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Highly Stereoselective Total Synthesis of Tylonolide, the Aglycon of the 16-Membered Macrolide Antibiotic Tylosin. I. Construction of the C-1—C-8 Chiral Centers[1,2]

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In order to synthesize tylonolide, the aglycon of the 16-membered macrolide antibiotic tylosin, a Prelog–Djerassi lactone-type compound (**4**) corresponding to the C-1—C-9 segment was synthesized from D-glucose. Benzyl-type protecting groups for hydroxy functions, such as benzyl, 4-methoxybenzyl, and 3,4-dimethoxybenzyl groups, as well as some cyclic and acyclic stereocontrolled reactions, such as hydroboration, catalytic hydrogenation, and Grignard reaction, were successfully employed.

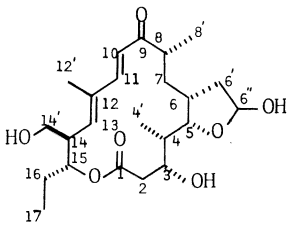
Keywords——macrolide antibiotic; tylosin; aglycon; tylonolide; chiral synthon; protecting group; acyclic stereocontrol; hydroboration; catalytic hydrogenation; Grignard reaction

In connection with our continuing interest in the area of chiral syntheses of complex polyketide-derived natural products such as macrolide and polyether ionophore antibiotics, we have extended our studies to the synthesis of tylonolide (**1**), the aglycon of a typical 16-membered ring macrolide antibiotic, tylosin, which has attracted much attention as a target molecule in current synthetic organic chemistry and is also an important therapeutic agent.[3]

In the preceding papers,[1,4] we reported a highly stereoselective synthesis of methynolide, the aglycon of the 12-membered macrolide antibiotic methymycin, from D-glucose through a synthetic methodology consisting of various means of stereochemical control in acyclic systems, selective use of suitable protecting groups, and efficient macrocyclization. This methodology was expected to be applicable for the synthesis of more complex macrolide and polyether antibiotics, and tylonolide (**1**)[5] was chosen as the next synthetic target in order to confirm its versatility. There are four precedents for the total synthesis of **1**, though the stereocontrol was quite unsatisfactory.[5] For the purpose of a highly stereoselective synthesis of **1** by our methodology, two segments i (**2**) and ii (**3**),[6] in which 4-methoxybenzyl (MPM)[7a,c] and 3,4-dimethoxybenzyl (DMPM)[7b,c] groups were used, respectively, for the protection of primary alcohols, seemed to be most suitable as intermediates.[8] In the present paper, we report the synthesis of a Prelog–Djerassi lactone-type compound (**4**) with all the chiral centers required for segment ii (**3**) from D-glucose, and in the subsequent paper, the synthesis of the two segments and tylonolide (**1**) itself will be reported.

Results and Discussion

Segment ii (**3**) has four contiguous chiral centers at C-3—C-6 and one isolated center at C-8. Since the configuration at C-4—C-8 is identical to that at C-2—C-6 of methynolide, the methodology employed in the synthesis of segment ii of methynolide[1,4] was directly applicable to the synthesis of **3**, which has only two differences, a protected hydroxyethyl group at C-6



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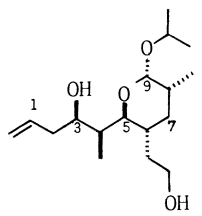

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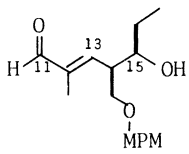
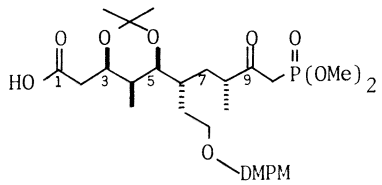


segment i

2



segment ii

3

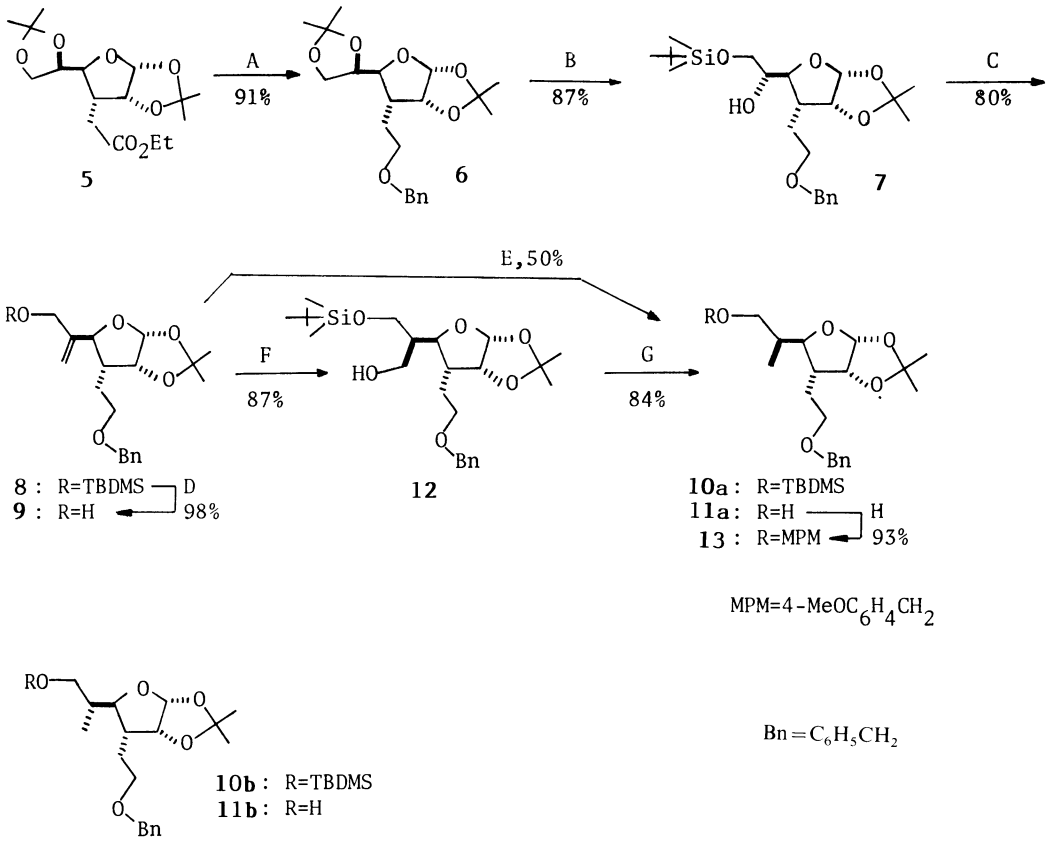
Chart 1

instead of a methyl group and an additional chiral center at C-3.

The known ester (**5**),[9] easily synthesized from D-glucose, was converted to **6** by lithium aluminum hydride (LAH) reduction followed by benzylation. The 5,6-acetonide[10] of **6** was selectively hydrolyzed with dilute sulfuric acid, and the primary alcohol of the resulting diol was selectively protected with the *tert*-butyldimethylsilyl (TBDMS) group under usual conditions to give the alcohol (**7**), which was subjected to Swern oxidation followed by Wittig reaction with a ylide prepared from methyltriphenylphosphonium bromide and *n*-butyllithium to give the olefin (**8**) in high yield.

Catalytic reduction of **8** over various catalysts, 5% platinum on carbon (Pt–C), 5% rhodium on alumina (Rh–Al_2O_3), and Wilkinson's catalyst [$(Ph_3P)_3RhCl$], gave mainly the expected product (**10a**), though the selectivity between **10a** and its isomer (**10b**) was always only about 3 : 1. The silyl protection of **8** was removed, and the resulting alcohol (**9**) was also hydrogenated, but no improvement was observed.[11] Therefore, a route *via* hydroboration was next examined. When **8** was treated with diborane in tetrahydrofuran and then with alkaline hydrogen peroxide, an acyclic stereocontrolled hydroboration[12] occurred smoothly and **12** was obtained in 92% yield[13] with 10 : 1 selectivity. The hydroboration at −30 °C gave a better result, with 87% yield and 16 : 1 selectivity. The alcohol (**12**) was tosylated, followed by LAH reduction to give **11a** in high yield. The primary alcohol of **11a** was then protected with MPM[8a,c] to give **13**. Thus the three contiguous chiral centers at C-4—C-6 of **1** were highly stereoselectively constructed.

The fourth chiral center at C-8 of **1** was introduced by the catalytic reduction of the unsaturated lactolide (**16**) as follows. The isopropylidene protection of **13** was removed with a rather strong acid, and the resulting diol was cleaved with sodium periodate to give the aldehyde (**14**), which was treated with a Wittig–Horner reagent based on trimethyl 1-phosphonopropionate[15] at −90 °C followed by treatment of the resulting (*Z*)-unsaturated ester with potassium carbonate in methanol to yield the cyclic α,β-unsaturated lactone (**15**). Although a so-called Prelog–Djerassi lactone-type compound was expected to be formed by the catalytic reduction of **15**, in order to increase the selectivity of the reduction, **15** was first

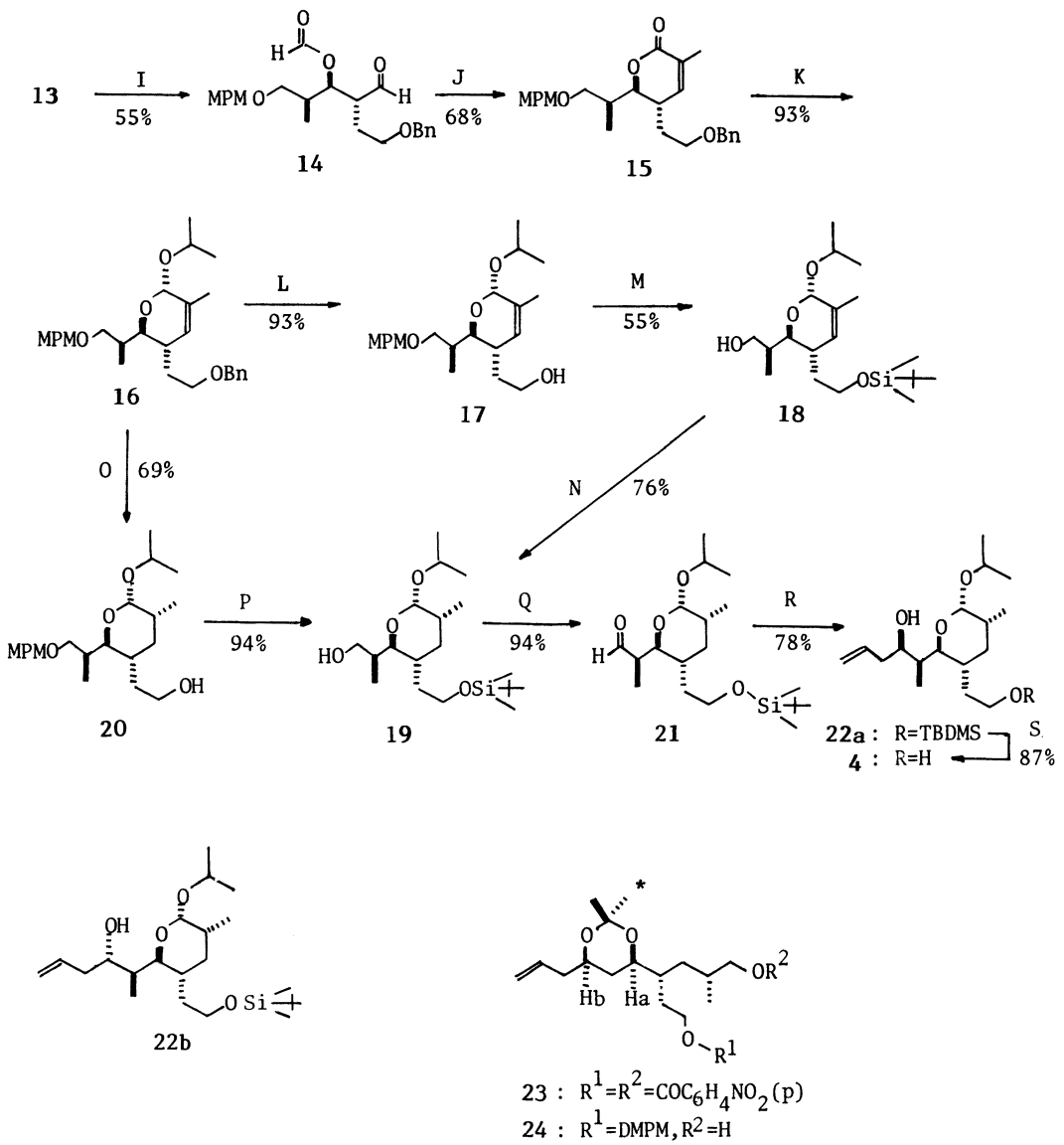


(A) 1) $LiAlH_4$, Et_2O–THF; 2) NaH, THF–DMSO, BnCl (B) 1) 2% H_2SO_4, MeOH; 2) TBDMSCl, imidazole, CH_2Cl_2, 0 °C (C) 1) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −70→0 °C; 2) $Ph_3P^+Me \cdot Br^-$, *n*-BuLi, THF (D) 2 N HCl, MeOH (E) Pt–C, H_2, benzene (F) B_2H_6, THF, −70→−5 °C, H_2O_2, NaOH (G) 1) TsCl, pyridine, 0 °C; 2) $LiAlH_4$, Et_2O (H) NaH, DMF–THF, MPMCl

Chart 2

converted to **16** and then subjected to the reduction. Treatment of **15** with diisobutylaluminum hydride (DIBAH) and then with camphorsulfonic acid (CSA) in isopropanol gave the anomerically pure α-lactolide (**16**) in excellent yield.[4a,16] After careful examination of various catalysts and conditions, the expected reduction product (**19**) was obtained by means of the following four-step conversion from **16**: selective removal of the benzyl protection by catalytic hydrogenation with Raney nickel (Ni)-W2 catalyst,[8c,17] TBDMS protection of the resulting alcohol (**17**), deprotection of the MPM group to give **18**,[4a] and reduction of the double bond of **18** over 5% Rh–Al_2O_3. The stereoselectivity of the reduction was 6.5 : 1.[18] However, when **16** was hydrogenated over more active Raney Ni-W4 catalyst, both the removal of the benzyl protection and the reduction of the double bond occurred simultaneously to give **20** with 6.7 : 1 selectivity. Conversion from **20** into **19** in the usual way proceeded in excellent yield.

The final chiral center at the C-3 of **1** was constructed by the Cram addition of a Grignard reagent[19] to the aldehyde (**21**), which was readily obtained from **19** by Swern oxidation. When **21** was treated with allylmagnesium bromide in ether at −90 °C, a diastereomeric mixture (6.7 : 1) of **22a** and **22b** mainly containing the Cram adduct (**22a**) was isolated in high yield.[20] After examination of several metal reagents under various conditions,



(I) 1) 4N H_2SO_4, dioxane, 65 °C; 2) $NaIO_4$, MeOH–H_2O (J) 1) $MeO_2CCHMePO(OMe)_2$, NaH, THF, −90→−10 °C; 2) K_2CO_3, MeOH (K) 1) DIBAH, toluene, −80 °C; 2) CSA, iso-PrOH (L) Raney Ni (W-2), H_2, EtOH (M) 1) TBDMSCl, imidazole, CH_2Cl_2; 2) DDQ, CH_2Cl_2, H_2O, iso-PrOH (N) Rh–Al_2O_3, H_2, 0 °C (O) Raney Ni (W-4), H_2, EtOH (P) 1) TBDMSCl, imidazole, CH_2Cl_2; 2) Pd–C, H_2, EtOAc or DDQ, CH_2Cl_2–H_2O (Q) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −80 °C→room temperature (R) $CrCl_2$, $LiAlH_4$, THF, $CH_2=CHCH_2I$ (S) *n*-Bu_4NF, THF

Chart 3

the stereoselectivity was found to be slightly improved (10 : 1) by reaction with allyl iodide in the presence of chromous chloride.[21] Removal of the TBDMS protection followed by chromatographic purification gave the expected product (**4**), whose structure was confirmed after its conversion to **23** *via* **24**.[22] In the nuclear magnetic resonance (NMR) spectrum of **23**, nuclear Overhauser enhancements (NOE) were observed between the axial methyl group

TABLE I. Grignard-Type Reactions of the Aldehyde (**21**)

Reagents	Solvent	Temperature (°C)	Product	
			22a : **22b**	Yield (%)
$CH_2=CH-CH_2-MgBr$	Et_2O	−90	6.7 : 1	90
$CH_2=CH-CH_2-MgBr$, CuI	Et_2O	−20	4 : 1	99
$CH_2=CH-CH_2-Li$	THF	−90	9 : 1	67
$CH_2=CH-CH_2-I$, $CrCl_2$	THF	0	10 : 1	78

(δ 1.33) (marked*) of the isopropylidene protecting group and either Ha (δ 3.61, 13%) or Hb (δ 3.81, 14%). All the chiral centers required for segment ii (**3**) were thus constructed from D-glucose. The total synthesis of tylonolide (**1**) using **4** as a chiral intermediate will be described in an accompanying paper.[23]

Experimental

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

3-*C*-(2-Benzyloxyethyl)-3-deoxy-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (6)——A tetrahydrofuran (THF) solution (250 ml) of **5** (40.4 g, 0.122 mol) was added dropwise to a stirred ice-cold ether solution (250 ml) of LAH (4.63 g, 0.122 mol) under an argon atmosphere. The reaction mixture was allowed to warm to room temperature, and stirring was continued overnight. The mixture was cooled again in an ice bath, and excess LAH was decomposed by the addition of MeOH (12 ml), then H_2O (5 ml), 15% NaOH (5 ml), and H_2O (5 ml). Precipitated inorganic salts were filtered off, and the filtrate was evaporated to leave a colorless oil (32.6 g), which was dissolved in THF (100 ml) and added dropwise under argon to a stirred dimethylsulfoxide (DMSO) solution (60 ml) of NaH (3.0 g, 0.125 mol). After evolution of hydrogen had ceased, $PhCH_2Cl$ (17.2 g, 0.136 mol) was added dropwise, and stirring was continued for an additional 4 h at room temperature. The reaction mixture was poured into chilled aqueous NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) as the eluent to give **6** as a colorless oil (42.1 g, 91%). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.35 (3H, s), 1.40 (3H, s), 1.49 (3H, s), 1.70—2.25 (3H, m), 3.40—3.90 (6H, m), 4.53 (2H, s), 4.60 (1H, t, J=3.5 Hz), 5.72 (1H, d, J=3.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 378 (M^+, 0.7), 363 (3.1), 277 (2.4), 219 (3.3), 219 (3.3), 91 (100). Exact MS m/z Calcd for $C_{16}H_{21}O_4$ (M^+-101): 277.14395. Found: 271.14358. $[\alpha]_D^{24}+54.6°$ (c=1.0, $CHCl_3$).

3-*C*-(2-Benzyloxyethyl)-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (7)——A stirred ice-cold MeOH solution (300 ml) of **6** (42.1 g, 0.111 mol) was treated with 2% H_2SO_4 (50 ml), and the solution was stirred for 40 h at room temperature. After neutralization with $NaHCO_3$, the reaction mixture was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated to leave an oil (34.6 g, 0.102 mol), which was dissolved in CH_2Cl_2 (200 ml) containing imidazole (15 g, 0.224 mol). The solution was cooled in an ice-bath, and a CH_2Cl_2 solution (50 ml) of TBDMS chloride (15.7 g, 0.104 mol) was added dropwise. After 3 h, the reaction mixture 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 (4 : 1) as the eluent to give **7** as a colorless oil (39.8 g, 87%). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 1.30 (3H, s), 1.49 (3H, s), 1.70—2.25 (3H, m), 2.61 (1H, d, J=4.0 Hz), 3.40—3.90 (6H, m), 4.53 (2H, s), 4.60 (1H, t, J=3.5 Hz), 5.72 (1H, d, J=3.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 452 (M^+, 0.2), 437 (0.6), 347 (3.1), 239 (7.6), 91 (100). Exact MS m/z Calcd for $C_{24}H_{40}O_6Si$ (M^+): 452.25936. Found: 452.25996.

3-*C*-(2-Benzyloxyethyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-methylene-α-D-*ribo*-hexofuranose (8)——A CH_2CH_2 solution (50 ml) of DMSO (12.4 g, 0.159 mol) was slowly added dropwise to a stirred CH_2CH_2 solution (200 ml) of oxalyl chloride (10.6 ml, 0.102 mol) under argon at below −60 °C, and then a CH_2CH_2 solution (120 ml) of **7** (34.7 g, 76.7 mmol) was similarly added at −70 °C. After 2 h at the same temperature, Et_3N (35 ml, 0.25 mol) was added, and the reaction mixture was allowed to warm gradually to 0 °C, then washed with H_2O, cold 0.5 N HCl, cold 2% NaOCl and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave the ketone as an oil (33.0 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.92 (9H, s), 1.32 (3H, s), 1.50 (3H, s), 1.73—2.20 (3H, m), 3.57 (1H, t, J=5.5 Hz), 4.29 (1H, d, J=10.0 Hz), 4.48 (2H, s), 4.57 (2H, s), 4.63 (1H, t, J=4.0 Hz), 5.80 (1H, d, J=3.5 Hz), 7.30 (5H, s). MS m/z (relative intensity): 435 (M^+-15, 0.2), 335 (3.2), 243 (1.8), 237 (4.6), 91 (100).

A 1.6 M hexane solution of *n*-butyllithium (32.5 ml, 52 mmol) was added dropwise to a stirred ice-cold suspension of methyltriphenylphosphonium bromide (23 g, 64 mmol) in THF (200 ml), and stirring was continued for 1 h at

room temperature. The stirred solution was again cooled in an ice bath, and a THF solution (60 ml) of the above ketone (13.0 g, 29 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was poured into cold NH_4Cl solution, 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 (5 : 1) as the eluent to give **8** as a colorless oil (10.9 g, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.91 (9H, s), 1.32 (3H, s), 1.51 (3H, s), 1.59—2.22 (3H, m), 3.59 (2H, t, J=6.0 Hz), 4.21 (2H, s), 4.28 (1H, d, J=11 Hz), 4.51 (2H, s), 4.60 (1H, t, J=4.0 Hz), 5.12 (1H, br s), 5.30 (1H, br s), 5.78 (1H, d, J=3.5 Hz), 7.32 (5H, s), MS m/z (relative intensity): 433 (M^+ − 15, 0.4), 333 (3.8), 241 (2.6), 227 (3.2), 225 (4.2), 143 (34), 91 (100). Exact MS m/z Calcd for $C_{24}H_{37}O_5Si$ (M^+ − 15): 433.24097. Found: 433.23917. $[\alpha]_D^{20}$ +39° (c=1.1, $CHCl_3$).

3-*C*-(2-Benzyloxyethyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-methylene-α-D-*ribo*-hexofuranose (9)——A solution of **8** (10.0 g, 22.3 mmol) in MeOH (50 ml) and 2 N HCl (10 ml) was stirred for 15 min at room temperature. After neutralization with $NaHCO_3$, the solution was evaporated *in vacuo*, and the residue was 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 (3 : 2) as the eluent to give **9** as a colorless oil (7.29 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.52 (3H, s), 1.60—2.26 (3H, m), 3.59 (2H, t, J=6.0 Hz), 4.13 (1H, d, J=10.5 Hz), 4.16 (1H, br s), 4.35 (1H, d, J=10.5 Hz), 4.50 (2H, s), 4.61 (1H, t, J=4.0 Hz), 5.12 (1H, d, J=1.0 Hz), 5.27 (1H, d, J=1.0 Hz), 5.80 (1H, d, J=3.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 334 (M^+, 0.3), 319 (1.1), 229 (1.9), 185 (2.3), 91 (100). Exact MS m/z Calcd for $C_{18}H_{23}O_5$ (M^+ − 15): 319.15452. Found: 319.15305.

3-*C*-(2-Benzyloxyethyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-methyl-β-L-talofuranose (11a)——(a) A benzene solution (300 ml) of **9** (4.5 g, 13.5 mmol) was hydrogenated in the presence of 5% Pt–C (400 mg) at ordinary temperature and pressure. After 3 h, the catalyst was filtered off, and the filtrate was evaporated to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–EtOAc (5 : 1) as the eluent to give two fractions. The first fraction gave 3-*C*-(2-benzyloxyethyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-methyl-α-D-allofuranose (**11b**) as a colorless oil (1.0 g, 23%). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=7.0 Hz), 1.30 (3H, s), 1.49 (3H, s), 1.60—2.25 (4H, m), 2.50 (1H, br s), 3.50—3.92 (5H, m), 4.52 (2H, s), 4.56 (1H, t, J=3.5 Hz), 5.74 (1H, d, J=4.0 Hz), 7.33 (5H, s). MS m/z (relative intensity): 336 (M^+, 0.35), 335 (0.85), 321 (1.9), 277 (2.2), 248 (1.4), 230 (1.2), 219 (2.3), 171 (5), 111 (9), 105 (10), 91 (100). Exact MS m/z Calcd for $C_{18}H_{25}O_5$ (M^+ − 15): 321.17017. Found: 321.17016.

The second fraction gave **11a** as a colorless oil (2.2 g, 50%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7.0 Hz), 1.30 (3H, s), 1.49 (3H, s), 1.50—1.70 (2H, m), 1.71—1.90 (2H, m), 1.91—2.18 (2H, m), 3.61 (2H, dd, J=7.0, 6.0 Hz), 3.65—3.71 (2H, m), 4.01 (1H, dd, J=10.0, 2.0 Hz), 4.53 (2H, s), 4.54 (1H, t, J=4.5 Hz), 5.73 (1H, d, J=4.0 Hz). MS m/z (relative intensity): 336 (M^+, 0.1), 321 (2.2), 277 (1.8), 248 (1.8), 219 (2.2), 91 (100). Exact MS m/z Calcd for $C_{18}H_{25}O_5$ (M^+ − 15): 321.17017. Found: 321.16749. $[\alpha]_D^{20}$ +68 (c=1.5, $CHCl_3$).

(b) A stirred pyridine solution (40 ml) of **12** (13 g, 27.9 mmol) was treated with TsCl (12.0 g, 62.9 mmol) at room temperature. After 18 h, cold water was added. The mixture was stirred for 1 h in an ice bath, then poured into ice-water, and extracted with ether. The ether extract was washed with brine, 10% $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave 3-*C*-(2-benzyloxyethyl)-6-*O*-(*tert*-butyldimethylsilyl)-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-toluenesulfonyloxymethyl-β-L-talofuranose (16.5 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.84 (9H, s), 1.29 (3H, s), 1.46 (3H, s), 1.60—2.20 (4H, m), 2.44 (3H, s), 3.50—3.70 (4H, m), 3.78—4.35 (4H, m), 4.55 (2H, s), 5.62 (1H, d, J=3.5 Hz), 7.20—7.41 (7H, m), 7.78 (2H, d, J=8.5 Hz).

The above tosylate (16.0 g, 25.8 mmol) in ether (100 ml) was added dropwise to a stirred suspension of LAH (5.0 g, 0.132 mol) in anhydrous ether (200 ml) at room temperature. After 4 h, EtOAc was added to decompose excess LAH, then H_2O (5 ml), 15% NaOH (5 ml) and H_2O (15 ml) were added, and stirring was continued for 1 h. Precipitated inorganic salts were filtered off, and the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 2) as eluent to give **11a** as a colorless oil (7.6 g, 88%).

3-*C*-(2-Benzyloxyethyl)-5-*C*-(*tert*-butyldimethylsilyloxy)methyl-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-allofuranose (12)——A 1 M THF solution of B_2H_6 (35 ml) was added dropwise to a stirred THF solution (50 ml) of **8** (15.5 g, 34.6 mmol) at −70 °C, and the reaction mixture was allowed to gradually warm to −5 °C over a period of 6 h. After addition of MeOH to the stirred solution, 15% NaOH (7 ml) and 30% H_2O_2 (6 ml) were added at 0 °C. The reaction mixture was diluted with ether, 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) as the eluent to give **12** as a colorless oil (14.0 g, 87%). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.29 (3H, s), 1.48 (3H, s), 1.70—2.05 (3H, m), 2.06—2.20 (1H, m), 2.77 (1H, dd, J=7.0, 4.5 Hz), 3.61 (2H, t, J=6.0 Hz), 3.72—3.91 (4H, m), 3.97 (1H, dd, J=10.5, 4.0 Hz), 4.53 (2H, s), 4.55 (1H, t, J=4.0 Hz), 5.71 (1H, d, J=3.5 Hz), 7.32 (5H, s). MS m/z (relative intensity): 466 (M^+, 0.1), 451 (0.9), 351 (2.2), 243 (11), 91 (100). Exact MS m/z Calcd for $C_{25}H_{42}O_6Si$ (M^+): 466.2753. Found: 466.2726. $[\alpha]_D^{24}$ +45 (c=1.0, $CHCl_3$).

3-*C*-(2-Benzyloxyethyl)-3,5-dideoxy-1,2-*O*-isopropylidene-6-*O*-(4-methoxybenzyl)-5-*C*-methyl-β-L-talofuranose (13)——A solution of **11a** (12.5 g, 37.2 mmol) in THF (50 ml) was added dropwise to a stirred suspension of NaH (1.34 g, 55.8 mmol) in dimethylformamide (DMF) (30 ml) under argon at room temperature. After 2 h, MPM chloride (6.4 g, 40.9 mmol) was added, and stirring was continued overnight. Then Et_2NH (2 ml) was added at 50 °C. After 3 h, the reaction mixture was cooled, poured into cold aqueous NH_4Cl solution, and extracted with ether. 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 as the eluent to give **13** as a colorless oil (15.7 g, 93%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=7.0 Hz), 1.30 (3H, s), 1.49 (3H, s), 1.60—2.20 (4H, m), 3.39 (1H, dd, J=9.0, 4.0 Hz), 3.50 (1H, dd, J=9.0, 4.0 Hz), 3.58 (2H, t, J=7.0 Hz), 3.79 (3H, s), 3.98 (1H, dd, J=10.5, 2.5 Hz), 4.44 (2H, s), 4.52 (2H, s), 4.53 (1H, t, J=4.0 Hz), 5.71 (1H, d, J=4.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.32 (5H, s). MS *m/z* (relative intensity): 398 (M^+-58, 6.7), 307 (1.1), 289 (1.2), 277 (2.5), 219 (2.5), 121 (100), 91 (74). Exact MS *m/z* Calcd for $C_{24}H_{30}O_5$ (M^+-58): 398.20929. Found: 398.20818. $[\alpha]_D^{22}+35^\circ$ (c=1.2, $CHCl_3$).

(2*R*,3*R*,4*S*)-2-(2-Benzyloxyethyl)-3-formyloxy-5-(4-methoxybenzyloxy)-4-methylpentanal (14)——A solution of **13** (15.7 g, 34.3 mmol) in dioxane (170 ml) and 4 N H_2SO_4 (35 ml) was stirred for 4.5 h at 65 C. After cooling, the reaction mixture was neutralized with $NaHCO_3$ and evaporated *in vacuo*. The residue was extracted with CH_2Cl_2, 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 : 1) as the eluent to give the diol as a colorless oil (9.86 g, 68%). An aqueous solution of $NaIO_4$ (7.3 g, 34 mmol) was added to a sitrred ice-cold MeOH solution (100 ml) of the above diol (6.8 g, 16.3 mmol). After 2 h, the precipitates were filtered off, then the filtrate was concentrated *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 : 5) as the eluent to give **14** as a colorless oil (5.5 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=6.5 Hz), 1.70—2.25 (3H, m), 2.70—3.00 (1H, m), 3.20—3.35 (2H, m), 3.48 (2H, d, J=6.0 Hz), 3.79 (3H, s), 4.36 (2H, s), 4.44 (2H, s), 5.46 (1H, t, J=6.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.30 (5H, s), 8.07 (1H, s), 9.65 (1H, d, J=3.0 Hz). MS *m/z* (relative intensity): 396 (M^+-18, 0.1), 323 (0.2), 305 (0.5), 290 (0.8), 232 (1.5), 187 (2.0), 121 (100), 91 (42). IR ν_{max}^{neat} cm^{-1}: 1725. $[\alpha]_D^{20}+26$ (c=1.2, $CHCl_3$).

(2*Z*,4*S*,5*S*,6*S*)-4-(2-Benzyloxyethyl)-5-hydroxy-2,6-dimethyl-7-(4-methoxybenzyloxy)hept-2-enoic Acid δ-Lactone (15)——A THF solution (10 ml) of trimethyl α-phosphonopropionate (9.4 g, 48 mmol) was added dropwise to a stirred suspension of NaH (576 mg, 24 mmol) in THF (100 ml) under argon at 0 C. After evolution of hydrogen had ceased, the solution was cooled to −90 C, and a THF solution (20 ml) of **14** (5.5 g, 13 mmol) was added dropwise. The reaction mixture was allowed to warm to −10 °C during 5 h, and then aqueous NH_4Cl was added in order to quench the reaction. The whole mixture was extracted with ether, and the extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was dissolved in MeOH (50 ml). This solution was stirred and K_2CO_3 (1.0 g) was added at room temperature, then after 10 h NH_4Cl (1.0 g) was added. The reaction mixture was evaporated *in vacuo*, and the residue was 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 : 4) as the eluent to give **15** as a colorless oil (3.82 g, 68%). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J=7.5 Hz), 1.53—1.70 (1H, m), 1.75—1.90 (1H, m), 1.88 (3H, t, J=2.0 Hz), 2.05—2.22 (1H, m), 2.63—2.83 (1H, m), 3.37 (1H, dd, J=9.5, 6.0 Hz), 3.53 (1H, t, J=9.5 Hz), 3.57 (2H, t, J=5.5 Hz), 3.80 (3H, s), 4.37 (1H, dd, J=10.0, 3.0 Hz), 4.41 (1H, s), 4.42 (1H, s), 4.48 (1H, s), 4.49 (1H, s), 6.49 (1H, q, J=1.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.18—7.39 (7H, m). MS *m/z* (relative intensity): 424 (M^+, 0.8), 333 (5.6), 191 (29), 121 (100). Exact MS *m/z* Calcd for $C_{26}H_{32}O_5$ (M^+): 424.22493. Found: 424.22590. IR ν_{max}^{neat} cm^{-1}: 1710. $[\alpha]_D^{20}+58^\circ$ (c=1.0, $CHCl_3$).

(2*S*,5*S*,6*S*)-2-Benzyloxyethyl-5,6-dihydro-2-isopropyloxy-6-[2-(4-methoxybenzyloxy)-1(*S*)-methylethyl]-3-methyl-2*H*-pyran (16)——A 1 M hexane solution of DIBAH (12 ml) was added to a stirred toluene solution (50 ml) of **15** (4.27 g, 10.1 mmol) under argon at −80 C. After 1 h, MeOH was added to decompose the reagent, and the reaction mixture was allowed to warm to room temperature and then extracted with ether. The ether extract was washed with 0.5 N HCl, 10% $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to leave an oil, which was dissolved in iso-PrOH (20 ml). CSA (100 mg) was added to the above solution, and the mixture was stirred for 1 h at room temperature. After addition of Et_3N, the reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 5) as the eluent to give **16** as a colorless oil (4.40 g, 93%). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=7.0 Hz), 1.15 (3H, d, J=6.0 Hz), 1.18 (3H, d, J=6.5 Hz), 1.30—1.55 (1H, m), 1.60—1.80 (1H, m), 1.67 (3H, s), 2.05—2.22 (1H, m), 2.25—2.55 (1H, m), 3.37 (1H, dd, J=9.0, 7.5 Hz), 3.52 (1H, t, J=9.0 Hz), 3.55 (2H, t, J=6.5 Hz), 3.75 (1H, dd, J=9.0, 2.0 Hz), 3.80 (3H, s), 3.94 (1H, qq, J=6.5, 6.0 Hz), 4.38 (1H, d, J=12.0 Hz), 4.46 (1H, d, J=12.0 Hz), 4.48 (2H, s), 4.77 (1H, s), 5.56 (1H, s), 6.86 (2H, d, J=9.0 Hz), 7.20—7.34 (7H, m). MS *m/z* (relative intensity): 468 (M^+, 0.2), 425 (0.3), 408 (0.8), 347 (0.8), 332 (1.2), 304 (1.3), 287 (24), 229 (10), 223 (10), 121 (100), 91 (73). Exact MS *m/z* Calcd for $C_{29}H_{40}O_5$ (M^+): 468.28753. Found: 468.28745. $[\alpha]_D^{16}+58^\circ$ (c=1.0, $CHCl_3$).

5,6-Dihydro-5(*S*)-(2-hydroxyethyl)-2(*S*)-isopropyloxy-6(*R*)-[2-(4-methoxybenzyloxy)-1(*S*)-methyl-1(*S*)-ethyl]-3-methyl-2*H*-pyran (17)——An EtOH solution (5 ml) of **16** (135 mg, 0.29 mmol) was hydrogenated in the presence of Raney Ni W-2 (2 ml of EtOH suspension) at ordinary temperature and pressure. After 48 h, the catalyst was filtered off, and the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 5—2 : 3) to give the recovered **16** (20.4 mg, 15%) and **17** as a colorless oil (86 mg, 79%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7.0 Hz), 1.16 (3H, d, J=6.0 Hz), 1.19 (3H, d, J=6.5 Hz), 1.30—2.45 (5H, m), 1.69 (3H, s), 3.20—4.10 (6H, m), 4.44 (2H, ABq, J=11 Hz), 4.78 (1H, s), 5.57 (1H, s), 6.86 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz). MS *m/z* (relative intensity): 335 (M^+-43, 0.7), 320 (1.8), 259 (6), 197 (15), 147 (13), 121 (100). Exact MS *m/z*

Calcd for $C_{19}H_{27}O_5$ (M^+-43): 335.18581. Found: 335.18774.

5(*S*)-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-5,6-dihydro-6(*R*)-(2-hydroxy-1(*S*)-methyl-1(*S*)-ethyl)-2(*S*)-isopropyloxy-3-methyl-2*H*-pyran (18)——TBDMS chloride (50 mg, 0.32 mmol) was added to a stirred CH_2Cl_2 solution (2 ml) of **17** (86 mg, 0.23 mmol) and imidazole (50 mg, 0.75 mmol) at room temperature. After 15 min, the reaction mixture was evaporated, and the residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 15) as the eluent to give 5(*S*)-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5,6-dihydro-2(*S*)-isopropyloxy-6(*R*)-[2-(4-methoxybenzyloxy)-1(*S*)-methyl-1(*S*)-ethyl]-3-methyl-2*H*-pyran as a colorless oil (108 mg, 96%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.19 (6H, t, J=7.0 Hz), 1.30—2.45 (4H, m), 1.70 (3H, s), 3.20—3.90 (6H, m), 3.79 (3H, s), 4.43 (2H, s), 4.69 (1H, s), 5.60 (1H, s), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0). MS m/z (relative intensity): 449 (M^+-43, 0.1), 338 (0.9), 311 (6.0), 253 (6.0), 121 (100). Exact MS m/z Calcd for $C_{25}H_{41}O_5Si$ (M^+-43): 449.27228. Found: 449.27157.

DDQ (100 mg, 0.44 mmol) was added to a stirred cold solution of the above TBDMS compound (108 mg, 0.22 mmol) in CH_2Cl_2 (4 ml) containing iso-PrOH (0.2 ml) and H_2O (0.2 ml) in an ice bath. After 25 min, the reaction mixture was poured into 10% $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with 10% $NaHCO_3$, 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 : 10) as the eluent to give **18** as a colorless oil (46 mg, 57%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 0.99 (3H, d, J=7.0 Hz), 1.25 (6H, t, J=7.0 Hz), 1.30—2.45 (5H, m), 1.71 (3H, s), 3.30—4.00 (6H, m), 4.72 (1H, s), 5.30 (1H, s). MS m/z (relative intensity): 313 (M^+-59, 3.2), 297 (1.4), 284 (1.2), 255 (52), 185 (16), 163 (27), 75 (100). Exact MS m/z Calcd for $C_{17}H_{33}O_3Si$ (M^+-59): 313.21985. Found: 313.22087.

5(*R*)-(2-Hydroxyethyl)-2(*S*)-isopropyloxy-6(*S*)-[2-(4-methoxybenzyloxy)-1(*S*)-methyl-1(*S*)-ethyl]-3(*R*)-methyltetrahydropyran (20)——An EtOH solution (10 ml) of **16** (655 mg, 1.40 mmol) was hydrogenated in the presence of Raney Ni W-4 (10 ml of EtOH suspension) at ordinary temperature and pressure for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 3) as the eluent to give **20** as a colorless oil (366 mg, 69%). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz), 1.07 (3H, d, J=6.0 Hz), 1.14 (3H, d, J=6.0 Hz), 1.20—1.82 (7H, m), 2.97 (1H, m), 3.31 (1H, dd, J=9.0, 7.0 Hz), 3.47 (1H, dd, J=9.0, 7.0 Hz), 3.60—3.95 (4H, m), 3.80 (3H, s), 4.37 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.5 Hz), 4.61 (1H, d, J=3.5 Hz), 6.87 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 322 (M^+-58, 0.1), 321 (0.9), 320 (2.7), 275 (1.6), 247 (2.5), 208 (3.0), 199 (15), 137 (18), 121 (100). Exact MS m/z Calcd for $C_{19}H_{28}O_4$ (M^+-60): 320.19872. Found: 320.19872. IR ν_{max}^{neat} cm^{-1}: 3400. $[\alpha]_D^{16}+97°$ (c=1.3, $CHCl_3$).

The 3(*S*)-epimer (61 mg, 11%) was next obtained. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7.0 Hz), 1.03 (3H, d, J=7.5 Hz), 1.10 (3H, d, J=6.0 Hz), 1.16 (3H, d, J=5.5 Hz), 1.20—2.25 (7H, m), 3.20—4.05 (5H, m), 3.80 (3H, s), 4.42 (2H, ABq, J=11.0 Hz), 4.53 (1H, s), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0). MS m/z (relative intensity): 320 (M^+-60, 5), 274 (2), 247 (6.7), 208 (4), 199 (13), 121 (100). Exact MS m/z Calcd for $C_{19}H_{28}O_4$ (M^+-60): 320.19872. Found: 320.19950.

5(*R*)-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-6(*S*)-(2-hydroxy-1(*S*)-methyl-1(*S*)-ethyl)-2(*S*)-isopropyloxy-3(*R*)-methyltetrahydropyran (19)——(a) An ether solution (3 ml) of **18** (39 mg, 0.10 mmol) was hydrogenated in the presence of 5% Rh–Al_2O_3 (18 mg) at 0 °C under ordinary pressure for 5 h. After removal of the catalyst by filtration, the filtrate was evaporated to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 10) to give **19** as a colorless oil (34 mg, 76%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.83 (3H, d, J=7.0 Hz), 0.89 (9H, s), 1.00 (3H, d, J=7.5 Hz), 1.15 (3H, d, J=6.5 Hz), 1.22 (3H, d, J=6.5 Hz), 1.15—1.35 (2H, m), 1.50—2.05 (5H, m), 2.74 (1H, dd, J=9.0, 2.5 Hz), 3.55—3.95 (6H, m), 4.64 (1H, d, J=3.0 Hz). MS m/z (relative intensity): 374 (M^+, 0.3), 315 (7.1), 297 (5.5), 257 (61), 100 (100). Exact MS m/z Calcd for $C_{17}H_{35}O_3Si$ (M^+-59): 315.23550. Found: 315.23511. IR ν_{max}^{neat} cm^{-1}: 3400. $[\alpha]_D^{16}+123.5°$ (c=1.2, $CHCl_3$).

(b) A CH_2Cl_2 solution (100 ml) of **20** (4.3 g, 11.4 mmol), imidazole (1.5 g, 22.4 mmol), and TBDMS chloride (2.1 g, 13.4 mmol) was stirred for 1 h at room temperature. The reaction mixture 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 EtOAc–hexane (1 : 20) to afford the TBDMS ether as a colorless oil (5.64 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.82 (3H, d, J=7 Hz), 0.88 (9H, s), 0.89 (3H, d, J=7 Hz), 1.07 (3H, d, J=6 Hz), 1.14 (3H, d, J=6 Hz), 1.20—2.20 (6H, m), 3.31 (1H, dd, J=9, 7 Hz), 3.47 (1H, dd, J=9, 7 Hz), 3.60—3.95 (4H, m), 3.79 (3H, s), 4.41 (2H, ABq, J=10.5 Hz), 6.86 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz). MS m/z (relative intensity): 435 (M^+-59, 0.1), 434 (0.4), 377 (0.6), 313 (6.2), 181 (5.0), 163 (4.0), 121 (100). Exact MS m/z Calcd for $C_{25}H_{42}O_4Si$ (M^+-60): 434.28519. Found: 434.28250.

An EtOAc solution (70 ml) of the TBDMS ether (5.64 g, 11.4 mmol) was hydrogenated over 10% Pd–C (1.0 g) at ordinary temperature and pressure for 2 d. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 20) to give **19** as a colorless oil (4.05 g, 95%).

(c) DDQ (18 mg, 0.079 mmol) was added to a stirred cold CH_2Cl_2 solution (2 ml) of the above TBDMS ether (23.2 mg, 0.047 mmol) containing H_2O (0.1 ml) in an ice bath. After 1.5 h, the reaction mixture was poured into 10% $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with 10% $NaHCO_3$, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 20) to give **19**

as a colorless oil (16.2 mg, 92%).

2(*R*)-5(*R*)-[2-(*tert*-Butyldimethylsilyl)ethyl]-2(*S*)-isopropyloxy-3(*R*)-methyl-6(*S*)-tetrahydropyranylpropanal (21)——A solution of DMSO (180 mg, 2.31 mmol) in CH_2Cl_2 was added dropwise to a stirred CH_2CH_2 solution (5 ml) of $(COCl)_2$ (190 mg, 1.5 mmol) at −80 C, and then a solution of **19** (277 mg, 0.74 mmol) in CH_2Cl_2 was similarly added. After 1 h, Et_3N (300 mg, 2.97 mmol) was added, and the reaction mixture was allowed to warm gradually to room temperature, then washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave crude **21** as a colorless oil (259 mg, 94%), which was subjected to the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.84 (3H, d, J=7.0 Hz), 0.89 (9H, s), 1.05 (3H, d, J=6.5 Hz), 1.09 (3H, d, J=7.5 Hz), 1.18 (3H, d, J=6.5 Hz), 1.20—1.85 (6H, m), 2.61 (1H, dq, J=1.5, 6.5 Hz), 3.55—3.82 (3H, m), 4.20 (1H, dd, J=10.5, 3.0 Hz), 4.57 (1H, d, J=3.5 Hz), 9.67 (1H, s). IR ν_{max}^{neat} cm^{-1}: 1725.

5(*R*)-[5(*R*)-(2-Hydroxyethyl)-2(*S*)-isopropyloxy-3(*R*)-methyl-6(*S*)-tetrahydropyranyl]-4(*R*)-hydroxy-1-hexane (4)——(a) A stirred 1.4 M ether solution of allylmagnesium bromide (5 ml) was diluted with ether (10 ml) and cooled to −90 C. Next, a solution of **21** (451 mg, 1.21 mmol) in ether was added dropwise, and after 1.5 h, the reaction mixture was allowed to warm gradually to −5 C, then quenched by the dropwise addition of cold saturated NH_4Cl solution, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave a 6.7 : 1 mixture of **22a** and **22b** (450 mg, 90%), which was dissolved in THF (2 ml). To this solution, a 1 M THF solution of *n*-Bu_4NF (1.3 ml) was added. The mixture was stirred overnight at room temperature, and then evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2–Et_2O (15 : 1) to give **4** as a colorless oil (286.5 mg, 87%). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=7.0 Hz), 1.10—1.33 (2H, m), 1.21 (3H, d, J=6.0 Hz), 1.45—1.90 (5H, m), 2.15 (1H, dt, J=15.0, 7.5 Hz), 2.36 (1H, dt, J=15.0, 7.5 Hz), 3.55—4.00 (6H, m), 4.67 (1H, d, J=3.5 Hz), 5.00—5.20 (2H, m), 5.82 (1H, ddt, J=17.0, 10.0, 7.5 Hz). MS m/z (relative intensity): 269 (M^+ − 31, 0.1), 241 (2.5), 223 (5.0), 199 (8.5), 141 (33), 100 (100). Exact MS m/z Calcd for $C_{14}H_{25}O_3$ (M^+ − 59): 241.18034. Found: 241.18112. $[\alpha]_D^{16}$ + 165.5° (c=0.9, $CHCl_3$).

(b) LAH (37 mg, 1.0 mmol) was added in three portions to a stirred suspension of $CrCl_3$ (300 mg, 1.89 mmol) in THF (10 ml) at 0 C. The color of the reaction mixture changed from violet to dark brown. Stirring was continued for 5 min at 0 C and for 20 min at room temperature, then a THF solution (5 ml) of **21** (100 mg, 0.27 mmol) and allyl iodide (136 mg, 0.80 mmol) was added at room temperature with stirring. After 30 min, the reaction mixture was poured into aqueous $NaHCO_3$, and insoluble material was removed by filtration. The filtrate was extracted with CH_2Cl_2. Evaporation of the solvent left a 10 : 1 mixture of **22a** and **22b** (86 mg, 78%), which was converted to **4** as described above.

(4*R*,5*S*,6*S*,7*R*,9*R*)-5,9-Dimethyl-4,6-isopropylidenedioxy-10-(4-nitrobenzoyl)oxy-7-[2-(4-nitrobenzoyl)oxyethyl]-1-decene (23)——DDQ (7.0 mg, 0.031 mmol) was added to a stirred cold solution of **24** (10.7 mg, 0.024 mmol)[23] in CH_2Cl_2 (2 ml) and H_2O (0.1 ml) in an ice bath. After 1 h, the reaction mixture was poured into aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was subjected to silica gel thin layer chromatography (TLC) with EtOAc–hexane (1 : 2) to give (4*R*,5*S*,6*S*,7*R*,9*R*)-5,9-dimethyl-7-(2-hydroxyethyl)-4,6-isopropylidenedioxy-1-decen-10-ol as an oil (6.3 mg, 88%), which was dissolved in CH_2Cl_2 (0.5 ml). To this stirred solution, Et_3N (0.1 ml), 4-dimethylaminopyridine (DMAP; 5 mg), and 4-nitrobenzoyl chloride (30 mg, 0.16 mmol) were added at room temperature. After 4 h, the reaction mixture was worked up in the usual way to give **23** as a colorless oil (13 mg, quantitative). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7.0 Hz), 1.05 (3H, d, J=7.0 Hz), 1.10—1.40 (2H, m), 1.33 (3H, s), 1.36 (3H, s), 1.40—2.20 (5H, m), 2.10 (1H, dt, J=15.0, 7.0 Hz), 2.29 (1H, dt, J=15.0, 7.0 Hz), 3.61 (1H, dd, J=9.5, 1.5 Hz), 3.81 (1H, dt, J=2.0, 7.0 Hz), 4.12 (1H, dd, J=10.5, 7.0 Hz), 4.31 (1H, dd, J=10.5, 6.0 Hz), 4.35—4.55 (2H, m), 5.05 (1H, d, J=8.0 Hz), 5.11 (1H, d, J=15.0 Hz), 5.77 (1H, ddt, J=15.0, 8.0, 7.0 Hz), 8.20 (4H, d, J=9.0 Hz), 8.29 (4H, d, J=9.0 Hz). MS m/z (relative intensity): 583 (M^+, 14), 523 (2.6), 356 (9.0), 332 (5.6), 292 (5.6), 189 (30), 150 (51), 120 (50), 82 (100). Exact MS m/z Calcd for $C_{30}H_{35}N_2O_{10}$ (M^+): 583.22912. Found: 583.22767.

References and Notes

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