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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

22.* SYNTHESIS OF THE C^8–C^{13} FRAGMENT OF OLEANDONOLIDE

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The stereospecific synthesis of the C^8–C^{13} fragment of oleandonolide was carried out in 15 steps with an overall yield of 4.48%.

In the previous communication [1] we carried out a retrosynthetic analysis of oleandonolide, and α,β-methylglycoside (II) was chosen as the starting material for the synthesis of its C^8–C^{13} fragment in the form of aldehyde (I).

As seen from Scheme 1, the synthesis of the C^8–C^{13} fragment requires the conversion of the cyclic form of methylglycoside (II) to acyclic derivative (IX) without affecting the chiral centers and to form the correct configuration of the C^9 center during the transition from derivative (IX) to aldehyde (I) (see scheme at top of following page).

Debenzylation of (II), transglycosylation of alcohols (III) to allylglycosides (IV), and protection of the hydroxyl group in the latter afforded p-methoxybenzyl (MPM) ethers (V). Removal of the allyl protective group afforded free monosaccharide (VI). Later it was found that this compound may be obtained more simply by hydrolysis of MPM-ethers (Va) obtained from compound (III) in one step.

Reduction of (VI) to diol (VII), selective benzoylation of the primary alcohol group, silylation of the secondary hydroxyl group in (VIII), and removal of the O-benzoyl group in (IX) afforded primary alcohol (X), which was oxidized to aldehyde (XI), the C^9–C^{13} fragment of oleandonolide.

In analogy with the synthesis of the related fragment of lancanolide [3], we attempted to form the C^9 center in aldehyde (I) by addition of lithium bis(2-methylpropenyl) cuprate to aldehyde (XI). The addition of this reagent was stereospecific but with the inverse stereochemistry to that required at the C^9 center. In accordance with the data in [2], we hoped to convert it to the required stereochemistry by using the method of Mitsunobu [3].

*For previous communication, see [1].

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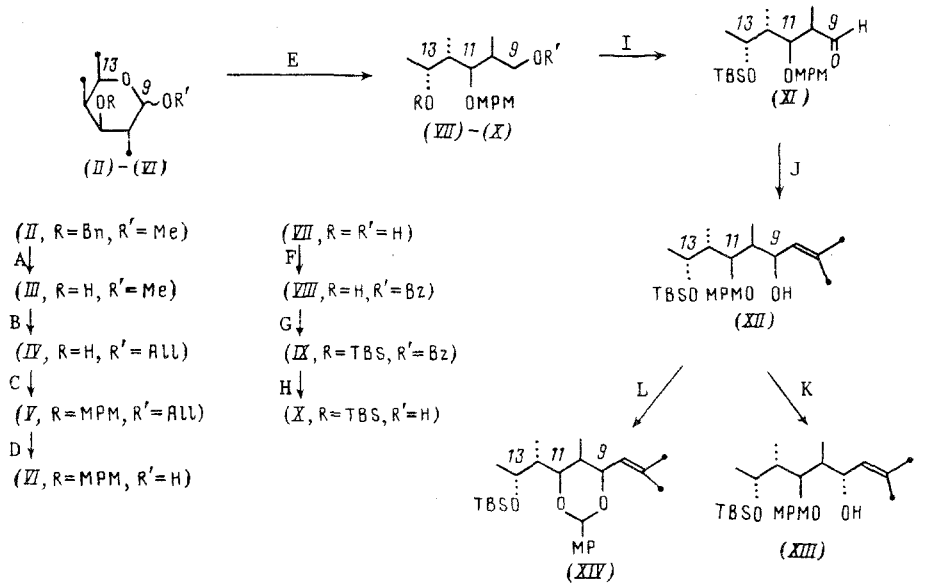
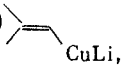
Scheme 1



Reagents: A) Ni—Ra, MeOH, Δ; B) AllOH, PPTS (cat.) Δ; C) MPMCl, NaH/DMF; D) *t*-BuOK, DMSO, 100°C, $Hg(OAc)_2$, Me_2CO—H_2O (8 : 2); E) $NaBH_4$/EtOH; F) BzCl, Py; G) TBSOTf, Et_3N, CH_2Cl_2; H) 15% NaOH, EtOH; I) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, —60°; J)  THF, —80°; K) *o*-$NO_2C_6H_4COOH$, Ph_3P, DEAD, Et_2O; L) DDQ, MS 3 Å-molecular sieve, CH_2Cl_2.

The configuration of the C^9 center in alcohol (XII) was confirmed by analysis of the PMR spectrum of cyclic derivative (XIV) [$J_{9,10}$ = 8 Hz, NOE (H_{ac}) H_9 8%, (H_{ac}) H_{11} 7.5%]. However, only 38% of the C^9 center of alcohol (XIV) underwent isomerization (PMR data) with this procedure [2], and we were unable to separate the mixture of alcohols (XII) and (XIII) that was formed.

Because of this, the scheme for synthesizing fragment C^8–C^{13} was modified. Thus, reaction of aldehyde (XI) with carbethoxymethylidenephosphorane according to Wittig gave rise exclusively to E-olefin (XV) (Scheme 2), which was readily hydroxylated to give a high yield of the chromatographically separable isomeric diols (XVI) and (XVII) in a ratio of 3:1. Analysis of the spectra of cyclic derivatives (XX) and (XVIII) showed that the former is the required 9,10-anti-isomer ($J_{9,10}$ = 10 Hz, NOE (H_{ac})H_8, H_{11} 7%) and that the latter has a 9,10-syn configuration ($J_{9,10}$ = 10 Hz, NOE (H_{ac}) H_9 8.7%, H_{11} 7.8%). Isomer (XVII) can be converted to aldehyde (XI) by periodate cleavage, and thus can be drawn into another conversion cycle (see Scheme 2).

Reduction of ester (XVI) afforded triol (XIX), whose treatment with dichlorodicyanobenzoquinone (DDQ) afforded acetal (XX). Cleavage of the diol group of compound (XX) by means of $Pb(OAc)_4$ afforded aldehyde (I), which is the C^8–C^{13} fragment of oleandonolide.

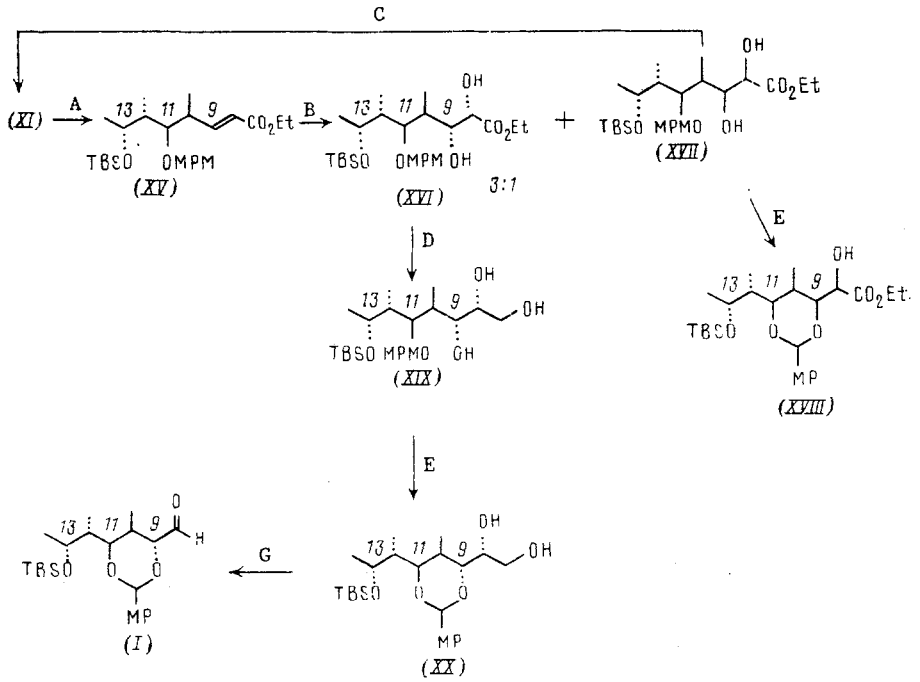
EXPERIMENTAL

For measurement of specific rotations and PMR spectra, purification of materials by means of HPLC, and preparation of solvents, see [1].

Methyl-α,β-2,4,6-trideoxy-2,4-di-C-methyl-D-galactopyranoside (III). A 50-g portion of Raney nickel was added to 3.9 g (14.77 mmoles) of compound (II) [4] in 200 ml MeOH, and the mixture was boiled for 2 h, with mixing, in a reflux condenser. It was then filtered, the residue was washed with MeOH, and the filtrate was evaporated in a fractionating column. Yield: 3.6 g (92%). The chromatographically pure compound was used in subsequent reactions without further purification.

Allyl-α-β-2,4,6-trideoxy-2,4-di-C-methyl-3-hydroxy-D-galactopyranoside (IV). A 0.4-g (10 mole %) portion of p-toluenesulfonic acid pyridinium salt (PPTS) was added to 3.6 g (13.6 mmoles) of compound (III) in 40 ml allyl alcohol, and the mixture was boiled for 4 h. The

Scheme 2



Reagents: A) $Ph_3P{=}CHCOOEt$, THF, Δ; B) OsO_4(cat.), NMO—H_2O, Me_2CO—H_2O (8:2); C) $NaIO_4$, THF—H_2O (4:1); D) $LiAlH_4$, Et_2O, —30 → 10°; E) DDQ, MS 3 Å, CH_2Cl_2; G) $Pb(OAc)_4$, CH_3CN, NaOAc, —20°.

allyl alcohol was distilled off, and the residue was recrystallized from hexane. Yield: 2.2 g (81.2%). PMR spectrum (δ, ppm, J, Hz): 0.93 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 6.75), 1.03 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.75), 1.17 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 2.0 m (2H, H^{10}, H^{12}), 3.60 d.d (1H, H^{11}, $J_{H^{11},H^{12}}$ = 4.75, $J_{H^{11},H^{10}}$ = 11), 4.01 m (1H, H^{13}), 4.12 d (2H, OCH_2-CH=CH_2-9), 4.67 d (1H, H^9, $J_{H^9,H^{10}}$ = 4), 5.23 m (2H, $OCH_2CH{=}CH_2$-9), 5.91 m (1H, $OCH_2CH{=}CH_2$-9).

Allyl-α,β-2,4,6-trideoxy-2,4-di-C-methyl-3-O-MPM-D-galactopyranoside (V). A 2.2-g (11.055-mmole) solution of compound (IV) in 5 ml DMF was added dropwise, with mixing, to a 1-g (41.66-mmole, 3-equiv.) suspension of sodium hydride in 20 ml DMF, and the reaction mixture was stirred for 1 h. Then 2.25 ml (16.6 mmoles) p-methoxybenzyl chloride was added, and the reaction mixture was stirred for 12 h; 150 ml of water was then added, and the mixture was extracted with ether (4 × 50 ml). The extract was washed with water and saturated sodium chloride, dried with Na_2SO_4, and evaporated in a vacuum; the residue was chromatographed in a system of 8% ether in benzene. Yield: 3.53 g (100%). Syrup. PMR spectrum (δ, ppm, J, Hz): 0.93 d, 1.03 d, 1.17 d (9H, 12-CH_3, 10-CH_3, 13-CH_3, $J_{CH_3,H^{12}}$ = 6.75, $J_{CH_3,H^{10}}$ = 6.75, $J_{CH_3,H^{13}}$ = 6.5), 2.0 m (2H, H^{10}, H^{12}), 3.60 d.d (1H, H^{11}, $J_{H^{11},H^{12}}$ = 4.75, $J_{H^{11},H^{10}}$ = 11), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.01 m (1H, H^{13}), 4.30 d and 4.55 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11, J_{gem} = 10), 4.12 m (2H, $OCH_2CH{=}CH_2$-9), 5.23 m (2H, $OCH_2CH{=}CH_2$-9), 5.91 m (1H, $OCH_2CH{=}CH_2$-9), 6.88 m and 7.28 m (4H, $CH_3OC_6H_4CH_2O$-11).

2,4,6-Trideoxy-2,4-di-C-methyl-3-O-MPM-α,β-D-galactopyranose (VI). a. A solution of 1.25 g (3.91 mmoles) of compound (V) and 0.66 g t-BuOK (1.5 equiv.) in 8 ml DMSO was heated with vigorous mixing for 2 h at 100°C. It was then cooled, diluted with water, and extracted with ether. The extract was washed with water and dried with Na_2SO_4. The solvent was evaporated in a vacuum, and the residue was dissolved in 100 ml of acetone—water (8:2). A 1.5-g (1.2-equiv.) portion of $Hg(OAc)_2$ was added, with mixing, the mixture was stirred for 5 h, and allowed to stand for 12 h. The mixture was evaporated in a vacuum, and the residue was dissolved in chloroform. The solution was washed with water and 10% KI, dried with Na_2SO_4, and the solvent was evaporated in a vacuum. Yield: 1.3 g (93.4%).

b. A 500-mg (2.89-mmole) solution of compound (II) in 3 ml DMF was added, with vigorous mixing, to 210 mg (3 equiv.) NaH in 2 ml DMF; then 350 μl (1.2 equiv.) of p-methoxybenzyl chloride (MPMCl) was added, and the mixture was stirred for 12 additional hours. The mixture was diluted with 10 ml water and extracted with ether. The extract was washed with water and dried with $MgSO_4$. The solvent was evaporated in a vacuum; the residue was dissolved in 5 ml of 80% aqueous AcOH and heated for 4 h at 60°C. The mixture was evaporated in a vacuum; the residue was neutralized with saturated $NaHCO_3$ and extracted with chloroform. The extract was washed with water and dried with $MgSO_4$. The solvent was evaporated in a vacuum, and the residue was chromatographed. Yield: 621 mg (77%).

2,4,6-Trideoxy-2,4-di-C-methyl-3-O-MPM-D-dulcite (VII). Three grams of $NaBH_4$ were added in 200-mg portions, with vigorous mixing over a period of 25 h, to 1.3 g (3.65 mmoles) of compound (VI) in 100 ml ethanol; then 50 ml of water was added, followed by dropwise addition of AcOH till neutralization. The mixture was extracted with chloroform; the extract was washed with saturated aqueous NaCl, dried with Na_2SO_4, and evaporated in a vacuum. The residue was passed through a silica gel layer; impurities were washed with benzene–ether (8:2), and the product was washed with ethyl acetate. Yield: 0.922 g (70.5%). Syrup, $[\alpha]_D^{25}$ −3.8° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.94 d (3H, 12-CH_3, $J_{CH_3,H^{12}} = 7$), 0.99 d (3H, 10-CH_3, $J_{CH_3,H^{10}} = 7$), 1.17 d (3H, 13-CH_3, $J_{CH_3,H^{13}} = 6.5$), 1.74 s (1H, H^{12}, $J_{H^{12},H^{13}} = 2$, $J_{H^{12},H^{11}} = 7$), 2.02 m (1H, H^{10}, $J_{H^{10},H^{11}} = 2$, $J_{H^{10},H^{9}a} = J_{H^{10},H^{9}b} = 7$), 3.57 m (1H, $H^{9}b$, $J_{H^{9}b,H^{9}a} = 12$), 3.59 d.d (1H, H^{11}, $J_{H^{11},H^{12}} = 7$), 3.64 m (1H, $H^{9}a$), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.16 d.q (1H, H^{13}), 4.56 d and 4.62 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11), $J_{gem} = 10$), 6.85 m and 7.25 m (4H, $CH_3OC_6H_4CH_2O$-11).

2,4,6-Trideoxy-2,4-di-C-methyl-3-O-MPM-1-O-benzoyl-D-dulcite (VIII). A 128 μl (1-equiv.) portion of benzoyl chloride was added dropwise, with mixing at −35°C, to 310 mg (1.10 mmoles) of compound (VII) in 4 ml pyridine. The reaction mixture was stirred at the same temperature for 1 h; it was then diluted with water and extracted with chloroform (3 × 20 ml) at about 20°C. The extract was washed with 1 M HCl and water, dried with Na_2SO_4, and evaporated in a vacuum; the residue was chromatographed. Yield: 396.3 mg (93%). Syrup, $[\alpha]_D^{25}$ +24.0° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.98 d (3H, 12-CH_3, $J_{CH_3,H^{12}} = 7$), 1.12 d (3H, 10-CH_3, $J_{CH_3,H^{10}} = 7$), 1.18 d (3H, 13-CH_3, $J_{CH_3,H^{13}} = 7$), 1.76 m (1H, H^{12}, $J_{H^{12},H^{13}} = 2$, $J_{H^{12},H^{11}} = 7$), 2.34 m (1H, H^{10}, $J_{H^{10},H^{9}a} = J_{H^{10},H^{9}b} = 7$, $J_{H^{10},H^{11}} = 4.5$), 3.60 d.d (1H, H^{11}), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.22 m (1H, H^{13}), 4.33 m (2H, $H^{9}a$, $H^{9}b$, $J_{H^{9}a,H^{9}b} = 11$, AB-system), 4.60 s (2H, $CH_3OC_6H_4CH_2O$-11), 6.85 m and 7.25 m (4H, $CH_3OC_6H_4CH_2O$-11), 7.55 m and 8,08 m (5H, C_6H_5COO-9).

2,4,6-Trideoxy-2,4-di-C-methyl-1-O-benzoyl-3-O-MPM-5-O-TBS-D-dulcite (IX). A 1.1-ml (3-equiv.) portion of triethylamine was added, with mixing at −25°C, to 396 mg (1.02 mmoles) of compound (VIII) in 5 ml dichloromethane; then 500 μl (1.1 equiv.) of TBSOTf was added. After 10 min the cooling was stopped and water was added; the aqueous layer was separated and extracted with chloroform. The extract was washed with saturated $NaHCO_3$ and water, dried with Na_2SO_4, and evaporated in a vacuum; the residue was chromatographed. Yield: 514 mg (100%). Syrup, $[\alpha]_D^{25}$ +44.44° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.09 s and 0.10 s (6H, t-Bu(CH_3)$_2$SiO-13), 0.83 d (3H, 12-CH_3, $J_{CH_3,H^{12}} = 7$), 0.91 d (3H, 10-CH_3, $J_{CH_3,H^{10}} = 7$), 0.92 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.19 d (3H, 13-CH_3, $J_{CH_3,H^{13}} = 6.5$), 1.61 m (1H, H^{12}, $J_{H^{12},H^{13}} = 2.5$, $J_{H^{12},H^{11}} = 7$), 2.34 m (1H, H^{10}, $J_{H^{10},H^{9}a} = J_{H^{10},H^{9}b} = 7$, $J_{H^{10},H^{11}} = 4.5$), 3.63 d.d (1H, H^{11}), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.30 m (1H, H^{13}), 4.33 m (2H, $H^{9}a$, $H^{9}b$, $J_{H^{9}a,H^{9}b} = 11$, AB-system), 4.51 d and 4.62 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11, $J_{gem} = 11$), 6.85 m and 7.25 m (4H, $CH_3OC_6H_4CH_2O$-11), 7.55 m and 8,08 (5H, C_6H_5COO-9).

2,4,6-Trideoxy-2,4-di-C-methyl-3-O-MPM-5-O-TBS-D-dulcite (X). A 5-ml portion of 15% NaOH was added to 514 mg (1.02 mmoles) of compound (IX) in 50 ml ethanol, and the mixture was boiled for 30 min. The solution was cooled and evaporated in a vacuum; the residue was chromatographed. Yield: 374 mg (92%). Syrup, $[\alpha]_D^{25}$ −8.66° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.096 s and 0.018 s (6H, t-Bu(CH_3)$_2$SiO-13), 0.83 d (3H, 12-CH_3, $J_{CH_3,H^{12}} = 7$),

0.91 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 7), 0.92 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.19 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 1.61 m (1H, H^{12}, $J_{H^{12},H^{13}}$ = 2.5, $J_{H^{12},H^{11}}$ = 7), 1.91 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2, $J_{H^{10},H^{9}}$ = 7), 3.63 m (1H, H^{11}), 3.65 m (2H, H^{9a}, H^{9b}, J_{gem} = 12, AB-system), 3.80 m (3H, $CH_3OC_6H_4CH_2O$-11), 4.30 d.q (1H, H^{13}), 4.51 d and 4.62 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11, J_{gem} = 11 Hz), 6.85 m and 7.25 m (4H, $CH_3OC_6H_4CH_2O$-11).

2,4,6-Trideoxy-2,4-di-C-methyl-3-O-MPM-5-O-TBS-D-galactose (XI). a. A solution of 80 µl (4.03 equiv.) of DMSO in 2 ml dichloromethane was added dropwise, with mixing in an argon atmosphere, to 50 µl (2.06 equiv.) oxalyl chloride in 2 ml dichloromethane at −60°C. After 5 min, 110 mg (0.28 mmole) of compound (X) in 3 ml dichloromethane was added to the reaction mixture. The mixture was stirred for 30 min, then 500 µl (12.8 equiv.) of triethylamine was added. After 5 min, the temperature was raised to 20°C, and 30 ml of chloroform was added. The mixture was washed with 1 M HCl and water, dried with Na_2SO_4, and evaporated in a vacuum; the residue was chromatographed. Yield: 111 mg (100%). Syrup, $[\alpha]_D^{25}$ −43° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.093 s and 0.102 s (6H, t-Bu$(CH_3)_2$SiO-13), 0.86 d (3H, 12-CH_3; $J_{CH_3,H^{12}}$ = 7.25), 0.93 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.13 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.5), 1.15 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 1.61 m (1H, H^{12}, $J_{H^{12},H^{13}}$ = 2, $J_{H^{12},H^{11}}$ = 7.25), 2.52 d.q (1H, H^{10}, $J_{H^{10},H^{11}}$ = 1.75), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.03 d.d (1H, H^{11}), 4.27 d and 4.37 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11, J_{gem} = 10), 4.35 m (1H, H^{13}), 6.86 m and 7.20 m (4H, $CH_3OC_6H_4CH_2O$-11), 9.89 s (1H, H^{9}).

b. A 97-mg (3-equiv.) portion of $NaIO_4$ was added to 75 mg (0.151 mmole) of compound (XVII) in 3 ml THF–water (4:1). The reaction mixture was stirred for 20 min, then 6 ml of chloroform and 5 ml water were added. The aqueous layer was separated and extracted with chloroform (2 × 4 ml). The extract was washed with water, dried with Na_2SO_4, and the solvent was evaporated in a vacuum; the residue was chromatographed. Yield: 50 mg (85%).

3,5,7-Trideoxy-3,5-di-C-methyl-4-O-MPM-6-TBS-1-isopropylidene-L-glucose (XII). A 10.8-ml portion of 1.115 N t-BuLi (12 mmoles, 6 equiv.) in pentane was added after 5 min to a vigorously mixed solution, cooled to −120°C in an argon atmosphere, of 810 mg (6 mmoles, 3 equiv.) isobutenyl bromide in 20 ml THF–ether–pentane (4:4:1). The mixture was stirred for 1 h at a temperature of −110 to −120°C. It was then heated to −90°C, and 15 ml ether, 309 mg (1.5 mmoles) of copper (I) bromide–dimethyl sulfide complex, and 2 ml dimethyl sulfide were added. The temperature was raised to −70°C, and 590 mg (1.5 mmoles) of compound (XI) in 6 ml ether was added. The mixture was stirred for 15 min and was decomposed by adding ammonium chloride solution. At about 20°C water was added; the aqueous layer was separated and extracted with ether (3 × 10 ml). The extract was washed with water and saturated NaCl, dried with Na_2SO_4, and evaporated in a vacuum; the residue was chromatographed. Yield: 366 mg (54%). Syrup, $[\alpha]_D^{25}$ +37.59° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.095 s (6H, t-Bu$(CH_3)_2$SiO-13), 0.82 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 7), 0.915 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.04 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 7), 1.18 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 1.62 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 1.75, $J_{H^{10},H^{9}}$ = 6.75), 1.70 m (6H, CH_3-7), 3.59 d.d (1H, H^{11}), 3.80 s (3H, $CH_3OC_6H_4CH_2O$-11), 4.25 m (1H, H^{13}), 4.45 m (1H, H^{9}), 4.41 d and 4.55 d (2H, AB-system of $CH_3OC_6H_4CH_2O$-11, J_{gem} = 11), 5.30 m (1H, H^{8}), 6.88 m and 7.27 m (4H, $CH_3OC_6H_4CH_2O$-11).

3,5,7-Trideoxy-2,4-O-(4-methoxybenzylidene)-3,5-di-C-methyl-6-O-TBS-1-isopropylidene-D-glycero-L-glucose (XIV). A 200-mg portion of MS 4 Å and 40 mg DDQ were added to a vigorously mixed solution of 70 mg (0.157 mmole) of compound (XII) in 2.5 ml dichloromethane. The mixture was stirred for 10 min, then a saturated $NaHCO_3$ solution was added. The layers were separated, and the aqueous layer was extracted with chloroform (2 × 5 ml). The extract was washed with water, dried with $MgSO_4$, and evaporated in a vacuum; the residue was chromatographed. Yield: 63 mg (91%). PMR spectrum (δ, ppm, J, Hz): 0.05 s (6H, t-Bu$(CH_3)_2$SiO-13), 0.78 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 6.75), 0.92 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.02 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.25), 1.10 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 1.56 m (1H, $J_{H^{12},H^{13}}$ = 1.5, $J_{H^{12},H^{11}}$ = 10), 1.57 m (1H, H^{10}, $J_{H^{10},H^{9}}$ = 8, $J_{H^{10},H^{11}}$ = 2.3), 1.75 m (6H, $(CH_3)_2$C=CH-9), 3.72 d.d (1H, H^{11}), 3.80 s (3H, $CH_3OC_6H_4CH$-11, 9), 4.33 d.q (1H, H^{13}), 4.57 d.d (1H, H^{9}),

5.38 m (1H, H^8), 5.52 s (1H, $CH_3OC_6H_4\underline{CH}$-11, 9), 6.88 m and 7.45 m (4H, ($CH_3OC_6\underline{H_4}CH$-11, 9)). Nuclear Overhauser effect (H_{ac}) H^9 = 8%, (H_{ac}) H^{11} = 7.5%.

2,4,6-Trideoxy-2,4-di-C-methyl-carbethoxymethylidene-3-O-MPM-5-O-TBS-D-galactose (XV). A 120-mg (2.42-equiv., 0.343-mmole) portion of carboxymethylidenephosphorane was added to 56 mg of aldehyde (XI) in 4.5 ml THF, and the mixture was boiled, with stirring, for 2.5 h. It was then cooled and evaporated in a vacuum. The residue was dissolved in benzene and passed through a silica gel layer; the reaction product was washed with benzene. The solution was evaporated in a vacuum, and the residue was chromatographed. Yield: 53 mg (78%). Syrup, $[\alpha]_D^{28}$ +14.33° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.095 s (6H, t-Bu($\underline{CH_3}$)$_2$SiO-13), 0.85 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 7), 0.915 s (9H, t-Bu(CH_3)$_2$SiO-13), 1.08 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.75), 1.17 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.25), 1.38 t (3H, J_{CH_3,CH_2} = 7.25, CH_3-CH_2O), 1.56 m (1H, H^{12}, $J_{H^{12},H^{13}}$ = 2.25, $J_{H^{12},H^{11}}$ = 9.2), 2.62 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2.75, J_{H^{10},H^9} = 7), 3.45 d.d (1H, H^{11}), 3.83 s (3H, $\underline{CH_3}OC_6H_4CH_2O$-11), 4.21 q (2H, $CH_3\underline{CH_2}O$, J_{gem} = 14), 4.3 m (1H, H^{13}), 4.43 m (2H, $CH_3OC_6H_4\underline{CH_2}O$-11), 5.88 d.d (1H, H^8, $J_{H^8,H^{10}}$ = 2), 6.87 m and 7.25 m (4H, $CH_3OC_6\underline{H_4}CH_2O$-11), 7.20 d.d (1H, H^9, J_{H^9,H^8} = 16).

4,6,8-Trideoxy-4,6-di-C-methyl-5-O-MPM-7-O-TBS-D-threo-L-galactooctanoic Acid Ethyl Ester (XVI) and 4,6,8-Trideoxy-4,6-di-C-methyl-5-O-MPM-7-O-TBS-D-threo-L-idooctanoic Acid Ethyl Ester (XVII). A 100-mg (0.736-mmole, 3.18-equiv.) portion of N-methylmorpholine N-oxide and 10 mg OsO_4 were added to 110 mg (0.232 mmole) of compound (XV) in 3 ml acetone–water (8:1). The homogeneous solution was kept for 2 h at about 20°C, then 12 ml chloroform and 500 mg $Na_2S_2O_5$ in 5 ml water were added; the mixture was shaken, and the layers were separated. The aqueous layer was extracted with chloroform (2 × 5 ml), the extract was dried with $MgSO_4$, the solvent was evaporated in a vacuum, and the residue was chromatographed. Yield: 78 mg (68%) of compound (XVI) and 26 mg (23%) of compound (XVII). (XVI): syrup, $[\alpha]_D^{30}$ +5.53° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.09 s and 0.10 s (6H, t-Bu($\underline{CH_3}$)$_2$SiO-13), 0.82 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 7), 0.91 s (9H, t-Bu(CH_3)$_2$SiO-13), 0.94 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 7), 1.19 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.25), 1.32 t (3H, $\underline{CH_3}CH_2O$, J_{CH_3,CH_2} = 7), 1.63 m (1H, H^{12}, $J_{H^{11},H^{12}}$ = 9.8, $J_{H^{12},H^{13}}$ = 1.8), 2.05 m (1H, H^{10}, J_{H^{10},H^9} = 10.5, $J_{H^{10},H^{11}}$ = 2), 3.83 s (3H, $\underline{CH_3}OC_6H_4CH_2O$-11), 3.92 d.d (1H, H^9, J_{H^9,H^8} = 1.75), 4.27 m (2H, $CH_3\underline{CH_2}O$), 4.30 m (1H, H^{13}), 4.60 d and 4.66 d (2H, AB-system of $CH_3OC_6H_4\underline{CH_2}O$-11, J_{gem} = 11), 6.87 m and 7.25 m (4H, $CH_3OC_6\underline{H_4}CH_2O$-11).

4,6,8-Trideoxy-4,6-di-C-methyl-5-O-MPM-7-O-TBS-D-threo-L-galactooctanol (XIX). A 53-mg (1.43-mmoles, 7.5-equiv.) portion of $LiAlH_4$ was added, with mixing, to 95 mg (0.191 mmole) of compound (XVI) in 3 ml ether at −30°C. The mixture was stirred for 1 h, then the temperature was raised to 10°C. The mixture was diluted with 5 ml ethyl acetate, then 53 μl of water was added followed by 53 μl of 15% aqueous NaOH and another 150 μl water. The mixture was filtered through a layer of $MgSO_4$, the precipitate was washed with ethyl acetate, the filtrate was evaporated, and the residue was chromatographed. Yield: 30 mg (35%) of compound (XIX). Syrup, $[\alpha]_D^{30}$ −4.53° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.082 s and 0.095 s (6H, t-Bu($\underline{CH_3}$)$_2$SiO-13), 0.82 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 7), 0.92 s (9H, t-Bu(CH_3)$_2$-SiO-13), 0.95 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.25), 1.2 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.25), 1.64 m (1H, $J_{H^{12},H^{11}}$ = 10, $J_{H^{12},H^{13}}$ = 1.75), 2.1 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2, J_{H^{10},H^9} = 11), 3.62 m (2H, H^{11}, H^8), 3.84 m (1H, H^9), 4.33 d.q (1H, H^{13}), 4.57 d and 4.66 d (2H, AB-system of $CH_3OC_6H_4\underline{CH_2}O$-11, J_{gem} = 11), 6.87 m and 7.25 m (4H, $CH_3OC_6\underline{H_4}CH_2O$-11).

4,6,8-Trideoxy-4,6-di-C-methyl-3,5-O-(4-methoxybenzylidene)-7-O-TBS-D-threo-L-idooctanoic Acid Ethyl Ester (XVIII). A 200-mg portion of MS 3 Å was added to 48 mg (0.0967 mmole) of compound (XVII) in 2 ml dichloromethane; then 24.2 mg (1.1 equiv.) DDQ was added with vigorous mixing and, after 10 min, 4 ml saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with chloroform (2 × 5 ml). The extract was washed with water, dried with $MgSO_4$, and evaporated in a vacuum; the residue was chromatographed. Yield: 43 mg (90%) of compound (XVIII). Syrup, $[\alpha]_D^{30}$ −12.7° (c 1.0). PMR spectrum (δ, ppm, J, Hz): −0.02 s and 0.018 s (6H, t-Bu($\underline{CH_3}$)$_2$SiO-13), 0.77 d (3H, 12-CH_3,

$J_{CH_3,H^{12}}$ = 7), 0.89 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.10 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.5), 1.15 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.75), 1.32 t (3H, CH_3CH_2O, J_{CH_3,CH_2} = 7), 1.56 m (1H, H^{12}, $J_{H^{12},H^{11}}$ = 10, $J_{H^{12},H^{13}}$ = 1.75), 1.73 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2, $J_{H^{10},H^{9}}$ = 9), 3.60 d.d (1H, H^{11}), 3.82 s (3H, $CH_3OC_6H_4CH$-9, 11), 4.0 d.d (1H, H^9, J_{H^9,H^8} = 2.25), 4.29 m (3H, H^{13} and CH_3CH_2O), 4.34 m (1H, H^8), 5.49 s (1H, $CH_3OC_6H_4CH$-9, 11), 6.91 m and 7.42 m (4H, $CH_3OC_6H_4CH$-9, 11). Nuclear Overhauser effect (H_{ac}) H^9 = 8.7%, (H_{ac}) H^{11} = 7.8%.

4,6,8-Trideoxy-4,6-di-C-methyl-5-O-(4-methoxybenzylidene)-7-O-TBS-D-threo-L-galacto-octanol (XX). A 200-mg portion of MS 3 Å was added to 30 mg (0.066 mole) of compound (XIX) in 2.5 ml dichloromethane; then 16.4 mg (0.072 mmole) DDQ was added with vigorous mixing. After 10 min, saturated $NaHCO_3$ was added; the aqueous layer was separated and extracted with chloroform (2 × 5 ml). The extract was washed with water, dried, and passed through a layer of $MgSO_4$ and aluminum oxide. The solvent was evaporated in a vacuum. Yield: 29.5 mg (98.8%); chromatographically and spectrally pure compound. Syrup, $[\alpha]_D^{31}$ −24.26° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.01 s (6H, t-Bu$(CH_3)_2$SiO-13), 0.77 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 6.5), 0.89 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.08 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.25), 1.25 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.25), 1.52 m (1H, H^{12}, $J_{H^{12},H^{13}}$ = 1.75, $J_{H^{12},H^{11}}$ = 10), 1.68 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2, $J_{H^{10},H^{9}}$ = 10), 3.57 d.d and 3.65 d.d (2H, H^{7a}, H^{7b}, J_{H^7,H^8} = 4.25 AB-system), 3.62 s (3H, $CH_3OC_6H_4CH$-9, 11), 3.68 m (1H, H^9, J_{H^9,H^8} = 2.5), 3.90 m (1H, H^{11}), 4.27 and (1H, H^8), 5.76 s (1H, $CH_3OC_6H_4CH$-9, 11), 6.92 m and 7.45 m (4H, $CH_3OC_6H_4CH$-9, 11). Nuclear Overhauser effect (H_{ac}) H^8 = 7%, (H_{ac}) H^{11} = 7%.

3,5,7-Trideoxy-3,5-di-C-methyl-2,4-O-(4-methoxybenzylidene)-5-O-TBS-D-glycero-L-manno-heptitol (I). A 200-mg portion of sodium acetate and (at −20°C) 87 mg (3 equiv.) $Pb(OAc)_4$ were added to a vigorously mixed solution of 29.5 mg (0.065 mmole) of compound (XX) in 2 ml acetonitrile. The mixture was stirred for 15 min and filtered through a layer of aluminum oxide; the product was washed with ether. The solution was evaporated, and the residue was chromatographed. Yield: 14 mg (51%). Syrup, $[\alpha]_D^{30}$ −67.5° (c 1.0). PMR spectrum (δ, ppm, J, Hz): 0.00 s and −0.05 s (6H, t-Bu$(CH_3)_2$SiO-13), 0.80 d (3H, 12-CH_3, $J_{CH_3,H^{12}}$ = 6.5), 0.86 s (9H, t-Bu$(CH_3)_2$SiO-13), 1.08 d (3H, 13-CH_3, $J_{CH_3,H^{13}}$ = 6.25), 1.26 d (3H, 10-CH_3, $J_{CH_3,H^{10}}$ = 6.25), 1.50 m (1H, H^{12}, $J_{H^{12},H^{11}}$ = 10, $J_{H^{12},H^{13}}$ = 1.75), 2.35 m (1H, H^{10}, $J_{H^{10},H^{11}}$ = 2.25, $J_{H^{10},H^{9}}$ = 10), 3.60 d.d (1H, H^{11}), 3.63 s (3H, $CH_3OC_6H_4CH$-9, 11), 4.23 d.d (1H, H^{13}), 4.28 d (1H, H^9), 5.71 s (1H, $CH_3OC_6H_4CH$-9, 11), 6.93 m and 7.48 m (4H, $CH_3OC_6H_4$-CH-9, 11), 10.05 s (1H, H^8).

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