), 3.33 (3H, s), 3.36 (3H, s), 3.47 (1H, dd, J=8.0, 2.0 Hz), 3.52 (1H, d, J=5.0 Hz), 3.58 (2H, s), 3.62 (1H, d, J=1.5 Hz), 3.80 (3H, s), 3.89 (1H, d, J=4.0 Hz), 4.52, 4.62 (1H each, ABq, J=10.5 Hz), 4.76, 4.82 (1H each, ABq, J=6.5 Hz), 4.80, 5.00 (1H each, ABq, J=6.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz). MS *m/z* (relative intensity): 697 (M^+ −15, 0.1), 457 (0.2), 311 (3.1), 269 (1.5), 121 (100). $[\alpha]_D^{24}$ +0.6° (c=0.80, $CHCl_3$). Exact MS *m/z* Calcd for $C_{25}H_{45}O_7$ (M^+ −255): 457.3165. Found: 457.3168.

Jones reagent (2.67 M, 37 μl, 0.099 mmol) was added to a stirred solution of the above alcohol (17.6 mg, 0.0247 mmol) in acetone (2 ml) at −17 °C. After 2 h, isopropanol was added. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2–MeOH (40:1) as the eluent to give the carboxylic acid (**27**) as a colorless oil (14.0 mg, 78%). IR ν_{max}^{neat} cm^{-1}: 1735, 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=7.5 Hz), 1.04 (3H, d, J=6.5 Hz), 1.08 (3H, t, J=7.5 Hz), 1.24 (3H, d, J=7.0 Hz), 1.27 (3H, s), 1.29 (3H, s), 1.31 (3H, s), 1.34 (3H, s), 1.43 (6H, s), 1.55—1.95 (7H, m), 2.67 (1H, dt, J=16.5, 7.0 Hz), 3.24 (1H, dd, J=7.0, 2.0 Hz), 3.34 (3H, s), 3.37 (3H, s), 3.43 (1H, dd, J=8.0, 2.5 Hz), 3.80 (3H, s), 3.84 (1H, d, J=2.0 Hz), 3.86 (1H, d, J=3.0 Hz), 3.89 (1H, d, J=3.5 Hz), 4.75, 4.80 (1H each, ABq, J=10.5 Hz), 4.85, 4.96 (1H each, ABq, J=6.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz). MS *m/z* (relative intensity): 471 (M^+ −255, 0.2), 457 (0.2), 413 (7.9), 121 (100). FD MS *m/z*: 727 (M^+ +1). $[\alpha]_D^{24}$ −1.7° (c=0.58, $CHCl_3$). Exact MS *m/z* Calcd for $C_{24}H_{39}O_9$ (M^+ −255): 471.2594. Found: 471.2577.

3,5:9,11-Di-*O*-isopropylidene-6,12-di-*O*-methoxymethyl-(9*S*)-9-dihydroerythronolide A Seco-acid (28) A solution of **27** (5.8 mg, 0.0080 mmol) in EtOH (2 ml) was hydrogenated in the presence of 10% Pd–C (10 mg) at 55 °C for 13 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave the seco-acid (**28**) as a colorless oil (4.8 mg, 99%). IR ν_{max}^{neat} cm^{-1}: 1730, 1715. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=6.5 Hz), 1.04 (3H, t, J=7.0 Hz), 1.09 (3H, d, J=6.5 Hz), 1.24 (3H, d, J=7.0 Hz), 1.27 (3H, s), 1.28 (3H, s), 1.34 (3H, s), 1.36 (3H, s), 1.43 (6H, s), 1.50—1.80 (4H, m), 1.80—2.10 (3H, m), 2.66 (1H, dt, J=17.0, 7.0 Hz), 3.29 (1H, dd, J=7.5, 2.0 Hz), 3.34 (3H, s), 3.41 (3H, s), 3.69 (1H, dd, J=10.5, 1.5 Hz), 3.86 (1H, d, J=2.0 Hz), 3.87 (1H, dd, J=9.0, 2.0 Hz), 3.93 (1H, d, J=4.5 Hz), 4.74, 4.82 (1H each, ABq, J=7.0 Hz), 4.78, 4.85 (1H each, ABq, J=7.5 Hz). MS *m/z* (relative intensity): 591 (M^+ −15, 0.1), 485 (0.1), 471 (0.3), 413 (1.2), 343 (2.8), 325 (2.7), 285 (7.1), 223 (14), 45 (100). $[\alpha]_D^{22}$ +18.2° (c=0.44, $CHCl_3$). Exact MS *m/z* Calcd for $C_{30}H_{55}O_{11}$ (M^+ −15): 591.3744. Found: 591.3770.

3,5:9,11-Di-*O*-isopropylidene-6,12-di-*O*-methoxymethyl-(9*S*)-9-dihydroerythronolide A (29) Et_3N (7.7 μl, 0.055 mmol) was added to a stirred solution of **28** (30.3 mg, 0.050 mmol) in THF (1 ml) at room temperature under argon. After 10 min, 2,4,6-trichlorobenzoyl chloride (8.0 μl, 0.050 mmol) was added, the stirring was continued for 2 h at room temperature, and then the solution was made up to 25 ml with toluene. The solution was added very slowly to a stirred solution of DMAP (151 mg, 1.25 mmol) in refluxing toluene (25 ml) over a period of 39 h under argon. The stirring was continued for 11 h. After being cooled, the reaction mixture was washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (4 : 1) as the eluent to give crude **29**, which was subjected to preparative TLC on silica gel. Development with *n*-hexane–EtOAc (4 : 1) gave pure **29** as a colorless solid (7.9 mg, 27%), mp 128—129 °C (from *n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.5 Hz), 1.02 (3H, d, J=6.5 Hz), 1.16 (3H, s), 1.18 (3H, d, J=6.0 Hz), 1.26 (3H, d, J=6.0 Hz), 1.29 (3H, s), 1.30 (3H, d, J=7.0 Hz), 1.05—1.40 (2H, m), 1.42 (3H, s), 1.43 (3H, s), 1.46 (6H, s), 1.45—1.68 (2H, m), 1.74—2.02 (2H, m), 2.03—2.29 (1H, m), 2.74 (1H, dq, J=10.5, 6.5 Hz), 3.10 (1H, d, J=11.0 Hz), 3.33 (3H, s), 3.39 (3H, s), 3.62 (1H, s), 3.78 (1H, d, J=10.5 Hz), 4.02 (1H, s), 4.69, 4.80 (1H each, ABq, J=7.0 Hz), 4.79, 4.87 (1H each, ABq, J=6.0 Hz), 5.47 (1H, dd, J=11.5, 2.0). MS *m/z* (relative intensity): 573 (M^+ − 15, 0.7), 481 (0.3), 413 (0.6), 253 (1.1), 45 (100). $[\alpha]_D^{22}$ −15.0° (c=0.18, $CHCl_3$). *Anal.* Calcd for $C_{31}H_{56}O_{10}$: C, 63.23; H, 9.58. Found: C, 63.45; H, 9.56. Exact MS *m/z* Calcd for $C_{30}H_{53}F_{10}O$ (M^+ − 15): 573.3638. Found: 573.3633.

(9S)-9-Dihydroerythronolide A (3) A solution of **29** (7.9 mg, 0.013 mmol) in AcOH (1 ml) and H_2O (0.5 ml) was stirred at 50—55 °C for 2 h. The solvent was evaporated off *in vacuo*. Benzene was added to the residue, and the solution was evaporated again *in vacuo* to leave **3** as a colorless solid (6.1 mg, 100%), which was recrystallized from $CHCl_3$–petroleum ether to give colorless needles, mp 201—203 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 2975, 2940, 1715, 1185, 1080, 975. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.5 Hz), 1.04 (3H, d, J=7.0 Hz), 1.05 (3H, s), 1.24 (3H, d, J=7.0 Hz), 1.24 (3H, s), 1.30 (6H, d, J=6.5 Hz), 1.12—1.35 (1H, m), 1.38—1.65 (4H, m), 1.76 (1H, s, OH), 1.94 (1H, dq, J=7.5, 1.5 Hz), 1.98—2.03 (1H, m), 2.52 (1H, s, OH), 2.79 (1H, dq, J=10.5, 6.5 Hz), 2.90 (1H, s, OH), 2.96 (1H, dt, J=9.5, 2.5 Hz), 3.39 (1H, s, OH), 3.41 (1H, d, J=7.5 Hz, OH), 3.49 (1H, dd, J=4.5, 1.5 Hz), 3.86 (1H, d, J=10.5 Hz), 3.96 (1H, s), 4.25 (1H, d, J=4.5 Hz, OH), 4.61 (1H, dd, J=11.0, 1.5 Hz). MS *m/z* (relative intensity): 402 (M^+ − 18, 0.3), 384 (1.6), 366 (1.9), 327 (5.2), 43 (100). $[\alpha]_D^{22}$ +10.8° (c=0.11, $CHCl_3$) (lit.,[17] mp 199—200 °C; $[\alpha]_D^{25}$ +9.5° (MeOH)).

References and Notes

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