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Highly Stereoselective Total Synthesis of Methynolide, the Aglycon of the 12-Membered Macrolide Antibiotic Methymycin. II. Kinetic Acetalization and Synthesis of the Seco-Acid[1,2]

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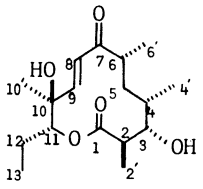
A highly stereoselective synthesis of the seco-acid (**3**) of methynolide (**1**), the aglycon of the 12-membered macrolide methymycin was carried out, starting from D-glucose *via* the Wittig–Horner coupling of the two segments i (**4**) (C-9—C-13) and ii (**5**) (C-1—C-8), which were synthesized by the use of *p*-methoxybenzyl and *p*-methoxybenzylidene acetal protecting groups for hydroxy functions.

Keywords——macrolide antibiotic; aglycon; methynolide; seco-acid; stereoselective synthesis; kinetic acetalization; protecting group; Wittig–Horner reaction

Many modern synthetic methodologies mainly consisting of means of acyclic stereocontrol, rather than classical cyclic stereocontrol, have recently been established and used to achieve marvelous total syntheses of biologically important natural products with highly complex structures such as macrolide and polyether antibiotics. Among many complex macrolides, methynolide (**1**), the aglycon of the 12-membered antibiotic methymycin, is a suitable first target in order to establish new synthetic methodologies,[3] because the structure of **1** is relatively less complex. In the preceding paper,[1] as the first step for the synthesis of **1**, we reported a highly stereoselective synthesis of a Prelog–Djerassi lactone-type versatile chiral



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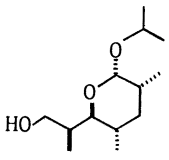

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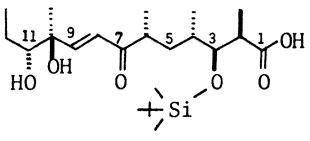

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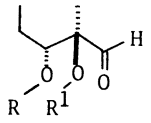
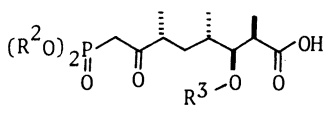


segment i



segment ii

4 : R, R^1 = MP, H

5 : R^2 = Et, R^3 = Si

Chart 1

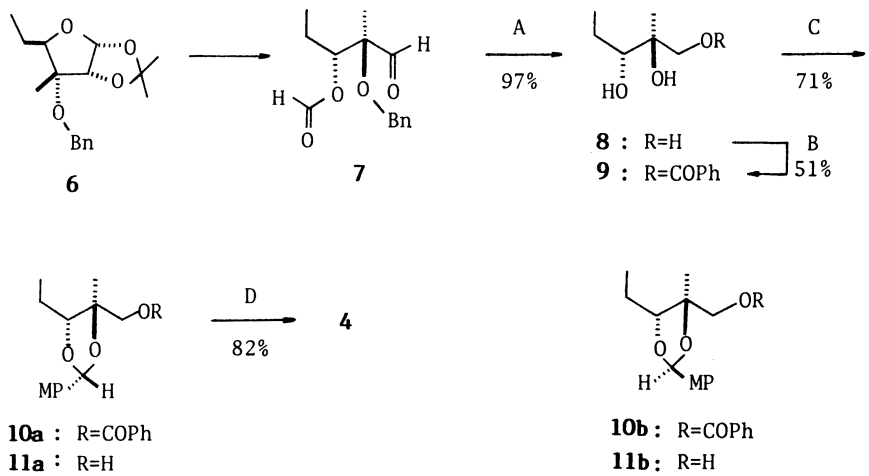
synthon (**2**), which has all the chiral centers required for segment ii and corresponds to the C-1—C-8 fragment of **1**, from D-glucose by using some stereocontrolled reactions and suitable protecting groups for hydroxy functions. In this paper we report the synthesis of both segments i (**4**) and ii (**5**) and their coupling to form the known seco-acid (**3**).

Results and Discussion

Synthesis of Segment i (4) *via* Kinetic Acetalization

The aldehyde (**7**)[4] corresponding to the segment i has already been synthesized from D-glucose *via* **6**[5] and utilized as a chiral synthon in our synthetic study of erythromycin A,[6] but **7** itself could not be used as segment i because the protecting groups of the two hydroxy functions were not suitable. It was very important to choose a protecting group for the 1,2-diol system that would be removable under conditions as mild as possible at the final synthetic step of **3**. For this purpose, *p*-methoxybenzylidene (MP acetal) protection rather than simple isopropylidene protection[7] was employed, and **7** was converted to **4** as follows.

Successive treatments of **7** with lithium aluminum hydride (LAH) and palladium on carbon (Pd–C) under a hydrogen atmosphere led to the triol (**8**), which was selectively benzoylated in pyridine to give the monobenzoate (**9**). Usual acid-catalyzed acetalization of the 1,2-diol of **9** with *p*-methoxybenzaldehyde in the presence of *p*-toluenesulfonic acid at room temperature gave a diastereoisomeric mixture of **10a** and **10b** in the ratio of 3.5 : 1.[8] Under acidic conditions two stereoisomeric acetals with respect to the benzylic carbon such as **10a** and **10b** must be in equilibrium to give a thermodynamically controlled mixture.[9,10] This disadvantage was overcome by the use of kinetically controlled acetalization with 4-methoxybenzyl methyl ether (MPMME) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[2a] When a mixture of **9** and MPMME in dichloromethane was reacted at room temperature for 30 min, **10a** was mainly obtained with excellent selectivity (39 : 1). Since 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) formed from DDQ is almost insoluble in the solvent,[12] the reaction mixture was kept almost neutral throughout the reaction and the acid-catalyzed equilibration would have been suppressed.[14] The benzoyl protection of **10a** was



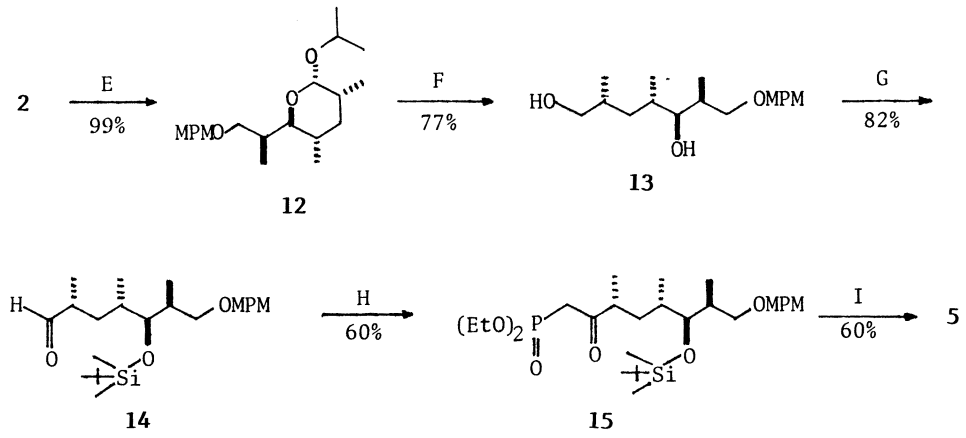
(A) 1) $LiAlH_4$, Et_2O, 0 °C; 2) Pd–C, H_2, EtOAc (B) BzCl, benzene, pyridine (C) 1) MPMME, DDQ, CH_2Cl_2; 2) KOH, MeOH (D) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, $-60 \rightarrow 0$ °C

Chart 2

removed with potassium hydroxide in aqueous methanol and the resulting primary alcohol (**11a**) was subjected to Swern oxidation to give the aldehyde (**4**: segment i).

Synthesis of Segment ii (5)

The hydroxy group of the Prelog–Djerassi lactone-type intermediate (**2**), synthesized highly stereoselectively from D-glucose,[1] was protected with a 4-methoxybenzyl (MPM) group[15] to give **12**, followed by acid hydrolysis of the acetal group and then calcium borohydride reduction to give the acyclic diol (**13**) in good yield. Three-step conventional conversion of **13**, *tert*-butyldimethylsilyl (TBDMS) protection of both the primary and secondary hydroxy groups, selective removal of the protection of the primary alcohol with a slight excess of a fluoride anion, and final Swern oxidation, gave the aldehyde (**14**) in high yield, and this product was treated with the lithio derivative of diethyl methylphosphonate, followed by immediate Swern oxidation of the resulting hydroxyphosphonate to give the ketophosphonate (**15**).[16] After removal of the MPM protection with DDQ in dichloromethane containing a small amount of water under usual conditions,[15] Jones oxidation of the resulting primary alcohol at 0 °C gave the carboxylic ketophosphonate (**5**: segment ii) in good yield.



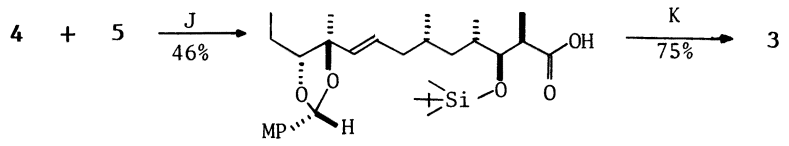
MPM = 4-$MeOC_6H_4CH_2$

(E) NaH, DMSO–THF, MPMCl (F) 1) 1 N HCl, THF, 50 °C; 2) $Ca(BH_4)_2$, EtOH (G) 1) TBDMSCl, imidazole, DMF, 90 °C; 2) Bu_4NF, THF; 3) $(COCl)_2$, DMSO–THF, Et_3N, −60→0 °C (H) 1) $(EtO)_2POMe$, *n*-BuLi, Et_2O, −78→0 °C; 2) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −60 °C (I) 1) DDQ, CH_2Cl_2–H_2O; 2) CrO_3, H_2SO_4, MeCOMe, 0 °C

Chart 3

Synthesis of Masamune's Seco-Acid (3)

The Wittig–Horner coupling[17] between the dilithio derivative of **5** and the aldehyde (**4**) proceeded smoothly in tetrahydrofuran (THF) at room temperature to afford the expected unsaturated ketone (**16**) in acceptable yield. Finally, the MP acetal protection of **16** was selectively removed without any detectable loss of the TBDMS protection by treatment with 0.4 N hydrochloric acid in dimethoxyethane at room temperature, and the expected seco-acid (**3**)[3b,c,g] was isolated in good yield.[7] Nuclear magnetic resonance (NMR) and high-resolution mass spectra of **3** were in complete agreement with those provided by Professor Ireland. Since **3** was converted to methynolide (**1**) and methymycin by Masamune *et al.*,[3b] a formal total synthesis of this macrolide antibiotic was thus completed in the present work.



16

(J) *n*-BuLi, THF (K) 0.4 N HCl, DME

Chart 4

Experimental

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

(2*S*,3*R*)-2-Methylpentane-1,2,3-triol (8)——Compound **7** (0.94 g, 3.76 mmol) was reduced with $LiAlH_4$ (0.21 g, 5.53 mmol) in ether (30 ml) at 0 °C for 1 h. Work-up in the usual way and chromatography on a silica gel column with hexane–EtOAc (1 : 1) gave (2*R*,3*S*)-2-benzyloxy-2-methylpentane-1,3-diol as a colorless oil (0.813 g, 97%). $[\alpha]_D^{15}$ +19.8° (*c* = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, *J* = 7.5 Hz), 1.07 (3H, s), 1.20—1.80 (2H, m), 2.64—2.88 (2H, m), 3.52—3.90 (3H, m), 4.55 (2H, s), 7.33 (5H, s). MS *m/z* (relative intensity): 193 (M^+ − 31, 3.0), 165 (3.5), 148 (1.8), 91 (100). Exact MS *m/z* Calcd for $C_{12}H_{17}O_2$ (M^+ − 31): 193.1228. Found: 193.1226.

An EtOAc solution (40 ml) of the diol (0.718 g, 3.21 mmol) was hydrogenated with 10% Pd–C (0.25 g) at ordinary temperature and pressure for 10 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to leave **8** as a colorless oil (0.437 g, 100%). $[\alpha]_D^{15}$ +30° (*c* = 1.16, $CHCl_3$). ^{1}H-NMR ($CDCl_3$–D_2O) δ: 1.08 (3H, t, *J* = 7 Hz), 1.20 (3H, s), 1.0—1.84 (2H, m), 3.34 (1H, dd, *J* = 2.5, 10 Hz), 3.39 (1H, d, *J* = 12 Hz), 3.52 (1H, d, *J* = 12 Hz). MS *m/z* (relative intensity): 103 (M^+ − 31, 28), 85 (13), 75 (85), 58 (80), 57 (73), 43 (100). Exact MS *m/z* Calcd for $C_5H_{11}O_2$ (M^+ − 31): 103.0759. Found: 103.0757.

(2*S*,3*R*)-1-Benzoyloxy-2-methylpentane-2,3-diol (9)——A solution of **8** (0.437 g, 3.26 mmol) and benzoyl chloride (0.55 g, 3.91 mmol) in benzene (4 ml) and pyridine (2 ml) was stirred at room temperature for 24 h. After addition of MeOH, the reaction mixture was diluted with benzene, washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (2 : 1) to afford **9** as a colorless oil (396 mg, 51%). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, *J* = 7.5 Hz), 1.28 (3H, s), 1.20—1.92 (2H, m), 2.20—2.80 (2H, br s), 3.44 (1H, dd, *J* = 2, 10 Hz), 4.40 (1H, d, *J* = 12 Hz), 4.54 (1H, d, *J* = 12 Hz), 7.30—7.70 (3H, m), 8.40 (2H, dd, *J* = 2, 8 Hz).

(2*S*,3*R*)-2,3-[(*R*)-(4-Methoxybenzylidene)dioxy]-2-methylpentanol (11a)——A solution of **9** (0.344 g, 1.45 mmol), 4-methoxybenzyl methyl ether (0.855 g, 5.78 mmol), and DDQ (0.721 g, 3.18 mmol) in anhydrous CH_2Cl_2 (20 ml) was stirred at room temperature for 30 min. After removal of the precipitates by filtration the filtrate was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo* to give a mixture mainly containing (2*S*,3*R*)-1-benzoyloxy-2,3-[(*R*)-(4-methoxybenzylidene)dioxy]-2-methylpentane (**10a**). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, *J* = 7 Hz), 1.47 (3H, s), 1.50—2.10 (2H, m), 3.80 (3H, s), 3.82 (1H, t, *J* = 6 Hz), 4.29 (1H, d, *J* = 12 Hz), 4.43 (1H, d, *J* = 12 Hz), 5.85 (1H, s), 6.87 (2H, d, *J* = 9 Hz), 7.44 (2H, d, *J* = 9 Hz), 7.30—7.70 (3H, m), 8.02 (2H, dd, *J* = 2.5, 8 Hz). MS *m/z* (relative intensity): 356 (M^+, 11), 355 (17), 221 (21), 137 (43), 135 (96), 105 (100). Exact MS *m/z* Calcd for $C_{21}H_{24}O_5$ (M^+): 356.1623. Found: 356.1620.

The above mixture (**10a,b**) was treated with KOH (1.0 g) in MeOH (12 ml) and water (2 ml) at room temperature for 1 h, then concentrated *in vacuo* and the residue was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (3 : 1) to afford a mixture of **11a** and **11b** (0.258 g, 71%). The ratio of **11a** and **11b** was determined to be 39 : 1 from the intensity ratio of the benzylic methine protons (**11a**: 5.84 ppm and **11b**: 6.12 ppm) in the NMR spectrum. $[\alpha]_D^{18}$ +8.0° (*c* = 1.12, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, *J* = 7 Hz), 1.35 (3H, s), 1.50—2.00 (2H, m), 3.48 (1H, dd, *J* = 7, 12 Hz), 3.68 (1H, dd, *J* = 5, 12 Hz), 3.81 (3H, s), 3.84 (1H, t, *J* = 5 Hz), 5.84 (1H, s), 6.90 (2H, d, *J* = 8.5 Hz), 7.42 (2H, d, *J* = 8.5 Hz). MS *m/z* (relative intensity): 252 (M^+, 14), 251 (19), 221 (33), 193 (15), 137 (100), 135 (51). Exact MS *m/z* Calcd for $C_{14}H_{20}O_4$ (M^+): 252.1361. Found: 252.1344.

(2*R*,3*R*)-2,3-[(*R*)-(4-Methoxybenzylidene)dioxy]-2-methylpentanal (4)——A solution of dimethylsulfoxide (DMSO) (0.165 g, 2.11 mmol) in CH_2Cl_2 (0.35 ml) was added dropwise to a stirred solution of oxalyl chloride (0.109 g, 0.858 mmol) in CH_2Cl_2 (1.7 ml) at −60 °C, and then a solution of **11** (0.19 g, 0.753 mmol) in CH_2Cl_2 (1 ml) was similarly added. After 1 h, NEt_3 (0.254 g, 2.52 mmol) was added. The reaction mixture was allowed to warm to 0 °C during 15 min, then poured onto a silica gel column. Elution with hexane–EtOAc (3 : 1) gave **4** as a colorless oil (0.154 g, 82%). IR ν_{max}^{neat} cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, *J* = 7 Hz), 1.40 (3H, s), 1.40—1.80 (2H, m), 3.83 (3H, s), 5.99 (1H, s), 6.94 (2H, d, *J* = 9 Hz), 7.50 (2H, d, *J* = 9 Hz). MS *m/z* (relative intensity): 250 (M^+, 4), 221 (47), 152 (12), 137 (100).

(2*S*,3*R*,5*S*,6*S*)-2-Isopropyloxy-3,5-dimethyl-6-[(1*S*)-2-(4-methoxybenzyl)oxy-1-methylethyl]tetrahydropyran

(12)——A solution of **2** (0.53 g, 2.30 mmol) in THF (5 ml) was added dropwise to a stirred suspension of NaH (110 mg, 4.58 mmol) in DMSO (3 ml). After evolution of hydrogen had ceased, MPMCl (700 mg, 4.47 mmol) was added dropwise at 0 °C, and the mixture was stirred at room temperature overnight, then treated with Et_2NH (0.2 ml) at 50 °C. After 3 h, the reaction mixture was poured into cold saturated NH_4Cl and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (5 : 1) to give **12** as a colorless oil (0.80 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=7 Hz), 0.80 (3H, d, J=7 Hz), 0.88 (3H, d, J=7 Hz), 1.07 (3H, d, J=7 Hz), 1.14 (3H, d, J=7 Hz), 1.00—2.20 (5H, m), 3.35 (1H, dd, J=7, 16 Hz), 3.50 (1H, dd, J=12, 16 Hz), 3.52 (1H, dd, J=2, 10 Hz), 3.80 (3H, s), 3.80 (1H, sept, J=7 Hz), 4.32 (1H, d, J=12 Hz), 4.48 (1H, d, J=12 Hz), 4.61 (1H, d, J=3 Hz), 6.85 (2H, d, J=9 Hz), 8.24 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 349 ($M^+ - 1$, 0.25), 290 (20), 217 (22), 169 (17), 134 (43), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{26}O_3$ ($M^+ - 60$): 290.1883. Found: 290.1882.

(2*R*,4*S*,5*S*,6*S*)-7-(4-Methoxybenzyl)oxy-2,4,6-trimethylheptane-1,5-diol (13)——A solution of **12** (800 mg, 2.28 mmol) in THF (10 ml) and 1 N HCl (3 ml) was heated at 50 °C. After 5 h, the reaction mixture was cooled, neutralized with $NaHCO_3$, and concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (3 : 1) to give the lactol (570 mg, 81%).

A solution of $NaBH_4$ (210 mg, 5.5 mmol) in EtOH (25 ml) was added dropwise to a stirred solution of $CaCl_2$ (610 mg, 5.5 mmol) in EtOH (30 ml) at −20 °C. After 30 min, the above lactol (570 mg, 1.85 mmol) in EtOH (10 ml) was added at −20 °C, and the resulting mixture was stirred for 3 h at room temperature. Excess $Ca(BH_4)_2$ was decomposed with 1 N HCl at 0 °C and the mixture was neutralized with $NaHCO_3$. After removal of the precipitates by filtration, the filtrate was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to leave an oil, which was dissolved in MeOH containing 1% AcOH and evaporated. This MeOH–AcOH treatment was repeated three times to decompose cyclic borates. The residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 1) to afford **13** as a colorless oil (546 mg, 95%). $[\alpha]_D^{18}$ − 14.5° (c=5.68, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, d, J=7 Hz), 0.95 (6H, d, J=7 Hz), 1.40—2.10 (5H, m), 2.70 (1H, br s), 3.20 (1H, br s), 3.30—3.70 (5H, m), 3.84 (3H, s), 4.46 (2H, s), 6.88 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 310 (M^+, 0.5), 292 (0.6), 171 (1.3), 150 (4.7), 137 (32), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{30}O_4$ (M^+): 310.2147. Found: 310.2140.

(2*R*,4*S*,5*S*,6*S*)-5-*tert*-Butyldimethylsilyloxy-7-(4-methoxybenzyl)oxy-2,4,6-trimethylheptanal (14)——A solution of **13** (546 mg, 1.76 mmol), TBDMS chloride (1.0 g, 6.64 mmol) and imidazole (500 mg, 7.35 mmol) in dimethylformamide (DMF) (5 ml) was stirred for 10 h at room temperature. To the resulting reaction mixture, containing the 1-monosilylate, TBDMSCl (500 mg, 3.32 mmol) and imidazole (300 mg, 4.41 mmol) were again added. The mixture was heated at 90 °C for 30 h, then cooled, poured into water (100 ml), and extracted with ether. The extract was dried (Na_2SO_4) and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (30 : 1) to give the 1,5-disilylate as a colorless oil (889 mg, 94%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (12H, s), 0.87 (3H, d, J=7 Hz), 0.89 (21H, s), 0.90 (3H, d, J=7 Hz), 1.00—2.10 (5H, m), 3.08—3.59 (4H, m), 3.62 (1H, dd, J=2, 5 Hz), 3.81 (3H, s), 4.41 (2H, s), 6.87 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 359 ($M^+ - 151$, 0.6), 323 (2.6), 227 (1.5), 187 (3.3), 121 (100). Exact MS *m/z* Calcd for $C_{19}H_{43}O_2Si_2$ ($M^+ - 151$): 359.2801. Found: 359.2790.

A solution of the disilylate (880 mg, 1.63 mmol) and a 1 M THF solution of Bu_4NF (1.8 ml, 1.8 mmol) in THF (10 ml) were mixed and allowed to stand for 10 h at room temperature, then concentrated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (5 : 1) to afford (2*R*,4*S*,5*S*,6*S*)-5-*tert*-butyldimethylsilyloxy-7-(4-methoxybenzyl)oxy-2,4,6-trimethylheptanol as a colorless oil (536 mg, 77%) from the first fraction. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.07 (3H, s), 0.88 (3H, d, J=7 Hz), 0.92 (9H, s), 0.93 (3H, d, J=7 Hz), 0.95 (3H, d, J=7 Hz), 1.20—2.20 (5H, m), 3.10—3.50 (5H, m), 3.72 (1H, dd, J=2.5, 4.5 Hz), 3.84 (3H, s), 4.43 (2H, s), 6.88 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 323 ($M^+ - 101$, 2.5), 187 (5.2), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{31}O_3Si$ ($M^+ - 101$): 323.2042. Found: 323.2053.

The second fraction gave the recovered starting diol (**13**: 68 mg, 13%).

A solution of DMSO (240 mg, 1.89 mmol) in CH_2Cl_2 (1.2 ml) was added dropwise to a stirred solution of $(COCl)_2$ (240 mg, 1.89 mmol) in CH_2Cl_2 (5 ml) at −60 °C, and then a solution of the above 5-monosilylate (530 mg, 1.25 mmol) in CH_2Cl_2 (1 ml) was similarly added. After 1 h, Et_3N (0.508 g, 5.03 mmol) was added and the reaction mixture was allowed to warm gradually to 0 °C, then washed with saturated NH_4Cl and water, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting oil was chromatographed on a silica gel column with hexane–EtOAc (5 : 1) to give **14** as a colorless oil (513 mg, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.01 (3H, s), 0.03 (3H, s), 0.88 (9H, s), 0.90 (3H, d, J=7 Hz), 0.94 (3H, d, J=7 Hz), 1.10 (3H, d, J=7 Hz), 1.40—2.10 (5H, m), 3.20 (1H, dd, J=6, 9 Hz), 3.35 (1H, dd, J=8, 9 Hz), 3.65 (1H, dd, J=3, 5 Hz), 3.82 (3H, s), 4.41 (2H, s), 6.88 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 9.50 (1H, d, J=3 Hz). MS *m/z* (relative intensity): 323 ($M^+ - 99$, 2.1), 259 (1.1), 241 (1.0), 187 (3.4), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{31}O_3Si$ ($M^+ - 99$): 323.2042. Found: 323.2041.

(3*R*,5*S*,6*S*,7*S*)-6-*tert*-Butyldimethylsilyloxy-1-diethylphosphono-8-(4-methoxybenzyl)oxy-3,5,7-trimethyloctan-2-one (15)——A 1.6 M hexane solution of *n*-BuLi (0.85 ml, 1.36 mmol) was added to a solution of diethyl

methanephosphonate (0.320 g, 1.51 mmol) in ether (3 ml) at −78 °C under argon was added and, after 10 min, a solution of **14** (0.308 g, 0.73 mmol) in ether (3 ml) was similarly added. The reaction mixture was allowed to warm to 0 °C during 1.5 h, then treated with saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave the hydroxyphosphonate as a crude oil (0.403 g, 96%). MS *m/z* (relative intensity): 574 (M^+, 0.15), 517 (1.3), 379 (0.9), 363 (0.9), 321 (1.5), 295 (1.9), 181 (8), 121 (100). Exact MS *m/z* Calcd for $C_{29}H_{55}O_7PSi$ (M^+): 574.3454. Found: 574.3435.

The hydroxyphosphonate (0.403 g, 0.702 mmol) in CH_2Cl_2 (3.5 ml) was subjected to the usual Swern oxidation with $(COCl)_2$ (0.116 g, 0.916 mmol), DMSO (0.176 g, 2.26 mmol) and NEt_3 (0.218 g, 0.916 mmol) in CH_2Cl_2 (2 ml) at −60 °C. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous NH_4Cl and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 2) to give **15** as a colorless oil (0.25 g, 62%). IR ν_{max}^{neat} cm^{-1}: 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (3H, s), 0.04 (3H, s), 0.85 (3H, d, J = 7 Hz), 0.88 (9H, s), 0.91 (3H, d, J = 7 Hz), 1.15 (3H, d, J = 7 Hz), 1.32 (6H, t, J = 7 Hz), 1.50—2.00 (5H, m), 2.84—3.00 (1H, m), 3.01 (1H, dd, J = 14, 22 Hz), 3.15 (1H, dd, J = 14, 22 Hz), 3.23 (1H, dd, J = 8, 9 Hz), 3.35 (1H, dd, J = 6, 9 Hz), 3.64 (1H, dd, J = 2.5, 5 Hz), 3.81 (3H, s), 4.13 (4H, quint, J = 7 Hz), 4.41 (2H, s), 6.87 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz). MS *m/z* (relative intensity): 515 ($M^+ - 57$, 0.3), 121 (100). Exact MS *m/z* Calcd for $C_{25}H_{44}O_7PSi$ ($M^+ - 57$): 515.2593. Found: 515.2606.

(2*R*,3*S*,4*S*,6*R*)-3-*tert*-Butyldimethylsilyloxy-8-diethylphosphono-7-oxo-2,4,6-trimethyloctanoic Acid (5)——A solution of **15** (0.241 g, 0.421 mmol) and DDQ (0.132 g, 0.581 mmol) in CH_2Cl_2 (10 ml) and water (0.5 ml) was stirred for 1 h at room temperature. After removal of the precipitates, the filtrate was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 2) to afford the alcohol (0.222 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.08 (3H, s), 0.83 (3H, d, J = 7 Hz), 0.91 (9H, s), 0.96 (3H, d, J = 6.5 Hz), 1.12 (3H, d, J = 7 Hz), 1.33 (6H, dt, J = 1.5, 7 Hz), 1.60—1.94 (3H, m), 2.92—3.20 (1H, m), 3.04 (1H, dd, J = 13, 23 Hz), 3.20 (1H, dd, J = 13, 23 Hz), 3.38 (1H, dd, J = 8, 11 Hz), 3.42 (1H, dd, J = 5, 11 Hz), 3.89 (1H, t, J = 3.5 Hz), 4.12 (4H, quint, J = 7 Hz), 4.78 (1H, br s). MS *m/z* (relative intensity): 395 ($M^+ - 57$, 60), 365 (25), 322 (30), 303 (22), 285 (20), 261 (84), 221 (27), 208 (95), 147 (85), 99 (70), 75 (85), 73 (100). Exact MS *m/z* Calcd for $C_{17}H_{36}O_6PSi$ ($M^+ - 57$): 395.2018. Found: 395.2002.

A 2.67 M solution of Jones reagent (0.2 ml, 0.534 mmol) was added to a solution of the above alcohol (0.138 g, 0.305 mmol) in acetone (12 ml) at 0 °C. After 10 min, the reaction was quenched with iso-PrOH, and the solution was diluted with water (3 ml) and extracted with ether. The extract was washed with cold brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (1 : 4) to afford 5 as a colorless oil (0.105 g, 74%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 0.99 (3H, d, J = 7 Hz), 1.33 (6H, t, J = 8 Hz), 1.60—2.00 (3H, m), 2.63 (1H, quint, J = 7 Hz), 2.80—3.04 (1H, m), 3.17 (2H, d, J = 23.5 Hz), 3.86 (1H, dd, J = 2.5, 8 Hz), 4.16 (2H, quint, J = 8 Hz), 4.18 (2H, quint, J = 8 Hz). MS *m/z* (relative intensity): 451 ($M^+ - 15$, 0.8), 409 (23), 391 (8), 261 (35), 221 (13), 208 (100), 198 (90), 79 (73). Exact MS *m/z* Calcd for $C_{17}H_{34}O_7PSi$ ($M^+ - 57$): 409.1811. Found: 409.1794.

(2*R*,3*S*,4*S*,6*R*,8*E*,10*S*,11*R*)-3-*tert*-Butyldimethylsilyloxy-10,11-[(*R*)-(4-methoxybenzylidene)dioxy]-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic Acid (16)——A 1.6 M hexane solution of *n*-BuLi (0.031 ml, 0.05 mmol) was added to a solution of **5** (9.5 mg, 0.02 mmol) in THF (0.5 ml) at 0 °C and, after 10 min, a solution of **4** (20 mg, 0.08 mmol) in THF (0.1 ml) was similarly added. The mixture was allowed to stand for 1 h at 0 °C, then for 13 h at room temperature. After addition of 5% aqueous KH_2PO_4, the mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil, which was purified by silica gel thin layer chromatography (TLC) with CH_2Cl_2–MeOH (24 : 1) to give **16** (5.3 mg, 46%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 0.90 (3H, d, J = 7 Hz), 1.06 (3H, t, J = 7 Hz), 1.08 (2H, d, J = 7 Hz), 1.14 (2H, d, J = 7 Hz), 1.49 (3H, s), 1.57 (2H, quint, J = 7 Hz), 1.70—1.92 (1H, m), 2.50—2.84 (2H, m), 3.80—3.88 (2H, m), 3.82 (3H, s), 5.89 (1H, s), 6.41 (1H, d, J = 15 Hz), 6.82 (1H, d, J = 15 Hz), 6.92 (2H, d, J = 9 Hz), 7.45 (1H, d, J = 9 Hz). MS *m/z* (relative intensity): 562 (M^+, 0.3), 561 (0.5), 369 (55), 351 (18), 137 (45), 135 (60), 75 (100).

(2*R*,3*S*,4*S*,6*R*,8*E*,10*S*,11*R*)-3-*tert*-Butyldimethylsilyloxy-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic Acid (3)——A solution of **16** (4.4 mg, 0.0078 mmol) in DME (0.3 ml) and 0.4 N HCl (0.15 ml) was allowed to stand for 2 h at 18 °C, and then diluted with water (0.2 ml). After addition of NaCl (for salting-out), the mixture was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was separated by TLC on silica gel to give **3** (2.6 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.91 (9H, s), 0.96 (3H, d, J = 7 Hz), 1.02 (3H, t, J = 7 Hz), 1.11 (3H, d, J = 7 Hz), 1.14 (3H, d, J = 7 Hz), 1.36 (3H, s), 1.45—1.90 (5H, m), 2.50—2.88 (2H, m), 3.49 (1H, dd, J = 2, 10.5 Hz), 3.81 (1H, dd, J = 2, 7.5 Hz), 6.48 (2H, d, J = 9 Hz), 6.89 (2H, d, J = 9 Hz). MS *m/z* (relative intensity): 408 ($M^+ - 36$, 1.2), 384 (2), 369 (9), 311 (7), 75 (100). Exact MS *m/z* Calcd for $C_{23}H_{44}O_6Si$ ($M^+ - 75$): 369.2097. Found: 369.2088.

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References and Notes

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8) The configurations of **10a** and **10b** were tentatively determined on the basis of the chemical shifts of the benzylic methine protons to be 5.85 and 6.13 ppm, respectively.[9a]
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10) This presented a problem, namely when **4** (3.5 : 1 mixture) was coupled with segment ii (**5**), the structural determination of the crude product (**16**) was almost impossible because of its very complicated NMR spectrum.
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14) The following mechanistic scheme may explain this kinetic acetalization, in which the acid-catalyzed back reaction from iv to iii may be suppressed under near-neutral conditions.[2a] However, prolonged treatment with DDQ caused a slow acid-catalyzed equilibration owing to the presence of a trace of DDHQ. The ratio of **10a** and **10b** fell to 15 : 1 when the reaction was quenched after 1.5 h.

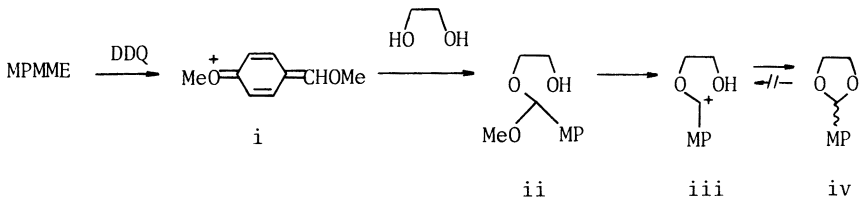

Chart 5

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