[Chem. Pharm. Bull. 35(6)2228—2237(1987)]

Highly Stereoselective Total Synthesis of Pikronolide, the Aglycon of the First Macrolide Antibiotic Pikromycin. Crucial Role of Benzyl-Type Protecting Groups Removable by 2,4-Dichloro-5,6-dicyanobenzoquinone Oxidation[1,2]

NORIYUKI NAKAJIMA, TATSUYOSHI TANAKA, TATSUO HAMADA, YUJI OIKAWA, and OSAMU YONEMITSU*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

(Received September 19, 1986)

The first total synthesis of pikronolide, the aglycon of pikromycin, isolated as the first macrolide antibiotic, is described. Two segments i (**5**: C-1—C-10) and ii (**6**: C-11—C-15) were synthesized highly stereoselectively from D-glucose and coupled by Yamaguchi's method to give the ester (**17**), which was subjected to macrocyclization by means of the intramolecular Wittig–Horner reaction developed by Nicolaou, and the 14-membered cyclic enone (**18**) was isolated in excellent yield. Removal of protecting groups and Swern oxidation gave pikronolide (**2**). In this synthesis, 3,4-dimethoxybenzyl, 4-methoxybenzyl, and benzyl protecting group for hydroxy function played a crucial role.

Keywords——macrolide antibiotic; pikromycin; aglycon; pikronolide; acyclic stereocontrol; protecting group; esterification; Wittig–Horner reaction; 2,4-dichloro-5,6-dicyanobenzoquinone oxidation; stereoselective synthesis

In the preceding papers,[1,3] we reported highly stereoselective syntheses of methynolide and tylonolide to exemplify some of the advantageous features of our synthetic methodology. In the present paper, we report the first total synthesis of pikronolide (**2**), the aglycon of the 14-membered macrolide antibiotic pikromycin (**1**), which was isolated from a strain of *Streptomyces* by Brockmann and Henkel as the first macrolide antibiotic in 1950.[4] However, all attempts at the total synthesis of pikronolide (**2**)[5] as well as pikromycin (**1**) itself during the past 35 years or more have been unsuccessful, because the construction of the β-hydroxyketone system at C-3—C-5[6] of **1** is extremely difficult.[7] Even under very mild hydrolytic conditions (pH 6.5, 60 °C), **1** readily gives the 4,5-anhydro compound, kromycin (**3**).[7b,8] This facile elimination into the α,β-unsaturated ketone system was explained in terms of the *anti*-periplaner disposition of the C-4 hydrogen and the glycoside linkage.[7b] For the total synthesis of **2**, it is essential to avoid such a side reaction. Therefore, the C-3 ketone must be constructed in the final synthetic stage, and we decided to synthesize **4** as a final intermediate. Selection of protecting groups, R^1—R^3, of **4** obviously holds the key to success in the total synthesis of **2**. Differentiation among the three protecting groups and selective deprotection without any effect on the other functional groups and substituents are critical requirements. We chose 3,4-dimethoxybenzyl (DMPM),[9,10] 4-methoxybenzyl (MPM),[10,11] and benzyl (Bn)[10,12] as R^1, R^2, and R^3, respectively. The utility of these protecting groups, removable by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), was shown by their use at crucial synthetic steps described in the preceding papers.[1,3]

In the methynolide synthesis, the oxidative removal of Bn protection of a tertiary hydroxy function[12a] was successfully applied at the final step.[3c] In the tylonolide synthesis,

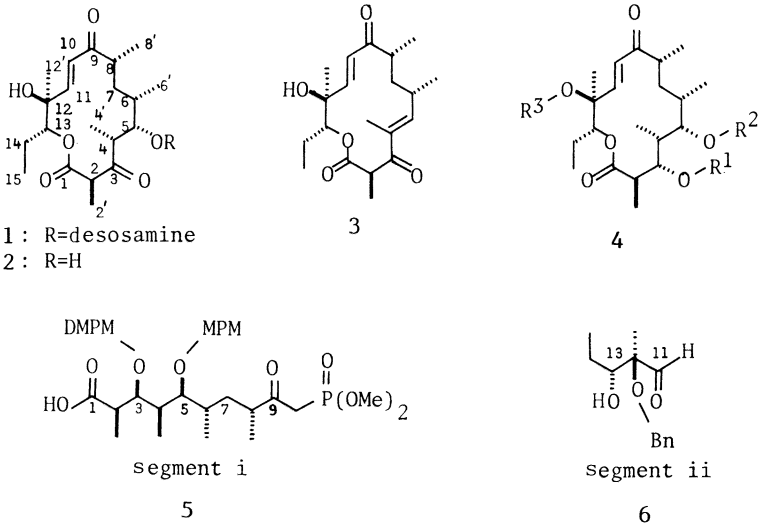


Chart 1

not only the selective oxidation of MPM and DMPM protecting groups, but also the selective removal of a Bn protecting group by hydrogenolysis with Raney nickel (Ni)[10,12b] was demonstrated.[1,3d]

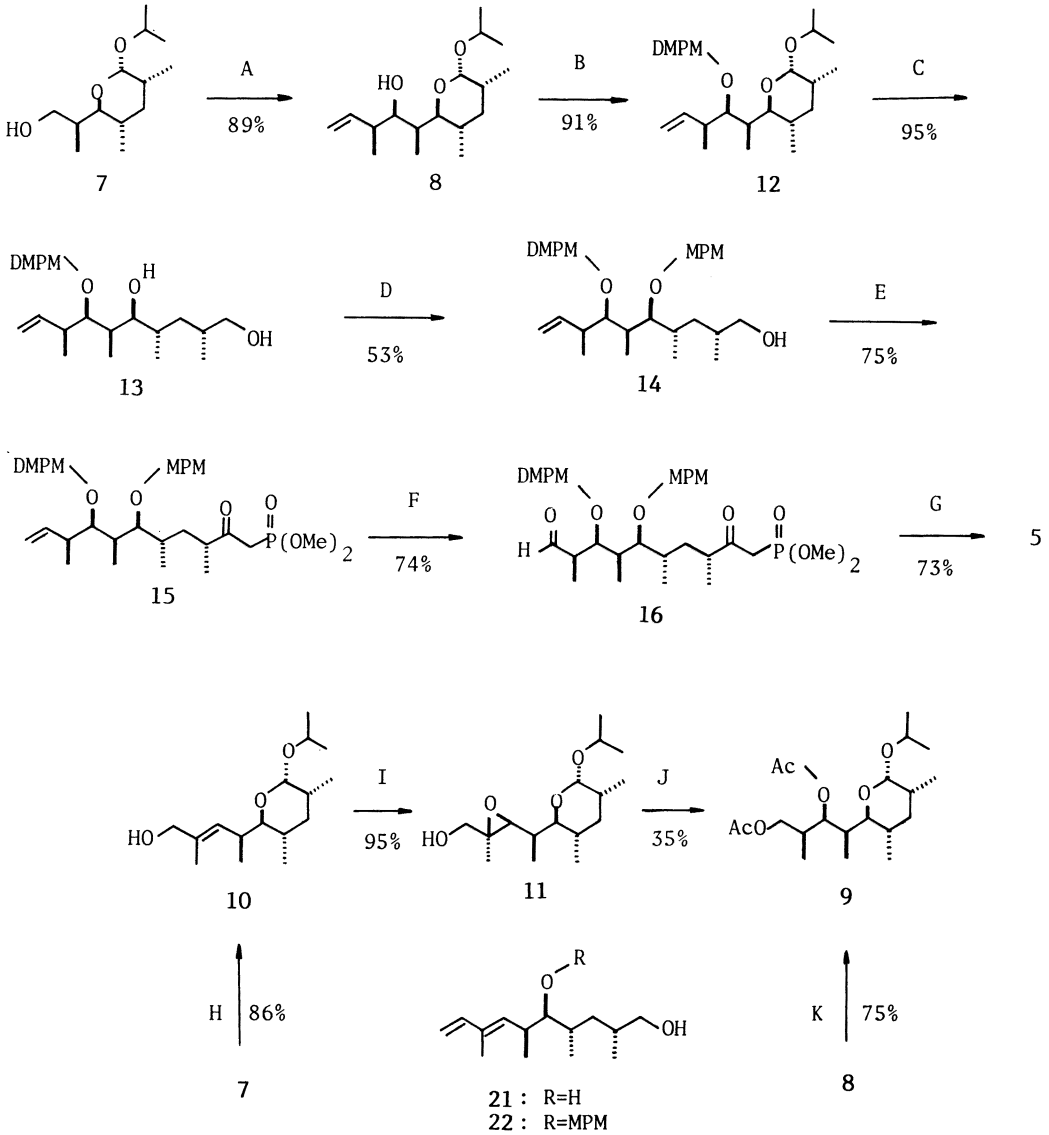
In the present first total synthesis of **2**, the selective removal of DMPM, MPM, and Bn protecting groups again played a decisive role. Segments i (**5**) and ii (**6**) were considered to be the most promising intermediates in the light of our synthetic methodology established in the syntheses of methynolide[3a-c] and tylonolide.[1,3d] In the syntheses of **5** and **6**, DMPM, MPM, and Bn protecting groups for the C-3, C-5 and C-12 hydroxy groups, respectively, were chosen. Segment ii (**6**) was readily synthesized from D-glucose as described in the previous paper,[3c] but the synthesis of the more complex segment i (**5**) was somewhat tedious.

Results and Discussion

The Prelog–Djerassi lactone equivalent compound (**7**), derived from D-glucose as a chiral intermediate for the synthesis of methynolide,[3a] already has four chiral centers corresponding to C-4, C-5, C-6, and C-8, and two additional chiral centers corresponding to C-2 and C-3 were introduced by an *erythro*-selective Cram addition of crotyl-tri-*n*-butyltin.[13] Swern oxidation[14] of the primary alcohol (**7**) readily gave the aldehyde, which was treated with excess boron trifluoride etherate ($BF_3 \cdot Et_2O$; 2.2. eq) and the tin reagent (2.4 eq)[13] at -90 °C. The addition of the reagent proceeded quite smoothly to give the expected product (**8**) having all-*syn* configurations of C-2, C-3, and C-4 with excellent yield and stereoselectivity ($>30:1$). The configuration of **8** was confirmed after conversion into the diacetate (**9**), which was also derived from **7** *via* another route involving the Sharpless asymmetric epoxidation.[15]

Oxidative cleavage of the double bond of **8** with ozone and reduction of the resulting aldehyde with sodium borohydride readily gave the diol, which was acetylated to give the diacetate (**9**). An authentic sample of **9** was synthesized as follows. The aldehyde, the Swern oxidation product of **7**, was subjected to the Wittig reaction with a stable ylide, followed by lithium aluminium hydride reduction to give the allyl alcohol (**10**), which was treated with *tert*-butyl hydroperoxide, L-(+)-diethyltartrate, and titanium (IV) isopropoxide,[15] and the expected epoxy alcohol (**11**) was isolated in excellent yield. Reductive ring opening of the epoxide (**11**) took place on treatment with sodium cyanoborohydride in the presence of boron

trifluoride etherate[16] to give mainly the expected 1,3-diol together with the 1,2-diol.[17] Acetylation of the 1,3-diol gave the diacetate (**9**). Both samples of **9** were identical in terms of their nuclear magnetic resonance (NMR) spectra.



(A) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-70\,^{\circ}C \rightarrow$room temperature; 2) $MeCH=CHCH_2SnBu_3$, $BF_3 \cdot Et_2O$, $-90\,^{\circ}C \rightarrow$room temperature (B) KH, DMSO, DMPMCl (C) 1) 1 N HCl, THF, 50 °C; 2) $CaCl_2$, $NaBH_4$, EtOH (D) 1) $Me_2C(OMe)_2$, CSA; 2) MPMCl, KCH_2SOMe, DMSO; 3) 0.1 N HCl (E) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-70\,^{\circ}C \rightarrow$room temperature; 2) $MePO(OMe)_2$, *n*-BuLi, THF, $-90 \rightarrow -20\,^{\circ}C$; 3) PDC, DMF (F) 1) OsO_4, NMO, MeCOMe; 2) $NaIO_4$, MeOH–H_2O (G) CrO_3, H_2SO_4, MeCOMe, $-20\,^{\circ}C$ (H) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-70\,^{\circ}C \rightarrow$room temperature; 2) $Ph_3P=CMeCO_2Et$, $(CH_2Cl)_2$, reflux; 3) $LiAlH_4$, Et_2O, 0 °C (I) (+)DET, TBHP, $(PrO)_4Ti$, CH_2Cl_2–toluene, $-23\,^{\circ}C$ (J) 1) $NaBH_3CN$, $BF_3 \cdot Et_2O$, THF; 2) Ac_2O, Et_3N, DMAP (K) 1) O_3, CH_2Cl_2, $-78\,^{\circ}C$; 2) $NaBH_4$, MeOH; 3) Ac_2O, Et_3N, DMAP

Chart 2

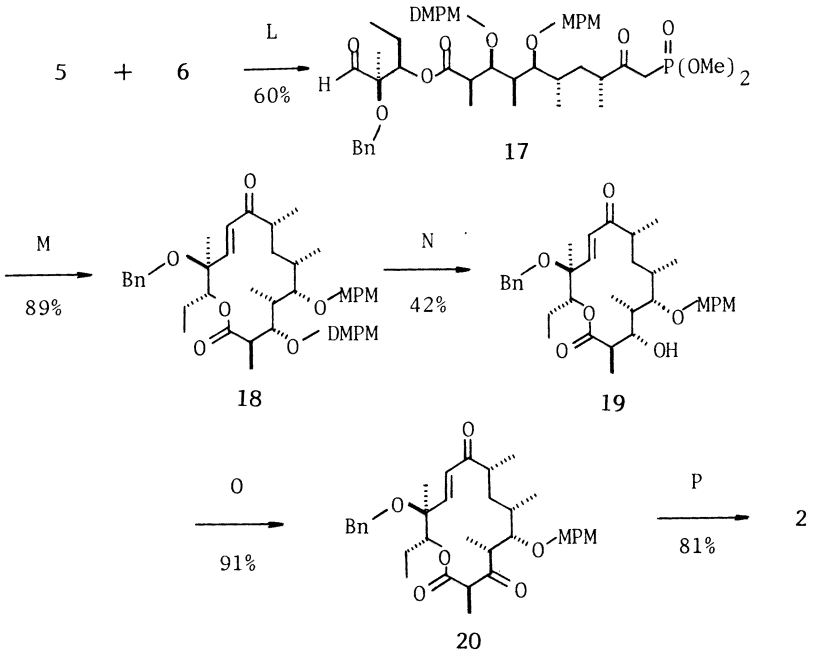
The DMPM protection of the secondary alcohol of **8** was rather difficult. No reaction occurred under usual conditions with sodium hydride and DMPM chloride.[10] Treatment of **8** with a large excess (10—20 eq) of potassium hydride and then DMPM chloride gave the expected DMPM ether (**12**), but the reproducibility of the reaction was poor. However, DMPM protection proceeded very rapidly upon reverse addition of the reagents (see below) to give **12** in excellent yield. The isopropyl protection of **12** was removed with 1 N hydrochloric acid, followed by reduction of the resulting hemiacetal with calcium borohydride to give the open-chain diol (**13**).

The primary alcohol of **13** was first protected as an acetal with the methoxyisopropyl group by treatment with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA), and then protection of the remaining secondary alcohol was examined. The MPM protection of the secondary alcohol at a sterically crowded position was quite difficult, and almost no reaction occurred under usual conditions.[10] Treatment with a large excess of sodium hydride (or dimsyl sodium) and MPM chloride gave only a mixture of dienes, **21** and **22**. However, when the chloride was first added to a dimethyl sulfoxide solution of the above acetal of **13** and then dimsyl potassium was added in two portions (reverse addition), the MPM protection proceeded quite rapidly to give the ether, which was treated with 0.1 N hydrochloric acid to remove the acetal protection, and the expected alcohol (**14**) was isolated in 50—60% yield.

Compound **14** was converted to segment i (**5**) in essentially the same way as described in the previous papers for the syntheses of methynolide[3b,c] and tylonolide.[1] Oxidation of the primary alcohol of **14** by Swern's method readily gave the aldehyde, which was treated with the lithio derivative of dimethyl methylphosphonate[19] at −80 °C followed by oxidation with pyridinium dichromate (PDC) in dimethylformamide (DMF)[20] to give the ketophosphonate (**15**). In order to convert **15** into **5** (segment i), the double bond of **15** was first oxidized directly to the carboxylic acid under Lemieux-von Rudloff's conditions,[21] which were successfully applied in the synthesis of tylonolide,[1] but the yield of **5** was unfortunately less than 10%, because the benzylic positions of the MPM and DMPM protecting groups were not stable enough to this oxidation. Therefore, stepwise oxidation *via* the aldehyde (**16**) was next examined. Oxidation of **15** with osmium tetroxide (OsO_4) in the presence of *N*-methylmorpholine *N*-oxide (NMO) followed by oxidative cleavage of the resulting diol with sodium metaperiodate ($NaIO_4$) gave the aldehyde (**16**), which was oxidized with the Jones reagent at −20 °C for 5 min to give segment i (**5**) in good yield.[22]

Coupling of the two segments i (**5**) and ii (**6**) proceeded smoothly by the Yamaguchi method[23] using 2,4,6-trichlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP) in toluene, and the expected ester (**17**) bearing both aldehyde and ketophosphonate functions was subjected to an intramolecular Wittig–Horner type macrocyclization by Nicolaou's method[24] using a large excess of powdered potassium carbonate and 18-crown-6 in toluene at 80 °C. The cyclization proceeded extremely smoothly and was completed within only 1 h to afford the expected 14-membered enone (**18**) in excellent yield.

For the purpose of conversion of **18** into pikronolide (**2**), it was necessary to remove selectively the DMPM protecting group at C-3 with minimum loss of the MPM and Bn protecting groups and other functional groups. Deprotection of DMPM groups with DDQ usually proceeds with excellent selectivity,[1,9,25] but unfortunately, **18** gave unsatisfactory results with less than 4 : 1 selectivity, and the expected product (**19**) was isolated in poor yield. However, the isolated **19** was converted to **2** very smoothly. Swern oxidation of **19** readily gave the C-3 keto compound (**20**) in excellent yield. Finally, when **20** was further treated with a large excess of DDQ in dichloromethane containing a small amount of water at room temperature, the MPM protecting group at C-5 was removed quite rapidly within 5 min; the clean deprotection of the Bn group at the C-12 proceeded rather slowly and required 19 h to



(L) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene (M) K_2CO_3, 18-crown-6, toluene, 80 °C (N) DDQ, toluene–H_2O, 0 °C (O) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −65→−55 C (P) DDQ, CH_2Cl_2–H_2O

Chart 3

complete. Surprisingly, during the reaction with DDQ, no trace of kromycin (**3**) was detected, and pikronolide (**2**) was isolated in high yield. The first total synthesis of **2** was thus achieved with a very high overall stereoselectivity (>86%) for the construction of the new chiral centers at C-2, C-4, C-6, C-8, and C-12.[26]

Experimental

Physical data were measured as described in the previous paper.[3a]

(3*S*,4*R*,5*S*)-4-Hydroxy-5-[2(*S*)-isopropyloxy-3(*R*),5(*S*)-dimethyl-6(*S*)-tetrahydroxypropanyl]-3-methylhexane (8)——Dry dimethyl sulfoxide (DMSO) (Me_2SO, 1.23 ml, 1.73 mmol) in CH_2Cl_2 (7 ml) was added dropwise during 15 min to an efficiently stirred solution of oxalyl chloride (0.75 ml, 8.7 mmol) in dry CH_2Cl_2 (15 ml) cooled to below −65 °C under an argon atmosphere. After 15 min at −70 °C, a solution of **4** (1.0 g, 4.34 mmol) was added to the mixture during 10 min. Stirring was continued at −70 °C for 30 min, then Et_3N (4.8 ml, 34 mmol) was added dropwise, and after removal of the cooling bath, the reaction mixture was allowed to warm to room temperature (over *ca.* 1 h). Then H_2O (20 ml) was added. The organic layer was separated, and the aqueous layer was extracted with ether (30 ml × 2), and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (9 : 1) as the eluant to give the aldehyde (0.95 g, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.18 (3H, d, J=7 Hz), 2.53 (1H, dq, J=2.5, 7 Hz), 3.74 (1H, sept, J=7 Hz), 4.05 (1H, dd, J=10, 2.5 Hz), 4.59 (1H, d, J=3.5 Hz), 9.68 (1H, s).

A stirred solution of the above aldehyde (0.95 g, 4.16 mmol) in dry CH_2Cl_2 (60 ml), cooled at −93 °C under nitrogen, was treated with $BF_3 \cdot Et_2O$ (1.15 ml, 9.3 mmol) in CH_2Cl_2 (5 ml). After 10 min, crotyl-tri-*n*-butyltin (4 ml, 10 mmol) in CH_2Cl_2 (20 ml) was added to the mixture. The rate of addition of $BF_3 \cdot Et_2O$ and crotyl-tri-*n*-butyltin was controlled to keep the temperature below −90 °C. The mixture was stirred at below −90 °C for 15 min, and the reaction was quenched with saturated NH_4Cl (10 ml). The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane–EtOAc (30 : 1) as the eluant to afford **8** as a colorless oil (1.1 g, 94%). ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, d, J=7 Hz), 0.82 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.09 (3H, d, J=6 Hz), 1.10 (3H, d, J=7 Hz), 1.23 (3H, d, J=7 Hz), 1.56—1.88 (2H, m), 1.92 (1H, ddq, J=

2, 1.5, 7 Hz), 2.32 (1H, tq, J=9, 7 Hz), 3.41 (1H, dd, J=9, 1.5 Hz), 3.59 (1H, dd, J=10, 2 Hz), 3.83 (1H, sept, J=7 Hz), 4.67 (1H, d, J=3 Hz), 4.97 (1H, dd, J=10, 2 Hz), 5.03 (1H, dd, J=17, 2 Hz), 5.62 (1H, ddd, J=17, 10, 9 Hz). MS m/z (relative intensity): 267 (M^+-17, 0.15), 225 (6), 169 (60), 100 (100). FD-MS m/z (relative intensity): 285 (M^++1, 28), 229 (100), 178 (17), 169 (15). Exact MS m/z Calcd for $C_{17}H_{33}O_3$ (M^++1): 285.2430. Found: 285.2437. Calcd for $C_{14}H_{25}O_2$ (M^+-59): 225.1855. Found: 225.1866. IR ν_{max}^{neat} cm^{-1}: 3500. $[\alpha]_D^{21}+112°$ (c=1.0, $CHCl_3$).

4(*S*)-[2(*S*)-Isopropyloxy-3(*R*),5(*S*)-dimethyl-6(*S*)-tetrahydropyranyl]-2-methyl-2(*E*)-pentenol (10)——A solution of the aldehyde (40 mg, 0.175 mmol), derived from **7**, and $Ph_3P=C(Me)CO_2Et$ (254 mg, 0.7 mmol) in $(CH_2Cl)_2$ (2 ml) was refluxed for 48 h. The Wittig reagent (254 mg, 0.7 mmol) was added again and refluxing was continued for an additional 24 h. After removal of the solvent *in vacuo*, the residue was purified on a silica gel column with hexane–EtOAc (50 : 1) as the eluant to give the oily α,β-unsaturated ester (51.4 mg, 94%).

A solution of the ester (33 mg, 0.105 mmol) in ether (0.2 ml) was added to a stirred solution of $LiAlH_4$ (6 mg, 0.158 mmol) in ether (1 ml) at 0 °C under an argon atmosphere. After 50 min, H_2O (6 μl), 15% NaOH (6 μl), and H_2O (20 μl) were successively added, and the resulting precipitates were removed by filtration. After evaporation of the solvent, the residue was purified through a short silica gel column with hexane–EtOAc (3 : 1) to afford **10** as a colorless oil (27.3 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=7 Hz), 0.84 (3H, d, J=7 Hz), 0.95 (3H, d, J=7 Hz), 1.07 (3H, d, J=7 Hz), 1.12 (3H, d, J=7 Hz), 1.69 (3H, d, J=1.5 Hz), 2.66 (1H, ddq, J=9, 3.5, 7 Hz), 3.37 (1H, dd, J=8.5, 3.5 Hz), 3.80 (1H, sept, J=7 Hz), 3.96 (2H, s), 4.66 (1H, d, J=2 Hz), 5.58 (1H, dq, J=9, 1.5 Hz). IR ν_{max}^{neat} cm^{-1}: 3325. MS m/z (relative intensity): 211 (M^+-75, 6), 171 (67.5), 129 (99), 100 (70), 71 (76), 58 (96), 43 (100). $[\alpha]_D^{15}+146.2°$ (c=1.07, $CHCl_3$).

2(*R*),3(*S*)-Epoxy-4(*S*)-[2(*S*)-isopropyloxy-3(*R*),5(*S*)-dimethyl-6(*S*)-tetrahydropyranyl]-2(*S*)-methylpentanol (11)——A solution of L(+)-diethyl tartrate (31 mg, 0.15 mmol) in CH_2Cl_2 (0.4 ml) was added gradually *via* a syringe to a cold solution (−26 °C) of titanium (IV) isopropoxide (30 μl, 0.1 mmol) in CH_2Cl_2 (0.4 ml). After 10 min at −26 °C, **10** (27.3 mg, 0.09 mmol) in CH_2Cl_2 (0.4 ml) and 3 M *tert*-butyl hydroperoxide (63 μl, 0.18 mmol) in toluene were both added dropwise to the solution. The mixture was allowed to stand for 24 h at −23 °C and then saturated Na_2SO_4 (0.2 ml) was added. The reaction mixture was warmed to room temperature, then celite was added with vigorous stirring, and after 1 h, the celite was filtered off. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give an oil, which was chromatographed on a silica gel column with hexane–EtOAc (5 : 1) as the eluant to give **11** as a colorless oil (27 mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=7 Hz), 0.82 (3H, d, J=7 Hz), 1.08 (3H, d, J=6 Hz), 1.09 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 1.32 (3H, s), 1.22—1.50 (2H, m), 1.50—1.85 (4H, m), 3.16 (1H, d, J=9 Hz), 3.44 (1H, dd, J=10, 2.5 Hz), 3.49 (1H, dd, J=12, 8.5 Hz), 3.69 (1H, dd, J=12, 5 Hz), 3.78 (1H, sept, J=7 Hz), 4.64 (1H, d, J=3.5 Hz). IR ν_{max}^{neat} cm^{-1}: 3400. MS m/z (relative intensity): 284 (M^+-18, 0.3), 244 (5.5), 171 (8.8), 100 (100), 58 (89), 43 (81). $[\alpha]_D^{16.5}+124.7°$ (c=0.97, $CHCl_3$).

(2*S*,3*R*,4*S*)-1,3-Diacetoxy-4-[2(*S*)-isopropyloxy-3(*R*),5(*S*)-dimethyl-6(*S*)-tetrahydropyranyl]-2-methylpentane (9)——(a) Ozone was introduced into a CH_2Cl_2 solution (0.5 ml) of **8** (10 mg, 0.0352 mmol) at −78 °C. After the color of the solution had changed to blue, the reaction was continued for a further 20 min, and then the reaction mixture was treated with a 10% solution of $NaBH_4$ in MeOH (0.1 ml). After 15 min at −78 °C, the mixture was allowed to warm to room temperature, then quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to leave an oil, which was purified on a silica gel column with hexane–EtOAc (3 : 1) to afford the 1,3-diol as a colorless oil (7.6 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.5 Hz), 0.82 (3H, d, J=6.5 Hz), 0.97 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.5 Hz), 1.09 (3H, d, J=6.5 Hz), 1.24 (3H, d, J=6.5 Hz), 1.4—1.5 (2H, m), 1.8—1.92 (2H, m), 2.08 (1H, br s), 3.47 (1H, br s), 3.57 (1H, dd, J=10, 2 Hz), 3.62 (1H, dd, J=5.5, 3 Hz), 3.72 (1H, dd, J=6, 3 Hz), 3.80 (1H, sept, J=6.5 Hz), 4.66 (1H, d, J=3.5 Hz). IR ν_{max}^{neat} cm^{-1}: 3350. MS m/z (relative intensity): 270 (M^+-18, 0.2), 246 (2.5), 229 (3.5), 200 (1.5), 169 (7.1), 129 (15), 100 (100). Exact MS m/z Calcd for $C_{16}H_{30}O_3$ (M^+-18): 270.2194. Found: 270.2178.

The 1,3-diol was acetylated with Ac_2O, Et_3N and DMAP in the usual way to give **9** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6 Hz), 0.81 (3H, d, J=7 Hz), 0.84 (3H, d, J=6 Hz), 0.93 (3H, d, J=7 Hz), 1.08 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 1.21—1.44 (2H, m), 1.50—1.90 (2H, m), 1.90—2.10 (1H, m), 2.02 (3H, s), 2.06 (3H, s), 2.30 (1H, m), 3.43 (1H, dd, J=10, 2 Hz), 3.81 (1H, dd, J=11.5, 6.5 Hz), 3.83 (1H, sept, J=7 Hz), 3.94 (1H, dd, J=11.5, 8 Hz), 4.65 (1H, d, J=3.5 Hz), 5.25 (1H, dd, J=10.5, 2 Hz). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1752, 1730. $[\alpha]_D^{19}+47.6°$ (c=0.42, $CHCl_3$). MS m/z (relative intensity): 372 (M^+, 0.3), 330 (3.5), 131 (15), 122 (26), 100 (100), 58 (53), 43 (70). Exact MS m/z Calcd for $C_{20}H_{36}O_6$ (M^+): 372.2513. Found: 372.2486.

(b) $NaBH_3CN$ (24 mg, 0.384 mmol) and $BF_3\cdot Et_2O$ (31.5 μl, 0.256 mmol) were added to a stirred solution of **11** (9.6 mg, 0.032 mmol) in tetrahydrofuran (THF) (2.5 ml) under reflux. The reaction mixture was cooled to room temperature, poured into ice-cooled saturated $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, and dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was chromatographed on a silica gel column with hexane–EtOAc (10 : 1) as the eluant to give two oily fractions. The first fraction gave the 1,3-diol (3.4 mg, 35%), and the second fraction gave the 1,2-diol (2.0 mg, 21%). The 1,3-diol was readily converted to **9** in the usual way.

(3*S*,4*R*,5*S*)-4-(3,4-Dimethoxybenzyloxy)-5-[2(*S*)-isopropyloxy-3(*R*),5(*S*)-dimethyl-6(*S*)-tetrahydroxypyranyl]-3-methylhexene (12)——A 2.5 M potassium dimsyl anion solution [1 ml; prepared from KH (99 mg) and DMSO

(1 ml)] was slowly added dropwise to a DMSO solution (0.7 ml) of DMPM chloride (360 mg, 1.9 mmol) and **8** (68.4 mg, 0.24 mmol) with ice-cooling. After 5 min, the reaction mixture was poured into 0.1 N HCl, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (30 : 1) as the eluant to give **12** as a colorless oil (94.2 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=7 Hz), 0.82 (3H, d, J=7 Hz), 1.02 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.09 (3H, d, J=6 Hz), 1.18 (3H, d, J=6 Hz), 1.28 (1H, t, J=12 Hz), 1.40 (1H, dt, J=12, 4 Hz), 1.55—1.85 (2H, m), 1.96 (1H, dq, J=2.5, 7 Hz), 2.57 (1H, tq, J=1, 7 Hz), 3.38 (1H, d, J=2.5 Hz), 3.47 (1H, d, J=2.5 Hz), 3.85 (1H, sept, J=7 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.47 (1H, d, J=11 Hz), 4.54 (1H, d, J=11 Hz), 4.67 (1H, d, J=4 Hz), 5.09 (1H, ddd, J=11, 2, 1 Hz), 5.13 (1H, ddd, J=17, 2, 1 Hz), 6.03 (1H, ddd, J=17, 11, 7 Hz), 6.80 (1H, d, J=8 Hz), 6.88 (1H, dd, J=8, 2 Hz), 6.92 (1H, d, J=2 Hz). $[\alpha]_D^{21}$ +56.5° (c=0.92, $CHCl_3$). MS m/z (relative intensity): 434 (M^+, 0.6), 374 (0.8), 166 (12), 151 (100). Exact MS m/z Calcd for $C_{26}H_{42}O_5$ (M^+): 434.3036. Found: 434.3053.

(2*R*,4*S*,5*S*,6*R*,7*R*,8*S*)-7-(3,4-Dimethoxybenzyloxy)-2,4,6,8-tetramethyl-9-decene-1,5-diol (13)——A solution of **12** (0.66 g, 1.52 mmol) in 1 N HCl (4 ml) and THF (12 ml) was stirred at 50 °C for 12 h. After neutralization with solid $NaHCO_3$, the reaction mixture was evaporated to dryness. CH_2Cl_2 and water were added to the residue, and the CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 several times, and the organic layers were combined and dried over $MgSO_4$. After evaporation of the solvent, purification of the residue on a silica gel column with hexane–EtOAc (7 : 1) as the eluant afforded recovered **12** (66 mg, 10%) and the lactol as a colorless oil (522 mg, 87%). MS m/z (relative intensity): 392 (M^+, 0.7), 374 (M^+-18, 1), 166 (5), 151 (100). Exact MS m/z Calcd for $C_{23}H_{36}O_5$ (M^+): 392.2564. Found: 392.2566.

A solution of $CaCl_2$ (1 g, 8.8 mmol) in EtOH was cooled at −40 °C, and $NaBH_4$ (0.5 g, 13.3 mmol) in EtOH (20 ml) was added dropwise. NaCl separated out at once as a fine solid. After 30 min, an EtOH solution of the above lactol (520 mg) was added to the resulting $Ca(BH_4)_2$ solution. The reaction mixture was stirred for 3 h at room temperature, then excess $Ca(BH_4)_2$ was decomposed by addition of 1 N HCl, and the mixture was neutralized with Na_2CO_3. After removal of the precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated *in vacuo* to leave **13** as a colorless oil (0.51 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=7 Hz), 0.90 (3H, d, J=7 Hz), 0.94 (3H, d, J=7 Hz), 1.14 (3H, d, J=7 Hz), 1.5—2.1 (6H, m), 2.64 (1H, dq, J=8, 7 Hz), 3.35 (1H, dd, J=11, 3 Hz), 3.39 (1H, d, J=4 Hz), 3.46 (1H, d, J=3 Hz), 3.59 (1H, dd, J=11, 5.5 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.45 (1H, d, J=11 Hz), 4.66 (1H, d, J=11 Hz), 5.02 (1H, ddd, J=10.5, 1, 0.5 Hz), 5.06 (1H, ddd, J=17.5, 2, 1 Hz), 6.87 (1H, ddd, J=17.5, 10.5, 8 Hz), 6.72—6.80 (3H, m). IR ν_{max}^{neat} cm^{-1}: 3400. $[\alpha]_D^{19.5}$ −46.4° (c=1.38, $CHCl_3$). MS m/z (relative intensity): 394 (M^+, 0.5), 167 (4), 151 (100). Exact MS m/z Calcd for $C_{23}H_{38}O_5$ (M^+): 394.2720. Found: 394.2731.

(2*R*,4*S*,5*R*,6*R*,7*R*,8*S*)-7-(3,4-Dimethoxybenzyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-decenol (14)——A 2,2-dimethoxypropane (20 ml) solution of **13** (1.2 g, 2.33 mmol) and CSA (40 mg) was stirred at room temperature for 30 min. Et_3N (1 ml) was added to quench the reaction and evaporation of the solvent gave an acetal (1.4 g). This acetal was dissolved in DMSO (14 ml), and MPM chloride (4.3 ml, 10 eq) was added, then a 2.5 M dimsyl potassium solution (14 ml; prepared from KH and DMSO at room temperature) was added dropwise to the mixture with vigorous stirring. The reaction mixture was poured into 0.1 N HCl, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography with hexane–EtOAc (3 : 1) as the eluant to give **14** as a colorless oil (0.82 g, 53%). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=7 Hz), 0.95 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.10 (3H, d, J=7 Hz), 1.38 (1H, m), 1.49 (1H, ddd, J=12.5, 9.5, 3.5 Hz), 1.56 (1H, m), 1.75 (1H, m), 1.85 (1H, m), 2.02 (1H, ddq, J=5.5, 5, 7 Hz), 2.58 (1H, ddq, J=8, 6.5, 7 Hz), 3.17 (1H, t, J=5.5 Hz), 3.28 (1H, dd, J=6.5, 5 Hz), 3.38 (1H, dd, J=11, 6 Hz), 3.50 (1H, dd, J=11, 4.5 Hz), 3.80 (3H, s), 3.87 (6H, s), 4.44 (1H, d, J=11 Hz), 4.49 (2H, s), 4.57 (1H, d, J=11 Hz), 4.99 (1H, ddd, J=10.5, 2, 1 Hz), 5.05 (1H, ddd, J=17.5, 2, 1 Hz), 5.84 (1H, ddd, J=17.5, 10.5, 8 Hz), 6.81—6.91 (5H, m), 6.86 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz). IR ν_{max}^{neat} cm^{-1}: 3450. $[\alpha]_D^{23.5}$ −11.8° (c=1.32, $CHCl_3$). MS m/z (relative intensity): 393 (M^+-121, 3), 363 (0.8), 227 (7), 167 (16), 151 (100), 121 (66). FI-MS m/z (relative intensity): 515 (M^++1, 33.5), 514 (M^+, 100), 122 (13), 121 (8). Exact MS m/z Calcd for $C_{23}H_{37}O_5$ (M^+-121): 393.2641. Found: 393.2656.

Dimethyl (3*R*,5*S*,6*R*,7*R*,8*R*,9*S*)-8-(3,4-Dimethoxybenzyloxy)-6-(4-methoxybenzyloxy)-2-oxo-3,5,7,9-tetramethyl-10-undecenylphosphonate (15)——Dry DMSO (0.42 ml, 5.9 mmol) in CH_2Cl_2 (1 ml) was added to a stirred solution of oxalyl chloride (0.21 ml, 2.33 mmol) in CH_2Cl_2 (5 ml) at −70 °C during 5 min. After 15 min, **14** (300 mg, 0.58 mmol) in dry CH_2Cl_2 (3 ml) was added. Stirring was continued for 30 min at −70 °C, then Et_3N (1 ml) was added dropwise, and after 15 min, the reaction mixture was allowed to warm to room temperature. After 1 h at room temperature, the reaction mixture was quenched with H_2O, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (10 : 1) to afford (2*R*,4*S*,5*S*,6*R*,7*R*,8*S*)-7-(3,4-dimethoxybenzyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8,-tetramethyl-9-hexenal as a colorless oil (284 mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7 Hz), 1.04 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.56—2.16 (2H, m), 2.40 (1H, m), 2.52 (1H, m), 3.14 (1H, dd, J=7, 4 Hz), 3.24 (1H, dd, J=7, 4 Hz), 3.80 (3H, s), 3.88 (6H, s), 4.38 (1H, d, J=11 Hz), 4.47 (2H, s), 4.60 (1H, d, J=11 Hz), 5.00 (1H, ddd, J=10.5, 2, 1 Hz), 5.04 (1H, ddd, J=18, 2, 1 Hz), 5.80 (1H, ddd, J=18, 10.5, 8 Hz), 6.86 (2H, d, J=9 Hz), 6.88 (3H, d, J=6 Hz), 7.24 (2H, d, J=9 Hz), 9.52 (1H, d, J=3 Hz). IR ν_{max}^{neat} cm^{-1}: 1720. MS m/z (relative

intensity): 391 ($M^+ - 121$, 3), 361 (1.3), 167 (14), 151 (100), 121 (53). Exact MS *m/z* Calcd for $C_{23}H_{35}O_5$ ($M^+ - 121$): 391.2485. Found: 391.2493.

A 1.6 M *n*-BuLi solution in hexane (2.25 ml) was added to a stirred solution of dimethyl methylphosphonate (0.52 ml, 4.8 mmol) in THF at −90 °C. After 45 min, the above aldehyde (0.16 g, 1.2 mmol) in THF (3 ml) was added dropwise, and the reaction mixture was gradually warmed to −20 °C during 8 h. After the reaction had been quenched with saturated NH_4Cl solution, the whole mixture was extracted with ether, and the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the β-hydroxyphosphonate as an oil (0.69 g, 91%). MS *m/z* (relative intensity): 515 ($M^+ - 121$, 2.4), 485 ($M^+ - 151$, 0.5), 349 (4), 235 (16), 151 (100), 121 (69). Exact MS *m/z* Calcd for $C_{26}H_{44}O_8P$ ($M^+ - 121$): 515.2775. Found: 515.2791.

PDC (2 g, 5.5 mmol) was added to a stirred solution of the β-hydroxyphosphonate (0.69 g, 1.1 mmol) in DMF (12 ml) at room temperature. After 5.5 h, the reaction mixture was poured into H_2O and then extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 2) to give 597 mg (86.5%) of the ketophosphonate (**15**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.12 (3H, d, J=7 Hz), 1.15 (3H, d, J=7 Hz), 1.65—1.80 (1H, m), 1.90 (1H, ddd, J=14, 10.5, 2.5 Hz), 2.04 (1H, ddq, J=7.5, 7, 3.5 Hz), 2.56 (1H, ddq, J=8, 7.5, 7 Hz), 2.90 (1H, ddq, J=10.5, 7, 3.5 Hz), 3.09 (1H, dd, J=23, 14.5 Hz), 3.19 (1H, dd, J=23, 14.5 Hz), 3.19 (1H, dd, J=7, 3.5 Hz), 3.33 (1H, dd, J=7.5, 3.5 Hz), 3.77 (1H, d, J=11 Hz), 3.78 (1H, d, J=11 Hz), 3.80 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 4.40 (1H, d, J=11 Hz), 4.45 (1H, d, J=11 Hz), 4.50 (1H, d, J=11 Hz), 4.58 (1H, d, J=11 Hz), 4.99 (1H, dd, J=10.5, 2 Hz), 5.05 (1H, ddd, J=17.5, 2, 1 Hz), 5.91 (1H, ddd, J=17.5, 10.6, 8 Hz), 6.9—6.96 (5H, m), 7.1—7.3 (2H, m). IR ν_{max}^{neat} cm^{-1}: 1710. $[\alpha]_D^{25}$ +15° (c=1.11, $CHCl_3$). MS *m/z* (relative intensity): 513 ($M^+ - 121$, 1.9), 483 (0.4), 347 (6.6), 311 (5.2), 233 (7.7), 151 (100), 121 (60).

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(3,4-Dimethoxybenzyloxy)-10-dimethoxyphosphono-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-oxo-decanal (16)——NMO (0.34 g, 2.52 mmol) was added to a stirred solution of **15** (0.53 g, 0.84 mmol) in a 1 : 4 mixture of acetone and H_2O (6 ml) at room temperature and then a *tert*-BuOH solution of OsO_4 (0.02 eq) was further added. After 1 h, 10% $Na_2S_2O_4$ solution (3 ml) and celite was added with vigorous stirring, and the celite was filtered off. The filtrate was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was washed with 0.1 N HCl and brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–MeOH (20 : 1) as the eluant to give 467 mg (74%) of the diol as an oil.

The diol was dissolved in MeOH (6 ml) and treated with $NaIO_4$ (282 mg, 1.32 mmol) in H_2O (3 ml) at 0 °C. The reaction mixture was stirred for 30 min at room temperature, then diluted with water, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and concentrated *in vacuo* to give **16** as an oil (447 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.13 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 2.5—3.24 (4H, m), 2.98 (1H, dd, J=22.5, 14 Hz), 3.21 (1H, dd, J=22.5, 14 Hz), 3.75 (3H, d, J=11 Hz), 3.77 (3H, d, J=11 Hz), 3.80 (3H, s), 3.87 (6H, s), 4.32 (1H, d, J=11 Hz), 4.39 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.53 (1H, d, J=11 Hz), 6.83 (3H, s), 6.87 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 9.76 (1H, d, J=1 Hz). IR ν_{max}^{neat} cm^{-1}: 1715, 1710.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(3,4-Dimethoxybenzyloxy)-10-dimethoxyphosphono-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-oxodecanoic Acid (5)——A stirred acetone solution (5.7 ml) of **16** (242 mg, 0.38 mmol), cooled at −20 °C, was treated dropwise with 2.67 M Jones reagent (285 μl, 0.38 mmol). After 5 min, 2-propanol (1 ml) was added to quench the reaction, and the reaction mixture was allowed to warm to room temperature. Ether and H_2O were then added. The organic layer was separated, and the aqueous layer was extracted with ether and CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved again in ether, and then extracted with saturated $NaHCO_3$. The alkaline extract was neutralized with saturated NH_4Cl and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), and concentrated *in vacuo* to afford **5** (180 mg, 72.5%) as a colorless oil, which was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.34 (3H, d, J=7 Hz), 1.63 (1H, m), 1.82 (1H, m), 1.94 (1H, ddq, J=3, 1, 7 Hz), 2.67 (1H, dq, J=0.5, 7 Hz), 2.76 (1H, dq, J=9.5, 7 Hz), 3.08 (1H, dd, J=8.5, 1 Hz), 3.18 (1H, br s), 3.25 (1H, br s), 3.55 (1H, d, J=9.5 Hz), 3.78 (3H, d, J=11.5 Hz), 3.78 (3H, s), 3.84 (3H, d, J=11.5 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.32 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.48 (1H, d, J=11 Hz), 4.67 (1H, d, J=11 Hz), 6.83 (2H, d, J=8.5 Hz), 6.82—6.90 (3H, m), 7.20 (2H, d, J=8.5 Hz). IR ν_{max}^{neat} cm^{-1}: 1735, 1710. $[\alpha]_D^{16.5}$ 0° (c=2.63, $CHCl_3$). MS *m/z* (relative intensity): 531 ($M^+ - 121$, 1.6), 501 (0.4), 329 (8.6), 233 (8.6), 180 (12), 151 (69), 121 (100). Exact MS *m/z* Calcd for $C_{25}H_{40}O_{10}P$ ($M^+ - 121$): 531.2360. Found: 531.2330.

(1*R*,2*R*)-2-Benzyloxy-1-ethyl-2-formylpropyl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(3,4-Dimethoxybenzyloxy)-10-dimethoxyphosphono-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-oxodecanate (17)——2,4,6-Trichlorobenzoyl chloride (30.5 μl, 0.21 mmol) was added dropwise to a stirred solution of **5** (113 mg, 0.173 mmol) and Et_3N (29 μl, 0.19 mmol) in THF (3 ml) at room temperature. After 1 h, precipitated $Et_3N \cdot HCl$ was filtered off and the filtrate was evaporated *in vacuo* to leave an oil, which was dissolved in toluene (2 ml). To this stirred solution, a mixture of **6** (77 mg, 0.346 mmol) and DMAP (21 mg, 0.173 mmol) in toluene (0.83 ml) was added. After 4 h, the reaction mixture was diluted with ether, washed with brine and saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 2) to give **17** as a colorless oil (88.5 mg, 60%).

^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz), 0.91 (3H, d, J=7 Hz), 1.06 (3H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.29 (3H, d, J=7 Hz), 1.32 (3H, s), 1.61 (2H, m), 1.77 (2H, m), 1.90 (2H, m), 2.75—2.90 (2H, m), 3.09 (1H, dd, J=22.5, 14.5 Hz), 3.15 (1H, dd, J=22.5, 14.5 Hz), 3.15 (1H, dd, J=6, 4 Hz), 3.74 (3H, d, J=11.5 Hz), 3.76 (3H, d, J=11.5 Hz), 3.79 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 4.41 (3H, d, J=11 Hz), 4.49 (1H, d, J=11 Hz), 4.54 (1H, d, J=11 Hz), 4.57 (1H, d, J=11 Hz), 5.22 (1H, dd, J=11, 3.5 Hz), 6.78—6.88 (3H, m), 6.85 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz), 7.30 (5H, m), 9.62 (1H, s). IR ν_{max}^{neat} cm^{-1}: 1740, 1735, 1710. $[\alpha]_D^{12}$ +20.6° (c=1.42, $CHCl_3$). MS m/z (relative intensity): 735 (M^+ −121, 1), 705 (0.2), 569 (3.6), 329 (9), 233 (11), 180 (7), 151 (91), 121 (100), 91 (36). FI-MS m/z (relative intensity): 856 (M^+, 36.6), 736 (73), 166 (100).

(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,13*R*,14*R*)-13-Benzyloxy-4-(3,4-dimethoxybenzyloxy)-14-ethyl-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11(*E*)-ene-2,10-dione (18)——A solution of **17** (2.9 mg) in toluene (1.5 ml) was added dropwise to a stirred suspension of K_2CO_3 (2.8 mg, 0.02 mmol) and 18-crown-6 (10.7 mg, 0.04 mmol) in toluene (2 ml) during 30 min at 80 °C. After 1 h at 80 °C, the reaction mixture was allowed to cool to room temperature, quenched by addition of saturated NH_4Cl (5 ml), and poured into ether (20 ml). This ether solution was washed with saturated KCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (3 : 1) as the eluent to give **18** as a colorless oil (2.2 mg, 89%). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz), 0.92 (3H, d, J=6 Hz), 1.07 (3H, d, J=7 Hz), 1.16 (3H, d, J=7 Hz), 1.20—1.30 (1H, m), 1.30 (3H, d, J=7 Hz), 1.39 (3H, s), 1.45—1.60 (1H, m), 1.76 (1H, t, J=12 Hz), 2.02 (1H, ddq, J=14, 7.5, 2.5 Hz), 2.08 (1H, m), 2.50—2.65 (1H, m), 2.69 (1H, dq, J=6, 7 Hz), 3.07 (1H, d, J=8 Hz), 3.40 (1H, dd, J=6, 2.5 Hz), 3.79 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 4.30 (2H, d, J=11 Hz), 4.31 (1H, d, J=11 Hz), 4.41 (1H, d, J=11 Hz), 4.46 (1H, d, J=11 Hz), 4.68 (1H, d, J=11 Hz), 5.01 (1H, dd, J=11, 2 Hz), 6.37 (1H, d, J=15.5 Hz), 6.80—6.90 (3H, m), 7.00 (1H, d, J=15.5 Hz), 7.19 (1H, d, J=9 Hz), 7.29 (1H, d, J=9 Hz), 7.29 (5H, m). IR ν_{max}^{neat} cm^{-1}: 3450, 1735, 1700. $[\alpha]_D^{16.5}$ −4.2° (c=1.64, $CHCl_3$). MS m/z (relative intensity): 609 (M^+ −121, 3), 579 (1), 335 (4), 167 (7), 151 (100), 121 (86), 91 (42). FI-MS m/z (relative intensity): 730 (M^+, 100), 580 (14), 136 (12). Exact MS m/z Calcd for $C_{36}H_{49}O_8$ (M^+ −121): 609.3429. Found: 609.3410.

(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,13*R*,14*R*)-13-Benzyloxy-14-ethyl-4-hydroxy-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11(*E*)-ene-2,10-dione (19)——DDQ (7.6 mg, 0.032 mmol) was added to a stirred ice-cold solution of **18** (24.4 mg, 0.0334 mmol) in toluene (1 ml) and H_2O (0.05 ml). After being stirred for 4.5 h at 0 °C, the reaction mixture was quenched by addition of saturated $NaHCO_3$, and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated to leave an oil, which was subjected to preparative thin layer chromatography (TLC) on silica gel (benzene : EtOAc = 15 : 1, three times development) to give **19** (6.4 mg, 33%, net 42%). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.5 Hz), 1.02 (6H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.28 (3H, d, J=7 Hz), 1.38 (3H, s), 1.90 (1H, m), 1.94 (1H, ddd, J=14, 7, 2 Hz), 2.66 (1H, dq, J=8.5, 7 Hz), 2.70 (1H, d, J=2.5 Hz), 2.78 (1H, dquint, J=8, 7 Hz), 3.51 (1H, t, J=4.5 Hz), 3.75 (1H, d, J=8.5 Hz), 3.81 (1H, s), 4.30 (1H, d, J=11 Hz), 4.41 (1H, d, J=11 Hz), 4.42 (1H, d, J=11 Hz), 4.45 (1H, d, J=11 Hz), 5.14 (1H, dd, J=11, 2.5 Hz), 6.28 (1H, d, J=16.5 Hz), 6.79 (1H, d, J=16.5 Hz), 6.89 (2H, d, J=9 Hz), 7.27 (2H, d, J=9 Hz), 7.23—7.37 (5H, m). IR ν_{max}^{neat} cm^{-1}: 3450, 1730, 1695. $[\alpha]_D^{13.5}$ −2.6° (c=1.0, $CHCl_3$). MS m/z (relative intensity): 472 (M^+ −108, 0.15), 401 (0.7), 336 (4.8), 121 (100), 91 (34.5). FI-MS m/z (relative intensity): 580 (M^+, 100), 121 (11.7). Exact MS m/z Calcd for $C_{28}H_{40}O_5$ (M^+ −108): 472.2825. Found: 472.2833.

(3*R*,5*R*,6*S*,7*S*,9*R*,13*R*,14*R*)-14-Ethyl-13-benzyloxy-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyl-1-oxacyclotetradec-11(*E*)-ene-2,4,10-trione (20)——A solution of DMSO (16.3 μl, 0.23 mmol) in CH_2Cl_2 (50 μl) was added to a stirred solution of oxalyl chloride (10 μl, 0.164 mmol) in dry CH_2Cl_2 (0.2 ml) at −70 °C. After 15 min, a CH_2Cl_2 solution of **19** (10 mg, 0.017 mmol) was added to the reaction mixture. Stirring was continued for 30 min at −65 °C, and then Et_3N (48 μl, 0.345 mmol) was added. After 70 min at −65—−55 °C, the reaction mixture was quenched with saturated NH_4Cl, then allowed to warm to room temperature during 1 h, and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column with hexane–EtOAc (3 : 1) as the eluant to afford **20** as a viscous oil (9.1 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.5 Hz), 1.01 (3H, d, J=7 Hz), 1.08 (3H, d, J=6.5 Hz), 1.27 (3H, d, J=7.5 Hz), 1.38 (3H, d, J=7 Hz), 1.40 (3H, s), 1.89 (1H, m), 2.75 (1H, dq, J=14, 7 Hz), 2.77 (1H, dq, J=6.5, 7 Hz), 3.80 (3H, s), 3.83 (1H, q, J=7 Hz), 3.93 (1H, dd, J=13.5, 6.5 Hz), 4.32 (1H, d, J=11.5 Hz), 4.43 (1H, d, J=11.5 Hz), 4.50 (2H, s), 5.09 (1H, dd, J=11, 2.5 Hz), 6.20 (1H, d, J=16.5 Hz), 6.73 (1H, d, J=16.5 Hz), 6.87 (1H, d, J=9 Hz), 7.27 (1H, d, J=9 Hz), 7.32 (5H, m). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1715, 1695, 1630. MS m/z (relative intensity): 578 (M^+, 0.1), 470 (0.8), 399 (0.8), 334 (4), 163 (5), 121 (100), 91 (42). FI-MS m/z (relative intensity): 578 (M^+, 100), 138 (22), 122 (24). Exact MS m/z Calcd for $C_{35}H_{46}O_7$ (M^+): 578.3244. Found: 578.3255.

Pikronolide (2)——DDQ (22 mg, 0.097 mmol) was added to a stirred solution of **20** (5.4 mg, 0.0934 mmol) in a mixture of CH_2Cl_2 and H_2O (20 : 1, 0.5 ml) at room temperature. After 19 h, the reaction mixture was directly chromatographed on a silica gel column with hexane–EtOAc (2 : 1—1 : 1) as the eluant to give **2** as a colorless solid (2.7 mg, 81%), mp 140—141.5 °C (EtOAc–hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz, C-15), 1.02 (3H, d, J=7 Hz, C-6′), 1.11 (3H, d, J=6 Hz, C-8′), 1.19—1.31 (1H, m, C-4′), 1.24 (3H, d, J=7 Hz, C-4′), 1.34 (3H, s, C-12′), 1.40—1.60 (1H, m, C-14), 1.44 (3H, d, J=7 Hz, C-2′), 1.45—1.59 (1H, m, C-7), 1.79 (1H, ddq, J=14, 2.5, 7 Hz, C-14), 1.94 (1H, m, C-6), 1.95 (1H, d, J=4.5 Hz, C-5 OH), 2.83 (1H, dq, J=12, 6 Hz, C-8), 2.93 (1H, dq, J=5.5, 7 Hz,

C-4), 2.94 (1H, s, C-12 OH), 3.79 (1H, q, $J=7$ Hz, C-2), 3.97 (1H, ddd, $J=5.5$, 4.5, 4 Hz, C-5), 5.00 (1H, dd, $J=11$, 2.5 Hz, C-13), 6.30 (1H, d, $J=16$ Hz, C-10), 6.71 (1H, d, $J=16$ Hz, C-11). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3450, 1740, 1695, 1635. $[\alpha]_D^{18.5}+66.3^\circ$ ($c=0.187$, MeOH). MS m/z (relative intensity): 368 (M^+, 0.6), 350 (14), 310 (3.4), 292 (4.6), 267 (4.2), 254 (7.5), 178 (47), 122 (100), 109 (85). Exact MS m/z Calcd for $C_{20}H_{32}O_6$ (M^+): 368.2198. Found: 368.2196

Acknowledgments The authors are grateful to Professor M. Yamaguchi, Kyushu University, for providing his precious reagent and for helpful discussions. We are also indebted to Mr. N. Kakusawa for technical assistance.

References and Notes

1) Chiral Synthesis of Polyketide-Derived Natural Products. XVI. For part XV, see: T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, *Chem. Pharm. Bull.*, **35**, 2219 (1987).
2) A preliminary report on this work: N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 4645 (1986).
3) *a*) Y. Oikawa, T. Tanaka, K. Horita, I. Noda, N. Nakajima, N. Kakusawa, T. Hamada, and O. Yonemitsu, *Chem. Pharm. Bull.*, **35**, 2184 (1987); *b*) Y. Oikawa, T. Tanaka, T. Hamada, and O. Yonemitsu, *ibid.*, **35**, 2196 (1987); *c*) T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada, and O. Yonemitsu, *ibid.*, **35**, 2203 (1987); *d*) T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, *ibid.*, **35**, 2209 (1987).
4) H. Brockmann and W. Henkel, *Naturwissenschaften*, **37**, 138 (1950); *idem, Chem. Ber.*, **84**, 284 (1951).
5) Pikronolide (**2**) was also isolated from the fermentation broth of *Streptomyces venezuelae* MCRL-0379: *a*) I. Maezawa, T. Hori, A. Kinumaki, and M. Suzuki, *J. Antibiot.*, **26**, 771 (1973); *b*) I. Maezawa, A. Kinumaki, and M. Suzuki, *ibid.*, **27**, 84 (1974).
6) Unless otherwise noted, the numberings are based on that of pikronolide (**2**).
7) *a*) S. Masamune, *Aldrichimica*, **11**, 23 (1978); *b*) T. Kaiho, S. Masamune, and T. Toyoda, *J. Org. Chem.*, **47**, 1612 (1982).
8) *a*) H. Brockmann and R. Strufe, *Chem. Ber.*, **86**, 876 (1953); *b*) H. Brockmann and R. Oster, *ibid.*, **90**, 605 (1957); *c*) R. Anliker and K. Gubler, *Helv. Chim. Acta*, **40**, 119, 1768 (1957).
9) Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **25**, 5393 (1984).
10) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, *Tetrahedron*, **42**, 3021 (1986), and references cited therein.
11) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).
12) *a*) Y. Oikawa, K. Horita, and O. Yonemitsu, *Tetrahedron Lett.*, **26**, 1541 (1985); *b*) Y. Oikawa, T. Tanaka, K. Horita, and O. Yonemitsu, *ibid.*, **25**, 5397 (1984).
13) *a*) Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 7107 (1980); *b*) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, and K. Maruyama, *Tetrahedron*, **40**, 2239 (1984); *c*) G. E. Keck and D. E. Abbot, *Tetrahedron Lett.*, **25**, 1879 (1984).
14) A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).
15) *a*) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980); *b*) B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *ibid.*, **103**, 464 (1981); *c*) K. B. Sharpless, C. H. Behrens, T. Katsuki, A. W. M. Lee, V. S. Martin, M. Takatani, S. M. Viti, F. J. Walker, and S. S. Woodard, *Pure Appl. Chem.*, **55**, 589 (1983).
16) R. O. Hutchints, I. M. Jaffer, and W. Bungoyne, *J. Org. Chem.*, **46**, 5215 (1981).
17) Reduction with excess sodium bis(2-methoxyethoxy)aluminum hydride[18] in refluxing xylene also gave the expected 1,3-diol, though the yield was very poor (6%).
18) *a*) J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, **23**, 2719 (1982); *b*) S. M. Viti, *ibid.*, **23**, 4541 (1982).
19) E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5654 (1966).
20) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, **1977**, 399.
21) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **30**, 1701, 1710 (1955).
22) Segment i (**5**) obtained by the Jones oxidation was contaminated with a small amount of a further oxidation product (3%) at the benzylic position of the DMPM group to the dimethoxybenzoyl group. Oxidation of **16** with other reagents such as PDC, RuO_2, n-Bu_4NMnO_4, Pt–O_2, *etc.* gave very poor results. Compound **5** was obtained in the pure state from **15** by the following five-step conversion: OsO_4 oxidation to the diol, *tert*-butyldimethylsilyl protection of the primary alcohol, Swern oxidation (using trifluoroacetic anhydride) of the secondary alcohol, removal of the silyl protection, and finally oxidative cleavage of the keto-alcohol with $NaIO_4$. However, the overall yield of **5** was less than 10%.
23) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
24) *a*) K. C. Nicolaou, S. P. Seitz, and M. R. Pavia, *J. Am. Chem. Soc.*, **104**, 2030 (1982); *b*) W. C. Still and V. J. Novack, *ibid.*, **106**, 1148 (1984); *c*) *Cf.*, P. A. Aristoff, *J. Org. Chem.*, **46**, 1954 (1981).
25) The DMPM protecting group of the acetate of **14** was also removed with excellent selectivity (22:1) by treatment with DDQ (1.2 eq) in toluene–H_2O (20:1) at $-5^\circ C$.
26) The stereoselectivities at C-4, C-6, C-8, and C-12 were reported in the previous paper.[3c]