A Chiral Synthesis of D-*myo*-Inositol 1-Phosphate Starting from L-Quebrachitol

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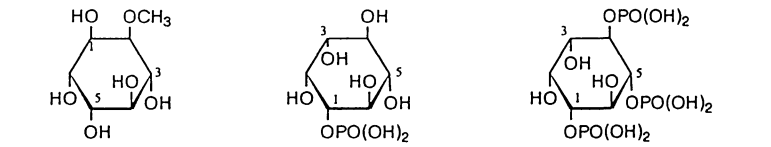
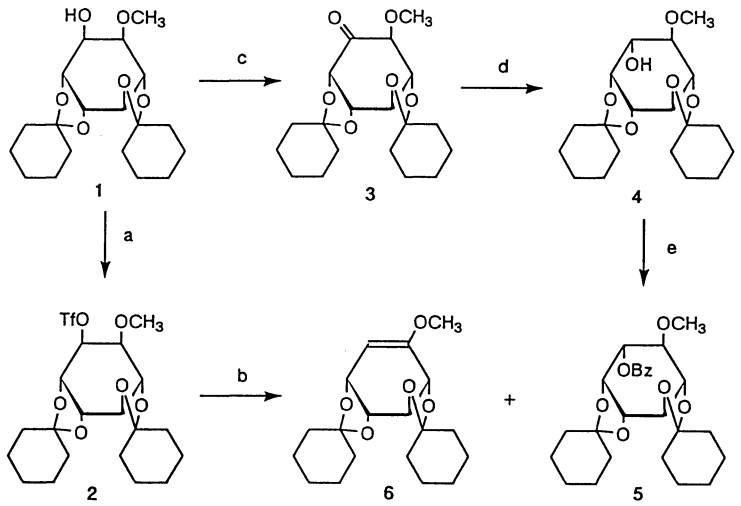
A naturally occurring optically active cyclitol, L-quebrachitol (1L-2-*O*-methyl-*chiro*-inositol), was stereoselectively transformed into *myo*-inositol derivatives via an oxidation–reduction process. The methyl ether was cleaved chemoselectively with $AlCl_3$–NaI in the presence of a *cis*-cyclohexylidene moiety with D-*myo*-inositol 1-phosphate being efficiently obtained.

Inositol phosphates have recently attracted considerable attention due to their important role in the transmembrane signalling process in the cell.[1] For example, D-*myo*-inositol 1,4,5-triphosphate ($Ins(1,4,5)P_3$) acts as the intracellular second messenger for calcium mobilization. A number of synthetic methods have appeared so far starting from *myo*-inositol, which is a naturally occurring optically inactive cyclitol.[2] A cumbersome optical resolution process is thus necessary for the syntheses of chiral inositol phosphates. L-Quebrachitol (1L-2-*O*-methyl-*chiro*-inositol) is one of the naturally occurring optically active inositols, obtained from an exudate of the rubber tree, and is currently of widespread interest as a new chiral source in organic synthesis.[3,4] Paulsen and his co-workers have reported the syntheses of branched-chain cyclitols,[5] and



Scheme 1.



Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, 0 °C, 1 h; (b) PhCOOCs, 18-Crown-6, DMF, 100 °C, 10 h; (c) RuO_2, $NaIO_4$, K_2CO_3, CH_3CN–CCl_4–H_2O, r.t. 3 h; (d) $NaBH_4$, THF–H_2O, 0 °C, 20 min; (e) PhCOCl, Et_3N, CH_2Cl_2, r.t. 3h.

Scheme 2.

Chida and Ogawa the syntheses of natural products such as Bengamide E.[6] Although the chiral syntheses of L-*myo*-inositol 1-phosphate[7] as well as L-*myo*-inositol 1,4,5-triphosphate[8] from L-quebrachitol have already been reported, no effective transformation of L-quebrachitol into biologically intriguing D-*myo*-inositol phosphates has been developed. Two difficulties have to be overcome in order to readily obtain optically active *myo*-inositol derivatives from L-quebrachitol; 1) chemoselective demethylation of the 2-OMe group in the presence of protecting groups, 2) stereospecific inversion of the configuration at C-1, that is, transformation of *chiro*-inositol into *myo*-inositol. We wish to report herein an efficient synthesis of D-*myo*-inositol 1-phosphate[9] as well as some chiral *myo*-inositol derivatives starting from L-quebrachitol, a synthesis involving stereoselective conversion of *chiro*-inositol to *myo*-inositol and subsequent $AlCl_3$–NaI promoted chemoselective demethylation of the methyl ether.[10]

Results and Discussion

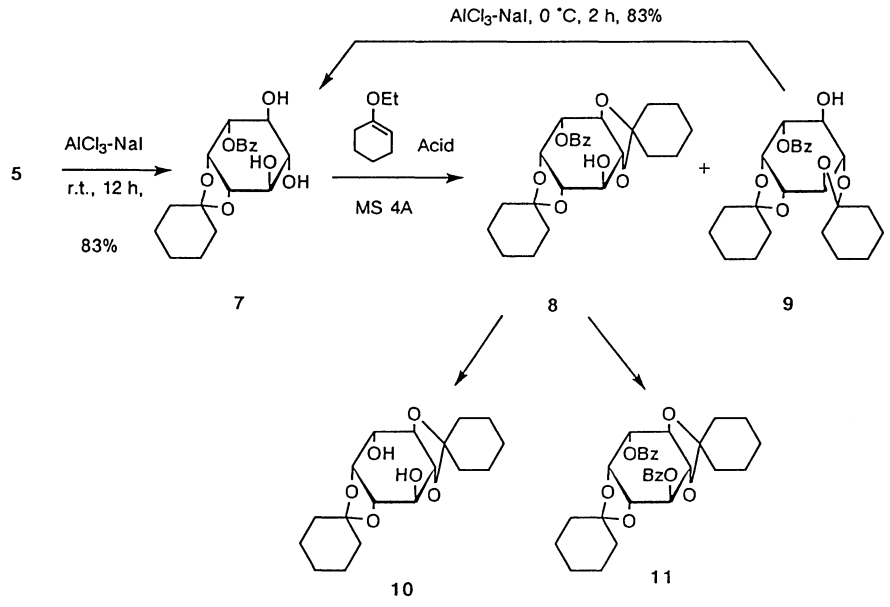
The first step in our approach towards the preparation of D-*myo*-inositol 1-phosphate from L-quebrachitol consisted of stereospecific inversion at C-1 of 1L-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol (**1**), readily available from L-quebrachitol in a single step.[7] The Mitsunobu inversion (EtOCON=NCOOEt, PPh_3, PhCOOH) of **1** was attempted, but no reaction took place.

Next, S_N2 displacement of *chiro*-inositol 1-trifluoromethanesulfonate (**2**) with benzoic acid metal salt was examined and the results are shown in Table 1. Treatment of **2** with cesium benzoate in the presence of 18-Crown-6[11] in toluene at 100 °C for 10 h gave a *myo*-inositol benzoate **5** in 56% yield together with 41% of the elimination product **6**. Other metal salts such as those of potassium or sodium were less satisfactory. Although the successful S_N2 displacement of the trifluoromethanesulphonate moiety of inositol with carboxylate ions has been reported,[12] clean S_N2 displacement of **2** did not take place due to the concurrent E2 elimination. Oxidation of the 1-OH group was studied. Most reproducible and high-yielding results were obtained with the Sharpless-modified RuO_2 oxidation (RuO_2–$NaIO_4$ in CCl_4–CH_3CN–H_2O)[13] and **3** was quantitatively obtained. Because the ketone was rather labile and was slightly decomposed during SiO_2 column

Table 1. S_N2 Displacement of *chiro*-Inositol Triflate **2**

$$\mathbf{2} \xrightarrow[\text{PhCOOM}]{\text{(4—6 equiv)}} \mathbf{5}+\mathbf{6}$$

Run	M	Additive	Conditions		Solvent	Yield of **5**/%	Yield of **6**/%
			°C	h			
1	Cs	18-Crown-6	100	10	Toluene	56	41
2	Cs	—	80	3	DMF	48	48
3	Na	—	45	2	DMF	37	46
4	K	18-Crown-6	80	4	DMF	18	85



Scheme 3.

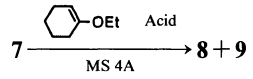
purification, it should be used immediately without purification. Reduction of the ketone with $NaBH_4$ followed by benzoylation afforded *myo*-inositol benzoate **5** in 93% yield from **1** with high stereoselectivity (97>3). One recrystallization gave pure *myo*-inositol benzoate **5** in high yield.

Chemoselective cleavage of the methyl ether of **5** was next investigated. For the cleavage of inositol methyl ethers, strongly acidic conditions such as HI[4a] and BCl_3[7] had been employed. Ley recently reported $BF_3 \cdot OEt_2$-*n*-$Bu_4N \cdot I$ mediated demethylation of *O*-methyl-penta-*O*-benzoyl-*chiro*-inositol which proceeded with a moderate yield.[14] Although we attempted the demethylation methods previously described along with other methods such as $AlCl_3$–EtSH[15] and Me_3SiCl–NaI[16] for the demethylation of **5**, most of the protecting groups were cleaved under these reaction conditions. Chemoselective demethylation of the methyl ether in preference to the *cis*-cyclohexylidene group was realized by the treatment of **5** with $AlCl_3$ (10 equiv) and NaI (10 equiv) in CH_3CN[17] at room temperature with a triol **7** being obtained in 83% yield.

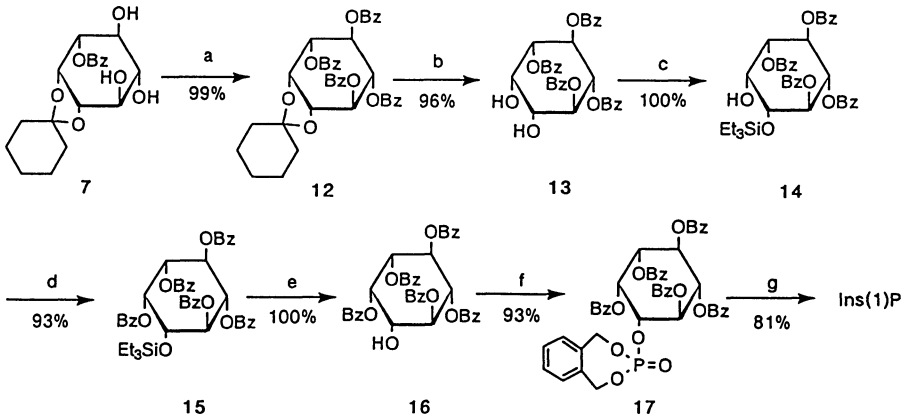
Regioselective protection of the 4,5-OH groups was next studied as shown in Table 2. The triol **7** was treated with ethoxycyclohexene in the presence of *p*-TsOH to give a mixture of the 1,2:4,5-di-*O*-cyclohexylidene derivative **8** and its 1,2:5,6-isomer **9** (Run 1). Since the latter isomer could be transformed into **7** in 83% yield by treatment with $AlCl_3$–NaI in CH_3CN at 0 °C for 2 h, **8** could be obtained in a good yield from **7** by recycling. Debenzoylation of **8** afforded **10**, which is an important chiral intermediate for the syntheses of optically active *myo*-inositol phosphates such as D-*myo*-inositol 1,4,5-triphosphate,[18] D-*myo*-inositol 1,3,4,5-tetraphosphate,[19] D-*myo*-inositol 1,4-diphosphate,[20] and *myo*-inositol phospholipids.[21] Benzoylation of **8** afforded **11**, which is also a crucial chiral intermediate for the syntheses of a number of optically active *myo*-inositol phosphates.[22]

With *myo*-inositol triol **7** synthesized, we next tried to synthesize Ins(1)P. The results are shown in Scheme 4. Perbenzoylation of **7** and subsequent acid hydrolysis of the *cis*-cyclohexylidene group (CF_3COOH, MeOH, r.t.) afforded a diol **13** in 96% yield. Selective protection of the equatorial OH group was accomplished with triethylsilyl moiety (Et_3SiCl, pyridine, 0 °C) to give **14** quantitatively, which on benzoylation of the axial OH group gave pentabenzoate **15** in 93% yield. The triethylsilyl group was readily deprotected by the action of *p*-TsOH in 80% aqueous acetic acid quantitatively.

Table 2. Effects of the Acid on the Cyclohexylidenation



Run	Acid	Solvent	Conditions °C h	Yield of **8**/%	Yield of **9**/%
1	*p*-TsOH	DMF	80 2	32	61
2	$BF_3 \cdot OEt_2$	CH_2Cl_2	0 0.5	20	34
3	CF_3SO_3H	CH_2Cl_2	0 3	16	20



Reagents and conditions: (a) PhCOCl, NEt_3, DMAP, CH_2Cl_2; (b) CF_3COOH, MeOH, r.t.; (c) Et_3SiCl, pyridine, 0 °C; (d) PhCOCl, NEt_3, DMAP, CH_2Cl_2; (e) *p*-TsOH, 80% AcOH; (f) i) 1*H*-Tetrazole, *o*-xylene-α,α'-diyl *N,N*-diethylphosphoramidite, CH_2Cl_2, ii) H_2O, iii) *m*-CPBA; (g) i) 10% Pd/C, H_2, MeOH, ii) NaOMe, MeOH, r.t.

Scheme 4. Synthesis of D-*myo*-inositol 1-phosphate.

Phosphorylation of the resultant OH group was achieved according to the newly developed method[23] (*o*-xylene-α,α'-diyl *N,N*-diethylphosphoramidite and 1*H*-tetrazole, followed by *m*-CPBA oxidation). Deprotection of the phosphate moiety by hydrogenolytic conditions, and subsequent deprotection of the benzoyl group afforded D-*myo*-inositol 1-phosphate, which was isolated as its crystalline dicylohexylamine salt in 81% yield. No migration of the phosphate moiety was detected by 270 MHz ^{1}H NMR. The present method for the synthesis of Ins(1)P is very efficient since; 1) excellent yields of all reactions make purifications of products very easy; and 2) an optical resolution process is not necessary. Additionally, the compounds thus produced would be useful precursors for syntheses of optically active cyclitols, in particular, chiral inositol phosphates.

The present study demonstrates the usefulness of L-quebrachitol as a chiral source for the synthesis of optically active cyclitol derivatives.

Experimental

The melting points were recorded on a Yamato melting point apparatus and are uncorrected. NMR spectra were observed with a JEOL GSX-270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi EPI G-3 spectrometer. Specific rotations were recorded with a Union PM-101 digital polarimeter.

S_N2 Displacement of 2. To a solution of **1**[7] (694 mg, 1.96 mmol) in CH_2Cl_2 (10 ml) were added successively pyridine (0.40 ml, 4.95 mmol) and trifluoromethanesulfonic anhydride (0.50 ml, 2.97 mmol) at 0 °C. After being stirred at that temperature for 1 h, the reaction mixture was quenched by addition of H_2O and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to dryness. The remaining oil of 1L-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-1-*O*-trifluoromethylsulfonyl-*chiro*-inositol (**2**) was used immediately without purification. A solution of **2** (38.8 mg, 0.0798 mmol), cesium benzoate[11] (134 mg, 0.529 mmol), and 18-Crown-6 (44.2 mg, 0.119 mmol) in toluene (2.5 ml) was heated at 100 °C for 10 h. After being allowed to cool to room temperature, the reaction mixture was quenched by addition of cold water and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The remaining oil was purified by preparative TLC (SiO_2, hexane : ethyl acetate=4 : 1) to give D-3-*O*-benzoyl-1,2:5,6-di-*O*-cyclohexylidene-4-*O*-methyl-*myo*-inositol (**5**) and 1L-1,2:3,4-di-*O*-cyclohexylidene-5-*O*-methyl-5-cyclohexene-(1,2,4/3)-pentol (**6**) in 56 and 41% respectively.

5. R_f 0.40 (hexane : ethyl acetate=4 : 1); mp 118—119 °C (hexane–ethyl acetate); IR (nujol) 1705, 1255, 1100, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22—1.80 (20H, m, $(CH_2)_{10}$), 3.56 (3H, s, CH_3), 3.60 (1H, dd, $J_{4,5}$=7.7 Hz, $J_{5,6}$=10.4 Hz, H-5), 3.67 (1H, dd, $J_{3,4}$=1.3 Hz, H-4), 4.23 (1H, dd, $J_{1,6}$=7.0 Hz, H-6), 4.47 (1H, t, $J_{1,2}$=7.0 Hz, H-1), 4.54 (1H, dd, $J_{2,3}$=3.7 Hz, H-2), 5.48 (1H, dd, H-3), 7.40—7.63 (3H, m, aromatic), and 7.98—8.16 (2H, m, aromatic); $[\alpha]_D^{22}$ −7.21° (*c* 2.22, $CHCl_3$). Found: C, 68.09; H, 7.46%. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47%.

6. R_f 0.30 (hexane : ethyl acetate=4 : 1); mp 139—141 °C; IR (nujol) 1620, 1350, 1315, 1260, 1220, and 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20—1.90 (20H, m, $(CH_2)_{10}$), 3.65 (3H, s, OCH_3), 3.76 (1H, t, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3), 4.08 (1H, ddd, $J_{4,6}$=2.0 Hz, $J_{1,4}$=1.0 Hz, H-4), 4.31 (1H, dd, $J_{1,2}$=7.0 Hz, H-2), 4.63 (1H, dd, $J_{1,6}$=3.5 Hz, H-6), 4.89 (1H, ddd, H-1), ^{13}C NMR ($CDCl_3$; internal standard of $CDCl_3$ as 77.00) δ=23.40, 23.48, 23.67, 23.96, 24.94, 25.11, 34.55, 35.95, 36.41, 37.56, 55.45, 72.91, 74.37, 74.60, 80.68, 90.38, 111.04, 114.17, and 156.18; $[\alpha]_D^{28}$ −26.5° (*c* 1.82, $CHCl_3$).

D-1,2:5,6-Di-*O*-cyclohexylidene-4-*O*-methyl-*myo*-inositol (4). To a vigorously stirred solution of **1** (2.0 g, 5.64 mmol) in CCl_4 (20 ml), CH_3CN (20 ml), and distilled water (20 ml) were successively added RuO_2 (52.6 mg, 0.395 mmol), K_2CO_3 (0.975 g, 7.05 mmol), and $NaIO_4$ (3.02 g, 14.1 mmol) in H_2O. After the vigorous stirring was continued for 3 h at room temperature, 2-propanol (4 ml) was added to the reaction mixture, which was filtered over Celite pad, and the filtrate extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give 2L-2,3:4,5-*O*-di-*O*-cyclohexylidene-6-*O*-methyl-(4,6/2,3,5)-pentahydroxycyclohexanone (**3**) as an oil quantitatively. To a solution of crude **3** (1.99 g, 5.64 mmol) in THF (30 ml) and H_2O (10 ml) was added $NaBH_4$ (0.213 g, 5.64 mmol) at 0 °C. After being stirred for 20 min, the reaction mixture was extracted with Et_2O, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated to give **4** (1.88 g) as an oil in 94% yield. The crude ketone was used without purification in the following step. IR ($CHCl_3$) 3570, 1160, 1100, and 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30—1.80 (20H, m, $(CH_2)_{10}$), 2.68 (1H, brs, OH), 3.45 (1H, dd, $J_{4,5}$=7.7 Hz, $J_{5,6}$=10.1 Hz, H-5), 3.50 (3H, s, CH_3), 3.66 (1H, dd, $J_{3,4}$=1.9 Hz, $J_{4,5}$=7.7 Hz, H-4), 3.97 (1H, dd, $J_{2,3}$=3.4 Hz, H-3), 4.16 (1H, dd, $J_{1,6}$=7.2 Hz, H-6), 4.34 (1H, t, $J_{1,2}$=7.2 Hz, H-1), and 4.39 (1H, dd, $J_{1,2}$=7.2 Hz, $J_{2,3}$=3.4 Hz, H-5); $[\alpha]_D^{29}$ −1.99° (*c* 10.7, $CHCl_3$). Found: C, 64.31; H, 8.61%. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53%.

D-3-*O*-Benzoyl-1,2:5,6-di-*O*-cyclohexylidene-4-*O*-methyl-*myo*-inositol (5). To a solution of **4** (3.05 g, 8.61 mmol), Et_3N (1.92 ml, 13.8 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (25 ml) was added benzoyl chloride (1.50 ml, 12.9 mmol) at 0 °C. After the stirring was continued at room temperature for 3 h, 10% HCl solution was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated to afford an oil, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 9) to give **5** as crystals in 93% yield. One recrystallization of the crystals from a mixture of hexane and ethyl acetate (v/v=7 : 1) gave pure **5** as crystals.

D-3-*O*-Benzoyl-1,2-*O*-cyclohexylidene-*myo*-inositol (7). To a solution of **5** (1.25 g, 2.73 mmol) in CH_3CN (30 ml) was added powdered $AlCl_3$ (3.63 g, 27.3 mmol) and NaI (4.09 g, 27.3 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at room temperature for 12 h, and ice water was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was successively washed with brine, 10% Na_2SO_3, and brine, dried over Na_2SO_4, concentrated in vacuo to leave an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2 : methanol=10 : 1) to afford **7** as crystals in 83% yield. Mp

198—200 °C (methanol); IR (nujol) 3490, 1700, 1275, 1105, and 700 cm^{-1}; ^1H NMR ($CDCl_3$: DMSO-d_6=95 : 5, v/v) δ=1.25—1.75 (10H, m, $(CH_2)_5$), 2.62—3.20 (3H, m, OH×3), 3.36 (1H, dd, $J_{4,5}$=10.0 Hz, $J_{5,6}$=11.0 Hz, H-5), 3.73 (1H, dd, $J_{1,6}$=8.0 Hz, H-6), 3.98 (1H, t, $J_{3,4}$=10.0 Hz, H-4), 4.09 (1H, dd, $J_{1,2}$=6.0 Hz, H-1), 4.53 (1H, t, $J_{2,3}$=6.0 Hz, H-2), 5.23 (1H, dd, H-3), 7.40—7.65 (3H, m, aromatic), and 8.05—8.20 (2H, m, aromatic); $[\alpha]_D^{22}$ +53.3° (*c* 1.22, ethanol). Found: C, 62.53; H, 6.66%. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64%.

D-3-*O*-Benzoyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (8) and D-3-*O*-benzoly-1,2:5,6-di-*O*-cyclohexylidene-*myo*-inositol (9). A mixture of **5** (38.9 mg, 0.107 mmol) and ethoxycyclohexene (45.6 mmol, 0.321 mmol) in DMF (0.8 ml) was heated at 80 °C for 2 h in the presence of *p*-toluenesulfonic acid (2.0 mg, 0.0107 mmol) and Molecular Sieves 4A. The reaction mixture was quenched by addition of sat. $NaHCO_3$ solution and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo to leave an oil, which was subjected to column chromatography (SiO_2, ethyl acetate : hexane=1 : 4) to obtain **8** and **9**, in 32% and 61% yield respectively.

8. R_f 0.30 (ethyl acetate : hexane=1 : 3); IR (nujol) 3500, 1700, 1260, 1100, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20—1.80 (20H, m, $(CH_2)_{10}$), 2.20—2.70 (1H, brs, OH), 3.48 (1H, dd, $J_{4,5}$=9.6 Hz, $J_{5,6}$=10.6 Hz, H-5), 3.95 (1H, dd, $J_{1,6}$=6.9 Hz, H-6), 4.13 (1H, dd, $J_{1,2}$=5.4 Hz, H-1), 4.19 (1H, dd, $J_{3,4}$=10.6 Hz, $J_{4,5}$=9.6 Hz, H-4), 4.72 (1H, t, $J_{2,3}$=5.4 Hz, H-2), 5.36 (1H, dd, H-3), 7.40—7.65 (3H, m, aromatic), and 8.10—8.20 (2H, m, aromatic); $[\alpha]_D^{26}$ +49.0° (*c* 1.51, $CHCl_3$), (lit, $[\alpha]_D^{20}$ +17.0° (*c* 2.1, $CHCl_3$)).[23a] Found: C, 67.59; H, 7.17%. Calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26%.

9. R_f 0.35 (ethyl acetate : hexane=1 : 3); IR (nujol) 3500, 1710, 1260, 1100, 1040, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30—1.76 (20H, m, $(CH_2)_{10}$), 3.03 (1H, d, *J*=4.2 Hz, OH), 3.58 (1H, dd, $J_{4,5}$=8.3 Hz, $J_{5,6}$=10.6 Hz, H-5), 4.08 (1H, dd, $J_{1,6}$=7.4 Hz, H-6), 4.15—4.25 (1H, m, H-4), 4.46 (1H, t, $J_{1,2}$=7.4 Hz, H-1), 4.65 (1H, dd, $J_{2,3}$=3.7 Hz, H-2), 5.27 (1H, dd, $J_{3,4}$=3.7 Hz, H-3), 7.40—7.64 (3H, m, aromatic), and 8.02—8.12 (2H, m, aromatic); $[\alpha]_D^{26}$ +1.8° (*c* 2.44, $CHCl_3$). Found: C, 67.50; H, 7.12%. Calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26%.

Conversion of 9 to 7. A solution of **9** (184.1 mg, 0.414 mmol) in CH_3CN (4 ml) was treated with $AlCl_3$ (275.7 mg, 2.07 mmol) and NaI (310.4 mg, 2.07 mmol) at 0 °C for 2 h. Ice water was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and 10% Na_2SO_3 solution, concentrated to give an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2 : ethyl acetate=1 : 3) to afford **7** in 83% yield.

D-1,2:4,5-Di-*O*-cyclohexylidene-*myo*-inositol (10). An ester **8** (71.7 mg, 0.161 mmol) was dissolved in a mixture of H_2O (0.2 ml) and methanol (2 ml) and treated with powdered KOH (90.5 mg, 1.61 mmol). After being stirred at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2, and washed with water. Removal of the solvent afforded an oil, which was purified by column chromatography to give **10** quantitatively. Mp 182—183 °C, (lit, 165—167 °C);[24b] IR (nujol) 1090 and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32—1.78 (20H, m), 2.44 (1H, d, *J*=9.1 Hz, OH), 2.61 (1H, brs, OH), 3.32 (IH, t, $J_{4,5}$=$J_{5,6}$=10.2 Hz, H-5), 3.82 (1H, t, $J_{3,4}$=10.2 Hz, H-4), 3.80—3.90 (1H, m, H-6), 3.98 (1H, dd, $J_{2,3}$=5.1 Hz, H-3), 4.07 (1H, t, $J_{1,6}$=$J_{1,2}$=5.1 Hz, H-1), and 4.47 (1H, t, H-2); $[\alpha]_D^{26}$ −26.4° (*c* 1.25, $CHCl_3$) (lit, $[\alpha]_D$ −16.0° (*c* 3.15, $CHCl_3$),[20] lit, $[\alpha]_D^{20}$ −5.6° (*c* 1.53, $CHCl_3$)).[24b] Found: C, 63.60; H, 8.39%. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29%.

D-1,2:4,5-Di-*O*-cyclohexylidene-3,6-di-*O*-benzoyl-*myo*-inositol (11). To a solution of **8** (27.5 mg, 0.0619 mmol) in CH_2Cl_2 (1 ml) were added a catalytic amount of DMAP, triethylamine (13.8 μl, 0.099 mmol), and benzoyl chloride (10.8 μl, 0.0929 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed successively with 0.5 mol dm^{-3} HCl, H_2O, and brine. The organic layer was dried over anhydrous $NaSO_4$ and evaporated to give an oil, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 5) to afford **11** in 72% yield. Mp 258—260 °C (lit, 267—269 °C);[24a] IR (nujol) 1700, 1260, 1160, 1100, 1060, and 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22—1.92 (20H, m, $(CH_2)_{10}$), 3.70 (IH, dd, $J_{4,5}$=10.5 Hz, $J_{5,6}$=9.5 Hz, H-5), 4.36 (1H, dd, $J_{1,6}$=6.7 Hz, $J_{1,2}$=4.6 Hz, H-1), 4.38 (1H, t, $J_{3,4}$=10.5 Hz, H-4), 4.76 (1H, t, $J_{2,3}$=4.6 Hz, H-2), 5.40 (1H, dd, H-3), 5.58 (1H, dd, H-6), 7.38—7.63 (6H, m, aromatic), and 8.02—8.18 (4H, m, aromatic); $[\alpha]_D^{25}$ +28.9° (*c* 1.35, $CHCl_3$), (lit, $[\alpha]_D^{20}$ +6.7° (*c* 0.58, $CHCl_3$)).[24a]

D-1,2-*O*-Cyclohexylidene-3,4,5,6-tetra-*O*-benzoyl-*myo*-inositol (12). To a solution of **7** (81.0 mg, 0.222 mmol) in CH_2Cl_2 (1.5 ml) were added a catalytic amount of DMAP, triethylamine (0.149 ml, 1.07 mmol), and benzoyl chloride (0.116 ml, 0.999 mmol) at 0 °C. The reaction mixture was quenched by addition of 0.5 mol dm^{-3} HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give crystals, which was purified by column chromatography (SiO_2, CH_2Cl_2–hexane, 3 : 1) to afford **12** as crystals in 99% yield. Mp 239—239.5 °C; IR (nujol) 1700, 1250, 1080, 1050, and 680 cm^{-1}; ^1H NMR ($CDCl_3$: DMSO-d_6=95 : 5, v/v) δ=1.22—1.80 (10H, m, $(CH_2)_5$), 4.57 (1H, dd, $J_{1,6}$=7.2 Hz, $J_{1,2}$=5.8 Hz, H-1), 4.83 (1H, dd, $J_{2,3}$=4.0 Hz, H-2), 5.70 (1H, t, $J_{4,5}$=$J_{5,6}$=9.0 Hz, H-5), 5.73 (1H, dd, $J_{3,4}$=9.9 Hz, H-3), 5.90 (1H, dd, H-6), 6.20 (1H, dd, H-4), 7.20—7.58 (12H, m, aromatic), and 7.80—8.08 (8H, m, aromatic); $[\alpha]_D^{26}$ +29.3° (*c* 3.00, $CHCl_3$). Found: C, 70.94; H, 5.41%. Calcd for $C_{40}H_{36}O_{10}$: C, 71.00; H, 5.36%.

D-3,4,5,6-Tetra-*O*-benzoyl-*myo*-inositol (13). A solution of **12** (0.553 g, 0.817 mmol) in a mixture of trifluoroacetic acid (16 ml) and methanol (2 ml) was stirred at room temperature for 30 min. The solvent was evaporated to dryness to leave an oil, which was recrystallized from a mixture of ethyl acetate and hexane to obtain **13** as crystals. Mp 226—227 °C; IR (nujol) 3450, 1710, 1260, 1100, and 700 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-d_6) δ=2.40 (2H, brs, OH), 4.14 (1H, brd, $J_{1,6}$=10.1 Hz, H-1), 4.61 (1H, t, $J_{2,1}$=$J_{2,3}$=2.7 Hz, H-2), 5.47 (1H, dd, $J_{3,4}$=10.1 Hz, H-3), 5.86 (IH, t, $J_{4,5}$=$J_{5,6}$=10.1 Hz, H-5), 5.93 (1H, t, H-6), 6.33 (1H, t, H-4), 7.20—7.54 (12H, m, aromatic), and 7.75—8.07 (8H, m, aromatic). $[\alpha]_D^{18}$ +19.8° (*c* 1.01, $CHCl_3$). Found: C, 68.18; H, 4.85%. Calcd for $C_{34}H_{28}O_{10}$: C, 68.45; H, 4.73%.

D-3,4,5,6-Tetra-*O*-benzoyl-1-*O*-triethylsilyl-*myo*-inositol (14). To a solution of **13** (74.2 mg, 0.124 mmol) in pyridine (1.0 ml) was added triethylsilyl chloride (31.3 μl, 0.186 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched by addition of 1 mol dm^{-3} HCl solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to afford an oil, which was purified by column chromatography (SiO_2, ethyl

acetate : hexane=1 : 3) to afford **14** in 100% yield. Mp 162—163 °C; IR (nujol) 3450, 1710, 1260, 1090, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.54 (6H, q), 0.84 (9H, t), 2.87 (1H, s, OH), 4.20 (1H, dd, $J_{1,6}$=9.7 Hz, $J_{1,2}$=2.7 Hz, H-1), 4.42 (1H, t, $J_{2,3}$=2.7 Hz, H-2), 5.45 (1H, dd, $J_{3,4}$=10.1 Hz, H-3), 5.78 (1H, t, $J_{4,5}$=$J_{5,6}$=10.1 Hz, H-5), 5.99 (1H, t, H-6), 6.32 (1H, t, H-4), 7.18—7.54 (12H, m, aromatic), and 7.72—8.08 (8H, m, aromatic); $[\alpha]_D^{26}$ +22.4° (*c* 1.43 $CHCl_3$). Found: C, 67.27; H, 5.95%. Calcd for $C_{40}H_{42}O_{10}Si$: C, 67.59; H, 5.96%.

D-1,3,4,5,6-Penta-*O*-benzoyl-1-*O*-triethylsilyl-*myo*-inositol (15). To a solution of **14** (382.7 mg, 0.538 mmol) in CH_2Cl_2 (5.5 ml) were added a catalytic amount of DMAP, triethylamine (0.15 ml, 1.08 mmol), and benzoyl chloride (0.125 ml, 1.076 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched by addition of 0.5 mol dm^{-3} HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo to give crystals, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 6) to afford **15** as crystals in 93% yield. Mp 186—188 °C; IR (nujol) 1710, 1250, 1090, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.50 (6H, q), 0.77 (9H, t), 4.41 (1H, dd, $J_{1,6}$=9.7 Hz, $J_{1,2}$=3.2 Hz, H-1), 5.63 (1H, dd, $J_{2,3}$=3.2 Hz, $J_{3,4}$=9.7 Hz, H-3), 5.88 (1H, t, $J_{4,5}$=$J_{5,6}$=9.7 Hz, H-5), 6.07 (1H, t, H-2), 6.12 (IH, t, H-6), 6.24 (1H, t, H-4), 7.20—7.70 (15H, m, aromatic), and 7.75—8.82 (10H, m, aromatic); $[\alpha]_D^{26}$ +55.9° (*c* 1.11 $CHCl_3$). Found: C, 69.03; H, 5.72%. Calcd for $C_{47}H_{46}O_{11}Si$: C, 69.27; H, 5.69%.

D-1,3,4,5,6-Penta-*O*-benzoyl-*myo*-inositol (16). A solution of **15** (73.0 mg, 0.0896 mmol) in $CHCl_3$ (0.2 ml) was treated with 80% aq acetic acid (1 ml) and *p*-toluenesulfonic acid (25.6 mg, 0.134 mmol) at room temperature for 1 h. The reaction mixture was quenched by addition of water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated to give an oil, which was purified by column chromatography (SiO_2, ethyl acetate–hexane, 1 : 1) to afford **16** in 100% yield. Mp 135—136 °C; IR (nujol) 3450, 1710, 1260, 1080, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.87 (1H, s, OH), 4.32—4.48 (1H, m, H-1), 5.66 (1H, dd, $J_{2,3}$=2.7 Hz, $J_{3,4}$=10.5 Hz, H-3), 5.92—6.20 (2H, m, H-5, H-6), 6.18 (1H, t, $J_{2,1}$=2.7 Hz, H-2), 6.23—6.32 (1H, m, H-4), 7.20—7.70 (15H, m, aromatic), and 7.78—8.22 (10H, m, aromatic); $[\alpha]_D^{26}$ +65.2° (*c* 1.15, $CHCl_3$). Found: C, 69.88; H, 4.82%. Calcd for $C_{41}H_{32}O_{11}$: C, 70.28; H, 4.60%.

D-2,3,4,5,6-Penta-*O*-benzoyl-1-*O*-(*o*-xylene-α,α'-diyldioxyphosphoryl)-*myo*-inositol (17). To a solution of **16** (237.2 mg, 0.339 mmol) in CH_2Cl_2 (5 ml) were added 1*H*-tetrazole (40.3 mg, 0.575 mmol) and *o*-xylene-α,α'-diyl *N,N*-diethylphosphoramidite (122 mg, 0.506 mmol) at room temperature. After 10 min, ion exchanged water (0.122 ml, 6.77 mmol) was added and stirring was continued for 10 min. The reaction mixture was allowed to cool at −40 °C and *m*-chloroperbenzoic acid (0.117 g, 0.677 mmol) was added. After being stirred at room temperature for 10 min, the reaction mixture was quenched by addition of H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was successively washed with brine, 10% Na_2SO_3, and sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated to give an oil, which was purified by column chromatography (SiO_2, ethyl acetate : hexane=1 : 2) to afford **17** in 93% yield. Mp 126—127 °C; IR (nujol) 1710, 1240, 1080, 1000, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.65—5.07 (4H, d, CH_2×2), 5.38 (1H, ddd, $J_{1,6}$=$J_{1,2}$=3.7 Hz, J_{1P}=10.2 Hz, H-1), 5.70 (1H, dd, $J_{2,3}$=3.7 Hz, $J_{3,4}$=10.2 Hz, H-3), 5.93 (1H, t, $J_{4,5}$=$J_{5,6}$=10.2 Hz, H-5), 6.25 (1H, dd, H-6), 6.28 (1H, t, H-4), 6.37 (1H, t, H-2), 6.95—7.74 (19H, m, aromatic), and 7.75—8.22 (10H, m, aromatic); $[\alpha]_D^{26}$ +22.7° (*c* 1.19, $CHCl_3$). Found: C, 66.98; H, 4.62%. Calcd for $C_{49}H_{39}O_{14}P$: C, 66.67; H, 4.45%.

D-*myo*-Inositol 1-Phosphate Dicyclohexylammonium Salt. A solution of **17** (191.7 mg, 0.217 mmol) in CH_3OH (3 ml) was treated with 10% Pd–C (50 mg) under H_2 atmosphere at room temperature overnight. The catalyst was filtered off and the filtrate was evaporated to dryness, which residue was dissolved in dry CH_3OH (3.5 ml) and NaH (60%, 0.10 mg) was added. After stirring at room temperature overnight, the reaction mixture was partitioned between CH_2Cl_2 and H_2O, and aqueous layer was washed with Et_2O and treated with Amberlite IR 120B (H^+). The acidic solution was washed once with Et_2O, cyclohexylamine (0.1 ml) added and evaporated to dryness in vacuo. The residue was recrystallized from H_2O–CH_3OH to give needles. Mp 190.5—192.5 °C, (lit, mp 190—192 °C);[7] ^1H NMR (D_2O, internal standard of HDO as 4.64) δ=0.90—1.28 (10H, m), 1.42—1.90 (10H, m), 2.80—3.10 (2H, m, NCH×2), 3.16 (1H, t, $J_{4,5}$=$J_{5,6}$=9.8 Hz, H-5), 3.39 (1H, dd, $J_{2,3}$=2.5 Hz, $J_{3,4}$=9.8 Hz, H-3), 3.47 (t, H-4), 3.57 (1H, $J_{1,6}$=9.8 Hz, H-6), 3.72 (1H, dt, $J_{1,2}$=2.5 Hz, $J_{1,P}$=9.8 Hz, H-1), 4.05 (1H, t, H-2); $[\alpha]_D^{28}$ +3.9° (*c* 3.0, H_2O), (lit, $[\alpha]_D^{20}$ +3.55° (*c* 1, H_2O)).[9c]

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