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Highly Stereoselective Total Synthesis of Tylonolide, the Aglycon of the 16-Membered Macrolide Antibiotic Tylosin. II. Total Synthesis of Tylonolide by Virtue of 4-Methoxybenzyl and 3,4-Dimethoxybenzyl Protection[1,2]

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

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

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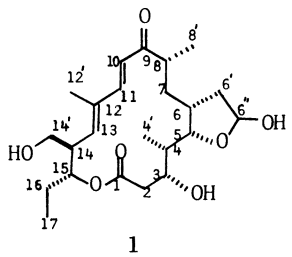
Tylonolide, was synthesized from D-glucose *via* coupling and cyclization of two segments i (**2**) (C-11—C-17) and ii (**3**) (C-1—C-10), which were synthesized from diacetoneglucose. A Prelog–Djerassi lactone-type compound was an intermediate in the synthesis of the latter segment. Esterification of the two segments by Yamaguchi's method followed by macrocyclization by use of the Wittig–Horner reaction gave the 16-membered cyclic enone, whose protecting groups were removed to afford tylonolide. In this total synthesis, 4-methoxybenzyl and 3,4-dimethoxybenzyl protecting groups played an important role.

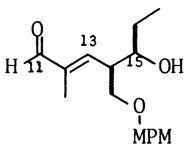
Keywords——macrolide antibiotic; tylosin; aglycon; tylonolide; esterification; macrocyclization; Wittig–Horner reaction; protecting group; 2,3-dichloro-5,6-dicyanobenzoquinone oxidation; stereoselective synthesis

For the purpose of the highly selective total synthesis of complex natural products such as macrolide and polyether antibiotics, it is essential to apply the most suitable protection for many functional groups as well as to use highly regio- and stereo-controlled reactions. As a part of our recent synthetic studies on such complex natural products, we have attempted the highly stereoselective total synthesis of tylonolide (**1**)[3] from D-glucose by means of our new synthetic methodology recently established in the synthesis of methynolide.[4]

Segments i (**2**) and ii (**3**) seemed to be the most suitable intermediate in our general strategy and, in the preceding paper,[1] the synthesis of the chiral synthon (**12**) was reported. In the present paper, we describe a new total synthesis of **1** through syntheses of **2** and **3**, coupling of these two segments, and selective removal of 4-methoxybenzyl (MPM)[5,6] and

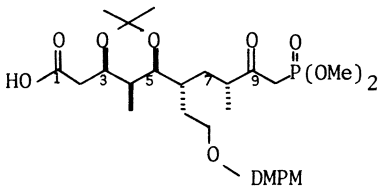


1



segment i

2



segment ii

3

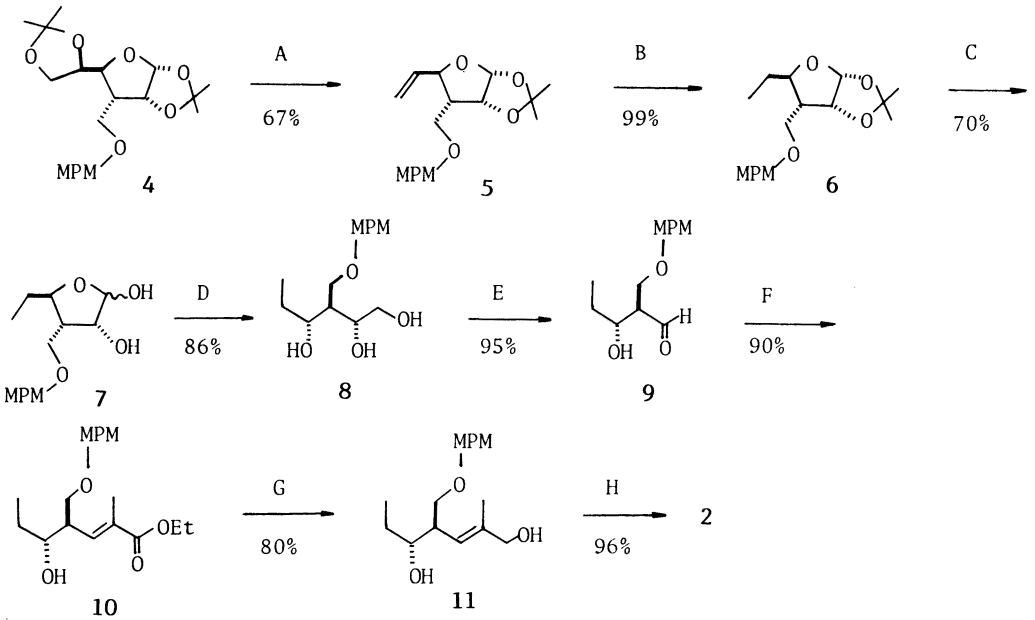
MPM = 4-$MeOC_6H_4CH_2$
DMPM = 3,4-$(MeO)_2C_6H_3CH_2$

Chart 1

3,4-dimethoxybenzyl (DMPM)[6,7] protecting groups by the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at crucial points in the final stage.

Synthesis of Segment i

Segment i (**2**), corresponding to C-11—C-17 of **1**,[8] was rather easily synthesized from D-glucose *via* the MPM ether (**4**).[9,10] The isopropylidene protection of the 5,6-side chain[12] was selectively removed in methanol with 2% sulfuric acid,[13] and the resulting diol was converted to the ditosylate, which was subjected to reductive elimination with sodium iodide in methyl ethyl ketone in the usual way to give the olefin (**5**). Catalytic reduction of **5** over 10% palladium on carbon (Pd–C) gave **6** in quantitative yield. Removal of the 1,2-isopropylidene protection[12] in tetrahydrofuran (THF) with 4.5 N hydrochloric acid gave the lactol (**7**), which was reduced to the triol (**8**) by treatment with calcium borohydride[14] in high yield.[15] The 1,2-diol was readily cleaved with sodium metaperiodate to give the aldehyde (**9**) in excellent yield. When **9** was treated with a stable ylide[16] in benzene at 60 °C, a smooth Wittig reaction proceeded, and the expected (*E*)-α,β-unsaturated ester (**10**) was isolated in high yield.[17,18] Lithium aluminum hydride (LAH) reduction of the ester (**10**) gave the allyl alcohol (**11**), which was oxidized with manganese dioxide in dichloromethane to give the α,β-unsaturated aldehyde (**2**) (segment i) in excellent yield.



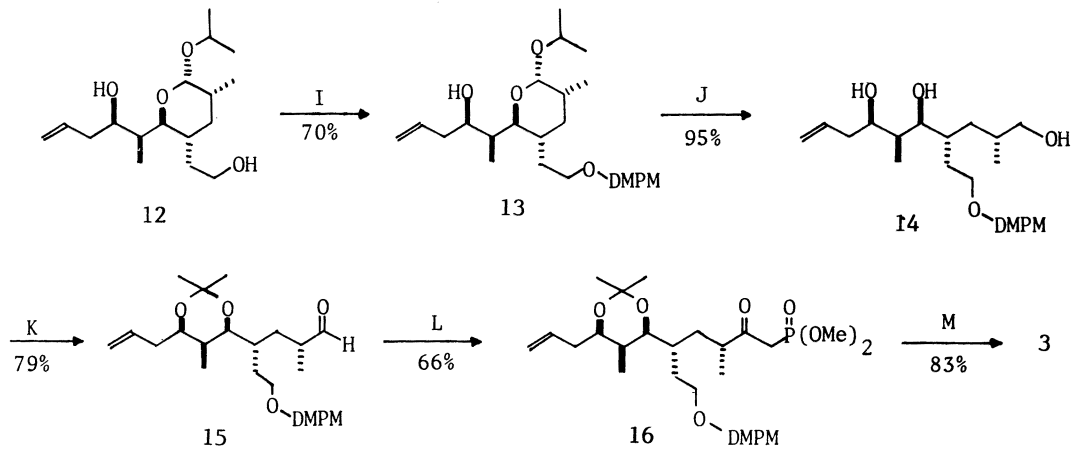
(A) 1) 2% H_2SO_4, MeOH; 2) TsCl, Et_3N, DMAP, CH_2Cl_2; 3) NaI, MeCOEt, reflux (B) Pd–C, H_2, EtOAc (C) 4.5 N HCl, THF, 50 °C (D) $CaCl_2$, $NaBH_4$, EtOH (E) $NaIO_4$, MeOH–H_2O (F) $Ph_3P{=}CMeCO_2Et$, benzene, 60 °C (G) $LiAlH_4$, THF, 0 °C (H) MnO_2, CH_2Cl_2

Chart 2

Synthesis of Segment ii

In the previous paper,[1] the chiral intermediate (**12**) having all the chiral centers required for segment ii was synthesized from D-glucose. The primary alcohol of **12** was protected with a DMPM group[6,7] to give **13** in 70% yield,[19] and then the acetal of **13** was hydrolyzed in THF with 1 N hydrochloric acid. The resulting lactol was reduced to the triol (**14**) by treatment with calcium borohydride[14] in quantitative yield.[20] The 1,3-diol group of **14** was protected as an

acetonide group with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) in 85% yield, and the remaining primary alcohol was subjected to Swern oxidation[21] to give the aldehyde (**15**) in 98% yield. The Wittig–Horner reaction of **15** with the lithio derivative of dimethyl methylphosphonate[22] gave almost quantitatively a hydroxy phosphonate, which was immediately oxidized with pyridinium dichromate (PDC)[23] in dimethylformamide (DMF) to give the ketophosphonate (**16**).[24] Finally, among various possible oxidation methods of the terminal olefin of **16** into the carboxylic group, Lemieux-von Rudloff oxidation with potassium permanganate and sodium periodate[26] gave a good result, and the expected segment ii (**3**) was isolated in 83% yield.



(I) NaH, DMSO–THF, DMPMCl (J) 1) 1 N HCl, THF, 50 °C; 2) $CaCl_2$, $NaBH_4$, EtOH (K) 1) $(MeO)_2CMe_2$, CSA, benzene; 2) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −80 °C→room temperature (L) 1) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −70→−30 °C; 2) PDC, DMF (M) $NaIO_4$, $KMnO_4$, $NaHCO_3$, MeCOMe–H_2O

Chart 3

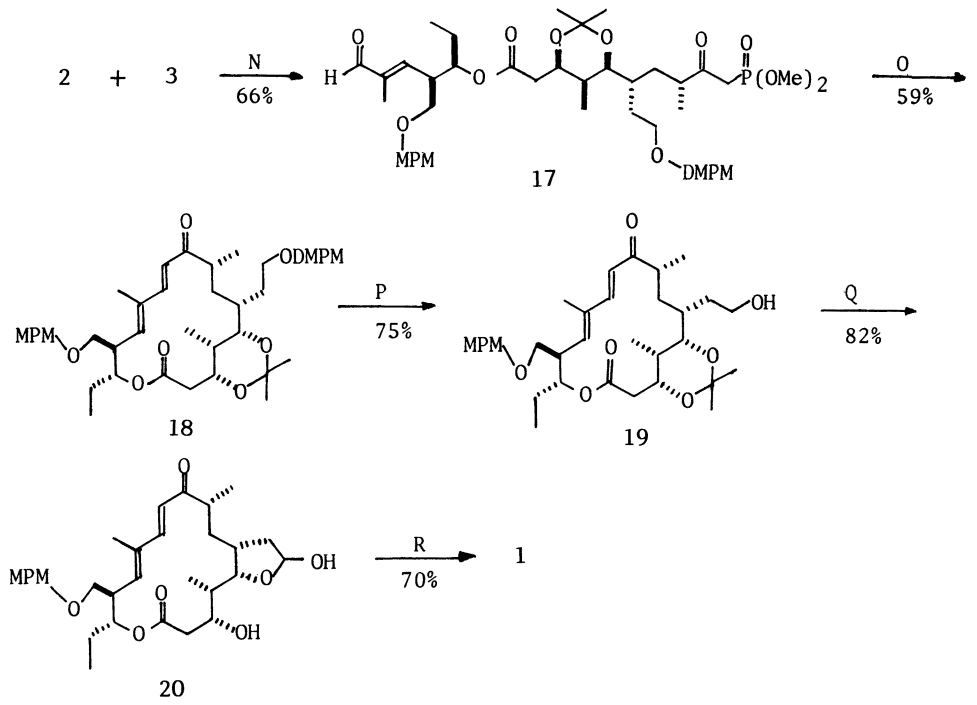
Coupling of the Two Segments and Synthesis of Tylonolide

The macrolactonization of seco-acids is commonly used for the synthesis of macrolides.[27] Wittig–Horner coupling between the two segments i (**2**) and ii (**3**) was first examined in order to obtain a seco-acid, but all attempts were unsuccessful. Therefore, we decided to reverse the order of reactions, namely esterification between **2** and **3** was first examined, and the resulting ester was subjected to intramolecular Wittig–Horner reaction.

When **2** and **3** were coupled in a rather concentrated solution (more than 1 M) with dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP), the expected ester (**17**) was obtained in 61% yield, but unfortunately complete separation from impurities could not be achieved. However, the Yamaguchi method[27g] gave a much better result. When **2** and **3** were condensed with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine and DMAP, the esterification was completed within only 1 h at room temperature to give the ester (**17**) in 66% yield.

The intramolecular Wittig–Horner coupling of **17** was carried out under Aristoff[28]–Nicolaou[3b] conditions, namely when a 1 mM solution of **17** in toluene was heated at 100 °C in the presence of 18-crown-6 (12 eq) and potassium carbonate (6 eq), the starting material (**17**) disappeared after 12 h, and the expected 16-membered enone (**18**) was isolated in 59% yield.

Selective removal of DMPM protecting groups in the presence of MPM protecting groups by DDQ oxidation has been clearly demonstrated in many cases.[6,7] When an ice-cold



(N) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, THF (O) K_2CO_3, 18-crown-6, toluene, 100 °C (P) DDQ, CH_2Cl_2–H_2O–benzene, 5 °C (Q) 1) PDC, CH_2Cl_2; 2) 0.5 N HCl, THF (R) DDQ, CH_2Cl_2–H_2O

Chart 4

solution of **18** in dichloromethane–water (20 : 1) was treated with a slight excess of DDQ (1.2 eq), the selective deprotection of the DMPM group occurred smoothly, and the monoalcohol (**19**) was isolated in 75% yield. PDC oxidation[23] of the primary alcohol of **19** gave the aldehyde (94%), and the remaining acetonide was immediately removed with 0.5 N hydrochloric acid to give the hemiacetal compound (**20**) in 90% yield. Finally, the MPM protecting group of **20** was easily removed by retreatment with DDQ under usual conditions,[5,6] and tylonolide (**1**) was isolated in 70% yield. This compound was identical, in terms of its infrared (IR), nuclear magnetic resonance (NMR) and mass spectra (MS) with tylonolide derived from natural tylosin.[29,30] Stereoselectivities in this total synthesis of **1** from D-glucose for the construction of the new chiral centers at C-3, C-4, C-6, C-8, and C-14 were 91, 94, 100, 87, and 100%, respectively.

Experimental

Physical data were measured as described in the previous paper.[4a]

1,2-*O*-Isopropylidene-3-*C*-(4-methoxybenzyl)oxymethyl-3,5,6-trideoxy-α-D-*ribo*-hex-5-enofuranose (5)——A solution of **4** (3.52 g, 8.95 mmol) in MeOH (43 ml) and 2% H_2SO_4 (18 ml) was allowed to stand at room temperature for 15 h. After neutralization with $NaHCO_3$, the reaction mixture was evaporated *in vacuo*, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (2 : 1) to give the diol as a colorless oil (2.72 g, 86.5%). TsCl (1.68 g), Et_3N (2 g) and DMAP (50 mg) were added to a stirred CH_2Cl_2 solution (50 ml) of the diol (1.31 g, 3.8 mmol) at room temperature. After 19 h, the reaction mixture was diluted with CH_2Cl_2, washed with 1 N HCl, 10% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave a pale yellow oil, which was dissolved in MeCOEt and heated under reflux with NaI (3.42 g) for 24 h. The reaction mixture was evaporated *in*

vacuo to leave an oil, which was extracted with CH_2Cl_2. The extract was washed with $Na_2S_2O_3$ solution and H_2O, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 3) to give **5** as a colorless solid (0.91 g, 77%). Recrystallization from ether–hexane gave colorless needles, mp 54—56 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, s), 1.51 (3H, s), 1.94—2.23 (1H, m), 3.40 (1H, dd, J=9.5, 5.0 Hz), 3.75 (1H, dd, J=9.5, 9.0 Hz), 3.80 (3H, s), 4.20 (1H, dd, J=10.5, 9.0 Hz), 4.46 (2H, s), 4.74 (1H, t, J=4.0 Hz), 5.15—5.39 (2H, m), 5.65—6.00 (1H, m), 5.83 (1H, d, J=4.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz). MS *m/z* (relative intensity): 320 (M^+, 0.2), 305 (0.3), 262 (3.5), 137 (41), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{24}O_5$: 320.1623. Found: 320.16241. *Anal.* Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.33; H, 7.55.

1,2-*O*-Isopropylidene-3-*C*-(4-methoxybenzyl)oxymethyl-3,5,6-trideoxy-α-D-*ribo*-hexofuranose (6)——An EtOAc solution (30 ml) of **5** (1.38 g, 4.31 mmol) was hydrogenated with 10% Pd–C (100 mg) at ordinary temperature and pressure for 30 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave **6** as a colorless oil (1.36 g, 98.5%). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.0 Hz), 1.20—2.15 (3H, m), 1.32 (3H, s), 1.49 (3H, s), 3.44 (1H, dd, J=9.5, 6.0 Hz), 3.65—3.91 (2H, m), 3.81 (3H, s), 4.47 (2H, s), 4.70 (1H, t, J=4.0 Hz), 5.79 (1H, d, J=3.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz). $[\alpha]_D^{15}$ +50° (c=1.3, $CHCl_3$). MS *m/z* (relative intensity): 307 (M^+ − 15, 0.4), 264 (2.9), 203 (1.0), 138 (58), 121 (100). Exact MS *m/z* Calcd for $C_{17}H_{23}O_5$ (M^+ − 15): 307.15452. Found: 307.15520.

3-*C*-(4-Methoxybenzyl)oxymethyl-3,5,6-trideoxy-α-D-*ribo*-hexofuranose (7)——A solution of **6** (1.63 g, 5.06 mmol) in THF (30 ml) and 4.5 N HCl (10 ml) was heated at 50 °C for 5.5 h. After neutralization with $NaHCO_3$, the reaction mixture was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with EtOAc–hexane (2 : 1) to give **7** (1.0 g, 70%). Recrystallization from ether–hexane gave colorless crystals, mp 61—64 °C. MS *m/z* (relative intensity): 282 (M^+, 0.8), 264 (1.2), 203 (1.2), 137 (43), 121 (100). Exact MS *m/z* Calcd for $C_{15}H_{22}O_5$ (M^+): 282.14669. Found: 282.14862. *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.80; H, 7.85. Found: C, 63.66; H, 7.81.

(2*R*,3*R*,4*S*)-2-(4-Methoxybenzyl)oxymethyl-1,2,4-trihydroxyhexane (8)——A solution of $NaBH_4$ (400 mg, 10.5 mmol) in EtOH (50 ml) was added dropwise to a cold stirred EtOH solution (50 ml) of $CaCl_2$ (1.1 g) at −20 °C under argon. The resulting $Ca(BH_4)_2$ solution was stirred for 30 min below −10 °C, then a solution of **7** (900 mg, 3.19 mmol) in EtOH was added and the mixture was stirred at room temperature for 1 h. The reducing agent was decomposed with 4 N HCl, and the solution was neutralized with $NaHCO_3$. After removal of precipitates by filtration, the filtrate was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was dried and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–EtOH (20 : 1) to give **8** as a colorless oil (777 mg, 86%). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz), 1.30—1.70 (2H, m), 1.88 (1H, dq, J=4, 6 Hz), 3.52 (1H, dd, J=5, 9.5 Hz), 3.58 (1H, dd, J=3.5, 9.5 Hz), 3.65 (1H, dd, J=5, 11.5 Hz), 3.72 (1H, dd, J=4, 11.5 Hz), 3.75—3.88 (1H, m), 3.81 (3H, s), 3.98 (1H, dt, J=4.5, 5 Hz), 4.41 (2H, s), 6.88 (2H, d, J=9 Hz), 7.22 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 284 (M^+, 0.5), 266 (3.8), 178 (1.8), 150 (2.6), 137 (44), 121 (100). Exact MS *m/z* Calcd for $C_{15}H_{24}O_5$ (M^+): 284.16235. Found: 284.16259. $[\alpha]_D^{15}$ +7.8° (c=1.3, $CHCl_3$).

(2*S*,3*R*)-3-Hydroxy-2-[(4-methoxybenzyl)oxymethyl]pentanal (9)——A solution of $NaIO_4$ (430 mg, 2.0 mmol) in H_2O (3.5 ml) was added to a stirred MeOH solution (10 ml) of **8** (194 mg, 0.68 mmol) at room temperature. After 1 h, the precipitate was filtered off, and the filtrate was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2, and the solution was dried over Na_2SO_4, then evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 1) to give **9** as a colorless oil (164 mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.0 Hz), 1.60 (2H, quint, J=7.0 Hz), 2.45—2.63 (1H, m), 2.80 (1H, br s), 3.67—4.20 (3H, m), 3.81 (3H, s), 4.46 (2H, s), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 9.87 (1H, d, J=1.5 Hz). MS *m/z* (relative intensity): 252 (M^+, 0.4), 234 (0.4), 194 (1.8), 175 (10), 137 (92), 121 (100). Exact MS *m/z* Calcd for $C_{14}H_{20}O_4$ (M^+): 252.13614. Found: 252.13501. IR ν_{max}^{neat} cm^{-1}: 3400, 1720. $[\alpha]_D^{15}$ +6.9° (c=1.3, $CHCl_3$).

Ethyl 5(*R*)-Hydroxy-4(*R*)-(4-methoxybenzyl)oxymethyl-2-methyl-2(*E*)-heptenoate (10)——A benzene solution (20 ml) of **9** (545 mg, 2.16 mmol) and recrystallized 1-carboethoxyethylidenetriphenylphosphorane[16] (1.6 g, 4.4 mmol) was heated at 60 °C for 10 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 2) to give **10** as a colorless oil (653 mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.30 (3H, t, J=7.0 Hz), 1.25—1.60 (2H, m), 1.86 (3H, d, J=1.5 Hz), 2.50 (1H, br s), 2.60—2.90 (1H, m), 3.53 (1H, dd, J=12.0, 1.0 Hz), 3.63 (1H, dd, J=12.0, 2.5 Hz), 3.70—3.95 (1H, m), 3.81 (3H, s), 4.19 (2H, q, J=7.0 Hz), 4.45 (2H, s), 6.81 (1H, dq, J=10.0, 1.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz). IR ν_{max}^{neat} cm^{-1}: 3450, 1705. $[\alpha]_D^{16.5}$ −17° (c=4.4, $CHCl_3$). MS *m/z* (relative intensity): 336 (M^+, 0.4), 263 (0.8), 200 (10), 121 (100). Exact MS *m/z* Calcd for $C_{19}H_{28}O_5$ (M^+): 336.19364. Found: 336.19474.

1,5(*R*)-Dihydroxy-4(*R*)-(4-methoxybenzyl)oxymethyl-2-methyl-2(*E*)-heptene (11)——A THF solution of **10** (454 mg, 1.35 mmol) was added dropwise to a cold stirred suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (5 ml) under argon in an ice-bath. After 1 h, the reaction was quenched by the addition of MeOH, then H_2O (0.1 ml), 15% NaOH (0.1 ml) and H_2O (0.3 ml) were added, and the mixture was stirred for 1 h. After removal of precipitated inorganic salts by filtration, the filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column with EtOAc–hexane (2 : 1) to give **11** as a colorless solid (339 mg, 86%). Recrystallization from benzene–

hexane gave colorless needles, mp 78—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.5 Hz), 1.42 (2H, quint, J=7.5 Hz), 1.69 (3H, d, J=1.5 Hz), 1.78 (2H, br s), 2.60—2.75 (1H, m), 3.44—3.62 (2H, m), 3.72 (1H, dt, J=3.0, 7.5 Hz), 3.81 (3H, s), 4.03 (2H, d, J=1.0 Hz), 4.50 (1H, dq, J=10.5, 1.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.24 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 294 (M^+, 1.4), 155 (2.8), 138 (22), 121 (100). Exact MS m/z Calcd for $C_{17}H_{26}O_4$ (M^+): 294.18307. Found: 294.18409. *Anal.* Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.22; H, 9.00.

5(*R*)-Hydroxy-4(*R*)-(4-methoxybenzyl)oxymethyl-2-methyl-2(*E*)-heptenal (2)——A CH_2Cl_2 solution (2 ml) of **11** (17.0 mg, 0.058 mmol) was stirred with active MnO_2 (100 mg, 1.15 mmol) at room temperature for 1 h. After removal of the precipitate by filtration, the filtrate was evaporated *in vacuo* and chromatographed on a silica gel column with EtOAc–hexane (1 : 3) to leave **2** as a colorless oil (16.2 mg, 96%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.20—1.60 (2H, m), 1.75 (3H, d, J=1.0 Hz), 2.7 (1H, br s), 2.89 (1H, ddt, J=10.0, 2.0, 5.0 Hz), 3.64 (2H, d, J=5.0 Hz), 3.80 (3H, s), 3.80—4.00 (1H, m), 4.45 (2H, s), 6.67 (1H, dd, J=10.0, 1.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 9.41 (1H, s). IR ν_{max}^{neat} cm^{-1}: 3430, 1680.

5(*S*)-{5(*R*)-[2-(3,4-Dimethoxybenzyloxy)ethyl]-2(*S*)-isopropyloxy-3(*R*)-methyl-6(*S*)-tetrahydropyranyl}-4(*R*)-hydroxy-1-hexene (13)——A solution of **12** (144 mg, 0.48 mmol) in THF (2 ml) was added dropwise to a stirred suspension of NaH (100 mg, 2.5 mmol) in dimethyl sulfoxide (DMSO) (2 ml) at room temperature. After 1 h, DMPM chloride (93.3 mg, 0.50 mmol) was added, and stirring was continued for 10 h. Then Et_3N (1 ml) was added, and after 30 min, the reaction mixture was poured into saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 5) to give **13** as a colorless oil (151.2 mg, 70%). ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, d, J=7 Hz), 0.91 (3H, d, J=7 Hz), 1.09 (3H, d, J=6 Hz), 1.22 (3H, d, J=6 Hz), 1.15—1.35 (1H, m), 1.47 (1H, dt, J=12.5, 4 Hz), 1.62 (1H, br s), 1.57—1.90 (4H, m), 2.14 (1H, dt, J=13.5, 7 Hz), 2.34 (1H, dt, J=13.5, 7 Hz), 3.40—3.55 (2H, m), 3.73 (1H, dd, J=2, 10.5 Hz), 3.73 (1H, d, J=8 Hz), 3.87 (1H, sept, J=6 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.40 (1H, d, J=12 Hz), 4.46 (1H, d, J=12 Hz), 4.67 (1H, d, J=3 Hz), 5.03 (1H, d, J=10 Hz), 5.08 (1H, d, J=17 Hz), 5.79 (1H, ddt, J=10, 17, 7 Hz), 6.80—6.90 (3H, m). MS m/z (relative intensity): 450 (M^+, 1.0), 390 (3.1), 319 (1.5), 239 (2.2), 222 (19), 151 (100). Exact MS m/z Calcd for $C_{26}H_{42}O_6$ (M^+): 450.29809. Found: 450.29840. $[\alpha]_D^{16}$ +119° (c=0.9, $CHCl_3$).

Monoacetate (colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=6.5 Hz), 1.19 (3H, d, J=6.5 Hz), 1.20—2.10 (7H, m), 2.03 (3H, s), 2.27 (1H, dt, J=15.5, 7.5 Hz), 2.45—2.64 (1H, m), 3.46 (2H, t, J=6.5 Hz), 3.62 (1H, dd, J=5.0, 1.0 Hz), 3.80—4.05 (1H, m), 3.88 (3H, s), 3.89 (3H, s), 4.39 (1H, d, J=11.0 Hz), 4.45 (1H, d, J=11.0 Hz), 4.62 (1H, d, J=3.0 Hz), 4.95—5.10 (3H, m), 5.63—5.80 (1H, m), 6.83—6.90 (3H, m).

(4*R*,5*S*,6*S*,7*R*,9*R*)-7-[2-(3,4-Dimethoxybenzyloxy)ethyl]-5,9-dimethyl-4,6,10-trihydroxy-1-decene (14)——A solution of **13** (1.97 g, 4.37 mmol) in THF (50 ml) and 1 N HCl (15 ml) was heated at 50 °C for 2 h. After neutralization with $NaHCO_3$, the reaction mixture was evaporated *in vacuo* and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 1) to give the lactol as a colorless oil (1.70 g, 95%).

A solution of $NaBH_4$ (1.5 g, 40 mmol) in EtOH (100 ml) was added dropwise to a stirred cold EtOH solution (200 ml) of $CaCl_2$ (3.0 g, 27 mmol) at −10 °C. After 30 min, the above lactol (1.70 g, 4.16 mmol) in EtOH (50 ml) was added, and the stirred reaction mixture was allowed to warm to room temperature. After 1.5 h, 1 N HCl was added to decompose the reducing agent, and the mixture was neutralized with $NaHCO_3$. After removal of precipitated inorganic salts by filtration, the filtrate was evaporated *in vacuo* and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated *in vacuo* to leave an oil, which was dissolved in MeOH containing AcOH (0.5 ml) to decompose borates. After evaporation of the solvent *in vacuo*, the acidic residue was neutralized with $NaHCO_3$ and then extracted with CH_2Cl_2. The extract was dried and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column. Elution with EtOAc and then CH_2Cl_2–MeOH (10 : 1) gave **14** as a colorless oil (1.7 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7.0 Hz), 1.10—1.90 (7H, m), 2.05—2.42 (2H, m), 3.20—3.95 (9H, m), 3.88 (3H, s), 3.89 (3H, s), 4.42 (2H, s), 5.03—5.19 (2H, m), 5.29—5.90 (1H, m), 6.84—6.90 (3H, m). $[\alpha]_D^{16}$ +2.3° (c=1.6, $CHCl_3$). MS m/z (relative intensity): 410 (M^+, 1.5), 392 (1), 310 (1.5), 292 (1.5), 282 (2), 151 (100). Exact MS m/z Calcd for $C_{23}H_{38}O_6$ (M^+): 410.26679. Found: 410.26802.

(2*R*,4*R*,5*S*,6*S*,7*R*)-4-[2-(3,4-Dimethoxybenzyloxy)ethyl]-2,6-dimethyl-5,7-isopropylidenedioxy-9-decenal (15)——A benzene solution (50 ml) of **14** (1.70 g, 4.14 mmol), 2,2-dimethoxypropane (5 ml) and CSA (20 mg) was stirred at room temperature for 3 h. The reaction mixture was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 3) to give an oil. The oil was dissolved in CH_2Cl_2 and the solution was shaken with 1 N HCl. Evaporation of the solvent gave (4*R*,5*S*,6*S*,7*R*,9*R*)-7-[2-(3,4-dimethoxybenzyloxy)ethyl]-5,9-dimethyl-4,6-isopropylidenedioxy-1-decen-10-ol as a colorless oil (1.56 g, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=6.5 Hz), 0.85 (3H, d, J=6.5 Hz), 1.05—2.00 (8H, m), 1.41 (3H, s), 1.42 (3H, s), 2.01—2.42 (2H, m), 3.20—3.95 (6H, m), 3.88 (3H, s), 3.89 (3H, s), 4.43 (2H, s), 5.05 (1H, br d, J=10.0 Hz), 5.08 (1H, br d, J=17.0 Hz), 5.53—5.79 (1H, m), 6.84—6.88 (3H, m). MS m/z (relative intensity): 450 (M^+, 1.5), 398 (1.5), 310 (3.5), 204 (3.1), 151 (100). Exact MS m/z Calcd for $C_{26}H_{42}O_6$ (M^+): 450.29809. Found: 450.29810. $[\alpha]_D^{15}$ +16° (c=2.0, $CHCl_3$).

A solution of DMSO (95 mg, 1.2 mmol) in CH_2Cl_2 (1 ml) was added to a cold stirred CH_2Cl_2 solution of $(COCl)_2$ (77 mg, 0.6 mmol) at −80 °C, and then the above alcohol (182 mg, 0.40 mmol) in CH_2Cl_2 was similarly added. After 1 h, Et_3N (134 mg, 1.3 mmol) was added, then the reaction mixture was allowed to warm to room temperature, washed with H_2O, 0.5 N HCl, brine and aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to leave **15** as an oil (172 mg, 94%). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=7.0 Hz), 1.10—2.70 (9H, m), 1.35 (3H, s), 1.38 (3H, s), 3.41—3.95 (4H, m), 3.88 (3H, s), 3.89 (3H, s), 4.42 (2H, s), 5.04 (1H, br d, J=10.0 Hz), 5.08 (1H, br d, J=17.0 Hz), 5.53—5.87 (1H, m), 6.84—6.88 (3H, m), 9.55 (1H, d, J=2.0 Hz). IR ν_{max}^{neat} cm^{-1}: 1720.

Dimethyl (3*R*,5*R*,6*S*,7*S*,8*R*)-5-[2-(3,4-Dimethoxybenzyloxy)ethyl]-3,7-dimethyl-6,8-isopropylidenedioxy-2-oxo-10-undecenylphosphonate (16)——A 1.6 M BuLi hexane solution (440 μl) was added to a stirred THF solution (6 ml) of dimethyl methylphosphonate (120 μl, 1.0 mmol) at −70 °C under argon. After 30 min, **15** (172 mg, 0.40 mmol) in THF was added dropwise, then the reaction mixture was allowed to warm to −30 °C, quenched by the addition of saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to leave the hydroxyphosphonate as a colorless oil (215 mg, 98%), which was dissolved in DMF (6.5 ml). PDC (500 mg) was added to the resulting solution, and the mixture was stirred for 1 d. Further PDC (500 mg) was added and stirring was continued for 5 h. The reaction mixture was poured into H_2O and extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (2 : 1) to give **16** as a colorless oil (146 mg, 67%). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=7.0 Hz), 1.06 (3H, d, J=7.0 Hz), 1.10—1.90 (6H, m), 1.40 (3H, s), 1.41 (3H, s), 2.11 (1H, dt, J=15.0, 7.0 Hz), 2.29 (1H, dt, J=15.0, 7.0 Hz), 2.84—3.04 (1H, m), 3.15 (2H, d, J=22.0 Hz), 3.45—3.90 (4H, m), 3.74 (3H, d, J=1.0 Hz), 3.80 (3H, d, J=10.0 Hz), 3.88 (3H, m), 3.89 (3H, s), 4.41 (2H, s), 5.04 (1H, d, J=9.0 Hz), 5.10 (1H, d, J=15.0 Hz), 5.50—5.90 (1H, m), 6.82—6.89 (3H, m). IR ν_{max}^{neat} cm^{-1}: 1715. MS m/z (relative intensity): 570 (M^+, 0.7), 442 (0.5), 232 (12), 193 (12), 180 (23), 151 (100). Exact MS m/z Calcd for $C_{29}H_{47}O_9P$ (M^+): 570.29571. Found: 570.29603.

(3*R*,4*S*,5*S*,6*R*,8*R*)-6-[2-(3,4-Dimethoxybenzyloxy)ethyl]-10-(dimethoxyphosphono)-4,8-dimethyl-3,5-isopropylidenedioxy-9-oxodecanoic Acid (3)——A solution of **16** (95 mg, 0.16 mmol) in acetone, 10% aqueous $NaHCO_3$ (0.2 ml) and a solution of $KMnO_4$ (5 mg, 0.03 mmol) in H_2O (0.2 ml) were added successively to a stirred aqueous solution (5 ml) of $NaIO_4$ (340 mg, 1.6 mmol) at room temperature. After 5 h, the reaction mixture was filtered, then the filtrate was mixed with saturated NH_4Cl solution (10 ml), and the mixture was extracted with CH_2Cl_2. The extract was washed with aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave **3** as a colorless viscous oil (82 mg, 83%). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=7.0 Hz), 1.06 (3H, d, J=7.0 Hz), 1.10—2.00 (6H, m), 1.39 (3H, s), 1.44 (3H, s), 2.37 (1H, dd, J=16.0, 5.0 Hz), 2.58 (1H, dd, J=16.0, 8.0 Hz), 2.80—3.20 (1H, m), 3.14 (2H, d, J=22.0 Hz), 3.47 (2H, t, J=6.0 Hz), 3.72 (3H, d, J=1.0 Hz), 3.83 (3H, d, J=1.0 Hz), 3.85—4.00 (1H, m), 3.88 (3H, s), 3.89 (3H, s), 4.20—4.40 (1H, m), 4.41 (2H, s), 6.85 (3H, s). IR ν_{max}^{neat} cm^{-1}: 1720, 1710. $[\alpha]_D^{26.5}$ −5.6° (c=1.4, $CHCl_3$).

1(*R*)-Ethyl-5-formyl-2(*R*)-(4-methoxybenzyl)oxymethyl-3(*Z*)-pentenyl (3*R*,4*S*,5*S*,6*R*,8*R*)-6-[2-(3,4-Dimethoxybenzyl)oxyethyl]-10-(dimethoxyphosphono)-4,8-dimethyl-3,5-isopropylidenedioxy-9-oxodecanoate (17)——2,4,6-Trichlorobenzoyl chloride (10 μl, 0.06 mmol) was added dropwise to a stirred THF solution (0.5 ml) of **3** (35 mg, 0.059 mmol) and Et_3N (10 μl, 0.07 mmol) at room temperature under argon. After 20 min, the precipitates were filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in benzene (1 ml) and added dropwise to a stirred benzene solution (0.5 ml) of **2** (25 mg, 0.086 mmol) and DMAP (9 mg, 0.07 mmol) at room temperature. After 1 h, the reaction mixture was washed with brine and 10% $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and evaporated to leave an oil, which was subjected to silica gel preparative thin layer chromatography (TLC) with EtOAc–hexane (2 : 1) to give **17** as a colorless oil (34.1 mg, 66%). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=7.0 Hz), 0.86 (3H, t, J=7.5 Hz), 1.06 (3H, d, J=7.0 Hz), 1.10—2.00 (8H, m), 1.36 (3H, s), 1.41 (3H, s), 1.78 (3H, s), 2.21 (1H, dd, J=15.0, 4.0 Hz), 2.51 (1H, dd, J=15.0, 9.0 Hz), 2.85—3.25 (2H, m), 3.13 (2H, d, J=22.0 Hz), 3.38—3.60 (4H, m), 3.63—4.05 (2H, m), 3.74 (3H, d, J=1.0 Hz), 3.80 (6H, s), 3.87 (3H, s), 3.88 (3H, s), 4.32—4.45 (4H, m), 5.21 (1H, m), 6.45 (1H, d, J=10.0 Hz), 6.80—6.95 (5H, m), 7.20 (2H, d, J=9.0 Hz), 9.44 (1H, s). MS m/z (relative intensity): 741 (M^+ − 121, 0.9), 683 (1.5), 363 (2.0), 345 (3.3), 263 (10), 232 (15), 180 (22), 151 (100). Exact MS m/z Calcd for $C_{34}H_{52}O_{12}P$ (M^+ − 179): 683.31956. Found: 683.32219. IR ν_{max}^{neat} cm^{-1}: 1735, 1710, 1690. $[\alpha]_D^{26}$ +2.8° (c=1.3, $CHCl_3$).

6″-Dihydro-6″-*O*-(3,4-dimethoxybenzyl)-3,5-*O*-isopropylidene-14′-*O*-(4-methoxybenzyl)tylonolide (18)——A toluene solution (5 ml) of **17** (34.1 mg, 0.039 mmol) was added very slowly to a stirred suspension of K_2CO_3 (33 mg, 0.24 mmol) in toluene (50 ml) in the presence of 18-crown-6 (125 mg, 0.47 mmol) at 100 °C during 1 h, and stirring was continued at the same temperature for 20 h. After cooling to room temperature, the reaction mixture was mixed with saturated NH_4Cl solution and extracted with ether. The extract was washed with saturated KCl solution several times, dried over Na_2SO_4, and evaporated to leave an oil, which was purified by silica gel preparative TLC with EtOAc–hexane (1 : 2) to give **18** as a colorless oil (17.2 mg, 59%). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=7.0 Hz), 1.10—2.20 (8H, m), 1.13 (3H, d, J=6.5 Hz), 1.38 (3H, s), 1.43 (3H, s), 1.82 (3H, s), 2.34 (2H, t, J=5.0 Hz), 2.80—3.10 (3H, m), 3.40 (2H, t, J=6.5 Hz), 3.46 (2H, d, J=5.0 Hz), 3.81 (3H, s), 3.90 (3H, s), 3.90—4.20 (2H, m), 4.35—4.50 (4H, m), 4.99 (1H, dt, J=4.0, 7.5 Hz), 5.81 (1H, d, J=11.0 Hz), 6.17 (1H, d, J=16.0 Hz), 6.80—6.95 (5H, m), 7.17 (1H, d, J=16.0 Hz), 7.20 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 736 (M^+, 0.55), 600 (0.5),

585 (0.9), 512 (0.95), 376 (3.0), 165 (13), 151 (87), 121 (100). Exact MS *m/z* Calcd for $C_{34}H_{49}O_8$ ($M^+ - 151$): 585.34268. Found: 585.33994. FD-MS *m/z* (relative intensity): 736 (M^+, 100).

6''-Dihydro-3,5-*O*-isopropylidene-14'-*O*-(4-methoxybenzyl)tylonolide (19)——A 4% benzene solution on DDQ (77 μl, 3.1 mg, 0.014 mmol) was added to a stirred ice-cold solution of **18** (10.0 mg, 0.0136 mmol) in CH_2Cl_2 (1.0 ml) and H_2O (0.05 ml), and stirring was continued for 3 h at 0—5 °C. The reaction mixture was poured into aqueous $NaHCO_3$, then the organic layer was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was purified by silica gel TLC with EtOAc–hexane (1 : 1) to give **19** as a colorless oil (6.0 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=7.0 Hz), 0.89 (3H, t, J=7.0 Hz), 1.10—2.00 (8H, m), 1.18 (3H, d, J=6.5 Hz), 1.40 (3H, s), 1.45 (3H, s), 1.82 (3H, s), 2.34 (2H, t, J=6.5 Hz), 2.80—3.03 (3H, m), 3.40—3.80 (2H, m), 3.46 (2H, d, J=5.0 Hz), 3.81 (3H, s), 3.93 (1H, br s), 4.05 (1H, t, J=3 Hz), 4.20 (1H, m), 4.41 (2H, ABq, J=10.0 Hz), 5.01 (1H, dt, J=4.0, 7.5 Hz), 5.83 (1H, d, J=10.5 Hz), 6.21 (1H, d, J=16.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.15 (1H, d, J=16.0 Hz), 7.23 (2H, d, J=9.0 Hz). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720, 1680. MS *m/z* (relative intensity): 586 (M^+, 0.7), 528 (0.8), 450 (4.3), 392 (2.3), 135 (16), 121 (100). Exact MS *m/z* Calcd for $C_{34}H_{50}O_8$ (M^+): 586.35051. Found: 586.34885.

14'-*O*-(4-Methoxybenzyl)tylonolide Hemiacetal (20)——A CH_2Cl_2 solution (2 ml) of **19** (8.3 mg, 0.014 mmol) and PDC (30 mg, 0.08 mmol) was stirred at room temperature for 6 h. The reaction mixture was directly chromatographed on a silica gel column with ether to give 14'-*O*-(4-methoxybenzyl)-3,5-*O*-isopropylidenetylonolide as a colorless oil (7.5 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=6.5 Hz), 1.36 (3H, s), 1.43 (3H, s), 1.81 (3H, d, J=1.0 Hz), 2.70—3.10 (4H, m), 3.46 (2H, d, J=5.0 Hz), 3.81 (3H, s), 3.85—4.15 (2H, m), 4.41 (2H, s), 5.04 (1H, dt, J=4.0, 7.5 Hz), 5.85 (1H, d, J=10.5 Hz), 6.17 (1H, d, J=16.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.17 (1H, d, J=16.0 Hz), 7.25 (2H, d, J=9.0 Hz), 9.64 (1H, t, J=2.0 Hz). MS *m/z* (relative intensity): 584 (M^+, 0.4), 448 (2.0), 135 (17), 121 (100). Exact MS *m/z* Calcd for $C_{34}H_{48}O_8$ (M^+): 584.33486. Found: 584.33424.

This oil was dissolved in THF (2 ml) and 0.5 N HCl (0.5 ml) and stirred for 1 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 1) to give **20** as a colorless oil (5.6 mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7.5 Hz), 0.97 (3H, t, J=7.0 Hz), 1.10—2.25 (9H, m), 1.23 (3H, d, J=7.0 Hz), 1.80 (3H, d, J=1.0 Hz), 2.27—2.70 (2H, m), 2.75—3.12 (1H, m), 3.49 (2H, d, J=5.0 Hz), 3.60 (1H, d, J=10.5 Hz), 3.77—3.90 (1H, m), 3.81 (3H, s), 4.12 (1H, dd, J=10.0, 4.0 Hz), 4.44 (2H, s), 4.93 (1H, dt, J=2.0, 10.0 Hz), 5.35—5.60 (1H, m), 5.80 (1H, d, J=10.5 Hz), 6.33 (0.8H, d, J=16.0 Hz), 6.37 (0.2H, d, J=16.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.22 (2H, d, J=9.0 Hz), 7.23 (1H, d, J=16.0 Hz). MS *m/z* (relative intensity): 526 (M^+, 0.5), 508 (0.5), 405 (2.8), 387 (2.0), 207 (2.9), 135 (11), 121 (100). Exact MS *m/z* Calcd for $C_{31}H_{42}O_7$ (M^+): 526.29930. Found: 526.29386.

Tylonolide Hemiacetal (1)——A solution of **20** (5.6 mg, 0.010 mmol) and DDQ (3.5 mg, 0.015 mmol) in CH_2Cl_2 (1 ml) and H_2O (0.05 ml) was stirred at room temperature for 6 h, then poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to silica TLC with EtOAc–hexane (2 : 1) to give **1** as a colorless solid (3.0 mg, 70%), mp 103 °C. ^{1}H-NMR ($CDCl_3$) δ (500 MHz): 0.95 (3H, t, J=7 Hz, C-17), 1.02 (3H, d, J=7 Hz, C-8'), 1.05 (1H, ddd, J=4, 12, 16 Hz, C-7), 1.23 (3H, d, J=7 Hz, C-4'), 1.60—1.73 (3H, m, C-7(1H), C-16(2H)), 1.55 (1H, dq, J=7, 10 Hz, C-4), 1.80—1.95 (1H, m, C-6'), 1.80 (3H, s, C-12'), 1.94 (1H, dd, J=2, 17 Hz, C-2), 2.01—2.07 (1H, m, C-6), 2.19 (0.23H, dd, J=6, 13 Hz, C-6'), 2.27 (0.77H, dd, J=6, 13 Hz, C-6'), 2.45—2.65 (1H, m, C-8), 2.57 (1H, dd, J=11, 17 Hz, C-2), 2.88 (1H, ddt, J=5, 6, 10 Hz, C-14), 3.67 (1H, dd, J=2, 11 Hz, C-3), 3.68—3.77 (2H, m, C-14'), 3.80 (0.23H, dd, J=4, 10 Hz, C-5), 4.12 (0.77H, dd, J=4, 10 Hz, C-5), 4.93 (1H, dt, J=2.10 Hz, C-15), 5.42 (0.23H, d, J=6 Hz, C-6''), 5.50 (0.77H, dd, J=4, 6 Hz, C-6''), 5.80 (1H, d, J=10 Hz, C-13), 6.33 (0.77H, d, J=15 Hz, C-10), 6.37 (0.23H, d, J=15 Hz, C-10), 7.22 (1H, d, J=15 Hz, C-11). MS *m/z* (relative intensity): 424 (M^+, 2), 406 (17), 393 (12), 388 (12), 191 (39), 121 (100). Exact MS *m/z* Calcd for $C_{23}H_{36}O_7$ (M^+): 424.24605. Found: 424.24538.

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References and Notes

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18) The *E,Z*-configuration was determined from the chemical shifts in the NMR spectra (*E*, 6.83; *Z*, 6.73).
19) The di-DMPM product was also obtained in 14% yield, but its secondary DMPM group, not the primary one, was selectively deprotected by the treatment with DDQ at $-20\,^{\circ}C$[6] to give **13** in 70% yield. Therefore, the combined yield of **13** was *ca.* 80%.
20) Other reducing agents gave only unsatisfactory results. The reduction with $LiAlH_4$ or $(iso\text{-}Bu)_2AlH$ (DIBAH) was incomplete due to formation of insoluble precipitates. Because of their fairly strong basicity, $NaBH_4$ and $NaAlH_2(OC_2H_4OCH_3)_2$ (Red-Al) brought about epimerization of the C-8 methyl group.
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30) The synthetic tylonolide (**1**) was a 3.3:1 isomeric mixture with respect to the hemiacetal position. Tylonolide derived from natural tylosin by Grieco's method A[29a] was a 6:1 mixture (fine needles, mp 155—156 °C, after three recrystallizations from acetone–ether–hexane; lit.[29a] mp 102.5—103.5 °C or 157.5—158.5 °C). When its $CDCl_3$ solution was allowed to stand in an NMR tube at room temperature, isomerization (probably catalyzed by a trace of acid in the solvent) occurred to give a 3:1 mixture.