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Highly Stereoselective Total Synthesis of Methynolide, the Aglycon of the 12-Membered Macrolide Antibiotic Methymycin. I. Synthesis of a Prelog–Djerassi Lactone-Type Chiral Intermediate from D-Glucose[1,2]

YUJI OIKAWA, TATSUYOSHI TANAKA, KIYOSHI HORITA, ICHIO NODA, NORIYUKI NAKAJIMA, NAOKI KAKUSAWA, TATSUO HAMADA, and OSAMU YONEMITSU*

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

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For the highly stereoselective synthesis of methynolide (**2**), the aglycon of the 12-membered macrolide antibiotic methymycin (**1**), a Prelog–Djerassi lactone-type chiral intermediate (**7a**) bearing four chiral centers corresponding to the C-2, C-3, C-4, and C-6 positions was synthesized from D-glucose. In this synthesis, several stereocontrolled reactions such as hydroboration, catalytic hydrogenation, *etc.* were successfully applied. The utility of the 4-methoxybenzyl protecting group was also demonstrated.

Keywords——macrolide antibiotic; aglycon; methynolide; acyclic stereocontrol; hydroboration; catalytic hydrogenation; protecting group; stereoselective synthesis

Macrolide antibiotics with multiple chiral centers, owing to the presence of many substituents and functional groups, have received much recent synthetic attention because of their significant pharmacological and biological activities.[3] For the total synthesis of such complex compounds, new synthetic methodologies mainly consisting of means of stereochemical control in acyclic systems, selective use of suitable protecting groups, and efficient macro-cyclizations are primarily required.

As part of the synthetic effort directed towards polyketide-derived natural products, macrolide and polyether antibiotics, our attention has recently been focused on the chiral synthesis of some representative antibiotics, methymycin (**1**),[4] pikromycin,[5] erythromycin A,[6] tylosine,[7] iso-lasalocid A,[8] salinomycin,[9] *etc.*, from D-glucose as a chiral starting material.

In order to establish our synthetic methodology, which is widely applicable to the synthesis of complex antibiotics, and mainly consists of some acyclic stereocontrolled reactions and the use of benzyl-type protecting groups,[10] we first planned a highly stereoselective synthesis of methynolide (**2**),[11] the aglycon of the 12-membered macrolide antibiotic methymycin (**1**). Our retrosynthesis of **2**, consisting of two routes, route a *via* the lactonization of the known seco-acid (**3**) and route b *via* the Wittig–Horner reaction of **4**, is shown in Chart 1. Both segment i and segment ii for the synthesis of **3** or **4** were expected to be synthesized from a ulose (**5**). In the present paper, we report stereoselective syntheses of a Prelog–Djerassi lactone-type chiral intermediate (**7a**) from D-glucose *via* **5**.

Results and Discussion

The Prelog–Djerassi lactonic acid (**8**),[12] corresponding to the C-1—C-7 segment of **2**, has

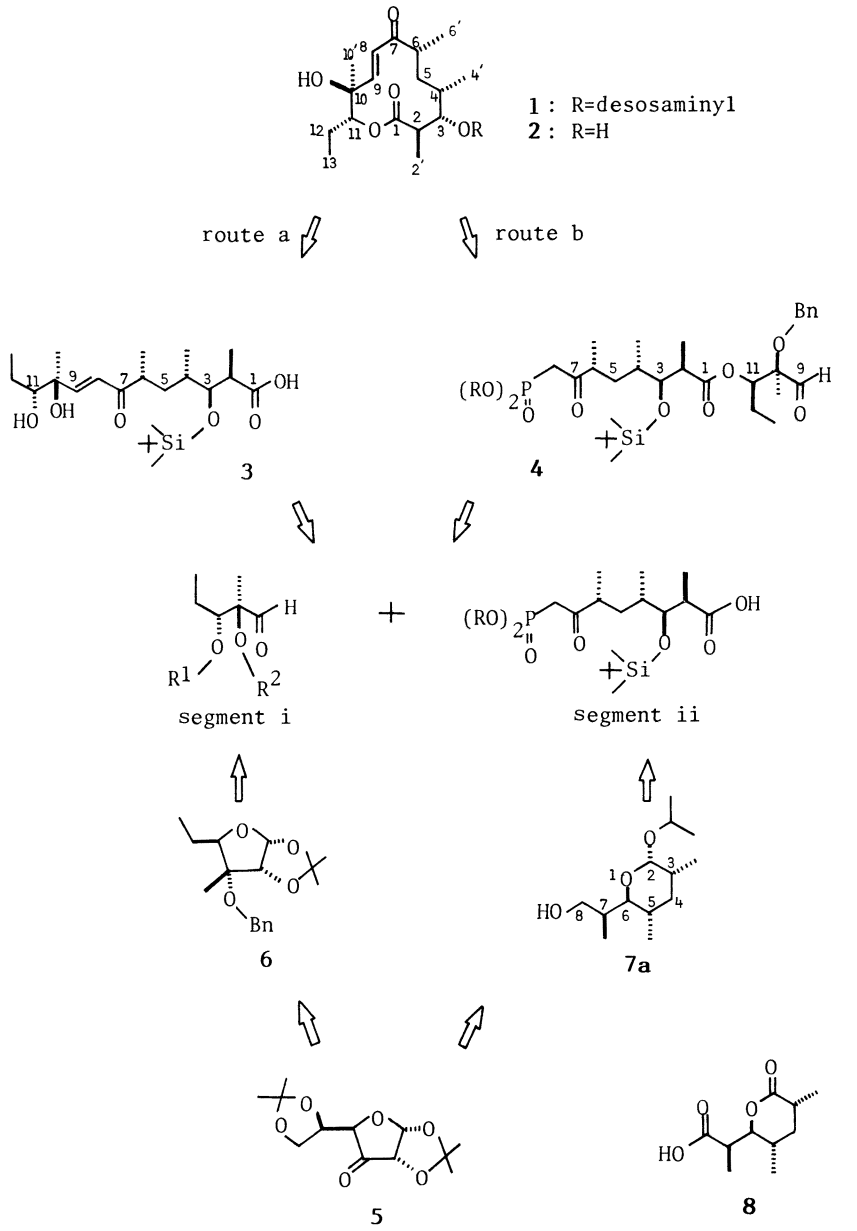
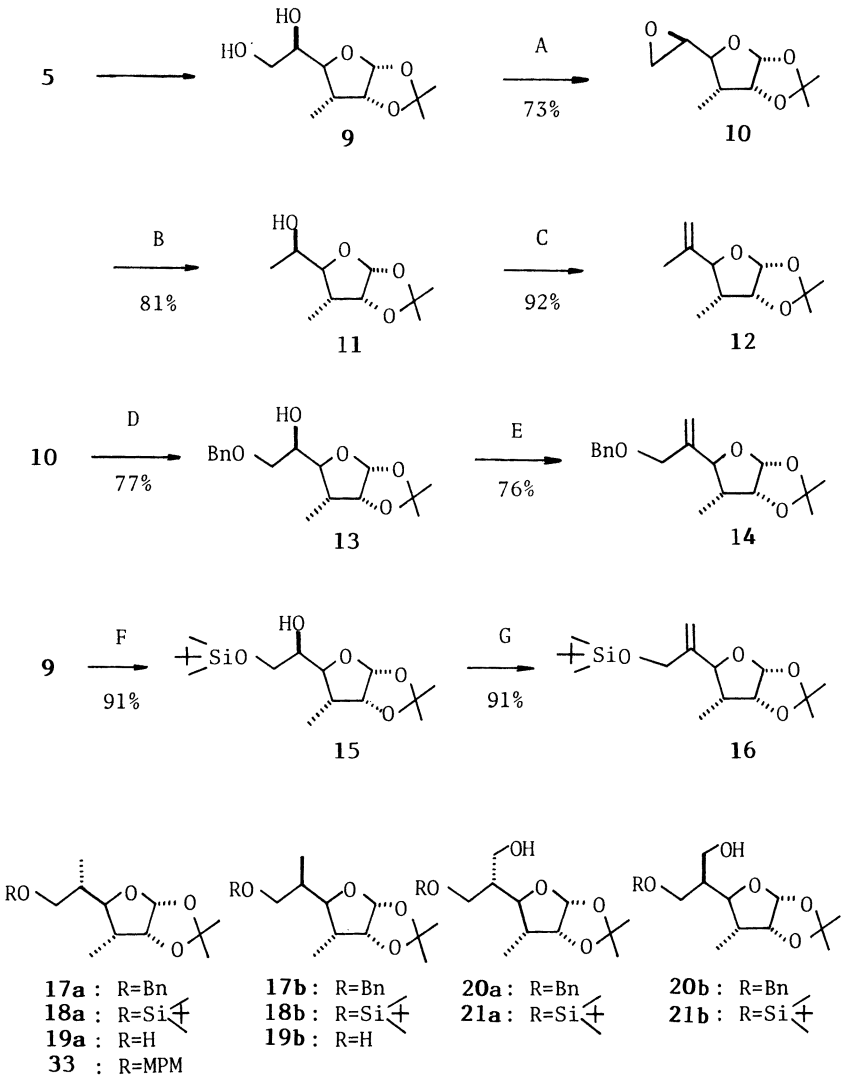


Chart 1

been a key compound for both the structure elucidation of **1** and subsequent synthetic efforts. The title compound (**7a**) is considered to be a more versatile synthetic equivalent of **8**.

For the synthesis of **7a**, we first synthesized the key intermediate (**19a**), with three contiguous chiral centers corresponding to C-2—C-4 of **2**, from D-glucose *via* catalytic reduction or hydroboration of **12**, **14**, or **16** with acyclic stereocontrol (Chart 2). The known diol (**9**),[13] derived from **5**, was converted to the epoxide (**10**) *via* a monotosylate. Reduction with lithium aluminium hydride (LAH) of **10** gave the secondary alcohol (**11**), which was oxidized with pyridinium chlorochromate (PCC) followed by the usual Wittig methylenation to give the olefin (**12**). On the other hand, nucleophilic ring opening of **10** with sodium



(A) 1) TsCl, pyridine; 2) K_2CO_3, MeOH (B) LAH, Et_2O (C) 1) PCC, molecular sieves, CH_2Cl_2; 2) $Ph_3P{=}CH_2$, THF (D) BnONa, DMSO–THF (E) 1) PCC, molecular sieves, CH_2Cl_2; 2) $Ph_3P{=}CH_2$, THF (F) TBDMSCl, imidazole, CH_2Cl_2 (G) 1) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, $-50\,°C$; 2) $Ph_3P^+Me{\cdot}Br^-$, *n*-BuLi, THF, 0 °C

Chart 2

benzyloxide gave the hydroxybenzyl ether (**13**), which was similarly converted to the second olefin (**14**) in reasonable yield. The third olefin (**16**) was also easily synthesized from **9** *via* three conventional reactions, selective *tert*-butyldimethylsilyl (TBDMS) protection of the primary alcohol, Swern oxidation of the secondary alcohol and the final Wittig methylenation.

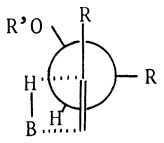
Hydrogenation of **14** over 10% palladium on charcoal (Pd–C) in ethyl acetate (EtOAc) gave a stereoisomeric mixture (1.3 : 1) with a slight excess of the desired isomer (**17a**). The ratio of **17a** and **17b** was improved to 4 : 1 by the use of 5% rhodium on alumina ($Rh–Al_2O_3$) catalyst, though this is still unsatisfactory (Table I). Almost no selectivity was observed in the hydrogenation of **16** over both Pd–C and $Rh–Al_2O_3$ catalysts; a *ca.* 1 : 1 mixture of **18a** and

TABLE I. Catalytic Hydrogenation and Hydroboration Results

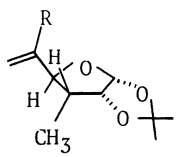
Substrate	Conditions	Product	
		Yield (%)	Ratio
14	10% Pd–C, H_2, EtOAc	**17a, b** (85)	1.3 : 1
14	Rh–Al_2O_3, H_2, EtOH	**17a, b** (100)	4 : 1
12	BH_3, THF	**19a, b** (59)	1 : 6.8
14	BH_3, THF	**20a, b** (82)	24 : 1
16	BH_3, THF	**21a, b** (91)	11 : 1
22	BH_3, THF	**25a, b** (65)	1 : 6.0
23	BH_3, THF	**26a, b** (75)	1 : 1.8
24	BH_3, THF	**27a, b** (69)	1 : 4

18b was obtained. Therefore, we turned our attention to hydroboration.

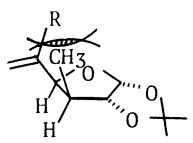
When **12** was treated with diborane, smooth hydroboration occurred to give a 6.8 : 1 mixture of **19b** and **19a**. Unfortunately, the major product was the undesired form. Recently, Still and Barrish[14] and Houk *et al.*[15] discussed transition state structures in the hydroboration of asymmetric allyl alcohol derivatives, and concluded that the conformation with the C–O bond *anti* to the double bond was most favorable, as shown in Chart 3. The result of hydroboration of **12** is consistent with their discussion, namely the *si*-face attack in the M-1 structure (Chrat 3) with diborane was predominant. For the same reason, better stereoselectivities (*re*-face attack of diborane) were obtained in the hydroboration of **14** and **16** to give mainly the desired products, **20a** (96 : 4) and **21a** (92 : 8), respectively (Table I).[16] Compounds **20a** and **21a**, without purification, were readily converted to the key intermediate (**19a**) by means of conventional reactions, tosylation, LAH reduction, *etc.* Benzyl protection of the primary alcohol of **19a** readily gave **17a**.



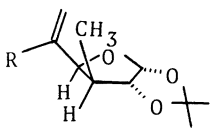
Still's model



M-1



M-2



M-3

12 : R= CH_3
14 : R= CH_2OBn
16 : R= $CH_2OSi\lessdot\!\!+$

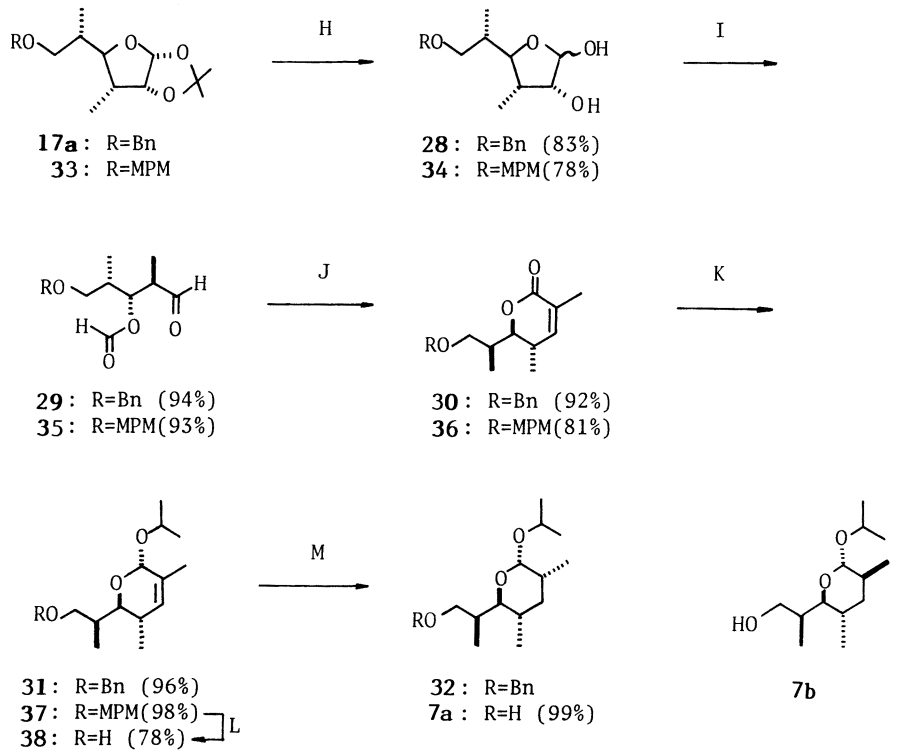
Chart 3

The three contiguous chiral centers corresponding to C-5—C-7 of the title compound (**7a**) [*i.e.*, to C-2—C-4 of **2**] were thus constructed, and the final chiral center at C-3 [C-6 of **2**] was introduced stereoselectively by hydrogenation of α-lactolide derivatives as follows (Chart 4).

The acetonide protection of **17a** was removed with hydrochloric acid and the resultant lactol (**28**) was oxidized with sodium periodate to give the aldehyde (**29**). When **29** was treated with the sodium salt of dimethyl 1-methoxycarbonylethylphosphonate at −90 °C, the Wittig–Horner reaction[17] proceeded quite smoothly to give the (*Z*)-α,β-unsaturated ester (9.6 : 1

stereoselectivity), which, without purification, was converted to the α,β-unsaturated lactone (**30**) by treatment with methanolic potassium carbonate. Catalytic reduction of the double bond of **30** was expected to give a so-called Prelog–Djerassi lactone-type compound, but in order to increase the stereoselectivity of the reduction, **30** was converted to the anomerically pure α-lactolide (**31**) *via* reduction with diisobutylaluminum hydride (DIBAH) followed by isopropyl protection of the resultant lactol.[18]

When **31** was hydrogenated over 10% Pd–C in EtOAc at 0 °C, **32** was obtained in high yield, though the stereoselectivity (6 : 1) was still unsatisfactory. Debenzylation of **32**, without purification, over Raney nickel (Ni) W-2[19] readily gave the title compound (**7a**) after chromatographic purification. When **31** was reduced over Rh–Al_2O_3 in ether, concomitant saturation of the benzyl group was unavoidable. After several examinations of substrates and catalysts in order to increase the stereoselectivity, an excellent result was obtained in the reduction of **38**, which was synthesized from the key intermediate (**19a**) *via* **33**—**37** by a method virtually identical with that described for **31**, forllowed by removal of the 4-methoxybenzyl (MPM) protection of **37** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The deprotection was smoothly carried out by a slight modification of the usual method,[10] namely in the presence of isopropanol, in good yield.[19] Hydrogenation of **38** over Rh–Al_2O_3 in ether gave the desired **7a** with excellent stereoselectivity (25 : 1) in quantitative yield. Compound **7a** has all the chiral centers required for segment ii, whose synthesis will be



17a: R=Bn
33: R=MPM

28: R=Bn (83%)
34: R=MPM(78%)

29: R=Bn (94%)
35: R=MPM(93%)

30: R=Bn (92%)
36: R=MPM(81%)

31: R=Bn (96%)
37: R=MPM(98%)
38: R=H (78%) ⟵ L

32: R=Bn
7a: R=H (99%)

7b

(H) 4N HCl, THF or dioxane, 40—45 °C (I) $NaIO_4$, MeOH–H_2O, 0 °C or $Pb(OAc)_4$, benzene (J) 1) $(MeO)_2POCH(Me)CO_2Me$, NaH, THF, −80→8 °C; 2) K_2CO_3, MeOH (K) 1) DIBAH, toluene, −80 °C; 2) CSA, iso-PrOH (L) DDQ, CH_2Cl_2–H_2O–iso-PrOH (M) a: **31**→**7a**; 1) Pd–C, H_2, EtOAc; 2) Raney Ni (W-2), H_2, EtOH b: **38**→**7a**; Rh–Al_2O_3, H_2, Et_2O

Chart 4

described in the following paper.

Experimental

Unless otherwise noted, physical data were measured as follows. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL FX-200 (200 MHz) or JEOL JNM GX-270 (270 MHz) instrument. Mass spectra (MS) were taken on a JEOL JMS D-300 or JEOL JMS-01 SG spectrometer. Infrared (IR) spectra were recorded on a JASCO IR-2 spectrometer.

5,6-Anhydro-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (10)——*p*-Toluenesulfonyl chloride (TsCl) (4.91 g, 25.7 mmol) was added portionwise to a stirred solution of **9**[13] (5.61 g, 25.7 mmol) in pyridine (36 ml) over a period of 7 h. After an additional 17 h, the reaction mixture was poured into ice-water (150 ml) and extracted with CH_2Cl_2. The extract was washed with 2 N HCl, brine and 5% $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was dissolved in MeOH (120 ml), and treated with K_2CO_3 (4 g) at room temperature for 40 min. The reaction mixture was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. 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 (4 : 1) to afford **10** as a colorless oil (3.78 g, 73.4%). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=7 Hz), 1.33 (3H, s), 1.50 (3H, s), 2.03 (1H, ddq, J=4.5, 10, 7 Hz), 2.68 (1H, dd, J=2.5, 5 Hz), 2.78 (1H, dd, J=4, 5 Hz), 2.92 (1H, ddd, J=2.5, 4, 6 Hz), 3.51 (1H, dd, J=6, 10 Hz), 4.57 (1H, dd, J=3.5, 4.5 Hz), 5.81 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 185 (M^+-15, 50), 157 (10), 99 (20), 59 (56), 43 (100). Exact MS m/z Calcd for $C_9H_{13}O_4$ (M^+-15): 185.0814. Found: 185.0811.

3,6-Dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (11)——A solution of **10** (6.78 g, 33.9 mmol) in Et_2O (17 ml) was added dropwise to a stirred ice-cold suspension of LAH (0.845 g, 22.2 mmol) in Et_2O (63 ml). The mixture was stirred for 5 h at 0 °C and then 1 h at room temperature. Usual work-up gave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (3 : 2) to afford **11** as a colorless oil (5.55 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=7 Hz), 1.21 (3H, d, J=7 Hz), 1.34 (3H, s), 1.52 (3H, s), 1.99 (1H, d, J=4 Hz), 2.10 (1H, ddq, J=5, 10, 7 Hz), 3.80 (1H, dd, J=3, 10 Hz), 4.20 (1H, ddq, J=3, 4, 7 Hz), 4.56 (1H, dd, J=4, 5 Hz), 5.77 (1H, d, J=4 Hz). MS m/z (relative intensity): 187 (M^+-15, 30), 157 (48), 99 (77), 71 (53), 59 (93), 43 (100). Exact MS m/z Calcd for $C_9H_{15}O_4$ (M^+-15): 187.0970. Found: 187.0982.

3,5,6-Trideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-methylene-α-D-*ribo*-hexofuranose (12)——A solution of **11** (0.554 g, 2.52 mmol) and PCC (1.20 g, 5.57 mmol) in CH_2Cl_2 (35 ml) with powdered 3 Å molecular sieves (4.2 g) was stirred for 6 h at room temperature. After removal of insoluble materials by filtration, the filtrate was evaporated *in vacuo* and the residue was extracted with ether. The extract was purified by passage through a silica gel column with ether to give the ketone as a colorless oil (0.463 g, 92%). IR ν_{max} cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7 Hz), 1.35 (3H, s), 1.51 (3H, s), 2.00 (1H, ddq, J=5, 11, 7 Hz), 4.08 (1H, d, J=11 Hz), 4.58 (1H, dd, J=3, 5 Hz), 5.91 (1H, d, J=3 Hz). MS m/z (relative intensity): 185 (M^+-15, 12), 157 (55), 99 (58), 85 (18), 71 (50), 59 (80), 43 (100). Exact MS m/z Calcd for $C_9H_{13}O_4$ (M^+-15): 185.0814. Found: 185.0812.

A tetrahydrofuran (THF) solution (1 ml) of the above ketone (0.290 g, 1.45 mmol) was added dropwise to a stirred solution of methylenetriphenylphosphorane, prepared from NaH (0.104 g, 4.33 mmol) in dimethylsulfoxide (DMSO) and methyltriphenylphosphonium bromide (1.65 g, 4.62 mmol), at 18 °C. After 2 h, the reaction mixture was poured into ice-cold saturated NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (3 : 2) as the eluent to afford **12** as a colorless oil (0.287 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J=7 Hz), 1.34 (3H, s), 1.53 (3H, s), 1.71 (3H, s), 1.88 (1H, ddq, J=4, 0.5, 7 Hz), 4.12 (1H, d, J=10.5 Hz), 4.57 (1H, dd, J=3.5, 4.0 Hz), 4.93—5.0 (2H, m), 5.83 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 198 (M^+, 4.7), 183 (25), 140 (12), 128 (15), 99 (18), 95 (27), 59 (100). Exact MS m/z Calcd for $C_{11}H_{18}O_3$ (M^+): 198.1256. Found: 198.1251.

6-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (13)——A THF solution (6 ml) of **10** (5.27 g, 26.3 mmol) was added to a stirred solution of sodium benzyloxide, prepared from NaH (0.942 g, 39.25 mmol) and benzyl alcohol (4.24 g, 39.35 mmol) in DMSO (13 ml) and THF (6 ml), at room temperature. After 13 h, the reaction mixture was poured into cold saturated NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (4 : 1) as the eluent to afford **13** as a colorless oil (6.274 g, 77%) $[\alpha]_D^{17}+19°$ (c=1.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7 Hz), 1.33 (3H, s) 1.51 (3H, s), 2.08 (1H, ddq, J=5, 10, 7 Hz), 2.42 (1H, d, J=4 Hz), 3.54 (1H, dd, J=7, 10 Hz), 3.65 (1H, dd, J=3, 10 Hz), 3.81 (1H, dd, J=5, 10 Hz), 3.82 (1H, dddd, J=3, 4, 5, 7 Hz), 4.53 (1H, d, J=12 Hz), 4.54 (1H, dd, J=4, 5 Hz), 4,58 (1H, d, J=12 Hz), 5.75 (1H, d, J=4 Hz), 7.34 (5H, s). MS m/z (relative intensity): 308 (M^+, 3), 293 (6), 250 (10), 157 (30), 99 (100). Exact MS m/z Calcd for $C_{17}H_{24}O_5$ (M^+): 308.1625. Found: 308.1621.

6-*O*-Benzyl-3,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-methylene-α-D-*ribo*-hexofuranose (14)——PCC (3.80 g, 17.6 mmol) and powdered molecular sieves 3 Å (12 g) were added to a stirred solution of **13** (2.371 g, 7.70 mmol) in CH_2Cl_2 (80 ml) at room temperature. After 24 h, the reaction mixture was filtered, and the filtrate was

concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (3 : 2) as the eluent to afford the ketone as a colorless oil (2.09 g, 89%). IR ν_{max}^{neat} cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7 Hz), 2.33 (3H, s), 1.50 (3H, s), 1.80—2.24 (1H, m), 4.18 (2H, d, J=11 Hz), 4.42 (2H, s), 4.54 (1H, dd, J=3.5, 4.5 Hz), 4.61 (1H, s), 5.83 (1H, d, J=3.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 306 (M^+, 0.25), 291 (1.6), 278 (2.0), 277 (2.6), 200 (6.1), 157 (50), 120 (15), 105 (20), 99 (75), 91 (100). Exact MS m/z Calcd for $C_{17}H_{22}O_5$ (M^+): 306.1467. Found: 306.1474.

A 1.85 M solution of BuLi in hexane (0.35 ml, 0.56 mmol) was added to a suspension of methyltriphenylphosphonium bromide (218 mg, 0.62 mmol) in THF (1 ml) at −10 °C, and the mixture was stirred for an additional 1 h at −10 °C and then for 2 h at room temperature. Next, a solution of the ketone (85 mg, 0.28 mmol) in THF (0.5 ml) was added dropwise at −10 °C and the reaction mixture was stirred overnight at room temperature, then poured into brine, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (6 : 1) as the eluant to give **14** as a colorless oil (72 mg, 85%). $[\alpha]_D^{17}$ +15.0° (c=3.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=7 Hz), 1.33 (3H, s), 1.52 (3H, s), 2.05 (1H, ddq, J=5, 10, 7 Hz), 4.01 (1H, d, J=13.5 Hz), 4.13 (1H, d, J=13.5 Hz), 4.23 (1H, d, J=10 Hz), 4.48 (1H, d, J=12 Hz), 4.54 (1H, dd, J=3.5, 5 Hz), 4.55 (1H, d, J=12 Hz), 5.24 (1H, s), 5.34 (1H, dd, J=1.5, 3 Hz), 5.79 (1H, d, J=3.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 289 (M^+ − 15, 4.0), 198 (14), 183 (27), 140 (9.5), 107 (25), 91 (100). Exact MS m/z Calcd for $C_{17}H_{21}O_4$ (M^+ − 15): 289.1440. Found: 289.1441.

6-*O*-*tert*-Butyldimethylsilyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (15)——*tert*-Butyldimethylsilyl chloride (8.15 g, 54.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **9** (11.68 g, 54.0 mmol) and imidazole (9.2 g, 135 mmol) in CH_2Cl_2 (60 ml) in an ice bath. After 1 h at room temperature, the reaction mixture was poured into saturated NH_4Cl. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (20 : 1) to give **15** as a colorless oil (16.1 g, 90.6%). ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.20 (3H, d, J=7 Hz), 1.33 (3H, s), 1.51 (3H, s), 1.90—2.08 (1H, m), 2.54 (1H, br s), 3.60—3.82 (4H, m), 4.54 (1H, dd, J=3.5, 4.5 Hz), 5.75 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 317 (M^+ − 15, 11), 275 (7), 217 (46), 190 (32), 157 (22), 117 (86), 99 (51), 89 (33), 75 (100). Exact MS m/z Calcd for $C_{15}H_{29}O_5Si$ (M^+ − 15): 317.1784. Found: 317.1777.

6-*O*-*tert*-Butyldimethylsilyl-3,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-methylene-α-D-*ribo*-hexofuranose (16)——DMSO (8 ml) was added dropwise to a stirred solution of oxalyl chloride (3.44 ml, 39.7 mmol) in CH_2Cl_2 (100 ml) at a temperature below −50 °C. After 5 min, a solution of **15** (11.0 g, 33.1 mmol) in CH_2Cl_2 (20 ml) was added. After 2 h at −50 °C, the mixture was treated with NEt_3 (24 ml), then allowed to warm to room temperature, and poured into brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent *in vacuo* left an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 25) to give 6-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-*C*-methyl-α-D-*ribo*-hexofuranos-5-ulose (10.5 g, 96%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.20 (3H, d, J=7.0 Hz), 1.34 (3H, s), 1.51 (3H, s), 1.91—2.10 (1H, m), 4.23 (1H, d, J=10.5 Hz), 4.25—4.59 (3H, m), 5.88 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 315 (M^+ − 15, 6), 273 (1.5), 215 (5), 157 (5), 117 (100).

A 1.6 M hexane solution of *n*-BuLi in hexane (254 ml, 0.407 mol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (70 g, 0.478 mol) in THF (2.5 l) at a temperature below 0 °C in an ice-salt bath. The reaction mixture was stirred for 5 h at room temperature, then cooled again to below 0 °C, and the above ulose (58.4 g, 0.177 mol) in THF was added. The mixture was stirred for 16 h, poured into saturated NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, and concentrated *in vacuo* to leave an oil, which was extracted with hexane. The hexane extract was evaporated *in vacuo* and the residue was chromatographed on a silica gel column. Elution with benzene–hexane (4 : 1) gave triphenylphosphine and further elution with EtOAc afforded **16** as a colorless oil (54.9 g, 95%). $[\alpha]_D^{20}$ +27.0° (c=0.98, MeOH). IR ν_{max}^{neat} cm^{-1}: 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.91 (9H, s), 1.04 (3H, d, J=7.0 Hz), 1.34 (3H, s), 1.52 (3H, s), 1.92—2.10 (1H, m), 4.00—4.32 (3H, m), 4.56 (1H, dd, J=3.5, 4.5 Hz), 5.04—5.16 (1H, m), 5.23—5.34 (1H, m), 5.80 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 313 (M^+ − 15, 6), 271 (7), 213 (30), 143 (100). Exact MS m/z Calcd for $C_{16}H_{29}O_4Si$ (M^+ − 15): 313.1837. Found: 313.1835. *Anal.* Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.05; H, 9.88.

3,5-Dideoxy-1,2-*O*-isopropylidene-3,5-di-*C*-methyl-β-L-talofuranose (19a) and 3,5-Dideoxy-1,2-*O*-isopropylidene-3,5-di-*C*-methyl-α-D-allofuranose (19b)——a) Hydrogenation of **14** with 10% Pd–C: An EtOAc solution (8 ml) of **14** (33 mg, 0.11 mmol) was hydrogenated with 10% Pd–C (20 mg) at 0 °C for 3 h under ordinary hydrogen pressure. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave an inseparable mixture of **17a** (see below) and **17b**, which was hydrogenated again in EtOAc (5 ml) with 10% Pd–C (20 mg) for 10 h at ordinary temperature and pressure. After removal of the catalyst by filtration, evaporation of the solvent left an oil, which was subjected to silica gel thin layer chromatography (TLC) to afford two fractions. The less polar fraction gave **19a** as a colorless oil (8.7 mg, 37%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7 Hz), 1.03 (3H, d, J=7 Hz), 1.32 (3H, s), 1.51 (3H, s), 1.60—2.40 (3H, m), 3.69 (2H, d, J=6 Hz), 3.93 (1H, dd, J=2.5, 10 Hz), 4.52 (1H, t, J=4 Hz), 5.75 (1H, d, J=4 Hz). MS m/z (relative intensity): 201 (M^+ − 15, 31), 157 (29), 99 (53), 59 (100). Exact MS m/z Calcd for $C_{10}H_{17}O_4$ (M^+ − 15): 201.1128. Found: 201.1119.

The more polar fraction gave **19b** (6.7 mg, 29%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7 Hz), 1.05 (3H, d, J=

7 Hz), 1.35 (3H, s), 1.52 (3H, s), 1.60—2.40 (3H, m), 3.68 (2H, d, J=6 Hz), 3.68 (1H, dd, J=5, 10 Hz), 4.53 (1H, t, J=4 Hz), 5.74 (1H, d, J=4 Hz). MS m/z (relative intensity): 201 (M^+-15, 32), 157 (42), 99 (63), 71 (45), 59 (100). Exact MS m/z Calcd for $C_{10}H_{17}O_4$ (M^+-15): 201.1127. Found: 201.1125.

b) Hydrogenation of **14** with 5% Rh–Al_2O_3: An EtOH solution (80 ml) of **14** (2.478 g, 8.15 mmol) was hydrogenated with 5% Rh–Al_2O_3 (1.0 g) at 8—10 °C under ordinary pressure. After removal of the catalyst by filtration, evaporation of the solvent left an oil, which was again hydrogenated with 10% Pd–C (0.5 g) in EtOH (80 ml) at ordinary temperature and pressure for 6 h. After removal of the catalyst by filtration, the filtrate was evaporated and chromatographed on a silica gel column with hexane–EtOAc (1 : 4) to afford **19a** (1.41 g, 80%) and **19b** (0.352 g, 20%).

c) Hydroboration of **12**: A THF solution (1 ml) of **12** (0.322 g, 1.63 mmol) was added to a stirred 1 M THF solution of BH_3–THF complex (6.5 ml, 6.5 mmol) at 0 °C under argon. After 1 h at 0—5 °C, the solution was successively treated with MeOH (0.8 ml), 3 N NaOH (1 ml), and 30% H_2O_2 (1 ml) at 0 °C and then brought to 50 °C for 25 min. The mixture was extracted with ether, and the extract was washed with 2 N HCl and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with Et_2O–hexane (4 : 1) to afford a mixture of **19a** and **19b** (0.207 g, 59%). The ratio of **19a** and **19b** was determined to be 1 : 6.8 from the C-4 proton signals (3.93 ppm for **19a** and 3.68 ppm for **19b**) in the NMR spectrum.

d) Hydroboration of **14**: A THF solution of 1 M BH_3–THF (4 ml, 4 mmol) was added to a solution of **14** (1.2 g, 3.95 mmol) in THF (20 ml) at −20 °C, and the solution was stirred for 9 h at −10 °C. The excess BH_3 was decomposed with MeOH (2 ml) at −10 °C, and 4 N NaOH (1.65 ml) and 70% *tert*-BuOOH (0.6 ml) were added to the resulting mixture at −10 °C. The mixture was stirred for 0.5 h at −10 °C, then evaporated *in vacuo*, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and evaporated to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (2 : 1) to give a mixture of **20a** and **20b** (1.03 g, 82%). The ratio of **20a** and **20b** was determined to be 24 : 1 from the anomeric proton signals (5.75 for **20a** and 5.71 for **20b**) in the NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J=6.5 Hz), 1.32 (3H, s), 1.49 (3H, s), 1.90—2.10 (2H, m), 2.68 (1H, dd, J=3, 8.5 Hz), 3.67 (1H, dd, J=6, 9 Hz), 3.70—3.88 (3H, m), 3.92 (1H, dd, J=3, 11 Hz), 4.54 (1H, dd, J=3.5, 4.5 Hz), 4.55 (2H, s), 3.75 (1H, d, J=3.5 Hz), 7.33 (5H, s).

The mixture (20 mg, 0.06 mmol) was treated with methanesulfonyl chloride (MsCl) (14 mg, 0.12 mmol) in CH_2Cl_2 (0.2 ml) and pyridine (0.1 ml) at room temperature. After 1.5 h, the solution was diluted with CH_2Cl_2, washed with cold 2 N HCl and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (3 : 2) to give a mixture of mesylates (19 mg, 76.5%), which (17.6 mg, 0.044 mmol) in Et_2O (0.5 ml) was reduced with LAH (45 mg, 1.18 mmol) at 0 °C for 6.5 h to give a mixture of **17a** and **17b** (9.6 mg, 71%). The mixture (9.6 mg, 0.031 mmol) was hydrogenated with 10% Pd–C (5 mg) in EtOH (0.2 ml) at room temperature for 6 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*, dissolved in Et_2O, and passed through a silica gel column to give a mixture of **19a** and **19b** (6.8 mg, 100%). The ratio of **19a** and **19b** was determined to be 24 : 1 from the NMR spectrum.

e) Reduction of **21a**: A solution of **21a** (44.7 g, 0.129 mol) and TsCl (36.9 g, 0.193 mol) in pyridine (220 ml) was allowed to stand overnight at room temperature, then poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with ice-cold 1 N HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give tosylate (61.6 g, 95%). $[\alpha]_D^{20}$ +13.3 ° (c=1.26, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.81 (9H, s), 1.06 (3H, d, J=7.0 Hz), 1.30 (3H, s), 1.46 (3H, s), 1.91—2.06 (2H, m), 2.44 (3H, s), 3.57 (2H, d, J=6.5 Hz), 3.81 (1H, dd, J=3.0, 10.5 Hz), 3.99 (1H, dd, J=6.0, 10.0 Hz), 4.48 (1H, t, J=4.0 Hz), 5.65 (1H, d, J=4.0 Hz), 7.34 (2H, d, J=8.0 Hz), 7.78 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 485 (M^+-15, 9.9), 443 (8), 385 (5.5), 229 (100). Exact MS m/z Calcd for $C_{23}H_{37}O_7SSi$ (M^+-15): 485.2046. Found: 485.2031.

The tosylate (51.3 g, 0.102 mol) in ether (250 ml) was added to a stirred ice-cold suspension of LAH (23.3 g, 0.616 mol) in ether (230 ml). After 5 h at room temperature, EtOAc, then water (23 ml), and 15% NaOH (23 ml) were added carefully. The resulting mixture was filtered through celite and the solid was washed with ether. The combined ether layers were dried ($MgSO_4$) and evaporated *in vacuo* to give an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 2) as the eluant to give **19a** as an oil (21.0 g, 95%).

5-*C*-(*tert*-Butyldimethylsilyloxy)methyl-1,3-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-β-L-talofuranose (21a) and 5-*C*-(*tert*-Butyldimethylsilyloxy)methyl-3,5-dideoxy-1,2,*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (21b)——A 1 M THF solution of BH_3–THF complex (6.55 ml, 6.6 mmol) was added to a stirred solution of **16** (2.15 g, 6.6 mmol) in THF (7 ml) at 0 °C under argon. After 1 h at 0 °C, the solution was cooled to −16 °C, and treated with 4.15 N NaOH (2.6 ml) and 70% aqueous *tert*-BuOOH solution (1.0 ml). After 3 h, the reaction mixture was diluted with ether, washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 16—1 : 5) to afford **21b** as a colorless oil (0.17 g, 7.5%) from the first fraction. $[\alpha]_D^{20}$ +30 ° (c=1.38, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.10 (3H, d, J=7.0 Hz), 1.32 (3H, s), 1.50 (3H, s), 1.82—2.13 (2H, m), 2.76 (1H, t, J=6.0 Hz), 3.74—4.17 (5H, m), 4.52 (1H, dd, J=3.5, 4.5 Hz), 5.74 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 331 (M^+-15, 9.9), 285 (5.5), 229 (100). Exact MS m/z Calcd for $C_{16}H_{31}O_5Si$ (M^+-15): 331.1943. Found: 331.1933.

The second fraction gave **21a** as a colorless oil (1.9 g, 84%). IR ν_{max}^{neat} cm^{-1}: 3400. $[\alpha]_D^{20}$ +41 ° (c=1.28, MeOH).

^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.06 (3H, d, J=7.0 Hz), 1.33 (3H, s), 1.50 (3H, s), 1.79—2.17 (2H, m), 2.79 (1H, dd, J=3.0, 8.5 Hz), 3.69—3.96 (5H, m), 4.55 (1H, t, J=4.0 Hz), 5.76 (1H, d, J=4.0 Hz). MS m/z (relative intensity): 331 (M^+-15, 6.4), 231 (12.3), 213 (8), 201 (12), 75 (100). Exact MS m/z Calcd for $C_{16}H_{31}O_5Si$ (M^+-15): 331.1943. Found: 331.1962.

6-*O*-Benzyl-3,5-dideoxy-1,2-*O*-isopropylidene-3,5-di-*C*-methyl-*β*-L-talofuranose (17a)——A solution of **19** (1.50 g, 7.13 mmol) in THF (8 ml) was added portionwise to a stirred suspension of NaH (0.24 g, 9.99 mmol) in DMSO (6 ml) was added portionwise at room temperature. After gas evolution had ceased, benzyl chloride (0.948 g, 7.49 mmol) was added. The reaction mixture was stirred for 20 h, poured into cold aqueous NH_4Cl, and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (4 : 1) to give **17a** as a colorless oil (2.00 g, 89%). $[\alpha]_D^{19}+19°$ (c=1.90, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=7.0 Hz), 1.02 (3H, d, J=7.0 Hz), 1.33 (3H, s), 1.51 (3H, s), 1.77—2.08 (2H, m), 3.41 (1H, dd, J=8.0, 14 Hz), 3.55 (1H, dd, J=8.0, 14 Hz), 3.91 (1H, dd, J=2.5, 10.5 Hz), 4.52 (1H, dd, J=3.5, 4.5 Hz), 4.53 (2H, s), 5.74 (1H, d, J=3.5 Hz), 7.32 (5H, s). MS m/z (relative intensity): 306 (M^+, 2.3), 291 (4.3), 248 (2.3), 231 (2.6), 157 (9.0), 91 (100). Exact MS m/z Calcd for $C_{18}H_{26}O_4$ (M^+): 306.1833. Found: 306.1829.

6-*O*-Benzyl-3,5-dideoxy-3,5-di-*C*-methyl-L-talofuranose (28)——A solution of **17a** (20.0 g, 65.4 mmol) in THF (750 ml) and 4 N HCl (250 ml) was allowed to stand for 10.5 h at 40 °C, then neutralized with $NaHCO_3$, and evaporated *in vacuo*. The residue was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 1) to afford **28** as a colorless oil (14.5 g, 83%). MS m/z (relative intensity): 248 (M^+-18, 5.3), 107 (28), 91 (100). Exact MS m/z Calcd for $C_{15}H_{20}O_3$ (M^+-18): 248.1412. Found: 248.1432.

5-*O*-Benzyl-2,4-dideoxy-3-*O*-formyl-2,4-di-*C*-methyl-L-lyxose (29)——A solution of $NaIO_4$ (8.75 g, 40.9 mmol) in water (60 ml) was added to a stirred solution of **28** (7.25 g, 27.3 mmol) in MeOH (110 ml) at 0 °C. After 1 h, the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was extracted with CH_2Cl_2, then the extract was dried ($MgSO_4$), and evaporated *in vacuo* to give **29** as an oil (6.8 g, 94.4%). IR ν_{max}^{neat} cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J=7.0 Hz), 1.13 (3H, d, J=7.5 Hz), 1.98—2.30 (1H, m), 2.75 (1H, ddq, J=2.5, 7.0, 7.5 Hz), 3.20 (1H, dd, J=2, 16 Hz), 3.40 (1H, d, J=16 Hz), 4.45 (2H, s), 5.42 (1H, dd, J=7.0, 7.5 Hz), 7.32 (5H, s), 8.01 (1H, s), 9.63 (1H, d, J=2.5 Hz). MS m/z (relative intensity): 264 (M^+, 0.3), 188 (2.4), 160 (5.1), 145 (3.3), 112 (12), 107 (8), 91 (100). Exact MS m/z Calcd for $C_{15}H_{20}O_4$ (M^+): 264.1361. Found: 264.1367.

(2*Z*,4*S*,5*S*,6*S*)-7-*O*-Benzyloxy-5-hydroxy-2,4,6-trimethylhept-2-enoic Acid *δ*-Lactone (30)——$(MeO)_2P(O)CH(Me)CO_2Me$ (2.7 g, 13.8 mmol) was added to a stirred suspension of NaH (270 mg, 11.2 mmol) in THF (50 ml) at 0 °C. After 1 h, the solution was cooled at −80 °C and then **29** (1.21 g, 4.58 mmol) in THF (20 ml) was added dropwise at below −80 °C. The solution was allowed to warm to 8 °C overnight, treated with saturated NH_4Cl, and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was dissolved in MeOH (30 ml) and treated with K_2CO_3 (0.5 g) at room temperature for 1 h. The reaction mixture was neutralized with NH_4Cl (0.5 g) ad evaporated *in vacuo*. The residue was extracted with benzene, then the extract was dried (Na_2SO_4), and evaporated to leave an oil, which was chromatographed on a silica gel column with hexane–EtOAc (8 : 1) to give **30** as a colorless oil (1.15 g, 92%). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=8 Hz), 1.08 (3H, d, J=8 Hz), 1.90 (3H, dd, J=1.5, 2 Hz), 1.95—2.36 (1H, m), 1.36—2.88 (1H, m), 3.48 (1H, dd, J=6, 10 Hz), 3.63 (1H, t, J=10 Hz), 4.27 (1H, dd, J=3, 12 Hz), 4.52 (2H, s), 6.32 (1H, dq, J=4, 2 Hz), 7.10 (5H, s). MS m/z (relative intensity): 274 (M^+, 6.7), 214 (7.5), 161 (37), 125 (38), 91 (100). Exact MS m/z Calcd for $C_{17}H_{22}O_3$ (M^+): 274.1570. Found: 274.1584.

(2*S*,5*S*,6*S*)-2*H*-5,6-Dihydro-2-isopropyloxy-3,5-dimethyl-6-[1(*S*)-methyl-2-benzyloxyethyl]pyran (31)——A 1 M toluene solution of DIBAH (49.3 ml, 49.3 mmol) was added to a stirred solution of **30** (9.0 g, 32.8 mmol) in toluene (360 ml) at −80 °C. The solution was then treated with MeOH (50 ml). After 40 min, the reaction mixture was allowed to warm to room temperature, and treated with brine (250 ml) and 1 N HCl (60 ml). The resulting mixture was extracted with ether, then the extract was washed with $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude lactol (9.0 g, 99.4%) as an oil. The lactol (9.0 g, 32.6 mmol) was treated with camphorsulfonic acid (CSA) (0.5 g, 2.15 mmol) in Me_2CHOH (90 ml) in 1 h at room temperature. After addition of NEt_3 (10 ml), the mixture was stirred for 10 min, concentrated *in vacuo*, and extracted with ether. The extract was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–hexane (1 : 10) to afford **31** as a colorless oil (10.0 g, 97%). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.16 (3H, d, J=6 Hz), 1.17 (3H, d, J=6 Hz), 1.68 (3H, t, J=2.0 Hz), 1.90—2.50 (2H, m), 3.45 (1H, dd, J=8, 16 Hz), 3.53 (1H, dd, J=8, 16 Hz), 3.64 (1H, dd, J=2, 12 Hz), 3.96 (1H, sept, J=6 Hz), 4.45 (1H, d, J=12 Hz), 4.57 (1H, d, J=12 Hz), 4.79 (1H, br s), 5.43 (1H, br s), 7.31 (5H, s). MS m/z (relative intensity): 318 (M^+, 1.3), 259 (6), 167 (10), 140 (50), 98 (100). Exact MS m/z Calcd for $C_{20}H_{30}O_3$ (M^+): 318.2196. Found: 318.2181.

(2*S*,3*R*,5*S*,6*S*)-2-Isopropyloxy-3,5-dimethyl-6-[1(*S*)-methyl-2-hydroxyethyl]tetrahydropyran (7a) and (2*S*,3*S*,-5*S*,6*S*)-2-Isopropyloxy-3,5-dimethyl-6-[1(*S*)-methyl-2-hydroxyethyl]tetrahydropyran (7b)——a) Hydrogenation of **31**: A solution of **31** (2.7 g, 8.49 mmol) in EtOAc (30 ml) was hydrogenated over 10% Pd–C (0.9 g) at ordinary

temperature and pressure for 21 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave **32** as an oil. MS *m/z* (relative intensity): 320 (M^+, 0.3), 278 (0.5), 260 (1.7), 91 (100). Exact MS *m/z* Calcd for $C_{17}H_{24}O_2$ ($M^+ - 60$): 260.1776. Found: 260.1767.

Compound **32** was dissolved in EtOH (15 ml) and hydrogenated again over Raney Ni W-2 (10 ml of precipitate in EtOH) for 24 h. After removal of the catalyst, the filtrate was concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with EtOAc–benzene (1 : 20) to afford **7a** as a colorless oil (1.7 g, 87%) from the first fraction. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=7 Hz), 0.83 (3H, d, J=7 Hz), 1.00 (3H, d, J=7 Hz), 1.10 (3H, d, J=6 Hz), 1.24 (3H, d, J=6 Hz), 1.50—2.04 (3H, m), 2.76 (1H, dd, J=3.5, 8 Hz), 3.50—3.84 (3H, m), 3.77 (1H, sept. J=6 Hz), 4.65 (1H, d, J=4 Hz). MS *m/z* (relative intensity): 171 ($M^+ - 59$, 43), 143 (26), 139 (19), 100 (19), 89 (40), 81 (36), 72 (74), 71 (82), 43 (100). Exact MS *m/z* Calcd for $C_{10}H_{19}O_2$ ($M^+ - 59$): 171.1385. Found: 171.1379.

The second fraction gave **7b** (0.234 g, 12%). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=6 Hz), 1.03 (3H, d, J=7 Hz), 1.12 (3H, d, J=6 Hz), 1.23 (3H, d, J=6 Hz), 1.40—2.10 (3H, m), 3.50—3.90 (3H, m), 3.88 (1H, sept, J=6 Hz), 4.57 (1H, s). MS *m/z* (relative intensity): 230 (M^+, 0.2), 188 (10), 171 (15), 119 (22), 100 (88), 89 (55), 82 (53), 69 (63), 58 (100). Exact MS *m/z* Calcd for $C_{13}H_{26}O_3$ (M^+): 230.1882. Found: 230.1881.

b) Hydrogenation of **38** with Pd–C: A solution of **38** (6 mg, 0.0263 mmol) in EtOAc (1 ml) at 0 °C was hydrogenated with 10% Pd–C (5 mg) for 9 h. After removal of the catalyst, evaporation of the solvent left an oil, which was chromatographed on a silica gel column with hexane–benzene (1 : 1) to give a mixture of **7a** and **7b** as a colorless oil (2.8 mg, 46%). The ratio of **7a** and **7b** was determined to be 5 : 1 from the anomeric proton signals (4.66 ppm for **7a** and 4.47 ppm for **7b**) in the NMR spectrum.

c) Hydrogenation of **38** with Rh–Al_2O_3: A solution of **38** (17 mg, 0.0745 mmol) in ether (3.5 ml) was hydrogenated with Rh–Al_2O_3 (20 mg) at room temperature overnight. After removal of the catalyst, the filtrate was evaporated to leave an oil, which was dissolved in EtOAc and passed through a silica gel column to give a 24 : 1 mixture of **7a** and **7b** (7.1 mg, 99%).

3,5-Dideoxy-1,2-*O*-isopropylidene-6-(4-methoxybenzyl)-3,5-dimethyl-β-L-talofuranose (33)——Compound **19a** (2.908 g, 13.46 mmol) was treated with NaH (0.387 g, 16.13 mmol) and 4-methoxybenzyl chloride (MPMCl) (2.53 g, 16.17 mmol) in DMSO (18 ml) as described for the preparation of **17a** to give **33** as a colorless oil (1.266 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=7 Hz), 1.02 (3H, d, J=7 Hz), 1.33 (3H, s), 1.50 (3H, s), 1.80—2.05 (2H, m), 3.39 (1H, dd, J=7.5, 9 Hz), 3.50 (1H, dd, J=6.5, 9 Hz), 3.80 (3H, s), 3.88 (1H, dd, J=2, 10 Hz), 4.43 (1H, d, J=11.5 Hz), 4.48 (1H, d, J=11.5 Hz), 4.52 (1H, dd, J=3.5, 5 Hz), 5.74 (1H, d, J=3.5 Hz), 6.86 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 336 (M^+, 2.6), 278 (1.3), 260 (1.0), 232 (1.5), 215 (1.1), 207 (3.0), 190 (4.0), 277 (2.8), 157 (8.0), 137 (52), 121 (100). Exact MS *m/z* Calcd for $C_{19}H_{28}O_5$ (M^+): 336.1936. Found: 336.1936.

6-*O*-(4-Methoxybenzyl)-3,5-dideoxy-3,5-di-*C*-methyl-L-talofuranose (34)——Compound **33** (4.50 g, 13.45 mmol) was hydrolyzed with 4 N HCl (30 ml) in dioxane (73 ml) at 45 °C for 100 min as described for the preparation of **28** to give **34** as a colorless oil (3.10 g, 78%). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (0.9H, d, J=7 Hz), 0.96 (2.1H, d, J=7 Hz), 1.04 (3H, d, J=9 Hz), 1.70—2.50 (3H, m), 2.64 (0.3H, d, J=7.5 Hz), 3.16 (0.7H, d, J=3.5 Hz), 3.20—3.70 (2H, m), 3.80 (3H, s), 3.80—4.20 (2H, m), 4.45 (2H, s), 5.21 (0.7H, d, J=3.5 Hz), 5.33 (0.3H, dd, J=4, 7.5 Hz), 6.88 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 296 (M^+, 0.2), 278 (1.5), 208 (2.0), 157 (4.1), 137 (47), 121 (100). Exact MS *m/z* Calcd for $C_{16}H_{24}O_5$ (M^+): 296.1623. Found: 296.1642.

2,4-Dideoxy-3-*O*-formyl-5-*O*-(4-methoxybenzyl)-2,4-di-*C*-methyl-L-lyxose (35)——Compound **34** (0.503 g, 1.70 mmol) was oxidized as described for the preparation of **29**, and purified by chromatography on a silica gel column with EtOAc–hexane (1 : 3) to give **35** as a colorless oil (0.465 g, 93%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=7 Hz), 1.10 (3H, d, J=7 Hz), 2.00—2.40 (1H, m), 2.74 (1H, ddq, J=2.5, 7.5, 7 Hz), 3.27 (1H, dd, J=7, 10 Hz), 3.38 (1H, dd, J=5.5, 10 Hz), 3.81 (3H, s), 4.38 (2H, s), 5.41 (1H, ddd, J=1, 5, 7.5 Hz), 6.89 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 8.09 (1H, d, J=1 Hz), 9.63 (1H, d, J=2.5 Hz). MS *m/z* (relative intensity): 294 (M^+, 1.5), 190 (1.3), 175 (1.9), 137 (13), 121 (100). Exact MS *m/z* Calcd for $C_{16}H_{22}O_5$ (M^+): 294.1467. Found: 294.1480.

(2*Z*,4*S*,5*S*,6*S*)-5-Hydroxy-7-*O*-(4-methoxybenzyl)-2,4,6-trimethylhept-2-enoic Acid δ-Lactone (36)——Compound **35** (0.465 g, 1.58 mmol) was reacted with the sodium salt of $(MeO)_2P(O)CH(Me)CO_2Me$ as described for the preparation of **30** to give **36** as a colorless oil (0.392 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=7 Hz), 1.05 (3H, d, J=7 Hz), 1.90 (3H, dd, J=1.5, 2 Hz), 2.00—2.15 (1H, m), 2.55—2.70 (1H, m), 3.40 (1H, dd, J=6, 9 Hz), 3.58 (1H, dd, J=8.5, 9 Hz), 3.81 (3H, s), 4.24 (1H, dd, J=2, 11 Hz), 4.42 (1H, d, J=12 Hz), 4.48 (1H, d, J=12 Hz), 6.34 (1H, dq, J=1.5, 3.5 Hz), 6.88 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 304 (M^+, 2.1), 289 (0.5), 217 (5.0), 191 (22), 121 (100). Exact MS *m/z* Calcd for $C_{18}H_{24}O_4$ (M^+): 304.1674. Found: 304.1684.

(2*S*,5*S*,6*S*)-2*H*-5,6-Dihydro-2-isopropyloxy-3,5-dimethyl-6-[1(*S*)-methyl-2-(4-methoxybenzyloxy)ethyl]pyran (37)——Compound **36** (0.314 g, 1.03 mmol) was reduced with DIBAH as described for the reduction of **30** to give the lactol as a colorless oil (0.318 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=7 Hz), 0.91 (3H, d, J=7 Hz), 1.73 (3H, t, J=2 Hz), 1.90—2.60 (2H, m), 3.34 (1H, dd, J=6.5, 9 Hz), 3.54 (1H, dd, J=7.5, 9 Hz), 3.70 (1H, dd, J=2, 10.5 Hz), 3.81 (3H, s), 4.46 (2H, s), 5.09 (1H, br s), 5.44 (1H, br s), 6.90 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 306 (M^+, 0.15), 288 (1.1), 167 (20), 152 (8), 137 (23), 121 (100), 99 (33). Exact MS *m/z* Calcd for $C_{18}H_{26}O_4$ (M^+): 306.1831. Found: 306.1846.

The above lactol (0.31 g, 0.89 mmol) was treated with iso-PrOH in the presence of CSA as described for the preparation of **31** to afford **37** as a colorless oil (0.341 g, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.16 (3H, d, J=6 Hz), 1.19 (3H, d, J=6 Hz), 1.67 (3H, t, J=1.5 Hz), 1.80—2.50 (2H, m), 3.39 (1H, dd, J=7.5, 9 Hz), 3.56 (1H, dd, J=6, 9 Hz), 3.64 (1H, dd, J=2, 10 Hz), 3.80 (3H, s), 3.94 (1H, sept, J=6 Hz), 4.39 (1H, d, J=12 Hz), 4.52 (1H, d, J=12 Hz), 4.78 (1H, br s), 5.42 (1H, br s), 6.86 (2H, d, J=9 Hz), 7.28 (2H, d, J=9 Hz). MS m/z (relative intensity): 348 (M^+, 0.4), 305 (1.3), 288 (0.5), 227 (0.8), 167 (19), 121 (100). Exact MS m/z Calcd for $C_{21}H_{32}O_4$ (M^+): 348.2300. Found: 348.2283.

(1*R*,4*S*,5*S*,6*S*)-3,4,6-Trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-ene (39) and Its Dimer (40)——DDQ (0.197 g 0.868 mmol) was added to a stirred solution of **37** (0.252 g, 0.724 mmol) in CH_2Cl_2 (20 ml) and water (1 ml) at room temperature. After 1.5 h, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–EtOAc (4 : 1) to give **40** as a colorless oil (41.5 mg, 34%) from the first fraction. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, d, J=7 Hz), 0.90 (6H, d, J=7 Hz), 1.68 (6H, t, J=2 Hz), 1.96—2.40 (4H, m), 3.26 (2H, dd, J=3, 4 Hz), 3.84 (2H, dd, J=2, 11 Hz), 4.07 (2H, dd, J=8, 11 Hz), 4.68 (2H, s), 5.43 (2H, s). MS m/z (relative intensity): 336 (M^+, 45), 254 (26), 167 (31), 123 (65), 109 (100). Exact MS m/z Calcd for $C_{20}H_{32}O_4$ (M^+): 336.2300. Found: 336.2283.

The second fraction gave **39** as a colorless oil (58.6 mg, 48%). ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.65 (3H, t, J=1.5 Hz), 2.00—2.30 (1H, m), 2.32—2.60 (3H, m), 3.50 (1H, d, J=11 Hz), 3.60 (1H, d, J=11 Hz), 3.63 (1H, dd, J=5, 12 Hz), 6.68—6.80 (1H, m). MS m/z (relative intensity): 168 (M^+, 15), 119 (25), 98 (22), 86 (65), 84 (100).

(2*S*,5*S*,6*S*)-2*H*-5,6-Dihydro-2-isopropyloxy-3,5-dimethyl-6-[1(*S*)-methyl-2-hydroxyethyl]pyran (38)——DDQ (16 mg, 0.07 mmol) was added to a CH_2Cl_2 solution (1.0 ml) of **37** (12 mg, 0.0344 mmol) containing Me_2CHOH (0.05 ml) and water (0.05 ml) at room temperature. After 2 h, the mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo* to leave an oil, which was purified by TLC on silica gel with hexane–EtOAc (1 : 1) to give **38** as a colorless oil (6.1 mg, 78%). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.18 (3H, d, J=6 Hz), 1.26 (3H, d, J=6 Hz), 1.58 (1H, br s), 1.68 (3H, t, J=2 Hz), 1.80—2.10 (1H, m), 2.10—2.44 (1H, m), 3.70 (1H, dd, J=2, 10 Hz), 3.82 (1H, d, J=10 Hz), 3.94 (1H, septet, J=6 Hz), 4.80 (1H, s), 5.44 (1H, br s). MS m/z (relative intensity): 228 (M^+, 0.3), 169 (20), 140 (28), 109 (40), 98 (100). Exact MS m/z Calcd for $C_{10}H_{17}O_2$ ($M^+ - 59$): 169.1228. Found: 169.1232.

References and Notes

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In contrast with the C-3-α-methyl compounds (**12**, **14**, **16**), the corresponding C-3-β-methyl compounds (**22**, **23**, **24**) showed rather opposite stereoselectivities in the formation of the hydroxy compounds (**25a**, **b**, **26a**, **b**, **27a**, **b**), probably because of steric repulsion between methyl groups in the transition structure (M-2) in Chart 3. The results are also shown in Table I. Details will be reported elsewhere.

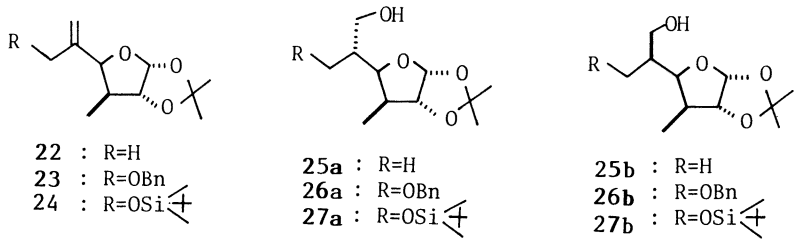

Chart 5

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20) When **37** was treated with DDQ under usual conditions for deprotection of MPM groups in dichloromethane containing a small amount of water,[10,21] a mixture of **39** and **40** instead of the desired **38** was obtained because the isopropyl protection of **38** was labile even to very weak acids. This disadvantage was overcome by the addition of isopropanol.

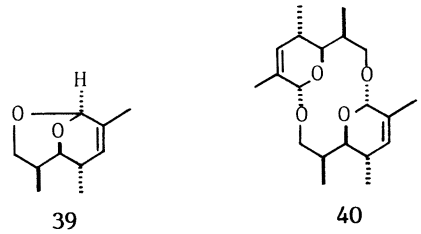

Chart 6

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