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SYNTHESIS OF 6-*O*-(α-D-MANNOPYRANOSYL)-D-*MYO*-INOSITOL : A FRAGMENT FROM *MYCOBACTERIA* PHOSPHOLIPIDS

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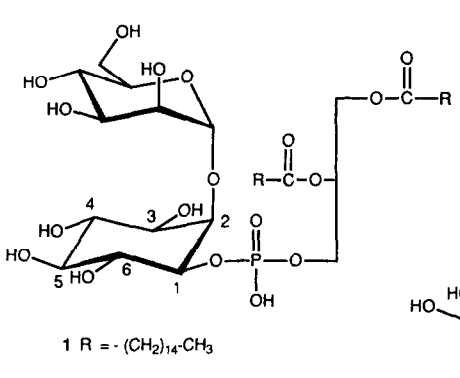
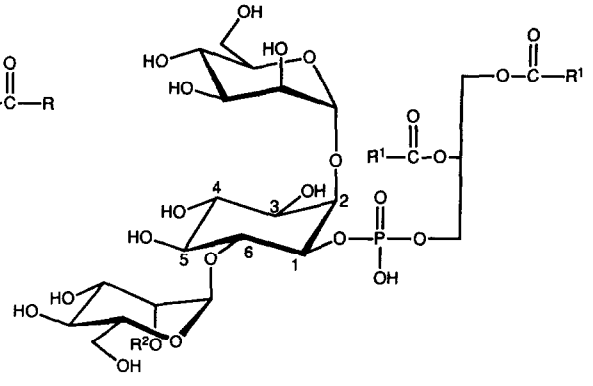
ABSTRACT. Condensation of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride (**12**) or ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**13**) with racemic 1,2-*O*-cyclohexylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol (**11**) gave, after deacylation and column chromatography, the enantiomorphs **16a** and **16b**. Benzylation, acid hydrolysis of the 1,2-*O*-cyclohexylidene group and regioselective allylation of **16b** led to **4b**, which was deblocked by deallylation and hydrogenolysis to give 6-*O*-(α-*O*-D-mannopyranosyl)-D-*myo*-inositol (**5b**). Any attempt to glycosylate the hydroxyl at the axial C-2 position of the *myo*-inositol moiety in **4b** with the mannopyranosyl fluoride **12** or the ethyl thiomannopyranoside **13** failed.

In an earlier report[1] from this laboratory, the synthesis of 1-*O*-(1,2-di-*O*-palmitoyl-*sn*-glycero-3-phosphoryl)-2-*O*-(α-D-mannopyranosyl)-D-*myo*-inositol (**1**) was described. The disubstituted D-*myo*-inositol derivative **1** is a fragment of a family of naturally occurring mycobacterial phospholipids **2a-b**, the structure of which was elucidated by Ballou *et al*[2].

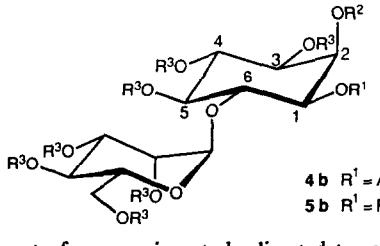


1 R = -$(CH_2)_{14}$-CH_3



2 **a** R^1 = -$(CH_2)_{14}$-CH_3, R^2 = -[α-(1-6)-D-Man*p*]$_{2-3}$
b R^1 = -$(CH_2)_{14}$-CH_3, R^2 = -[α-(1-6)-D-Man*p*]$_{2-3}$-α-(1-2)-D-Man*p*

3 R^1 = -$(CH_2)_{14}$-CH_3, R^2 = H

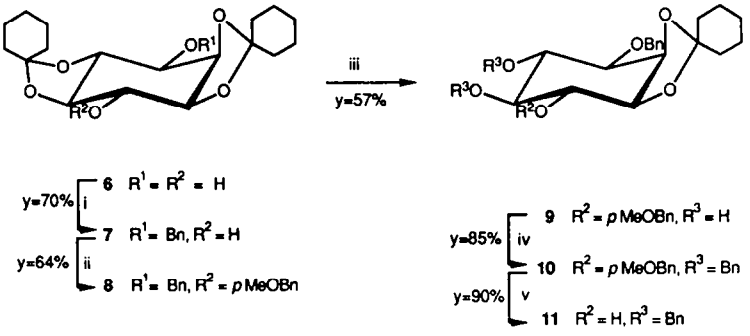


4b R^1 = All, R^2 = H, R^3 = Bn
5b R^1 = R^2 = R^3 = H

As part of an ongoing study directed towards the preparation of the trisubstituted D-*myo*-inositol fragment **3**, we now report a synthetic route to the D-*myo*-inositol mono-mannoside **5b**.

The original purpose of this study was to use the partially protected D-*myo*-inositol mono-mannoside **4b** (*i.e.* the precursor of **5b**) as the starting compound for the preparation of the trisubstituted D-*myo*-inositol **3**. Thus stereoselective mannosylation of the hydroxyl group at C-2 of **4b**, and subsequent removal of the allyl protecting group followed by the introduction of the phosphatidic unit, as described for the synthesis of **1**[1], would eventually lead to the target compound **3**. However, in executing this intended route to **3** an unexpected pitfall was met.

The synthetic route to **4b** comprises three distinct stages. The first one, the synthesis of the properly protected D(L)-*myo*-inositol acceptor **11** is depicted in Scheme 1. Regioselective benzylation of racemic 1,2:4,5-di-*O*

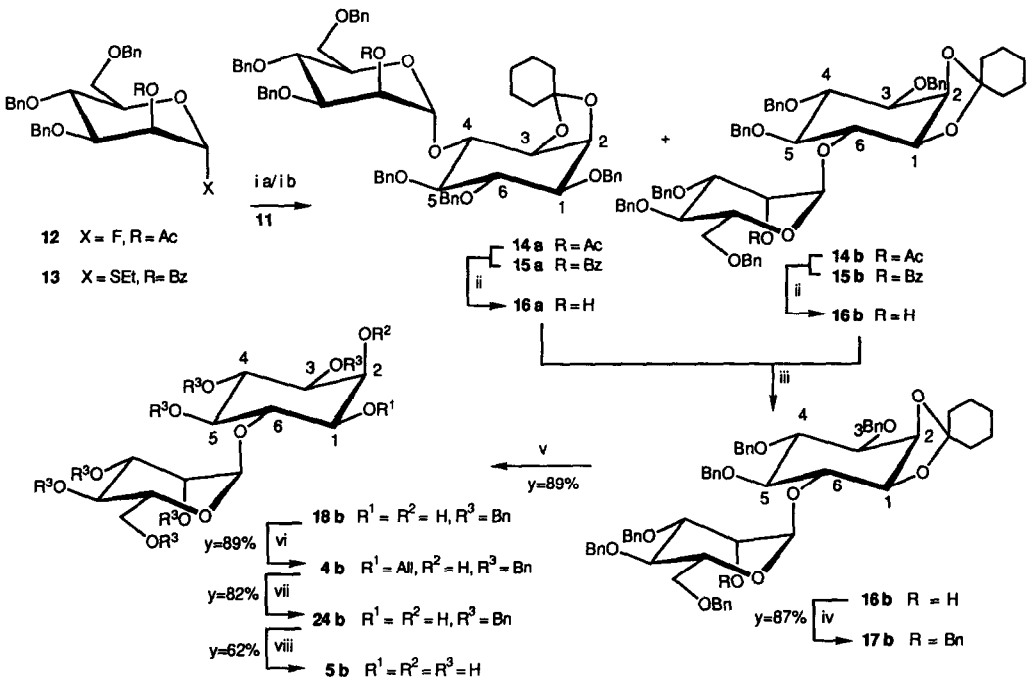


Scheme 1 Reagents : (i) BnBr / BaO, $Ba(OH)_2.8H_2O$ /DMF. (ii) *p* MeOBnCl /NaH / DMF (iii) *p*-TsOH /$HOCH_2CH_2OH$. (iv) BnBr /NaH /DMF . (v) DDQ / CH_2Cl_2 / H_2O.

cyclohexylidene derivative **6** with benzyl bromide, in the presence of barium oxide - barium hydroxide octahydrate[3], in *N,N*-dimethylformamide led to the isolation of the crystalline 3-*O*-benzyl derivative **7**, after separation from a small amount (3%) of the 3,6-di-*O*-benzyl derivative. In this respect, it is of interest to note that the reported[4] sodium hydride assisted regioselective benzylation of **6** was accompanied by an unacceptable amount of the 6-*O*-benzyl position isomer of **7**. Treatment of **7** with *para*-methoxybenzyl chloride[5] and sodium hydride yielded, after purification on silica gel, crystalline **8**. Selective removal of the *trans*-cyclohexylidene function in **8**, to give **9**, was effected by trans-ketalisation with ethylene glycol and catalytic *para*-toluenesulfonic acid[6]. Finally, benzylation of **9** (→ **10**) and subsequent removal[7] of the *para*-methoxybenzyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the isolation of racemic **11** in 76% overall yield for the two steps.

The next stage, which entails stereospecific 1,2-*trans* mannosylation of **11** with a donor having at C-2 a participating ester group followed by separation of the individual diastereoisomers thus obtained, is outlined in Scheme 2.

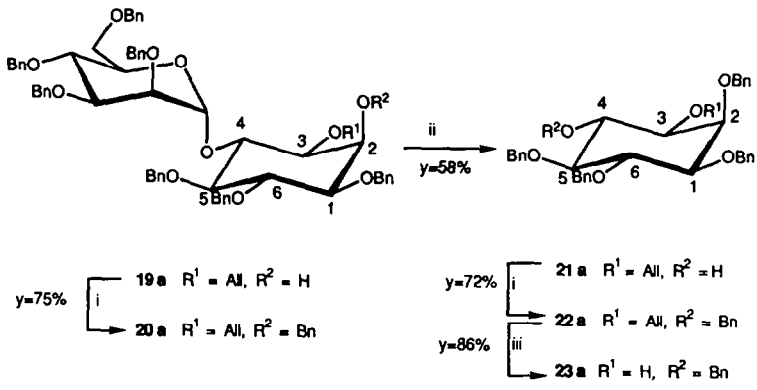
Thus glycosidation of acceptor **11** with the donor 2-*O*-acetyl-3,4,6-tri-*O*-α-D-mannopyranosyl fluoride (**12**)[8] in the presence of boron trifluoride etherate[9] gave, as expected[1], the α-linked diastereoisomers **14a-b** in 97% yield. It was also established that the condensation of **11** with ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**13**), using the recently developed promoter system *N*-iodosuccinimide and catalytic trifluoromethanesulfonic acid[10], proceeded stereospecifically, and led to the isolation of **15a-b** in a comparible yield. The ethyl thioglycoside **13** was easily prepared, according to a published procedure[11], by converting 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α/ß-D-



Scheme 2 Reagents : (i a) BF_3 Et_2O ; (i b) NIS/CF_3SO_3H. (ii) NaOMe or KOtBu/ MeOH, dioxane. (iii) Column chromatography. (iv) BnBr/ NaH/ DMF. (v) HCl/MeOH. (vi) Bu_2SnO/ MeOH; AllBr/ CsF/ DMF. (vii) a. Ir(COD)[PMePh.$_2$]$_2^+PF_6^-$/H_2; b: HgO/$HgCl_2$/ Acetone/H_2O. (viii) 10% Pd/C/H_2/isopropanol/H_2O.

mannopyranose[12] first to the corresponding α-chloride with the Vilsmeier-Haack reagent and additional treatment of the chloride with potassium ethyl mercaptide.

With respect to the separation of the individual diastereoisomers **14a-b** (**15a-b**) we anticipated, on the basis of earlier experimental evidence gathered during the synthesis of similarly protected mono-mannosylated D(L)-*myo*-inositols, that the diastereoisomer showing the highest R_f-value also contained the L-*myo*-inositol moiety. Unfortunately, no significant difference in R_f-values between **14a** and **14b** or **15a** and **15b** was observed. However, Zemplén deacetylation of **14a-b**, or potassium *tert*-butoxide assisted debenzoylation of **15a-b**, gave stereoisomers **16a-b** having an acceptable difference in R_f-value. In accordance with the above formulated rule of thumb we selected the enantiomorph **16b** (low R_f-value) for the preparation of the chiral pure D-*myo*-inositol containing target compound **4b**. To this end, **16b** was subjected to the following sequence of protecting group manipulations. Benzylation of **16b** gave **17b**, the *cis*-1,2-*O*-cyclohexylidene group of which was removed with dry hydrochloric acid in methanol[5]. Regioselective allylation of **18b**, to give **4b**, could be realized by treating the stannylidene-complex[13] of **18b** with allyl bromide in the presence of cesium fluoride[14]. The ^{1}H- and ^{13}C-NMR data of **4b** and fully deblocked **5b**, which was isolated after de-allylation[15] and hydrogenolysis of the allyl and benzyl groups (steps vii and viii in Scheme 2) from **4b** followed by purification (HiLoad Sephadex S100), were in complete accordance with the proposed structures. The presence in **16b**, and hence in **4b**, of the D-*myo*-inositol unit was corroborated indirectly as follows. Firstly, the dispensable enantiomorph **16a** (high R_f-value) was converted to **19a** by the same sequence of reactions as executed earlier (see Scheme 2) for the synthesis of **4b**.



Scheme 3 Reagents : (i) BnBr/NaH/DMF. (ii) HOAc, 3% HCl/H_2O. (iii) *p*-TsOH/Pd(C)/ MeOH/H_2O.

Secondly (see Scheme 3), benzylation of **19a**, and acid hydrolysis of the interglycosidic linkage[16] in **20a**, gave the inositol derivative **21a**. Benzylation of **21a**, and subsequent deallylation of **22a** with palladium on charcoal in the presence of catalytic *p*-toluenesulfonic acid[17], yielded penta-*O*-benzyl-*myo*-inositol **23a**, the specific optical rotation ($[\alpha]_D^{20}$-value) of which was the same as reported for 2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol[18].

The availability of **4b** opened the way to glycosylate the hydroxyl at C-2 with a mannopyranosyl donor. Unfortunately, contrary to expectation[1], glycosylation of acceptor **4b** with either donor **12** or **13**, under the conditions mentioned earlier in Scheme 2, was not successful. In the light of this disappointing result, we are at present exploring whether **3** may be attained by a reversed diglycosidation sequence : *i.e.* first glycosidation of HO-2, instead of HO-6, of a properly protected *myo*-inositol derivative. The results of this alternative synthetic route will be published in due course.

EXPERIMENTAL

Triethylamine, dichloromethane and 1,2-dichloroethane were dried by refluxing with calcium hydride (5 gram per litre) for 16 h and distilled. The liquids were stored over molecular sieves 0.4 nm. 1,2-Dichloroethane was redistilled from lithium aluminium hydride (2 gram per litre) before use. Methanol was dried by refluxing with magnesium methoxide, distilled and stored over molecular sieves 0.3 nm. Toluene and diethyl ether were distilled from phosphorous pentoxide and stored over sodium wire. *N,N*-dimethylformamide was stirred with calcium hydride (5 gram per litre) for 16 h at 20 °C, distilled under reduced pressure and stored over molecular sieves (0.4 nm). Triethyl ammonium bicarbonate (TEAB) was prepared by passing a stream of carbon dioxide gas through a cooled (ice-water bath) solution of triethylamine in de-ionized water (2 molar) until a neutral solution was obtained. Cesium fluoride was purchased from Fluka and *para*-methoxybenzyl chloride from Aldrich. Schleicher and Schüll DC Fertigfolien F1500 LS254 were used for TLC analysis. Compounds were detected under UV light or by spraying with 20% sulphuric acid in methanol, or with 1% potassium permanganate in 5% aqueous potassium carbonate for compounds containing a double bond or with a solution of ammonium molybdate (25 g) and ammonium cerium sulphate (10 g) in 10% aqueous sulphuric acid, followed by charring at 140 °C for a few minutes. Short column chromatography was performed on Kieselgel 60 (230-400 mesh ASTM, Merck). The HiLoad Sephadex S100 (HR 26/60) was eluted with 0.15 M TEAB, equipped with a HPLC pump (LKB 2150) with a flow of 1.5 ml/min. The fractions were detected by a differential refractometer (LKB 2142). ^{1}H-NMR spectra were measured at 300 MHz, using a Bruker WM-300 spectrometer interfaced with an ASPECT-2000 computer, operating in the Fourier transform mode. Correlated spectra were measured at 400 MHz, using a Bruker MSL-400 spectrometer interfaced with a ASPECT 3000-computer. ^{13}C-NMR spectra were measured at 50.1 MHz, using a JEOL JNM-FX 200 spectrometer, also equipped with an ASPECT-2000 computer, operating in the Fourier transform mode. Tetramethylsilane (TMS) was used as internal standard for samples in $CDCl_3$. Chemical shifts

are given in ppm (δ), relative to TMS. Optical rotations were measured at 20 °C using a Perkin Elmer 241 Polarimeter.

3-*O*-Benzyl-1,2:4,5-di-*O*-cyclohexylidene-D(L)-*myo*-inositol (7)

To a suspension of compound **6** (30 g, 88.2 mmol), barium oxide (27.6 g, 180 mmol) and barium hydroxide octahydrate (3.54 g, 11.25 mmol) in *N,N*-dimethylformamide (500 ml) benzyl bromide (11.8 ml, 99 mmol) was added. The mixture was stirred at room temperature for 4 days. T.l.c. analysis (dichloromethane/acetone, 97/3, v/v) showed the conversion of **6** (R_f 0.10) into **7** (R_f 0.29) and a byproduct, the dibenzylated derivative of compound **7**. The mixture was diluted with diethyl ether (350 ml) and neutralised with aqueous acetic acid. The mixture was washed with water (400 ml), aqueous sodium bicarbonate (400 ml, 10%, w/v) and water (400 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was purified by silica gel column (9x10 cm) chromatography. Elution was effected with *n*-hexane/ethyl acetate (2000 ml, 4:1 to 3:1, v/v). The appropriate fractions were pooled and concentrated *in vacuo*. The oil thus obtained was crystallised from diethyl ether/*n*-hexane to give **7** (27.1 g, 63 mmol) in 70% yield : m.p. 137-138 °C; R_f : 0.29 (dichloromethane/acetone, 97/3, v/v); ^1H NMR ($CDCl_3$) δ 7.60-7.21 (m, 5 H, H_{arom} benzyl), 4.90 (d, 1 H, CH_2 benzyl, JA,B 12.5 Hz), 4.81 (d, 1 H, CH_2 benzyl), 4.36 (t, 1 H, H-3, $J_{2,3}$ 4.4 Hz), 4.04 (t, 1 H, H-6, $J_{5,6}$ 9.5 Hz), 3.86 (dd, 1 H, H-1, $J_{1,2}$ 2.7 Hz, $J_{1,6}$ 6.7 Hz), 3.77 (dd, 1 H, H-4, $J_{4,5}$ 10.2 Hz), 3.26 (dd, 1 H, H-5), 2.41 (d, 1 H, OH), 1.9-1.3 (m, 20 H, 2 x cyclohex); ^{13}C NMR ($CDCl_3$) δ 137.9 (C_{arom} benzyl), 128.2-127.5 (CH_{arom} benzyl), 112.7 and 110.5 (C_{quat} cyclohex.), 81.1, 78.2, 76.5, 75.9 and 74.5 (CH *myo*-inositol), 71.4 (CH_2 benzyl), 37.6, 36.4, 36.1 and 35.0 (4 x $CH_{2\alpha}$ cyclohex.), 24.8, 23.8, 23.6 and 23.4 (2 x $CH_{2\gamma}$ and 4 x $CH_{2\beta}$, cyclohex.).

3-*O*-Benzyl-1,2:4,5-di-*O*-cyclohexylidene-6-*O*-*para*-methoxybenzyl-D(L)-*myo*-inositol (8)

To a cooled (0 °C) and stirred suspension of compound **7** (12.4 g, 28.8 mmol) and sodium hydride (1.0 g, 41.6 mmol) in *N,N*-dimethylformamide (150 ml) was added dropwise *para*-methoxybenzyl chloride (5.0 ml, 34.6 mmol). The suspension was stirred for 6 h at 20 °C. T.l.c. analysis (*n*-hexane/diethyl ether, 1:1, v/v) showed complete conversion of **7** (R_f 0.13) into **8** (R_f 0.43). After the addition of methanol to destroy excess sodium hydride, the reaction mixture was evaporated to dryness. The residue was taken up in diethyl ether (500 ml) and washed with water (200 ml), aqueous sodium bicarbonate (200 ml, 10%, w/v) and water (200 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oil, which crystallised from methanol upon standing, gave **8** (10.2 g, 18.6 mmol) in 64.3% yield : m.p. 137-139 °C; R_f : 0.53 (dichloromethane/acetone, 97/3, v/v); ^1H NMR ($CDCl_3$) δ 7.61-6.82 (m, 9 H, H_{arom} benzyl and *p*-methoxybenzyl), 4.90-4.78 (m, 4 H, CH_2 benzyl and *p*-methoxybenzyl), 4.32 (t, 1 H, H-2, $J_{2,3}$ 4.6 Hz), 4.01 (dd, 1 H, H-3, $J_{3,4}$ 6.4 Hz), 3.97 (d, 1 H, H-5, $J_{4,5}$ 9.1 Hz), 3.71 (dd, 1 H, H-1, $J_{1,2}$ 4.2 Hz), $J_{1,6}$ 10.2 Hz), 3.63 (dd, 1 H, H-4), 3.31 (dd, 1H, H-6, $J_{5,6}$ 9.2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.1 C_{arom}-OCH_3, *p*-methoxybenzyl), 138.1 (C_{arom} benzyl), 130.4 (C_{arom}, *p*-methoxybenzyl), 129.6-113.6 (CH_{arom} benzyl and *p*-methoxybenzyl), 112.6 and 110.3 (2 x C_{quat} cyclohex.), 80.5, 79.4, 78.7, 76.8, 76.2 and 74.6 (CH *myo*-inositol), 71.5 and 71.4 (CH_2 benzyl and *p*-methoxybenzyl), 37.4 36.4 and 35.3 (4 x $CH_{2\alpha}$ cyclohex.), 25.1, 25.0, 24.0, 23.9, 23.8 and 23.5 (4 x $CH_{2\beta}$ and 2 x $CH_{2\gamma}$).

Anal. Calc. for $C_{33}H_{42}O_7$: C, 71.98; H, 7.68. Found : C, 71.89; H, 7.72.

3-*O*-Benzyl-1,2-*O*-cyclohexylidene-6-*O*-*para*-methoxybenzyl-D(L)-*myo*-inositol (9)

To a solution of compound **8** (6.2 g, 11.3 mmol) in dichloromethane (100 ml) was added ethylene glycol (0.63 ml, 11.2 mmol) and *para*-toluenesulfonic acid monohydrate (0.2 g). After the appearance of a precipitate, the reaction was stopped by the addition of triethylamine (1 ml). The mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml), 1M sodium bicarbonate (100 ml) and water (100 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The solid was applied to a column of silica gel (70 g). The elution was carried out with a gradient of dichloromethane/methanol of 100:0 to 98:2, v/v. The appropriate fractions were pooled and concentrated *in vacuo* to give **9** (3.0 g, 6.5 mmol) as a crystalline product in 57.3% yield: m.p. 140-142 °C; R_f 0.12 (dichloromethane/acetone, 99/1, v/v); ^1H NMR ($CDCl_3$) δ 7.64-6.85 (m, 9 H, H_{arom} benzyl and *p*-methoxybenzyl), 4.92-4.58 (m, 4 H, CH_2 benzyl and *p*-methoxybenzyl), 4.32 (dd, 1 H, H-2, $J_{2,3}$ 4.9 Hz), 4.07 (dd, 1 H, H-3, $J_{3,4}$ 7.0 Hz), 3.94 (t, 1 H, H-5, $J_{4,5}$ 9.4 Hz), 3.80 (s, 3 H, OCH_3, *p*-methoxybenzyl), 3.55-3.50 (m, 2 H, H-2 and H-4, $J_{1,2}$ 2.7 Hz), 3.34 (t, 1 H, H-6, $J_{5,6}$ 9.6 Hz), 2.67 (d, 2 H, OH), 1.92-1.31 (m, 10 H, cyclohex.); ^{13}C NMR ($CDCl_3$) δ 158.8 (C_{arom}-OCH_3, *p*-methoxybenzyl), 137.8 (C_{arom} benzyl), 130.1 (C_{arom} *p*-methoxybenzyl), 129.1-113.1 (CH_{arom} benzyl and *p*-methoxybenzyl), 109.8 (C_{quat} cyclohex.), 72.8 and 72.0 (CH_2 benzyl and *p*-methoxybenzyl), 82.0, 78.3, 77.2, 73.3, 72.9 and 71.2 (CH *myo*-inositol), 34.5 (OCH_3, *p*-methoxybenzyl), 37.2 and 34.6 ($CH_{2\alpha}$ cyclohex.), 24.5, 23.4 and 23.2 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.).

3,4,5-Tri-*O*-benzyl-1,2-O-cyclohexylidene-6-*O*-*para*-methoxybenzyl-D(L)-*myo*-inositol (10)

To a cooled (0 °C) and stirred suspension of compound **9** (2.7 g, 5.75 mmol) and sodium hydride (0.6 g, 23.0

mmol) in *N,N*-dimethylformamide (100 ml) was added dropwise benzyl bromide (3.0 ml, 17.25 mmol). T.l.c. analysis (dichloromethane/acetone, 99:1), after stirring for 16 h at 20 °C, showed the conversion of **9** (R_f 0.12) into **10** (R_f 0.66). Methanol was added in order to destroy excess sodium hydride. The reaction mixture was evaporated to dryness, taken up in diethyl ether (400 ml) and washed with water (200 ml), aqueous sodium bicarbonate (200 ml, 10%, w/v) and water (200 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was purified by silica gel column (9x6 cm) chromatography. The elution was effected with *n*-hexane/diethyl ether (250 ml, 100:0 to 50:50, v/v). The appropriate fractions were pooled and concentrated *in vacuo* to give **10** (3.2 g, 85%) as an oil; R_f 0.53 (*n*-hexane/diethyl ether, 1/1, v/v); ^1H NMR ($CDCl_3$) δ 7.67-6.80 (m, 19 H, H_{arom} 3 x benzyl and *p*-methoxybenzyl), 4.85-4.65 (m, 8 H, 3 x CH_2 benzyl and *p*-methoxybenzyl), 4.27 (dd, 1 H, H-2, $J_{2,3}$ 5.6 Hz, $J_{1,2}$ 3.8 Hz), 4.08 (dd, 1 H, H-3, $J_{3,4}$ 7.0 Hz), 3.92 (t, 1 H, H-6, $J_{5,6}$ 8.4 Hz), 3.80 (dd, 1 H, H-4, $J_{4,5}$ 9.6 Hz), 3.79 (s, 3 H, OCH_3 *p*-methoxybenzyl), 3.69 (dd, 1 H,H-1, $J_{1,6}$ 8.5 Hz), 3.39 (dd, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 158.7 (C_{arom}-OCH_3 *p*-methoxybenzyl), 138.4, 138.3 and 138.0 (C_{arom} benzyl), 130.4 (C_{arom} *p*-methoxybenzyl), 129.1-113.1 (CH_{arom} benzyl and *p*-methoxybenzyl), 109.8 (C_{quat} cyclohex.), 82.0, 81.7, 80.5, 78.4, 76.9 and 73.6 (CH *myo*-inositol), 74.6, 74.4, 73.1 and 72.5 (4 x CH_2 benzyl and *p*-methoxybenzyl), 54.6 (OCH_3 *p*-methoxybenzyl), 37.0 and 34.7 ($CH_{2\alpha}$ cyclohex.), 24.7, 23.6 and 23.3 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.).

3,4,5-Tri-*O*-benzyl-1,2-*O*-cyclohexylidene-D(L)-*myo*-inositol (11)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (4.0 g) was added to a solution of compound **10** (3.2 g, 4.9 mmol) in a mixture of dichloromethane/water (200 ml, 19:1, v/v). T.l.c. analysis (dichloromethane/acetone, 99:1, v/v), after stirring for 1 h at 20 °C, showed the reaction to be complete. The reaction mixture was diluted with dichloromethane (100 ml) and washed with water (150 ml), aqueous sodium bicarbonate (3 x 150 ml, 10%, w/v) and water (150 ml). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The oily residue was purified by silica gel column (6x6 cm) chromatography and eluted with dichloromethane. The appropriate fractions were pooled and concentrated *in vacuo* to an oil, which crystallised upon standing, to give **11** in 90% yield (2.34 g, 4.41 mmol): m.p. 103 °C; R_f 0.41 (dichloromethane/acetone, 97:3, v/v); ^1H NMR ($CDCl_3$) δ 7.42-7.40 (m, 15 H, H_{arom} 3 x benzyl), 4.91-4.61 (m, 6 H, 3 x CH_2 benzyl), 4.31-4.28 (dd, 1 H, H-2, $J_{1,2}$ 2.4 Hz), 3.99-3.94 (dd, 1 H, H-4, $J_{3,4}$ 7.6 Hz), 3.90 (d, 1 H, H-5, $J_{4,5}$ 7.8 Hz), 3.89-3.86 (dd, 1 H, H-1, $J_{1,6}$ 9.8 Hz), 3.75-3.71 (dd, 1 H, H-3, $J_{2,3}$ 3.8 Hz), 3.28-3.22 (dd, 1 H, H-6, $J_{5,6}$ 7.8 Hz), 2.51 (bs, 1 H, OH), 1.85-1.30 (m, 10 H, cyclohexylidene); ^{13}C NMR ($CDCl_3$) δ 138.1, 138.0 and 137.9 (C_{arom} benzyl), 131.7-127.6 (CH_{arom} benzyl), 110.4 (C_{quat} cyclohex.), 81.8, 81.1, 77.8, 77.2, 74.2 and 73.4 (CH *myo*-inositol), 74.6, 74.4 and 72.9 (CH_2 benzyl), 37.2 and 34.8 ($CH_{2\alpha}$ cyclohex.), 24.8, 23.7 and 23.4 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.).

Anal. Calc. for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found : C, 74.37; H, 7.16.

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranosyl fluoride (12)

The title compound was obtained in a similar way as described in a previous paper[1].

Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (13)

To a solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranose (1.5 g, 3.0 mmol) in dry dichloromethane (50 ml) was added the chloroiminium ion[19], obtained from oxalyl chloride and *N,N*-dimethylformamide (2.0 g, 15.76 mmol). T.l.c. analysis (acetone/dichloromethane, 3:97, v/v), after stirring for 4 h at 20 °C, indicated the conversion of the starting compound (R_f 0.2) into the chloride (R_f 0.8) to be complete. The mixture was diluted with toluene (100 ml) and concentrated. The solid was taken up in a mixture of *n*-hexane/ethyl acetate (100 ml, 1/1, v/v), filtered over a pad of celite. The filtrate was concentrated and taken up in ethyl acetate (50 ml) and was added *via* a syringe to a mixture of potassium *t*-butoxide (0.44 g, 3.9 mmol) and ethyl mercaptane (0.3 ml, 3.9 mmol) in dry methanol (20 ml). After 1 h, t.l.c. analysis (acetone/dichloromethane, 3:97, v/v) showed complete conversion of the chloride (R_f 0.8) into the ethylthio compound (R_f 0.56). The reaction mixture was concentrated, coevaporated with pyridine and redissolved in pyridine (20 ml). Benzoyl chloride (0.46 ml, 3.90 mmol) was added to the reaction solution, and the mixture was stirred for 3 h at 20 °C when t.l.c. analysis (n-hexane/ethyl acetate, 2:3, v/v) showed the conversion of the starting compound (R_f 0.33) into **13** (R_f 0.66) to be complete. The reaction was stopped by the addition of water, after which the reaction mixture was concentrated. The oily residue was taken up in diethyl ether (50 ml) and washed with water, aqueous sodium bicarbonate (25 ml, 10%) and water (25 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. The syrup was purified by silica gel (2x4 cm) chromatography, eluted with *n*-hexane/ethyl acetate (200 ml, 2/1, v/v). The appropriate fractions were pooled and concentrated *in vacuo* to afford **13** (1.25 g, 2.10 mmol) as a yellow oil; ^{13}C NMR ($CDCl_3$) δ 165.4 (C=O, carbonyl Bz), 138.1 and 137.5 (3 x C_{arom} benzyl), 134.3-127.3 (CH_{arom} benzyl), 82.3 (C-1), 78.4, 74.3, 71.8, 70.6 (C-2, C-3, C-4, C-5), 68.8 (C-6), 25.4 (CH_2, SEt), 14.7 (CH_3, SEt); ^1H NMR ($CDCl_3$) δ 8.20-7.15 (m, 20 H, H_{arom} 3 x benzyl and benzoyl), 5.71-5.69 (dd, 1 H, H-2, $J_{2,3}$ 3.18 Hz), 5.44-5.43 (d, 1 H, H-1, $J_{1,2}$ 1.82 Hz), 4.89-4.49 (m, 6 H, 3 x CH_2 benzyl), 4.25-4.20 (dq, 1 H, H-5, $J_{5,6}$ 3.74 Hz), 4.17-4.10 (t, 1 H, H-6, $J_{6,6'}$ 9.05 Hz), 4.04-

4.00 (dd, 1 H, H-3, $J_{3,4}$ 9.08 Hz), 3.95-3.90 (dd, 1 H, H-6', $J_{5,6'}$ 9.67 Hz), 3.87-3.74 (dd, 1 H, H-4, $J_{4,5}$ 1.87 Hz).

3,4,5-Tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-(2'-*O*-acetyl-3',4',6'-tri-*O*-benzyl-α-D-mannopyranosyl)-D/L-*myo*-inositol (14a and 14b)

Compound **11** (2.0 g, 3.77 mmol) and **12** (2.3 g, 4.66 mmol) were dried by co-evaporation with toluene (2 x 25 ml). To a stirred solution of **11** and **12** together with activated molecular sieves (0.4 nm, 2.0 g) in dichloromethane (35 ml), under a blanket of nitrogen, boron trifluoride etherate (0.5 M, 1.0 ml) was added. T.l.c. analysis (*n*-hexane/diethyl ether, 1/1, v/v), after 1 h at 25 °C, revealed the formation of **14a** and **14b**. The reaction was stopped with triethylamine (1 ml). The solids were removed by filtration and the clear filtrate was evaporated to dryness. The residual oil was applied onto a column of silica gel (100 g), which was eluted with *n*-hexane/diethyl ether (500 ml, 100:0 to 50:50, v/v). The appropriate fractions were pooled and concentrated *in vacuo* to give a mixture of **14a** and **14b** as a colourless oil. Yield 3.67 g (3.66 mmol, 97%); R_f 0.38 and 0.33 (*n*-hexane/diethyl ether, 1/1, v/v); ^{13}C NMR ($CDCl_3$) δ 170.1 and 169.3 (C=O, carbonyl Ac), 138.6, 138.5, 138.2, 138.1, 138.0, 137.8, 137.7 and 137.6 (12 x C_{arom} benzyl), 128.1-127.0 (CH_{arom} benzyl), 110.6 and 110.1 (2 x C_{quat} cyclohex.), 98.2 and 95.9 (C-1), 82.3, 80.7, 80.6, 78.8, 78.3, 78.2, 77.4, 76.8, 76.6, 74.0, 73.9, 73.8, 73.4, 71.2, 71.0, 68.5 and 68.4 (CH myo-inositol and mannopyranosyl), 75.2, 74.8, 74.7, 74.6, 74.3, 73.3, 72.9, 72.8, 71.6, 71.3 and 68.3 (6 x CH_2 benzyl and C-6'mannopyranosyl), 34.8 and 34.4 (2 x $CH_{2\alpha}$ cyclohex.), 24.8, 23.7 and 23.5 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$), 20.9 and 20.8 (2 x CH_3 Ac).

Anal. Calc. for $C_{62}H_{68}O_{12}$: C, 74.08; H, 6.82. Found : C, 73.82; H, 6.97.

3,4,5-Tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-(2'-*O*-benzoyl-3',4',6'-tri-*O*-benzyl-α-D-mannopyranosyl)-D(L)-myo-inositol (15a and 15b)

Compound **11** (0.285 g, 0.5 mmol) and **13** (0.35 g, 0.6 mmol) were dried by co-evaporation with toluene (2 x 10 ml). To a cooled (0 °C) and stirred solution of **11**, **13** and molecular sieves (0.4 nm, 0.5 g) in dichloroethane was added, under a blanket of argon, a stock solution of *N*-iodosuccinimide (0.1 M, 6 ml) and trifluoromethanesulfonic acid (0.12 equiv.) in diethyl ether/dichloroethane (10, ml, 1/1, v/v). T.l.c. analysis (16% ethyl acetate/toluene), after 15 min at 0 °C, showed the formation of **15a/15b**. The reaction was stopped with triethylamine (0.25 ml). The solids were removed by filtration over a pad of celite and the clear filtrate was washed with sodium thiosulfate (100 ml, 20%, w/v), aqueous sodium bicarbonate (100 ml, 10%, w/v) and water (2 x 100 ml). The organic solution was dried over magnesium sulfate and concentrated *in vacuo* to dryness. The oily residue was applied onto a column of silica gel and eluted with a mixture of *n*-hexane/ethyl acetate (300 ml, 4:1, v/v). The appropriate fractions were concentrated and the oil thus obtained was purified by Sephadex LH-20 column chromatography. Elution was effected with a mixture of methanol/dichloromethane (1/2, v/v) to give a mixture of **15a** and **15b** as a colourless oil in 96% yield (0.51 g, 0.48 mmol); R_f 0.81 and 0.79 (16% ethyl acetate/toluene); ^{13}C NMR ($CDCl_3$) δ 166.1 and 165.7 (C=O, carbonyl Bz), 139.3, 139.2, 138.9, 138.8, 138.7, 138.6, 138.4 and 138.3 (14 x C_{arom} benzyl and benzoyl), 133.4-127.7 (CH_{arom} benzyl and benzoyl), 111.3 and 110.8 (C_{quat}, cyclohex.), 98.8 and 96.7 (C-1'), 82.9, 81.5, 81.4, 79.4, 79.1, 78.9, 78.2, 77.5, 77.4, 74.7, 74.5, 74.1, 73.1 and 69.6 (CH *myo*-inositol and mannopyranosyl), 75.9, 75.7, 75.5, 75.4, 75.2, 75.0, 73.9, 73.6, 73.5, 72.0, 71.7 and 69.3 (CH_2 benzyl and C-6'), 37.8 37.7, 35.4 and 35.2 ($CH_{2\alpha}$ cyclohex.), 25.5 24.3 and 24.2 ($CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.).

3,4,5-Tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-(3',4',6'-tri-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (16a) and 3,4,5-tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-(3',4',6'-tri-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (16b)

Methanolic sodium methoxide (1 M, 6.0 ml) was added to a solution of **14a** and **14b** (3.4 g, 3.39 mmol) in a mixture of dry methanol (50 ml) and dioxane (50 ml), and the mixture was stirred for 6 h at 20 °C. In a similar fashion, compounds **15a** and **15b** were debenzoylated by treatment with potassium *t*-butoxide (2 equiv.) in a mixture of methanol and dioxane for 4 h at 20 °C. Both solutions were neutralized with Dowex 50 XW4 (H^+-form) resin (100-200 mesh), filtered and concentrated *in vacuo*. The two diastereoisomers **16a** and **16b** were applied onto a column of silica gel (60 g), and eluted with a gradient of *n*-hexane/ethyl acetate (2000 ml, 90:10 to 60:40, v/v) to give **16a** (1.14 g, 1.18 mmol), $[\alpha]_D^{20}$ +23.9 ° (c 1 $CHCl_3$) and **16b** (1.11 g, 1.15 mmol), $[\alpha]_D^{20}$ +43.5 ° (c 1 $CHCl_3$) as colourless oils; R_f **16a** and **16b**, 0.50 and 0.45 (acetone/dichloromethane, 3:97, v/v), respectively; ^{13}C NMR ($CDCl_3$) of **16b** δ 138.5, 138.2, 138.1, 138.0 and 137.7(2x) (6 x C_{arom} benzyl), 128.7-125.0 (CH_{arom} benzyl), 110.5 (C_{quat} cyclohex.), 97.3 (C-1', $J_{C\text{-}1',H\text{-}1'}$ 172.9 Hz), 80.9, 80.8, 79.5, 78.7, 77.1, 76.7, 75.3, 74.2, 74.0 and 70.8 (C-2', C-3', C-4', C-5', C-1, C-2, C-3, C-4, C-5 and C-6), 75.0, 74.5, 74.4, 72.7, 72.6, 71.3 and 68.4 (6 x CH_2 benzyl and C-6'), 36.9 and 34.9 ($CH_{2\alpha}$ cyclohex.), 24.8, 23.7 and 23.4 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.); ^1H NMR ($CDCl_3$) δ 7.43-6.85 (m, 30 H, H_{arom} 6 x benzyl), 5.53 (d, 1 H, H-1', $J_{1',2'}$ 1.77 Hz), 4.83-4.33 (m, 12 H, 6 x CH_2 benzyl), 4.23 (dd, 1 H, H-2, $J_{1,2}$ 3.81 Hz, $J_{2,3}$ 5.46 Hz), 4.11-4.05 (m, 2 H, H-4 and H-2', $J_{3,4}$ 7.20 Hz, $J_{2',3'}$ 2.70 Hz), 4.01 (dd, 1 H, H-3), 3.98 (bt, 1 H, H-5'), 3.94 (dd, 1 H, H-3', $J_{3',4'}$ 8.68 Hz), 3.90-3.85 (m, 2 H, H-6 and H-4', $J_{5,6}$ 7.78 Hz), 3.67 (dd, 1 H, H-1, $J_{1,6}$ 8.30 Hz), 3.56 (dd, 1 H, H-6a', $J_{5,6a'}$ 3.35 Hz), 3.45 (dd, 1 H, H-6b', $J_{5,6b'}$ 1.62 Hz, $J_{6a',6b'}$ 11.05 Hz), 3.27 (dd, 1H, H-5, $J_{4,5}$ 9.76 Hz), 2.34 (s, 1 H, 2'-OH), 1.84-

1.32 (m, 10 H, cyclohex.).
^{13}C NMR ($CDCl_3$) of **16a** δ 138.4, 138.1(2x), 138.0(2x) and 137.9 (6 x C_{arom} benzyl), 128.7-125.0 (CH_{arom} benzyl), 109.9 (C_{quat} cyclohex.), 99.8 (C-1', $J_{C-1',H-1'}$ 171.4 Hz), 82.4, 80.7, 79.8, 79.0, 76.8, 76.6, 74.0, 73.4, 70.9 and 68.3 (C-2', C-3', C-4', C-5', C-1, C-2, C-3, C-4, C-5 and C-6), 74.7, 74.5, 74.3, 73.2, 72.6, 71.5 and 70.8 (6 x CH_2 benzyl and C-6'), 37.0 and 34.4 ($CH_{2\alpha}$ cyclohex.), 24.8, 23.6(2x) (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex.); ^{1}H NMR ($CDCl_3$) δ 7.51-6.94 (m, 30 H, H_{arom} 6 x benzyl), 5.29 (d, 1 H, H-1', $J_{1',2'}$ 1.38 Hz), 4.84-4.48 (m, 12 H, 6 x CH_2 benzyl), 4.21 (dd, 1 H, H-2, $J_{1,2}$ 3.77 Hz, $J_{2,3}$ 5.40 Hz), 4.03-3.79 (m, 8 H), 3.68-3.64 (m, 2 H), 3.36-3.30 (m, 1 H), 2.34 (s, 1 H, 2'-OH), 1.98-1.23 (m, 10 H, cyclohex.).

3,4,5-Tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (17a) and 3,4,5-tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (17b)

Benzyl bromide (0.2 ml, 1.15 mmol) was added to a cooled (0 °C) and stirred suspension of **16b** (1.0 g, 1.04 mmol) and sodium hydride (60 mg, 2.3 mmol) in *N,N*-dimethylformamide (10 ml). T.l.c. analysis (*n*-hexane/diethyl ether, 1:1, v/v), after stirring for 8 h at 20 °C, showed the conversion of **16b** (R_f 0.11) into **17b** (R_f 0.33). Methanol was added to destroy excess sodium hydride. The reaction mixture was evaporated to dryness, taken up in diethyl ether (30 ml) and washed with water (15 ml), aqueous sodium bicarbonate (15 ml, 10%, w/v) and water (15 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was purified by silica gel column (2x2 cm) chromatography. The elution was effected with a gradient of *n*-hexane/diethyl ether (250 ml, 100:0 to 40:60, v/v). The appropriate fractions were pooled and concentrated *in vacuo*, to give **17b** (1.0 g, 0.9 mmol) as an oil; R_f 0.64 (*n*-hexane/ethyl acetate, 2/3, v/v); +5.6° (c 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.5, 138.4, 138.3, 138.1 and 137.9 (C_{arom} benzyl), 128.8-127.0 (CH_{arom} benzyl), 110.6 (C_{quat} cyclohex), 96.1 (C-1'), 80.8, 79.4, 78.7, 77.5, 76.6, 74.8, 74.5 and 73.9 (C-2', C-3', C-4', C-5', C-1, C-3, C-4, C-5 and C-6), 75.0, 73.3, 73.2, 72.9, 72.0, 71.7 and 71.6 (7 x CH_2 benzyl and C-6'), 71.6 (C-2), 36.9 and 34.9 ($CH_{2\alpha}$ cyclohex), 24.9, 23.9 and 23.6 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex); ^{1}H NMR ($CDCl_3$) δ 7.49-6.95 (m, 35 H, H_{arom}7 x benzyl), 5.54 (d, 1 H, H-1', $J_{1',2'}$ 1.76 Hz), 4.91-4.32 (m, 14 H, 7 x CH_2 benzyl), 4.22 (dd, 1 H, H-2, $J_{1,2}$ 3.87 Hz, $J_{2,3}$ 5.67 Hz), 4.09-4.03 (m, 2 H, H-4 and H-4'), 3.98 (m, 1 H, H-5'), 3.93 (dd, 1 H, H-3, $J_{3,4}$ 6.93 Hz), 3.90 (m, 1 H, H-3'), 3.85 (dd, 1 H, H-6), 3.82 (dd, 1 H, H-2', $J_{2',3'}$ 3.12 Hz), 3.66 (dd, 1 H, H-1, $J_{1,6}$ 8.25 Hz), 3.60 (d, 1 H, H-6a', $J_{5',6a'}$ 4.02 Hz), 3.49 (dd, 1 H, H-6b', $J_{5',6b'}$1.71 Hz, $J_{6a',6b'}$ 11.21 Hz), 3.32 (dd, 1 H, H-5, $J_{5,6}$ 7.91 Hz, $J_{4,5}$ 9.96 Hz), 1.78-1.20 (m, 10 H, cyclohex.).
Compound **17a** was obtained in a similar way as described for **17b**; R_f 0.67 (*n*-hexane/ethyl acetate, 2/3, v/v); ^{13}C NMR ($CDCl_3$) of δ 139.1, 139.0, 138.9, 138.7 and 138.5 (C_{arom} benzyl), 129.2-125.5 (CH_{arom} benzyl), 110.5 (C_{quat} cyclohex), 98.7 (C-1'), 82.9, 81.3, 80.3, 79.3, 77.3, 77.1, 75.9, 75.0 and 73.8 (C-2', C-3', C-4', C-5', C-2, C-3, C-4, C-5 and C-6), 75.2, 74.8, 74.5, 73.6, 73.1, 72.3, 72.2 and 69.2 (7 x CH_2 benzyl and C-6'), 37.5 and 34.9 ($CH_{2\alpha}$ cyclohex), 25.3, 24.2 and 24.1 (2 x $CH_{2\beta}$ and $CH_{2\gamma}$ cyclohex).

3,4,5-Tri-*O*-benzyl-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (18a) and 3,4,5-tri-*O*-benzyl-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (18b)

A solution of acetyl chloride in methanol (0.5 M, 7.0 ml) was added to a solution of **17b** (0.85 g, 0.81 mmol) in a mixture of dry methanol (25 ml) and dioxane (25 ml). T.l.c. analysis (*n*-hexane/ethyl acetate, 2/3, v/v), after stirring for 48 h at 20 °C, showed complete conversion of **17b** (R_f 0.64) into **18b** (R_f 0.43). The solution was neutralized with triethylamine and concentrated *in vacuo*. The oily residue was purified by silica gel column (2x5 cm) chromatography. Elution was effected with a gradient of dichloromethane/methanol (200 ml, 100:0 to 98:2, v/v) to give **18b** (0.7 g, 0.72 mmol) as a colourless oil; $[\alpha]_D^{20}$ +27.4° (c 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.5, 138.2, 138.0 and 137.4 (C_{arom} benzyl), 128.9-125.1 (CH_{arom} benzyl), 96.9 (C-1'), 81.1, 79.8, 79.4, 76.3, 74.9, 74.8, 73.3, 71.2 and 70.1 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4' and C-5'), 75.7, 75.4, 74.7, 72.7, 72.1, 72.0, 71.4 and 68.8 (7 x CH_2 benzyl and C-6'); ^{1}H NMR ($CDCl_3$) δ 7.42-7.08 (m, 35 H, H_{arom} 7 x benzyl), 5.53 (d, 1 H, H-1', $J_{1',2'}$ 1.98 Hz), 4.86-3.84 (m, 14 H, 7 x CH_2 benzyl), 4.15-3.84 (m, 7 H), 3.54-3.24 (m 5 H), 2.93 (d, 1 H, OH, $J_{H,OH}$ 9.03 Hz), 2.60 (s, 1 H, OH).
Compound **18a** was obtained in a similar procedure as described for **18b**; R_f 0.51 (*n*-hexane/ethyl acetate, 2/3, v/v); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 138.0 and 137.8 (C_{arom} benzyl), 128.0-124.9 (CH_{arom} benzyl), 99.8 (C-1'), 83.8, 82.2, 80.7, 79.3, 79.2, 75.4, 74.6, 72.0, 70.7 and 69.4 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4' and C-5'), 75.3, 75.0, 74.5, 72.9, 72.1, 71.9, 71.5 and 69.1 (7 x CH_2 benzyl and C-6').

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-(2',3',4',5'-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (4b) and 1-*O*-allyl-3,4,5-tri-*O*-benzyl-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (19a)

A solution of **18b** (0.7 g, 0.73 mmol) and dibutyltin oxide (0.25 g, 0.96 mmol) in dry methanol (25 ml) was refluxed for 2.5 h and subsequently concentrated. The residue was co-evaporated with toluene (2 x 10 ml). The resulting oil was dissolved in *N,N*-dimethylformamide (20 ml) to which was added cesium fluoride (0.15 g, 0.99

mmol) and allyl bromide (0.10 ml, 1.16 mmol). T.l.c. analysis (*n*-hexane/ethyl acetate, 2/3, v/v), after stirring for 18 h at 20 °C, indicated complete conversion of **18b** (R_f 0.43) into **4b** (R_f 0.66). The solution was concentrated *in vacuo* and the oily residue was purified by silica gel column (2x3 cm) chromatography, eluted with n-hexane/ethyl acetate (400 ml, 1/1, v/v). The appropriate fractions were pooled and concentrated *in vacuo* to afford **4b** (0.65 g, 0.65 mmol) as a colourless oil; R_f 0.33 (*n*-hexane/ethyl acetate, 3/2); $[\alpha]_D^{20}$ +10.8° (c 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.4, 138.3, 137.8 and 137.7 (C_{arom} benzyl), 134.1 (-CH=, allyl), 128.1-126.8 (CH_{arom} benzyl), 117.3 (CH_2=, allyl), 97.9 (C-1'), 81.2, 81.1, 80.3, 79.7, 79.5, 75.0, 74.9, 74.7, 71.6 and 66.1 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4'and C-5'), 75.4, 74.5, 72.8, 72.2, 71.8, 71.7, 70.2, 68.4 and 65.8 (7 x CH_2 benzyl, CH_2 allyl and C-6'); ^1H NMR ($CDCl_3$) δ 7.48-7.02 (m, 35 H, H_{arom} 7 x benzyl), 5.84-5.71 (m, 1 H, -CH=, allyl), 5.51 (d, 1 H, H-1', $J_{1',2'}$ 1.78 Hz), 5.28-5.12 (m, 2 H, CH_2=, allyl), 4.91-4.23 (m, 14 H, 7 x CH_2 benzyl), 4.16 (t, 1 H, H-2, $J_{1,2}$ 2.52 Hz, $J_{2,3}$ 2.89 Hz), 4.13-3.86 (m, 7 H, H-4, H-6, H-3', H-4', H-5', -CH_2 allyl), 3.82 (dd, 1 H, H-2', $J_{2',3'}$ 2.96 Hz), 3.43-3.38 (dd, 1 H, H-6'), 3.35 (dd, 1 H, H-3, $J_{3,4}$ 9.50 Hz), 3.35-3.31 (dd, 1 H, H-6''), 3.26 (t, 1 H, H-5, $J_{4,5}$ 9.48 Hz, $J_{5,6}$ 9.83 Hz), 3.18 (dd, 1 H, H-1, $J_{1,6}$ 9.54 Hz), 2.36 (s, 1H, 2-OH).
Compound **19a** was obtained in a similar way asdescribed for **4b**; R_f 0.34 (*n*-hexane/ethyl acetate, 3/2, v/v); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.6, 138.4, 138.3, 137.8 (C_{arom} benzyl), 134.2 (-CH=, allyl), 128.8-125.1 (CH_{arom} benzyl), 118.0 (CH_2=, allyl), 98.3 (C-1'), 83.5, 81.0, 79.8, 79.4, 78.1, 75.5, 75.3 and 66.7 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4' and C-5'), 75.7, 74.5, 73.1, 72.4, 71.7, 71.5 and 69.3 (7 x CH_2 benzyl, CH_2 allyl and C-6').

1-*O*-Allyl-2,3,4,5-tetra-*O*-benzyl-6-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (20b) and 1-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-6-*O*-(2',3',4'.6'-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (20a)

Benzyl bromide (0.1 ml, 0.9 mmol) was to a cooled (ice-bath) and stirred suspension of compound **19** (0.6 g, 0.90 mmol) and sodium hydride (60 mg, 2.3 mmol) in *N,N*-dimethylformamide (25 ml). T.l.c. analysis (*n*-hexane/ethyl acetate, 4:1, v/v), after stirring for 4 h at 20 °C, showed conversion of **19b** (R_f 0.08) into **20b** (R_f 0.33). After the addition of methanol, the reaction mixture was evaporated to dryness, taken up in diethyl ether (40 ml), and washed with water (20 ml), aqueous sodium bicarbonate (20 ml, 10%, w/v) and water (20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The oily residue was purified by eluting the compound from a silica gel column (2x4 cm) with *n*-hexane/ethyl acetate (100 ml, 4:1, v/v). The appropriate fractions were pooled and concentrated *in vacuo*, to afford **20b** (0.5 g, 0.45 mmol) as an oil; R_f 0.40 (*n*-hexane/diethyl ether, 2:1, v/v); ^{13}C NMR ($CDCl_3$) δ 138.9, 138.6 and 138.1 (C_{arom} benzyl), 134.2 (-CH=, allyl), 128.1-125.1 (CH_{arom} benzyl), 116.8 (CH_2=, allyl), 98.1 (C-1'), 81.7, 81.6, 81.2, 80.7, 75.1, 74.7, 72.6 and 71.5 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4'and C-5'), 75.4, 74.6, 73.7, 72.9, 72.5, 71.9, 71.7, 70.3 and 68,5 (8 x CH_2 benzyl, CH_2 benzyl and C-6').
Compound **20a** was obtained in a similar way as described for **20b**; R_f 0.34 (*n*-hexane/ethyl acetate, 4:1); ^{13}C NMR ($CDCl_3$) δ 139.1, 138.8, 138.6, 138.5, 138.4 and 138.1 (C_{arom} benzyl), 134.4 (-CH=, allyl), 128.8-125.1 (CH_{arom} benzyl), 117.3 (CH_2=, allyl), 98.1 (C-1'), 84.2, 81.6, 80.5, 79.8, 79.1, 75.3, 74.8, 73.7 and 71.6 (C-1, C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4' and C-5'), 74.7, 74.5, 73.9, 73.1, 72.4, 71.7 and 69.2 (8 x CH_2 benzyl, CH_2 allyl and C-6').

1-*O*-Allyl-2,3,4,5-tetra-*O*-benzyl-D-*myo*-inositol (21b) and 1-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-*l*-*myo*-inositol (21a)

A solution of **20a** (0.4 g, 0.36 mmol) in acetic acid and 3% aqueous hydrochloric acid (15 ml, 9:1, v/v) was heated for 3 h at 100 °C. The reaction mixture was cooled and co-evaporated with toluene (4 x 50 ml). The oily residue was applied to column of silica gel (25 g). Elution was effected with a gradient of *n*-hexane/ethyl acetate (100 ml, 80:20 to 60:40, v/v) to give **21a** (120 mg, 0.21 mmol), $[\alpha]_D^{20}$ +6.9° (c 1 $CHCl_3$); R_f 0.66 (*n*-hexane/ethyl acetate, 2:3, v/v); ^{13}C NMR ($CDCl_3$) δ 138.7 and 138.2 (C_{arom} benzyl), 134.3 (-CH=, allyl), 128.2-127.3 (CH_{arom} benzyl), 117.2 (CH_2=, allyl), 83.3, 81.3, 81.0, 79.7, 73.4 and 72.6 (C-1, C-2, C-3, C-4, C-5 and C-6), 75.7, 75.2, 73.9, 72.8 and 71.0 (4 x CH_2 benzyl and CH_2 allyl); ^1H NMR ($CDCl_3$) δ 7.61-6.81 (m, 20 H, H_{arom} 4 x benzyl), 5.99-5.82 (m, 1 H, -CH=, allyl), 5.32-5.16 (m, 4 H, CH_2 benzyl and CH_2= allyl), 4.94-4.61 (m, 6 H, 3 x CH_2 benzyl), 4.13-3.98 (m, 5 H, -CH_2, allyl), 3.42-3.98 (m, 2 H), 3.42-3.12 (dd, 1 H), 2.54 (bs, 1 H, 6-OH).
Compound **21b** (90 mg, 0.16 mmol) was obtained in a similar procedure as described for **21a**; $[\alpha]_D^{20}$ -6.5° (c 1 $CHCl_3$).

1-*O*-Allyl-2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol (22b) and 1-*O*-allyl-2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol (22a) Benzyl bromide (0.05 ml, 0.42 mmol) was added to a cooled (ice bath) and stirred suspension of compound **21a** (100 mg, 0.18 mmol) and sodium hydride (30 mg, 1.1 mmol) in *N,N*-dimethylformamide (10 ml). T.l.c. analysis (*n*-hexane/ethyl acetate, 4:1, v/v), after stirring for 16 h at 20 °C, showed complete conversion of **21a** (R_f 0.38) into **22a** (R_f 0.89). Methanol was added and the solution was stirred for 0.5 h, evaporated to dryness and taken up in diethyl ether (25 ml). The organic layer was washed with water (10 ml), aqueous sodium bicarbonate (15 ml, 10%, w/v), water (10 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The oily residue was purified by silica gel column (2x2 cm) chromatography. The elution was effected with a

gradient of *n*-hexane/ethyl acetate (100 ml, 90:10 to 80:20, v/v). The appropriate fractions were pooled and concentrated *in vacuo*, to give **22a** (44 mg, 0.07 mmol); $[\alpha]_D^{20}$ −5.0° (c 1 $CHCl_3$); R_f 0.89 (*n*-hexane/ethyl acetate, 4:1, v/v); ^{13}C NMR ($CDCl_3$) δ 138.9 and 138.6 (C_{arom} benzyl), 135.0 (-CH=, allyl), 128.3-127.5 (CH_{arom} benzyl), 116.6 (CH_2=, allyl), 83.7, 81.7, 80.9, 80.8 and 74.5 (C-1, C-2, C-3, C-4, C-5 and C-6), 75.8, 74.1, 72.9 and 71.7 (5 x CH_2 benzyl and CH_2 allyl).
In a similar fashion, compound **22b** (34.2 mg, 0.05 mmol) was obtained; $[\alpha]_D^{20}$ 4.9° (c 1 $CHCl_3$).

2,3,4,5,6-Penta-*O*-benzyl-D-*myo*-inositol (23b) and 2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol (23a)
Para-toluenesulfonic acid monohydrate (30 mg) and Pd(C) (40 mg) were added to a solution of **23a** (44 mg, 0.07 mmol) in a mixture of methanol/water (5 ml, 11/1, v/v). T.l.c. analysis (*n*-hexane/ethyl acetate, 2:3, v/v), after 6 h at 80 °C, showed complete conversion of **22a** (R_f 0.34) into **23a** (R_f 0.09). The mixture, without cooling to room temperature, was filtered and neutralized with a few drops of triethylamine. The solution was evaporated to dryness and the residue was taken up in dichloromethane (25 ml). The organic layer was washed with water (15 ml), aqueous sodium bicarbonate (10 ml, 10%, w/v), water (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give **23a** (38 mg, 0.06 mmol); $[\alpha]_D^{20}$ +9.0° (c 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.7 and 138.6 (C_{arom} benzyl), 128.4-127.6 (CH_{arom} benzyl), 83.6, 82.1, 81.9, 81.1, 77.1, 72.4 (C-1, C-2, C-3, C-4, C-5 and C-6), 75.8, 75.7, 75.5, 74.7 and 72.4 (5 x CH_2 benzyl); ^1H NMR ($CDCl_3$) δ 7.40-7.25 (m, 25 H, 5 x H_{arom} benzyl), 5.02-4.60 (m, 10 H, 5 x CH_2 benzyl), 4.06 (dd, 1 H, H-4, $J_{4,5}$ 9.5 Hz), 4.03 (d, 1 H, H-2, $J_{2,3}$ 2.3 Hz), 3.81 (dd, 1 H, H-6, $J_{6,1}$ 9.5 Hz), 3.48 (dd, 1 H, H-5, $J_{5,6}$ 9.5 Hz), 3.48 (ddd, 1 H, H-1, $J_{1,2}$ 2.5 Hz, $J_{1,OH}$ 6.5 Hz), 3.46 (dd, 1 H, H-3, $J_{3,4}$ 9.5 Hz), 2.23 (d, 1 H, 1-OH).
Compound **23b** (24.4 mg, 0.04 mmol) was obtained in a similar way as described for **23a**; $[\alpha]_D^{20}$ -9.1° (c 1 $CHCl_3$).

3,4,5-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (24b)
Compound **4b** (0.45 g, 0.63 mmol) was dissolved in dichloroethane (8 ml). The solution was alternatingly degassed and placed under helium (3x). 1,5-Cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate (8 mg) was added, the solution was degassed and placed under helium (3x). The catalyst was activated by passing a stream of hydrogen for 2 min through the solution. Once again the reaction mixture was degassed and, thereafter, left under a gentle stream of helium for 4 h. T.l.c. analysis (*n*-hexane/ethylacetate, 4:1, v/v) showed complete conversion of the starting material **4b** (R_f 0.6) into the corresponding isomerized derivative (R_f 0.65). The solvent was evaporated and the catalyst was removed by column chromatography [silica gel (20 g); eluens: *n*-hexane/ethyl acetate (100 ml, 4:1, v/v)], to afford the homogeneous derivative (0.42 g).
The thus obtained compound was dissolved in acetone (18 ml) and water (1 ml). $HgCl_2$ (200 mg, 0.63 mmol) and HgO (220 mg, 1.0 mmol) were added. The suspension was stirred for 30 min at 20 °C. T.l.c. analysis (n-hexane/ethyl acetate, 4:1, v/v) showed complete conversion of the starting material (R_f 0.65) into **24b** (R_f 0.45). The solution was filtered over a pad of celite, diluted with dichloromethane (250 ml) and washed with 1M aqueous potassium iodide (3 x 125 ml) and water (125 ml). The organic layer was dried over magnesium sulfate and evaporated to dryness. The oily residue was purified by silica gel column (2x2 cm) chromatography. Elution was effected with dichloromethane. The appropriate fractions were pooled and concentrated *in vacuo* to give pure **24b**; ^{13}C NMR ($CDCl_3$) δ 138.6, 138.0, 137.9 and 137.7 (C_{arom} benzyl), 128.2-127.2 (CH_{arom} benzyl), 99.1 (C-1, $J_{C1\text{-}H1}$ 173.1 Hz), 81.2, 81.0, 79.6, 79.3, 76.3, 74.2, 73.3, 70.4, 70.1 and 68.1 (CH *myo*-inositol and mannopyranosyl), 74.7, 72.8, 72.0, 71.2 and 68.6 (7 x CH_2 benzyl and C-6); ^1H NMR ($CDCl_3$) δ 7.53-7.02 (m, 35 H, H_{arom}, 7 x benzyl), 5.52 (d, 1 H, H-1, $J_{1,2}$ 1.96 Hz), 4.89-4.27 (m, 14 H, 7 x CH_2 benzyl), 4.11-4.01 (m, 4 H), 3.95-3.78 (m, 3 H), 3.53-3.28 (m, 5 H), 2.87-2.65 (bdd, 2 H, 2 x OH).

6-*O*-(α-D-Mannopyranosyl)-D-*myo*-inositol (5b)
Compound **24b** (200 mg, 0.21 mmol) was dissolved in a mixture of water and isopropanol. After the addition of 200 mg Pd/C (10%), the suspension was kept under a blanket of hydrogen during 24 h at 1 atmosphere. T.l.c analysis (dichloromethane/methanol, 4:1, v/v) showed the conversion of the **24b** (R_f 0.62) into **5b** (R_f 0.05). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The remaining solids were purified by gel filtration (HiLoad Sephadex S100, HR 26/60). Elution was effected with 0.15 M TEAB. The appropriate fractions were pooled and concentrated *in vacuo*. Excess TEAB-solids were removed by repeatedly freezedrying of a solution of **5b** in de-ionized water. ^{13}C NMR (D_2O) of **5b** δ 102.0 (C-1', $J_{C\text{-}1',H\text{-}1'}$ 171.4 Hz, $J_{C\text{-}1',H\text{-}2'}$ 4.4 Hz), 80.8 (C-4'), 73.9 (C-5), 73.8 (C-5'), 73.6 (C-6), 73.5 (C-2), 72.6 (C-3), 72.0 (C-1), 71.5 (C-4') and 71.3 (C-2'), 67.6 (C-4), 61.7 (C-6'); ^1H NMR (D_2O) δ 5.17 (d, 1 H, H-1', $J_{1',2'}$ 1.79 Hz), 4.06 (dd, 1 H, H-2', $J_{2',3'}$ 3.29 Hz), 4.00 (t, 1 H, H-2, $J_{1,2}$ 2.77 Hz), 3.95 (m, 1 H, H-5', $J_{4',5'}$ 4.96 Hz, $J_{5',6'}$ 2.55 Hz and $J_{5',6''}$ 9.91 Hz), 3.83 (dd, 1 H, H-3', $J_{3',4'}$ 9.61 Hz), 3.80 (t, 1 H, H-4'), 3.80-3.75 (m, 2 H, H-6' and H-6''), 3.69 (t, 1 H, H-4, $J_{3,4}$ 9.80 Hz), 3.63 (dd, 1 H, H-3 $J_{2,3}$ 2.79 Hz), 3.62 (t, 1 H, H-6, $J_{5,6}$ 9.46 Hz), 3.50 (dd, 1 H, H-1, $J_{1,6}$ 9.98 Hz), 3.31 (t, 1 H, H-5, $J_{4,5}$ 9.17 Hz).

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