Synthetic Study of (9*S*)-9-Dihydroerythronolide A *via* Wittig–Horner Coupling of C1—C6 and C7—C15 Segments[1)]

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As part of a study directed at the total synthesis of (9*S*)-9-dihydroerythronolide A, Wittig–Horner coupling was carried out between the C7—C15 segment, (2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-2,4,6-trimethylnonanal synthesized from the C9—C15 triol, and the C1—C6 segment, diethyl (2*RS*,4*S*,5*R*,6*R*)-6-*tert*-butyldimethylsilyloxy-4-(3,4-dimethoxybenzyloxy)-2-oxo-1,3,5-trimethylhexylphosphonate synthesized from the C1—C5 diol, to obtain the C1—C15 enone, although the yield was poor.

Keywords macrolide antibiotic; erythromycin A; aglycone; erythronolide A; Wittig–Horner coupling; stereoselective synthesis; protecting group

Our continuing interest in the stereoselective synthesis of macrolide and polyether antibiotics by a common methodology developed in connection with the synthesis of some macrolide aglycones[2)] has led us to attempt a total synthesis of erythromycin A, and as the first approach we planned to synthesize (9*S*)-9-dihydroerythronolide A (**1**),[3)] which has already been converted to erythromycin A.[4)] Among several possible routes for the synthesis of **1**, a method *via* the Wittig–Horner reaction[5)] between the C7—C15 (**2**) and C1—C6 segments (**3**) seemed rather facile. In the preceding paper,[1)] improved and convenient syntheses of the C9—C15 (**4**) and C1—C5 segments (**5**) from D-glucose, propionaldehyde, and methallyl alcohol were described, and we report here the conversion of **4** and **5** into the actual C7—C15 (**6**) and C1—C6 segments (**7**), respectively, and then Wittig–Horner coupling between **6** and **7**.

Results and Discussion

Synthesis of the C7—C15 Segment (6) from 4 Although we recently synthesized **8** as a C7—C15 segment,[6)] protection of the 9,11-diol,[7)] not of the 11,12-diol, as a cyclic acetal was reported to be extremely important for the final macrolactonization.[3,4,8)] Hence, we decided to synthesize **6** instead of **8** from **4**, and we describe here two synthetic methods.

The primary alcohol of **4** was first benzoylated to give **9**, then the remaining diol was protected as the 1-(*p*-methoxyphenyl)ethylidene acetal (**10**),[9)] which is more labile to acid than acetonides. The primary alcohol was recovered by debenzoylation, and Swern oxidation gave the aldehyde (**11**). Treatment of **11** with the lithio derivative of ethyl β-trimethylsilylpropionate[10)] quantitatively gave **12** as a mixture of four compounds, which was mesylated and then treated with sodium ethoxide to give only the (*E*)-α,β-unsaturated ester (**13**) in high yield. Reduction of **13** with lithium aluminum hydride and epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) gave the unstable epoxide (**15**), which was immediately treated with the fluoride anion to give the expected olefin (**16**) as an 8 : 1 mixture with its isomer (**17**), reflecting stereoselectivity in the epoxidation. The crude olefin (**16**) was subjected to the next reaction without further purification. Assuming that the predominant conformation of **16** in dilute nonpolar solvents is as shown in A, with intramolecular hydrogen bonding, catalytic hydrogenation of the double bond of **16** in a dilute benzene solution would be expected to give mainly the desired product (**18**).[11)] Actually, hydrogenation of **16** over platinum charcoal gave mainly **18**, but selectivity between **18** and its isomer (**19**), separable thin-layer chromatographically, was only 4 : 1.

An alternative and more convenient synthesis of **18** was next examined. When the aldehyde (**11**) was treated with a stable ylide, the Wittig reaction proceeded quite smoothly and the (*E*)-α,β-unsaturated ester (**20**) was obtained in

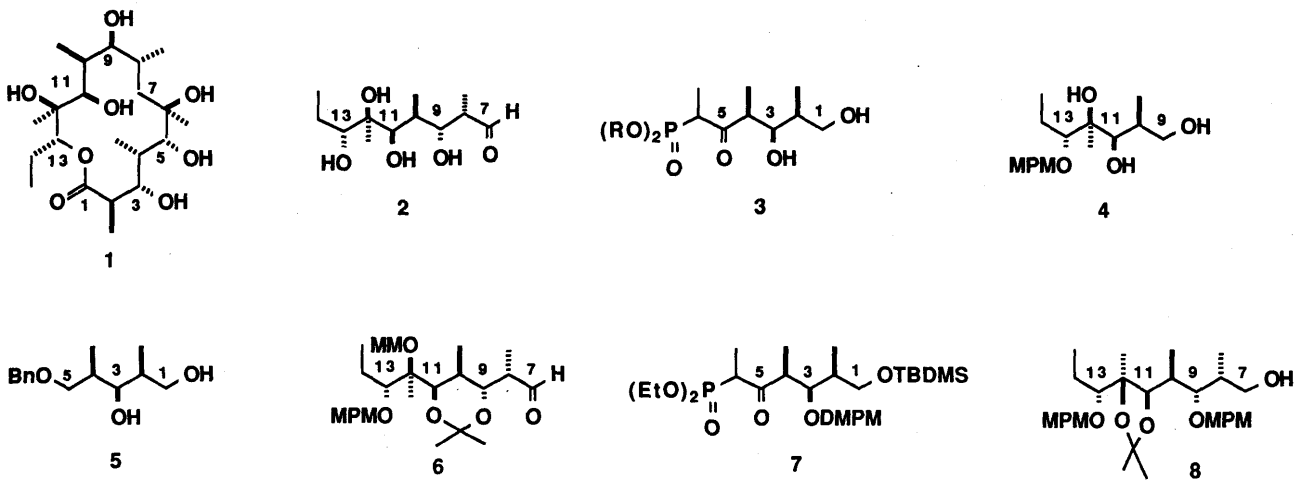
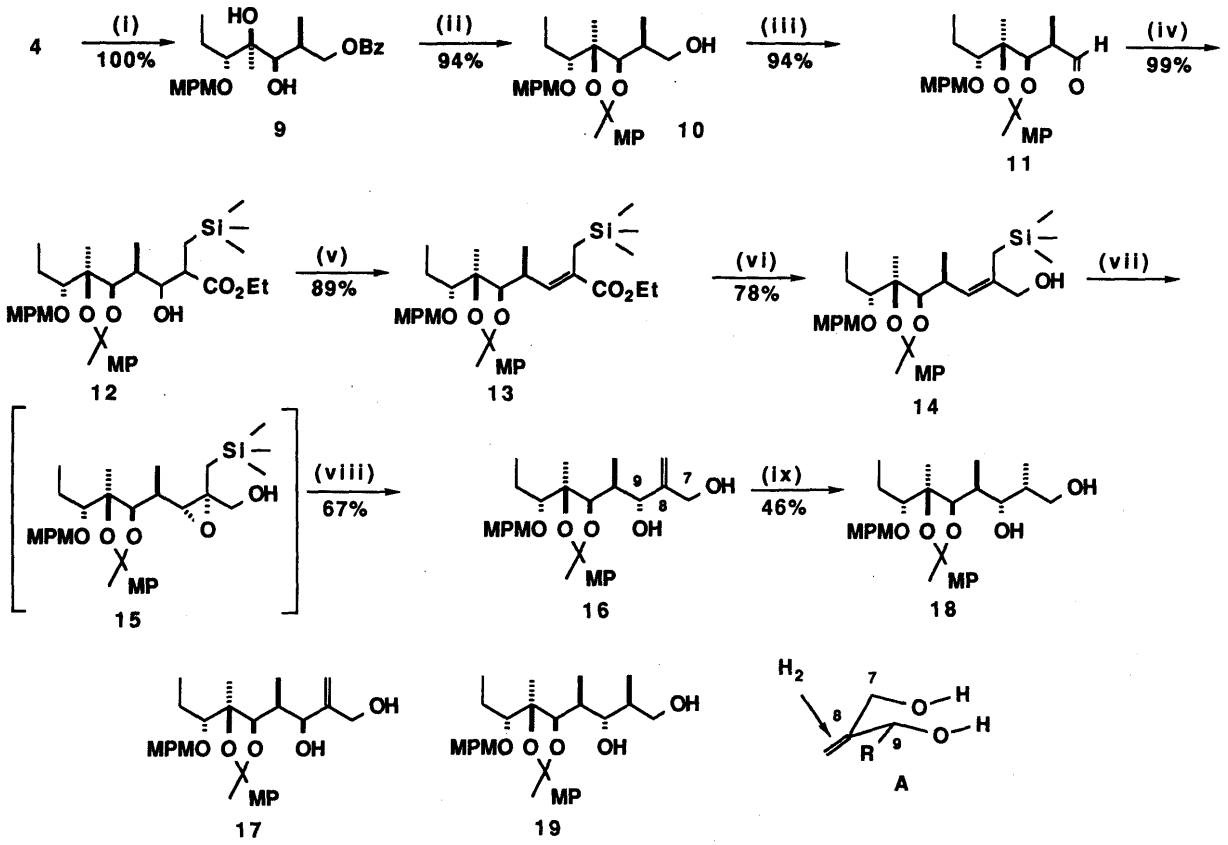
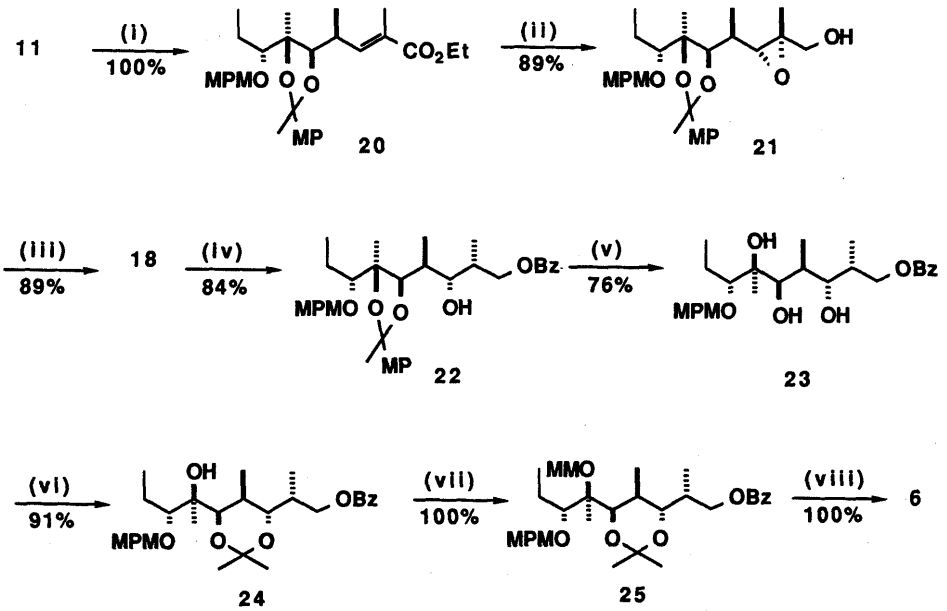


Chart 1



(i) BzCl, Py, CH_2Cl_2, room temperature, 10.5 h; (ii) a) *p*-$MeOC_6H_4CMe(OMe)_2$, CSA, CH_2Cl_2, room temperature, 2 h, b) 1 N KOH, MeOH, room temperature, 18 h; (iii) $(COCl)_2$, DMSO, Et_3N; (iv) $Me_3SiCH_2CH_2CO_2Et$, LDA, THF, −80— −20 °C, 2 h; (v) a) MsCl, Et_3N, benzene, 7 °C, 20 min (90%), b) NaOEt, THF, room temperature, 3.5 h (99%); (vi) LAH, Et_2O, 0 °C, 2 h; (vii) *m*-CPBA, CH_2Cl_2, −20 °C, 2.5 h; (viii) *n*-Bu_4NF, THF, room temperature, 5 h (8 : 1); (ix) 5% Pt–C, H_2, benzene, 10 °C.

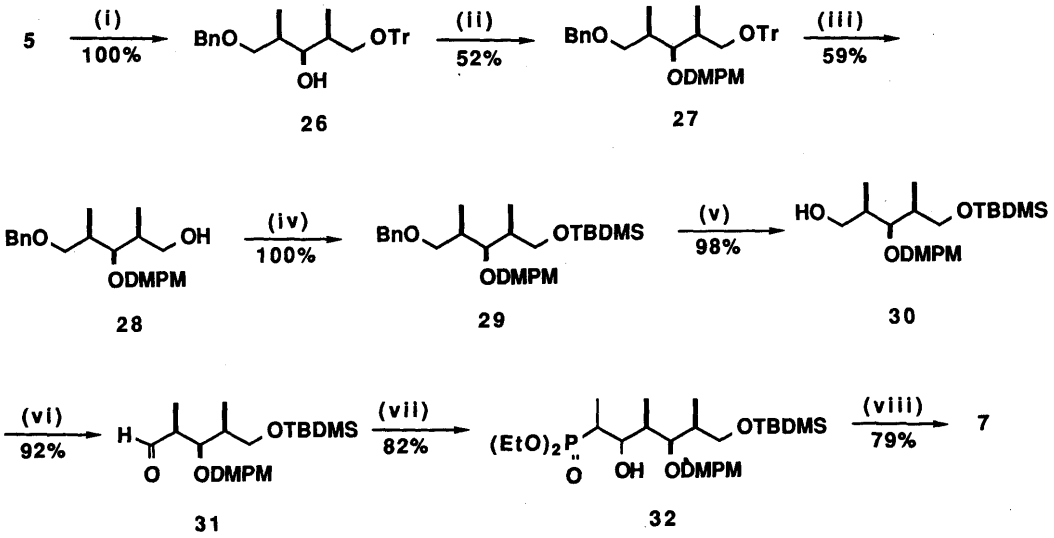
Chart 2



(i) $Ph_3P{=}CMeCO_2Et$, EDC, reflux, 45 h; (ii) a) LAH, Et_2O, 0 °C, 30 min (98%), b) *m*-CPBA, CH_2Cl_2, −15 °C (89%) (8 : 1); (iii) $NaBH_3CN$, BF_3–Et_2O, THF, reflux, 4 h; (iv) BzCl, Py, CH_2Cl_2, room temperature, 35 h; (v) 4 N HCl, THF, room temperature, 13 h; (vi) $MeOCMe{=}CH_2$, PPTS, CH_2Cl_2, room temperature, 25 min; (vii) MMCl, iso-Pr_2NEt, CH_2Cl_2, 45 °C, 12 h; (viii) a) 1 N NaOH, dioxane, 70 °C, 14 h, b) $(COCl)_2$, DMSO, Et_3N.

Chart 3

quantitative yield. After reduction of the ester group of **20**, the resulting (*E*)-allyl alcohol was treated with *m*-CPBA to give the epoxide (**21**) with 8 : 1 stereoselectivity, and this was used in the next reaction without purification. The anti-Markownikoff reductive ring opening of the epoxide (**21**) was one of the crucial steps in this total synthesis of **1**.

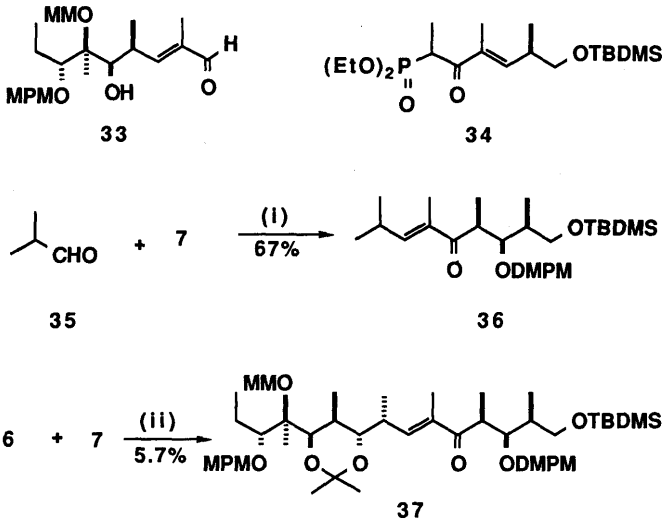


(i) TrCl, NEt_3, DMAP, CH_2Cl_2, room temperature, 12 h; (ii) DMPMCl, NaH, DMSO, room temperature, 17.5 h [76% based on consumed **26**]; (iii) 4 N HCl, THF, room temperature, 72 h [91% based on consumed **27**]; (iv) TBDMSCl, NEt_3, DMAP, CH_2Cl_2, room temperature, 45 h; (v) Raney Ni (W-2), EtOH, room temperature, 3 h; (vi) $(COCl)_2$, DMSO, NEt_3; (vii) $EtPO(OEt)_2$, *n*-BuLi, THF, −80— −10 °C, 5 h; (viii) $(COCl)_2$, DMSO, NEt_3 [94% based on consumed **32**].

Chart 4

Treatment of **21** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al)[12] or aluminum hydride,[13] *etc.* gave only poor results. However, when **21** was treated under modified Hutchins' conditions with a large excess of sodium cyanoborohydride ($NaBH_3CN$) in the presence of boron trifluoride etherate ($BF_3 \cdot Et_2O$) in refluxing tetrahydrofuran (THF),[14] completely regioselective reductive ring opening occurred to give only the desired 1,3-diol (**18**) in high yield.[15]

The primary alcohol of crude **18** was benzoylated to give **22**, which was treated with hydrochloric acid to give the triol (**23**). When **23** was treated with a large excess of 2-methoxypropene in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at room temperature,[16] the expected kinetic product, the 9,11-acetonide (**24**), not the 11,12-acetonide, was readily obtained in high yield. Methoxymethyl (MM) protection of the remaining tertiary alcohol gave **25**, which was treated with alkaline solution, and then the recovered primary alcohol was subjected to Swern oxidation to give the C7–C15 segment (**6**) in quantitative yield.



(i) *n*-BuLi, THF, 55 °C, 4.5 h; (ii) *n*-BuLi, Et_2O, room temperature, 16 h.

Chart 5

Synthesis of the C1–C6 Segment (7) from 5 In order to obtain a substrate corresponding to the C1–C6 segment (**3**) for the Wittig–Horner coupling[5] with the C7–C15 segment (**6**), **5** was converted to the β-ketophosphonate (**7**), for this reaction, selection of a suitable protecting group for the C3-hydroxy group was very important. We chose the 3,4-dimethoxybenzyl (DMPM) group, which is readily removable by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[17] The primary alcohol of **5** was first protected with the trityl group in the usual way to give **26**, and protection of the remaining secondary alcohol with the DMPM group[17a,c] gave **27**. The trityl protection of **27** was then substituted for the *tert*-butyldimethylsilyl (TBDMS) group by acid hydrolysis to **28** and subsequent TBDMS protection to give **29**.[18] Removal of the benzyl protection of **29** proceeded very smoothly with complete selectivity by hydrogenolysis over Raney nickel,[17b,c] and the mono-alcohol (**30**) readily gave the aldehyde (**31**), which was treated with the lithio derivative of diethyl ethanephosphonate,[19] followed by immediate Swern oxidation of the resulting hydroxyphosphonate (**32**) to give the ketophosphonate (**7**) as a 1 : 1 mixture with respect to the C6 position.

Wittig–Horner Coupling between 6 and 7 The Wittig–Horner reaction between an aldehyde and a carbanion of β-ketophosphonate is very important for the synthesis of α,β-unsaturated carbonyl compounds,[5] but because the reaction usually proceeds under strong basic conditions, serious side reactions are sometimes unavoidable. Use of lithium chloride (LiCl) and an amine was reported to give good results for the coupling of base-sensitive compounds.[20] Since both **6** and **7** seemed sensitive to strong base, the coupling with LiCl and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) was first examined under several con-

ditions, but unfortunately because of very poor reactivity, only β-elimination of both **6** and **7** catalyzed by DBU occurred to give **33** and **34**. Therefore, the coupling with *n*-butyllithium (*n*-BuLi) was next carefully examined. As a model reaction, **7** and isobutyraldehyde (**35**) were treated with *n*-BuLi in THF at 55 °C, when the coupling occurred rather smoothly to give **36** as a 4:1 (*E*:*Z*) mixture in fairly good yield. However, under similar conditions, **6** and **7** gave only **33** in 84% yield and 80% of **7** was recovered. After several unsuccessful attempts, only the reaction in absolute ether at room temperature gave a positive result to give the expected coupling product (**37**). Thus, the whole carbon skeleton of **1** was constructed, although the yield in the final step needs to be improved.

Experimental

Physical data were measured as described in the preceding paper.[1)]

(2*S*,3*R*,4*R*,5*R*)-1-Benzoyloxy-2,4-dimethyl-5-(4-methoxybenzyloxy)-heptan-3,4-diol (9) Benzoyl chloride (0.39 ml, 3.24 mmol) was added dropwise to a stirred solution of the triol (**4**) (0.50 g, 1.62 mmol) and pyridine (0.40 ml, 4.86 mmol) in CH_2Cl_2 (15 ml) at 0 °C, and the solution was stirred at room temperature for 10.5 h. MeOH was added to decompose the excess chloride, and after 30 min, the reaction mixture was washed successively with aqueous $KHSO_4$, brine, aqueous $NaHCO_3$, and 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 **9** as a colorless oil (0.69 g, 100%). IR ν_{max}^{neat} cm^{-1}: 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, *J*=7.5 Hz), 1.10 (3H, t, *J*=7.0 Hz), 1.12 (1H, dd, *J*=7.5, 4.0 Hz), 3.50 (1H, s), 3.78 (3H, s), 3.97 (1H, t, *J*=2.0 Hz), 4.18 (1H, dd, *J*=9.0, 6.5 Hz), 4.36 (1H, dd, *J*=9.0, 8.5 Hz), 4.61 (2H, s), 6.82 (2H, d, *J*=9.0 Hz), 7.21 (2H, d, *J*=9.0 Hz), 7.30—7.64 (3H, m), 8.02 (2H, dd, *J*=8.0, 1.5 Hz). MS *m*/*z* (relative intensity): 237 (M^+ − 179, 15), 219 (2.9), 193 (5.6), 138 (5.6), 122 (45), 121 (100). *Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.94; H, 7.85.

(2*S*,3*R*,4*R*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-3,4-[1-(4-methoxyphenyl)ethylidenedioxy]heptan-1-ol (10) A solution of **9** (0.93 g, 2.24 mmol), *p*-methoxyacetophenone dimethyl acetal (0.88 g, 4.48 mmol), and 10-camphorsulfonic acid (CSA) (0.09 g, 0.39 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 2 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), and evaporated *in vacuo* to leave the acetal as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, *J*=7.0 Hz), 1.08 (3H, s), 1.11 (3H, d, *J*=7.0 Hz), 1.57 (3H, s), 3.35 (1H, dd, *J*=8.0, 5.0 Hz), 3.75 (3H, s), 3.80 (6H, s), 4.25 (2H, d, *J*=5.0 Hz), 4.27 (1H, s), 4.49 (1H, d, *J*=12.0 Hz), 4.59 (1H, d, *J*=12.0 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.74 (1H, d, *J*=12.0 Hz), 6.76—7.50 (11H, m), 8.05 (2H, dd, *J*=8.0, 1.0 Hz). MS *m*/*z* (relative intensity): 548 (M^+, 0.25), 533 (6.5), 369 (20), 219 (85), 121 (100).

A 1 N KOH solution (4.5 ml) was added to a solution of the above acetal in MeOH (40 ml), and the solution was stirred at room temperature for 18 h. After removal of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2, and the resulting solution 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 the alcohol (**10**) as a colorless oil (0.94 g, 94%). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, *J*=7.0 Hz), 1.06 (3H, t, *J*=7.0 Hz), 1.06 (3H, s), 1.57 (3H, s), 3.40—3.60 (3H, m), 3.80 (6H, s), 4.12 (1H, d, *J*=5.0 Hz), 4.63 (2H, s), 6.83 (2H, d, *J*=9.0 Hz), 6.88 (2H, d, *J*=9.0 Hz), 7.29 (2H, d, *J*=9.0 Hz), 7.43 (2H, d, *J*=9.0 Hz). MS *m*/*z* (relative intensity): 444 (M^+, 0.5), 429 (3.0), 283 (1.0), 265 (30), 151 (60), 121 (100). Exact MS *m*/*z* Calcd for $C_{31}H_{42}O_7$ (M^+): 444.2511. Found: 444.2507.

(2*S*,3*R*,4*R*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-3,4-[1-(4-methoxyphenyl)ethylidenedioxy]heptanal (11) Dimethyl sulfoxide (DMSO) (0.39 ml, 5.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of oxalyl chloride (0.25 ml, 2.75 mmol) in CH_2Cl_2 (15 ml) at −50—−60 °C. After 15 min, a solution of **10** (0.94 g, 2.12 mmol) in CH_2Cl_2 (15 ml) was added. The solution was stirred at −50 °C for 30 min, then treated with Et_3N (1.1 ml, 8.25 mmol), and allowed to warm to room temperature. 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–CH_2Cl_2 (1:1) as the eluent to give the aldehyde (**11**) as a colorless oil (0.88 g, 94%). IR ν_{max}^{neat} cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s), 1.09 (3H, t, *J*=7.0 Hz), 1.13 (3H, d, *J*=7.0 Hz), 2.50 (1H, dquintet, *J*=7.0, 2.0 Hz), 3.41 (1H, dd, *J*=7.5, 5.0 Hz), 3.80 (6H, s), 4.39 (1H, d, *J*=7.0 Hz), 4.44 (1H, d, *J*=11.5 Hz), 4.55 (1H, d, *J*=11.5 Hz), 4.58 (1H, d, *J*=11.5 Hz), 4.69 (1H, d, *J*=11.5 Hz), 6.83 (2H, d, *J*=9.0 Hz), 6.87 (2H, d, *J*=9.0 Hz), 7.26 (2H, d, *J*=9.0 Hz), 7.40 (2H, d, *J*=9.0 Hz), 9.43 (1H, d, *J*=2.5 Hz). MS *m*/*z* (relative intensity): 442 (M^+, 0.5), 427 (2.0), 263 (10), 203 (35), 121 (100).

Ethyl (2*RS*,3*RS*,4*S*,5*R*,6*R*,7*R*)-4,6-Dimethyl-3-hydroxy-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2-trimethylsilylmethylnonanoate (12) A solution of ethyl β-trimethylsilylpropionate (0.315 g, 1.81 mmol) in THF (1 ml) was added dropwise to a stirred solution of lithium diisopropylamide (LDA) (1.76 mmol) in THF (3.5 ml) at −80—−83 °C under argon. After 45 min, a solution of **11** (0.572 g, 1.294 mmol) in THF (3 ml) was added dropwise, and then the reaction mixture was allowed to warm to −20 °C over a period of 2 h. After addition of a solution of AcOH (119 mg) in Et_2O (1 ml) at −20 °C, the reaction mixture was warmed to 0 °C and then extracted with Et_2O. The extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3:1) as the eluent to give a diastereoisomeric mixture of esters (**12**) as an oil (0.786 g, 99%). MS *m*/*z* (relative intensity): 601 (M^+ − 15, 1.0), 437 (6.0), 287 (15), 151 (25), 135 (30), 121 (100). Exact MS *m*/*z* Calcd for $C_{33}H_{49}O_8Si$ (M^+ − 15): 601.3196. Found: 601.3205.

Ethyl (2*E*,4*S*,5*R*,6*R*,7*R*)-4,6-Dimethyl-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2-trimethylsilylmethyl-2-nonenoate (13) A solution of mesyl chloride (0.156 g, 1.37 mmol) in benzene (0.5 ml) was added dropwise to a stirred solution of **12** (0.337 g, 0.547 mmol) and Et_3N (0.53 ml) in benzene (7 ml) at 7 °C. After 20 min, the reaction mixture was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3:1) as the eluent to give the mesylate as a colorless oil (0.34 g, 90%). IR ν_{max}^{neat} cm^{-1}: 1735 (sh), 1730, 1610. MS *m*/*z* (relative intensity): 694 (M^+, 0.2), 679 (3.0), 559 (7.0), 515 (20), 269 (15), 151 (30), 135 (50), 121 (100). Exact MS *m*/*z* Calcd for $C_{24}H_{39}O_8SSi$ (M^+ − 179): 515.2134. Found: 515.2109.

A solution of the mesylate (0.31 g, 0.446 mmol) in THF (5 ml) was added dropwise to a stirred solution of NaOEt (61 mg, 0.892 mmol) in THF (1 ml) at room temperature. After 3.5 h, the reaction mixture was neutralized with aqueous NH_4Cl, and extracted with CH_2Cl_2. The extracts were washed with water, dried (Na_2SO_4), and evaporated to give **13** as an oil (0.264 g, 99%). IR ν_{max}^{neat} cm^{-1}: 1710, 1615. ^{1}H-NMR ($CDCl_3$) δ: −0.06 (9H, s), 0.99 (3H, s), 1.05 (3H, t, *J*=7.0 Hz), 1.08 (3H, d, *J*=6.5 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.49 (1H, d, *J*=13.0 Hz), 1.58 (3H, s), 1.68 (1H, d, *J*=13.0 Hz), 2.28—2.50 (1H, m), 3.28 (1H, dd, *J*=7.0, 4.0 Hz), 3.80 (6H, s), 3.90 (1H, d, *J*=9.0 Hz), 4.14 (2H, q, *J*=7.0 Hz), 4.58 (2H, s), 6.33 (1H, d, *J*=10.0 Hz), 6.84 (2H, d, *J*=9.0 Hz), 6.86 (2H, d, *J*=9.0 Hz), 7.27 (2H, d, *J*=9.0 Hz), 7.46 (2H, d, *J*=9.0 Hz). MS *m*/*z* (relative intensity): 598 (M^+, 1.0), 583 (2), 419 (7), 269 (20), 223 (10), 151 (15), 135 (15), 121 (100). Exact MS *m*/*z* Calcd for $C_{34}H_{50}O_7Si$ (M^+): 598.3326. Found: 598.3335.

(2*E*,4*S*,5*R*,6*R*,7*R*)-4,6-Dimethyl-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2-trimethylsilylmethylnon-2-en-1-ol (14) $LiAlH_4$ (31 mg) was added to a stirred solution of **13** (0.24 g, 0.401 mmol) in Et_2O (6 ml) at 0 °C. After 2 h, usual work-up gave an oil, which was chromatographed on a silica gel column with *n*-hexane–EtOAc (3:1) as eluant to give the alcohol (**14**) as a colorless oil (0.174 g, 78%). ^{1}H-NMR ($CDCl_3$) δ: −0.04 (9H, s), 1.03 (3H, s), 1.04 (3H, d, *J*=6.5 Hz), 1.07 (3H, t, *J*=8.0 Hz), 1.26 (1H, d, *J*=14.0 Hz), 1.50 (1H, d, *J*=14.0 Hz), 1.57 (3H, s), 1.65—1.80 (2H, m), 2.22—2.35 (1H, m), 3.33 (1H, dd, *J*=8.0, 4.0 Hz, 3.80 (6H, s), 3.83 (1H, d, *J*=10.0 Hz), 4.52 (1H, d, *J*=11.0 Hz), 4.57 (1H, d, *J*=11.0 Hz), 4.60 (1H, d, *J*=11.0 Hz), 4.65 (1H, d, *J*=11.0 Hz), 4.99 (1H, d, *J*=10.0 Hz), 6.84 (2H, d, *J*=8.5 Hz), 6.88 (2H, d, *J*=8.5 Hz), 7.29 (2H, d, *J*=8.5 Hz), 7.47 (2H, d, *J*=8.5 Hz). MS *m*/*z* (relative intensity): 541 (M^+ − 15, 0.5), 377 (2), 227 (3), 223 (2), 209 (2), 121 (100). $[\alpha]_D^{22}$ +33.6° (*c*=0.60, $CHCl_3$).

(3*S*,4*S*,5*R*,6*R*,7*R*)-4,6-Dimethyl-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2-methylenenonane-1,3-diol (16) *m*-CPBA (76 mg, 0.374 mmol) was added to a stirred solution of **14** (0.104 g, 0.187 mmol) in CH_2Cl_2 (5 ml) at −20 °C. After 2.5 h, the solution was allowed to warm to 0 °C, washed successively with aqueous Na_2SO_3, aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated *in vacuo* to leave the crude epoxide (**15**) as an unstable oil. A 1 M solution of *n*-Bu_4NF in THF (0.32 ml) was added to a stirred solution of **15** in THF (3 ml) at room temperature. After 5 h, the reaction mixture was neutralized with aqueous NH_4Cl, and extracted with Et_2O. The extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (2:1) as the eluent to give an 8:1 mixture of **16** and **17** as an oil (63 mg, 67%), which was

subjected to the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=7.0 Hz), 1.04 (3H, s), 1.04 (3H, t, J=7.5 Hz), 1.59 (3H, s), 3.44 (1H, dd, J=8.0, 4.0 Hz), 3.81 (6H, s), 3.94—4.11 (2H, m), 4.12 (1H, d, J=7.5 Hz), 4.57 (1H, s), 4.59—4.74 (2H, m), 5.16 (1.78H, br s), 5.07 (0.22H, br s), 6.85 (2H, d, J=9.0 Hz), 6.89 (2H, d, J=9.0 Hz), 7.29 (2H, d, J=9.0 Hz), 7.44 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 500 (M^+, 0.12), 485 (1.5), 321 (3.7), 171 (35), 151 (50), 135 (30), 121 (100).

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-7-(4-Methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2,4,6-trimethylnonane-1,3-diol (18) (a) A solution of the 8:1 mixture of **16** and **17** (35 mg) in benzene (16 ml) was hydrogenated in the presence of 5% Pt–C (20 mg) at 8—10 °C under ordinary pressure for 1 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave an oil, which was subjected to preparative thin layer chromatography (TLC) on silica gel. Development with CH_2Cl_2–Et_2O (5:1) gave the diol (**18**) as a colorless oil (16 mg, 46%), and a mixture of **19** and a reduction product of **17** (6.5 mg, 19%). ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, d, J=7.0 Hz), 0.87 (3H, d, J=7.0 Hz), 1.05 (3H, s), 1.08 (3H, t, J=7.0 Hz), 1.58 (3H, s), 1.50—1.96 (4H, m), 3.47 (1H, dd, J=7.0, 5.0 Hz), 3.64 (2H, dd, J=4.5, 2.0 Hz), 3.60—3.80 (1H, m), 3.80 (6H, s), 4.50 (1H, d, J=1.5 Hz), 4.56, 4.69 (1H, each, ABq, J=10.5 Hz), 6.84 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.44 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 502 (M^+, 0.03), 487 (0.2), 427 (0.4), 305 (0.6), 173 (48), 151 (56), 121 (100). Exact MS m/z Calcd for $C_{29}H_{42}O_7$ (M^+): 502.2930. Found: 502.2926.

The diacetate of **18** was an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=7.0 Hz), 0.97 (3H, d, J=7.0 Hz), 0.99 (3H, s), 1.02 (3H, t, J=7.0 Hz), 1.56 (3H, s), 1.92 (3H, s), 2.04 (3H, s), 3.34 (1H, dd, J=9.0, 4.5 Hz), 3.80 (6H, s), 3.78—3.97 (2H, septet, J=11.0, 7.5 Hz), 4.22 (1H, s), 4.51 (1H, d, J=10.5 Hz), 4.88 (1H, d, J=10.5 Hz), 5.17 (1H, dd, J=7.5, 2.5 Hz), 6.85 (2H, d, J=9.0 Hz), 7.28 (2H, d, J=9.0 Hz), 7.46 (2H, d, J=9.0 Hz).

(b) $NaBH_3CN$ (3.54 g, 56 mmol) and then BF_3–Et_2O (3.55 ml, 28 mmol) were added dropwise to a stirred solution of **21** (2.34 g, 4.68 mmol) in dry THF (150 ml). The solution was stirred under reflux for 4 h, then poured into ice-cooled aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3:1) as the eluent to give an 8:1 mixture of **18** and its (2*S*,3*R*)-isomer as a colorless oil (2.09 g, 89%).

(c) The purified benzoate (**22**) was hydrolyzed in the usual way (1 N KOH/MeOH, room temperature, 4 h) to give **18** in quantitative yield.

Ethyl (2*E*,4*S*,5*R*,6*R*,7*R*)-7-(4-Methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2,4,6-trimethylnon-2-enoate (20) α-Ethoxycarbonylethylidenetriphenylphosphorane (2.90 g, 8.0 mmol) was added to a solution of **11** (0.88 g, 2.0 mmol) in dry ethylene dichloride (EDC) (40 ml), and the solution was stirred under reflux for 45 h. Evaporation of the solvent left an oil, which was chromtographed on a silica gel column with *n*-hexane–CH_2Cl_2 (1:1) as the eluent to give **20** as a colorless oil (1.07 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s), 1.06 (3H, t, J=7.0 Hz), 1.07 (3H, d, J=6.5 Hz), 1.26 (3H, d, J=7.0 Hz), 1.57 (3H, s), 1.50—1.90 (2H, m), 1.67 (3H, d, J=1.5 Hz), 2.30—2.70 (1H, m), 3.29 (1H, dd, J=7.0, 5.0 Hz), 3.80 (3H, s), 3.81 (3H, s), 3.94 (1H, d, J=9.5 Hz), 4.08, 4.21 (1H each, ABq, J=7.0 Hz), 4.58 (2H, s), 6.50 (1H, dd, J=10.0, 1.5 Hz), 7.27 (2H, d, J=9.0 Hz), 7.50 (2H, d, J=9.0 Hz), 7.84 (2H, d, J=9.0 Hz), 7.86 (2H, d, J=9.0 Hz).

(2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-2,3-Epoxy-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2,4,6-trimethylnonan-1-ol (21) $LiAlH_4$ (0.42 g, 11.0 mmol) was added to a stirred solution of **20** (2.90 g, 5.5 mmol) in dry Et_2O (120 ml) at −10 °C. The mixture was stirred at −10 °C for 30 min and then at 0 °C for 30 min. The excess hydride was decomposed with MeOH–H_2O at below 5 °C. Precipitated salts were filtered off and thoroughly washed with EtOAc. The EtOAc layer was dried (Na_2SO_4) and evaporated *in vacuo* to leave (2*E*,4*S*,5*R*,6*R*,7*R*)-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2,4,6-trimethylnon-2-en-1-ol as a colorless oil (2.62 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s), 1.06 (3H, t, J=7.5 Hz), 1.48 (3H, d, J=1.0 Hz), 1.57 (3H, s), 1.50—1.90 (2H, m) 2.16—2.64 (1H, m), 3.30 (1H, dd, J=7.5, 4.5 Hz), 3.80 (3H, s), 3.81 (3H, s), 3.87 (2H, d, J=9.5 Hz), 4.52, 4.65 (1H each, ABq, J=11.5 Hz), 5.10 (1H, dd, J=11.0, 1.0 Hz), 6.84 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.28 (2H, d, J=9.0 Hz), 7.46 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 484 (M^+, 0.1), 469 (0.8), 305 (8), 121 (100). Exact MS m/z Calcd for $C_{29}H_{40}O_6$ (M^+): 484.2824. Found: 484.2827.

m-CPBA (1.55 g, 7.58 mmol) was added to a stirred solution of the above alcohol (2.62 g, 5.41 mmol) in dry CH_2Cl_2 (100 ml) at −15 °C. After 5 h, the reaction mixture was allowed to warm to −5 °C over a period of 1 h, then washed successively with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, 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 an 8:1 mixture of the epoxide (**21**) and its stereoisomer as a colorless oil (2.41 g, 89%). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=5.0 Hz), 1.06 (3H, d, J=6.0 Hz), 1.07 (3H, s), 1.18 (3H, s), 1.58 (3H, s), 1.63—1.86 (3H, m), 2.99 (1H, d, J=9.5 Hz), 3.46 (1H, dd, J=8.0, 4.5 Hz), 3.56 (1H, dd, J=12.0, 4.5 Hz), 3.66 (1H, dd, J=12.0, 4.5 Hz), 3.80 (6H, s), 4.19 (1H, d, J=5.0 Hz), 4.58, 4.70 (1H each, ABq, J=11.0 Hz), 6.84 (2H, d, J=8.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 7.46 (2H, d, J=8.5 Hz). MS m/z (relative intensity): 501 (M^++1, 0.04), 500 (M^+, 0.2), 485 (0.4), 427 (0.6), 321 (3.7), 203 (13), 121 (100). *Anal.* Calcd for $C_{29}H_{40}O_7$: C, 69.58; H, 8.05. Found: C, 69.06; H, 8.19. Exact MS m/z Calcd for $C_{29}H_{40}O_7$ (M^+): 500.2775. Found: 500.2766.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-1-Benzoyloxy-7-(4-methoxybenzyloxy)-5,6-[1-(4-methoxyphenyl)ethylidenedioxy]-2,4,6-trimethylnonan-3-ol (22) A solution of **18** (2.09 g, 4.16 mmol), dry pyridine (1.01 ml, 12.5 mmol), and benzoyl chloride (0.97 ml, 6.32 mmol) in CH_2Cl_2 (80 ml) was stirred at room temperature for 35 h. MeOH (10 ml) was added to decompose the excess chloride. After 1 h, the reaction mixture was successively washed with aqueous $KHSO_4$, brine, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (8:1→4:1) as the eluent to give the benzoate (**22**) as a colorless oil (2.11 g, 84%). IR ν_{max}^{neat} cm^{-1}: 3500, 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=7.0 Hz), 1.05 (3H, s), 1.07 (3H, t, J=7.5 Hz), 1.57 (3H, s), 1.40—2.40 (5H, m), 3.45 (1H, dd, J=7.0, 5.5 Hz), 3.61 (1H, dd, J=9.0, 1.0 Hz), 3.79 (6H, s), 4.12 (1H, dd, J=11.0, 6.0 Hz), 4.39 (1H, dd, J=11.0, 7.5 Hz), 4.56 (1H, d, J=1.5 Hz), 4.63 (2H, s), 6.83 (2H, d, J=9.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.29 (2H, d, J=9.0 Hz), 7.43 (2H, d, J=9.0 Hz), 7.28—7.60 (3H, m), 8.04 (1H, d, J=8.0 Hz), 8.06 (1H, d, J=8.0 Hz). MS m/z (relative intensity): 606 (M^+, 0.1), 591 (0.4), 427 (2.5), 277 (36), 151 (31), 121 (100). $[\alpha]_D^{17}$ +3.5° (c=2.31, $CHCl_3$). *Anal.* Calcd for $C_{36}H_{46}O_8$: C, 71.26; H, 7.64. Found: C, 71.57; H, 7.80. Exact MS m/z Calcd for $C_{36}H_{46}O_8$ (M^+): 606.3193. Found: 606.3197.

(2*R*,3*S*,4*S*,5*R*,6*S*,7*R*)-1-Benzoyloxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylnonane-3,5,6-triol (23) A 4 N HCl solution (16 ml) was added to a stirred solution of **22** (1.88 g, 3.13 mmol) in THF (32 ml) at room temperature. After 13 h, the reaction mixture was poured into cold aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column with *n*-hexane–EtOAc (8:1→4:1) as the eluent to give recovered **22** (0.25 g, 13%) and the triol (**23**) as a colorless oil (1.13 g, 76%). IR ν_{max}^{neat} cm^{-1}: 3440, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=7.0 Hz), 1.05 (3H, d, J=4.5 Hz), 1.07 (3H, t, J=4.0 Hz), 1.11 (3H, s), 1.44—1.70 (2H, m), 1.81 (1H, quintet, J=7.5 Hz), 2.05—2.21 (1H, m), 2.77 (1H, s), 3.23 (1H, s), 3.33 (1H, dd, J=14.0, 8.5 Hz), 3.63 (1H, dd, J=7.0, 4.0 Hz), 3.79 (3H, s), 3.81 (1H, t, J=2.0 Hz), 4.12 (1H, dd, J=11.0, 6.0 Hz), 4.26 (1H, t, J=2.0 Hz), 4.44 (1H, dd, J=11.0, 7.5 Hz), 4.63 (3H, s), 6.87 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.38—7.48 (2H, m), 7.50—7.60 (1H, m), 8.02 (2H, d, J=8.5 Hz), 8.03 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 320 (M^+−154, 0.3), 277 (27), 155 (24), 121 (100). $[\alpha]_D^{18}$ +11.9° (c=1.42, $CHCl_3$). Exact MS m/z Calcd for $C_{19}H_{28}O_4$ (M^+−154): 320.1988. Found: 320.1991.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-1-Benzoyloxy-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylnonan-6-ol (24) 2-Methoxypropene (0.34 g, 3.5 mmol) and PPTS (8.8 mg, 0.035 mmol) were added to a stirred solution of **23** (166 mg, 0.35 mmol) in CH_2Cl_2 (10 ml) at room temperature. After 25 min, Et_3N (0.2 ml) was added, and the reaction mixture was evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–CH_2Cl_2 (1:1) and then CH_2Cl_2 as eluents to give **24** as a colorless oil (164 mg, 91%). IR ν_{max}^{neat} cm^{-1}: 3550, 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J=7.0 Hz), 1.07 (3H, t, J=7.0 Hz), 1.09 (3H, d, J=6.5 Hz), 1.16 (3H, s), 1.32 (3H, s), 1.36 (3H, s), 1.48—2.20 (4H, m), 2.22 (1H, s), 3.37 (1H, dd, J=6.0, 4.0 Hz), 3.50 (1H, dd, J=6.5, 3.0 Hz), 3.80 (3H, s), 4.04 (1H, d, J=4.0 Hz), 4.18, 4.37 (1H each, ABq, J=11.0 Hz), 4.42, 4.65 (1H each, ABq, J=11.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.32—7.60 (3H, m), 8.03 (2H, d, J=8.5 Hz), 8.05 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 360 (M^+−154, 0.2), 335 (1.0), 277 (55), 155 (46), 121 (100). $[\alpha]_D^{15}$ −12.9° (c=1.52, $CHCl_3$). Exact MS m/z Calcd for $C_{19}H_{27}O_5$ (M^+−179): 335.1858. Found: 335.1854.

(2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-1-Benzoyloxy-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-2,4,6-trimethylnonane (25) Diisopropylethylamine (13.4 ml, 76.8 mmol) and then methoxymethyl chloride (2.92 ml, 38.4 mmol) were added dropwise to a stirred solution of **24**

(987 mg, 1.92 mmol) in CH_2Cl_2 (30 ml) at room temperature. The solution was stirred at 45—50 °C for 12 h, and then H_2O was added. After 1 h, the reaction mixture was extracted with Et_2O. The extract was washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to give **25** as a colorless oil (1.081 g, 100%). IR ν_{max}^{neat} cm^{-1}: 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=7.0 Hz), 1.05 (3H, d, J=5.5 Hz), 1.08 (3H, t, J=7.5 Hz), 1.28 (3H, s), 1.32 (3H, s), 1.33 (3H, s), 1.65 (1H, quintet, J=7.5 Hz), 1.75—2.14 (3H, m), 3.36 (3H, s), 3.45 (1H, dd, J=5.0, 2.5 Hz), 3.48 (1H, dd, J=6.0, 2.5 Hz), 3.80 (3H, s), 3.93 (1H, d, J=4.0 Hz), 4.23 (1H, dd, J=11.0, 8.0 Hz), 4.28 (1H, dd, J=11.0, 8.0 Hz), 4.51, 4.62 (1H each, ABq, J=10.5 Hz), 4.79, 5.01 (1H each, ABq, J=7.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.38—7.50 (2H, m), 7.50—7.60 (1H, m), 8.03 (2H, d, J=8.5 Hz), 8.04 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 558 (M^+, 0.1), 513 (0.4), 469 (1.0), 455 (1.2), 321 (8.4), 121 (100). $[\alpha]_D^{15}$ −17.6° (c=1.57, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{46}O_8$: C, 68.79; H, 8.30. Found: C, 68.97; H, 8.32. Exact MS m/z Calcd for $C_{28}H_{37}O_6$ (M^+−89): 469.2591. Found: 469.2611.

(2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,5-Isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-2,4,6-trimethylnonanal (6) A 1 N NaOH solution (7.68 ml) was added to a stirred solution of **25** (1.081 g, 1.92 mmol) in dioxane (60 ml), and the resulting solution was stirred at 65—70 °C for 14 h. After evaporation of the solvent, the residue was dissolved in Et_2O. The Et_2O layer was washed with brine, dried (Na_2SO_4), and evaporated to leave (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-6-methoxymethoxy-2,4,6-trimethylnonanol as a colorless oil (881 mg, 100%). IR ν_{max}^{neat} cm^{-1}: 3420. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=7.0 Hz), 1.09 (3H, t, J=7.5 Hz), 1.29 (3H, s), 1.33 (3H, s), 1.38 (3H, s), 1.65 (1H, quintet, J=7.5 Hz), 1.75—2.00 (3H, m), 2.26 (1H, t, J=5.0 Hz), 3.36 (3H, s), 3.47 (1H, dd, J=8.0, 2.5 Hz), 3.51 (1H, dd, J=7.0, 2.5 Hz), 3.64 (2H, t, J=5.0 Hz), 3.80 (3H, s), 3.93 (1H, d, J=4.5 Hz), 4.50, 4.62 (1H each, ABq, J=10.5 Hz), 4.79, 5.00 (1H each, ABq, J=7.0 Hz), 6.87 (1H, d, J=9.0 Hz), 7.26 (1H, d, J=9.0 Hz). MS m/z (relative intensity): 454 (M^+, 0.2), 351 (1.6), 275 (1.6), 224 (4.8), 217 (20), 121 (100). $[\alpha]_D^{17}$ −9.5° (c=1.24, $CHCl_3$). Exact MS m/z Calcd for $C_{25}H_{42}O_7$ (M^+): 454.2930. Found: 454.2930.

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 −75 °C, and the solution was stirred at −60—−55 °C for 30 min. A solution of the above alcohol (50.8 mg, 0.112 mmol) in CH_2Cl_2 (3 ml) was added at −70 °C, and the mixture was stirred at −70—−55 °C. After 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 to leave the aldehyde (**6**) as a colorless oil (51.1 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=5.0 Hz), 1.09 (3H, t, J=7.0 Hz), 1.14 (3H, d, J=5.5 Hz), 1.26 (3H, s), 1.31 (3H, s), 1.35 (3H, s), 1.50—2.12 (3H, m), 2.20—2.56 (1H, m), 3.37 (3H, s), 3.48 (1H, dd, J=7.5, 3.0 Hz), 3.78 (1H, dd, J=7.0, 3.0 Hz), 3.80 (3H, s), 3.94 (1H, d, J=4.0 Hz), 4.47, 4.64 (1H each, ABq, J=11.0 Hz), 4.78, 5.01 (1H each, ABq, J=7.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 9.67 (1H, d, J=1.0 Hz).

(2*S*,3*S*,4*R*)-1-Benzyloxy-2,4-dimethyl-5-trityloxypentan-3-ol (26) Trityl chloride (1.38 g, 5.0 mmol) was added to a stirred solution of **5** (0.69 g, 2.9 mmol), Et_3N (0.93 ml, 6.7 mmol), and DMAP (36 mg, 0.29 mmol) in CH_2Cl_2 (35 ml) at room temperature, and the solution was stirred for 12 h. After addition of MeOH, the solution was stirred for 30 min, then evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–CH_2Cl_2 (1 : 1) as the eluent to give the alcohol (**26**) as a colorless oil (1.40 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=7.0 Hz), 1.09 (3H, d, J=7.0 Hz), 1.60—2.00 (2H, m), 2.68 (1H, d, J=3.0 Hz), 3.00 (1H, dd, J=9.5, 5.0 Hz), 3.17 (1H, dd, J=8.0, 5.0 Hz), 3.40 (2H, d, J=5.0 Hz), 3.68 (1H, dt, J=5.0, 3.0 Hz), 4.46 (2H, s), 7.08—7.52 (20H, m). MS m/z (relative intensity): 480 (M^+, 0.2), 403 (1.5), 259 (10), 243 (90), 91 (100).

(2*R*,3*S*,4*R*)-1-Benzyloxy-2,4-dimethyl-3-(3,4-dimethoxybenzyloxy)-5-trityloxypentane(27) A solution of oil-free NaH (84 mg, 3.5 mmol) in DMSO (10 ml) was stirred at 65—70 °C for 1 h under argon, and then cooled to room temperature. A solution of **26** (1.40 g, 2.9 mmol) in DMSO (10 ml) was added. After 1 h, DMPM chloride (0.81 g, 4.5 mmol) was added, and the stirring was continued for 17.5 h at room temperature. Et_2NH was added to decompose the excess DMPM chloride, then 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 (8 : 1) as the eluent to give the recovered alcohol (**26**) (0.45 g, 32%) and **27** as a colorless oil (0.95 g, 52%). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=7.0 Hz), 2.01 (2H, septet, J=6.0 Hz), 3.06 (2H, d, J=6.5 Hz), 3.28 (1H, dd, J=9.0, 6.0 Hz), 3.46 (1H, dd, J=9.0, 6.0 Hz), 3.66 (1H, t, J=5.5 Hz), 3.80 (3H, s), 3.85 (3H, s), 4.34 (2H, s), 4.48 (2H, s), 6.60—6.84 (3H, m), 7.08—7.54 (20H, m). MS m/z (relative intensity): 630 (M^+, 0.1), 539 (0.2), 538 (0.3), 387 (2.3), 243 (87), 151 (63), 91 (100).

(2*S*,3*R*,4*R*)-5-Benzyloxy-2,4-dimethyl-3-(3,4-dimethoxybenzyloxy)-pentan-1-ol (28) A solution of **27** (0.66 g, 1.05 mmol) and 4 N HCl (5.0 ml) in THF (15 ml) was stirred at room temperature. After 72 h, the solution was neutralized with aqueous $NaHCO_3$ and then 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 *n*-hexane–CH_2Cl_2 (1 : 1) and then CH_2Cl_2 as eluents to give recovered **27** (0.23 g, 35%) and the alcohol (**28**) as a colorless oil (0.24 g, 59%). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=7.5 Hz), 1.76—2.28 (3H, m), 3.38 (2H, dd, J=6.5, 3.5 Hz), 3.50—3.72 (2H, m), 3.61 (1H, t, J=5.0 Hz), 3.86 (6H, s), 4.47 (2H, s), 4.50 (2H, s), 6.72—6.96 (3H, m), 7.33 (5H, s). MS m/z (relative intensity): 388 (M^+, 1.4), 222 (4.2), 182 (5.9), 167 (36), 151 (100), 91 (61). *Anal.* Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.85; H, 8.34. Exact MS m/z Calcd for $C_{23}H_{32}O_5$ (M^+): 388.2250. Found: 388.2252.

(2*R*,3*S*,4*R*)-1-Benzyloxy-5-*tert*-butyldimethylsilyloxy-2,4-dimethyl-3-(3,4-dimethoxybenzyloxy)pentane (29) A solution of **28** (324 mg, 0.835 mmol), Et_3N (0.26 ml, 1.76 mmol), DMAP (10 mg, 0.084 mmol), and *tert*-butyldimethylsilyl chloride (227 mg, 1.51 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature. After 45 h, the solvent was evaporated off *in vacuo*. The residue was taken up in Et_2O, and this solution washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with *n*-hexane–CH_2Cl_2 (1 : 1) as the eluent to give **29** as a colorless oil (419 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.89 (9H, s), 0.95 (3H, d, J=5.0 Hz), 1.01 (3H, d, J=5.0 Hz), 1.99 (2H, dq, J=13.0, 6.5 Hz), 3.31 (1H, dd, J=9.0, 6.5 Hz), 3.54 (1H, dd, J=9.0, 6.5 Hz), 3.28—3.68 (2H, m), 3.56 (1H, t, J=5.5 Hz), 3.86 (6H, s), 4.48 (2H, s), 4.49 (2H, s), 6.72—6.94 (3H, m), 7.32 (5H, s). MS m/z (relative intensity): 503 (M^++1, 0.3), 502 (M^+, 1.0), 336 (0.3), 241 (1.7), 204 (2.4), 151 (100), 91 (60). Exact MS m/z Calcd for $C_{29}H_{46}O_5Si$ (M^+): 502.3114. Found: 502.3115.

(2*R*,3*S*,4*R*)-5-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-3-(3,4-dimethoxybenzyloxy)pentan-1-ol (30) A stirred solution of **29** (334 mg, 0.665 mmol) in EtOH (25 ml) was hydrogenated in the presence of Raney Ni (W-2) (*ca.* 12 ml) at room temperature for 3 h. The catalyst was removed by filtration with the aid of Celite and washed thoroughly with EtOH. The EtOH layer was evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (4 : 1) as the eluent to give the alcohol (**30**) as a colorless oil (267 mg, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.90 (9H, s), 0.94 (3H, d, J=4.0 Hz), 1.01 (3H, d, J=4.0 Hz), 1.72—2.20 (3H, m), 3.50 (2H, d, J=7.0 Hz), 3.50—3.72 (1H, m), 3.60 (2H, t, J=5.0 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.53 (2H, s), 6.72—6.96 (3H, m). MS m/z (relative intensity): 412 (M^+, 0.4), 246 (0.6), 167 (4.0), 151 (100). Exact MS m/z Calcd for $C_{22}H_{40}O_5Si$ (M^+): 412.2645. Found: 412.2650.

(2*S*,3*R*,4*R*)-5-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-3-(3,4-dimethoxybenzyloxy)pentanal (31) The alcohol (**30**) (306 mg, 0.743 mmol) was oxidized with oxalyl chloride (98 μl, 1.12 mmol), DMSO (158 μl, 2.23 mmol), and Et_3N (0.47 ml, 3.35 mmol) as indicated for the preparation of **11**. The crude product was chromatographed on a silica gel column with *n*-hexane–CH_2Cl_2 (1 : 1) and then CH_2Cl_2 as eluents to give the aldehyde (**31**) as a colorless oil (282 mg, 92%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 0.96 (3H, d, J=7.0 Hz), 1.15 (3H, d, J=7.0 Hz), 1.87 (1H, quintet, J=6.0 Hz), 2.72 (1H, ddq, J=7.0, 5.0, 1.0 Hz), 3.53 (2H, d, J=5.5 Hz), 3.87 (3H, s), 3.88 (3H, s), 3.96 (1H, t, 5.0 Hz), 4.46 (2H, s), 6.84 (3H, s), 9.79 (1H, d, J=1.0 Hz).

Diethyl (2*RS*,3*RS*,4*R*,5*S*,6*R*)-6-*tert*-Butyldimethylsilyloxy-4-(3,4-dimethoxybenzyloxy)-2-hydroxy-1,3,5-trimethylhexylphosphonate (32) A 1.6 M solution of *n*-BuLi in hexane (0.93 ml, 1.49 mmol) was added dropwise to a stirred solution of diethyl ethylphosphonate (307 mg, 1.85 mmol) in THF (10 ml) at −80—−70 °C. After 1 h, a solution of **31** (267 mg, 0.651 mmol) in THF (6 ml) was added dropwise at −80 °C. The solution was allowed to warm to 10 °C over a period of 5 h, then poured into aqueous NH_4Cl, and 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 *n*-hexane–EtOAc (2 : 1) as the eluent to give **32** (a mixture of four diastereoisomers) as a colorless oil (347 mg, 82%). IR ν_{max}^{neat} cm^{-1}: 3390.

Diethyl (2*RS*,4*S*,5*R*,6*R*)-6-*tert*-Butyldimethylsilyloxy-4-(3,4-dimethoxybenzyloxy)-2-oxo-1,3,5-trimethylhexylphosphonate (7) Compound **32** (187 mg, 0.325 mmol) was oxidized with oxalyl chloride (57 μl, 0.65 mmol),

DMSO (92 μl, 1.30 mmol), and Et_3N (0.27 ml, 1.95 mmol) as indicated for the preparation of **11**. The crude product was chromatographed on a silica gel column with CH_2Cl_2–MeOH (160 : 1) as the eluent to give recovered **32** (25 mg, 16%) and the β-ketophosphonate (**7**) (a mixture of two diastereoisomers) as a colorless oil (143 mg, 79%). IR ν_{max}^{neat} cm^{-1}: 1705. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.87 (3H, d, J=8.0 Hz), 0.89 (9H, s), 1.06—1.56 (12H, m), 1.54—1.92 (1H, m), 3.10—3.80 (5H, m), 3.87 (3H, s), 3.88 (2H, s), 3.89 (1H, s), 3.92—4.30 (4H, m), 4.40, 4.63 (0.67H each, ABq, J= 11.0 Hz), 4.52 (0.67H, s), 6.70—7.04 (3H, m). MS m/z (relative intensity): 560 (M^+ − 14, 0.2), 559 (0.4), 557 (1.7), 556 (5.3), 518 (1.9), 517 (5.5), 419 (12), 235 (18), 151 (100). Exact MS m/z for $C_{24}H_{42}O_8PSi$ (M^+ − 57): 517.2387. Found: 517.2393.

(2*R*,3*R*,4*S*)-1-*tert*-Butyldimethylsilyloxy-3-(3,4-dimethoxybenzyloxy)-2,4,6,8-tetramethylnon-6-en-5-one (36) A 1.6 M solution of *n*-BuLi in hexane (29 μl, 0.047 mmol) was added dropwise to a stirred solution of **7** (33.5 mg, 0.0584 mmol) in THF (1 ml) at −20 °C. After 10 min, isobutyraldehyde (**35**) (10.6 μl, 0.117 mmol) was added, and the solution was stirred at room temperature for 15.5 h. Isobutyraldehyde (**35**) (10.6 μl, 0.117 mmol) was again added, and the solution was stirred at 55 °C for 4.5 h, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was subjected twice to preparative TLC on silica gel with *n*-hexane–EtOAc (4 : 1) and CH_2Cl_2 as developing solvents to give **36** [a mixture of (*E*)- and (*Z*)-isomers] as a colorless oil (15.0 mg, 67%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.04 (3H, s), 0.85 (3H, d, J=7.0 Hz), 0.90 (9H, s), 1.04 (6H, d, J=6.5 Hz), 1.19 (3H, d, J=6.5 Hz), 1.40—1.80 (1H, m), 1.79 (2.4H, d, J=1.0 Hz), 1.93 (0.6H, d, J=1.0 Hz), 2.52—2.92 (1H, m), 3.28—3.68 (3H, m), 3.82 (1H, dd, J=7.0, 3.0 Hz), 3.87 (3H, s), 3.90 (3H, s), 4.49 (0.4H, s), 4.52 (1.6H, s), 5.43 (0.2H, dd, J=10.5, 1.0 Hz), 6.44 (0.8H, dd, J=9.5, 1.0 Hz), 6.68—6.96 (3H, m).

(2*R*,3*R*,4*S*,6*E*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-1-*tert*-Butyldimethylsilyloxy-3-(3,4-dimethoxybenzyloxy)-2,4,6,8,10,12-hexamethyl-9,11-isopropylidenedioxy-13-(4-methoxybenzyloxy)-12-methoxymethoxypentadec-6-en-5-one (37) A 1.6 M solution of *n*-BuLi in hexane (27 μl, 0.042 mmol) was added dropwise to a stirred solution **7** (28.7 mg, 0.05 mmol) in ether (1 ml) at −22 °C. The solution was allowed to warm to room temperature, and a solution of **6** (19.0 mg, 0.042 mmol) in Et_2O (1 ml) was added. After 16 h, the solution was poured into 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) as the eluent to give **37** as a colorless oil (1.8 mg, 5.7%). ^{1}H-NMR ($CDCl_3$) δ: 0.02 (3H, s), 0.04 (3H, s), 0.83 (3H, d, J= 7.0 Hz), 0.90 (9H, s), 1.04 (3H, d, J=2.5 Hz), 1.06 (3H, d, J=3.0 Hz), 1.07 (3H, t, J=7.5 Hz), 1.19 (3H, d, J=6.5 Hz), 1.25 (3H, s), 1.28 (3H, s), 1.30 (6H, s), 1.45—1.73 (3H, m), 1.73—1.90 (1H, m), 1.79 (3H, d, J=1.0 Hz), 3.19 (1H, dd, J=6.0, 5.0 Hz), 3.35 (3H, s), 3.38—3.68 (4H, m), 3.80 (3H, s), 3.86 (1H, dd, J=9.0, 2.5 Hz), 3.87 (3H, s), 3.88 (3H, s), 3.96 (1H, d, J= 3.5 Hz), 4.52 (3H, s), 4.50, 4.61 (1H each, ABq, J=10.5 Hz), 4.76, 5.01 (1H each, ABq, J=7.0 Hz), 6.60 (1H, dd, J=10.0, 1.0 Hz), 6.80—6.93 (3H, m), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 752 (M^+ − 120, 0.4), 751 (0.6), 585 (0.1), 551 (0.2), 525 (0.5), 467 (1.2), 283 (7.9), 151 (51), 121 (100), and **33** as a colorless oil (8.1 mg, 49%). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=8.0 Hz), 1.15 (3H, d, J=7.0 Hz), 1.26 (3H, s), 1.38—1.82 (2H, m), 1.75 (3H, d, J=1.0 Hz), 2.64—3.16 (1H, m), 3.39 (3H, s), 3.54 (1H, dd, J=11.0, 6.5 Hz), 3.80 (1H, d, J=7.0 Hz), 3.81 (3H, s), 4.58 (2H, s), 4.71, 4.79 (1H each, ABq, J=7.0 Hz), 6.51 (1H, dd, J=10.0, 1.0 Hz), 6.88 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz), 9.39 (1H, s).

References and Notes

1) Chiral synthesis of polyketide-derived natural products. 21. For part 20, see: H. Tone, M. Hikota, T. Hamada, T. Nishi, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1155 (1989).
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15) Compound **18** contained an isomeric (2*S*,3*R*)-1,3-diol in the ratio of 8 : 1, and was purified chromatographically after conversion into the benzoate (**22**). Under Hutchins' acidic conditions[14] the MP-ethylidene protecting group of **18** was gradually cleaved to give a tetrol. For example, when **21** was treated with $NaBH_3CN$ (12 mol eq) and $BF_3 \cdot Et_2O$ (16 eq) at room temperature, the yield of **18** decreased to 48%. In the preceding paper,[1] we recommended the use of a large excess of B_2H_6 in hexamethylphosphoramide (HMPA)–THF for the reduction of highly acid-sensitive substrates, but this method did not need to be used for the reduction of **21**.
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