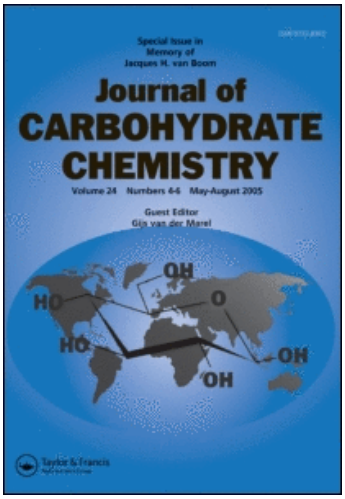

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IODONIUM ION-MEDIATED MANNOSYLATIONS OF *MYO*-INOSITOL : SYNTHESIS OF A *MYCOBACTERIA* PHOSPHOLIPID FRAGMENT

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ABSTRACT

Iodonium ion-mediated glycosylation of 1-*O*-allyl-3,4,5-tri-*O*-benzyl-6-*O*-*para*-methoxybenzyl-D/L-*myo*-inositol by ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside gave, after removal of the *para*-methoxybenzyl group and column chromatography, an α/β-mixture of the individual diastereoisomeric disaccharides. Subsequent stereospecific glycosylation of the α(1-2) linked mannopyranosyl-D-*myo*-inositol enantiomorph by the same ethyl 1-thiomannopyranoside donor afforded, after debenzoylation, benzylation and subsequent deallylation the partially benzylated 2,6-dimannopyranosyl-D-*myo*-inositol derivative, the HO-1 position of which was phosphorylated, *via* the *H*-phosphonate method, with 1,2-dipalmitoyl-*sn*-glycerol. Oxidation of the intermediate phosphonate diester, and subsequent hydrogenolysis of the *O*-benzyl groups, furnished the target compound 1-*O*-(1,2-dipalmitoyl-*sn*-glycero-3-phosphoryl)-2,6-di-*O*-α-D-mannopyranosyl-D-*myo*-inositol.

INTRODUCTION

As part of our continuous efforts directed towards the assembly of the 2,6-dimannopyranosyl-D-*myo*-inositol phospholipid **I** (Figure 1), which is a fragment of the *Mycobacteria* phospholipids **IIa-b**,[1] we reported the synthesis of 1-*O*-(1,2-di-palmitoyl-*sn*-glycero-3-phosphoryl)-2-*O*-α-D-mannopyranosyl-D-*myo*-inositol[2] (**III**) and 6-*O*-(α-D-mannopyranosyl)-D-*myo*-inositol[3] (**IV**). Furthermore, it was established that

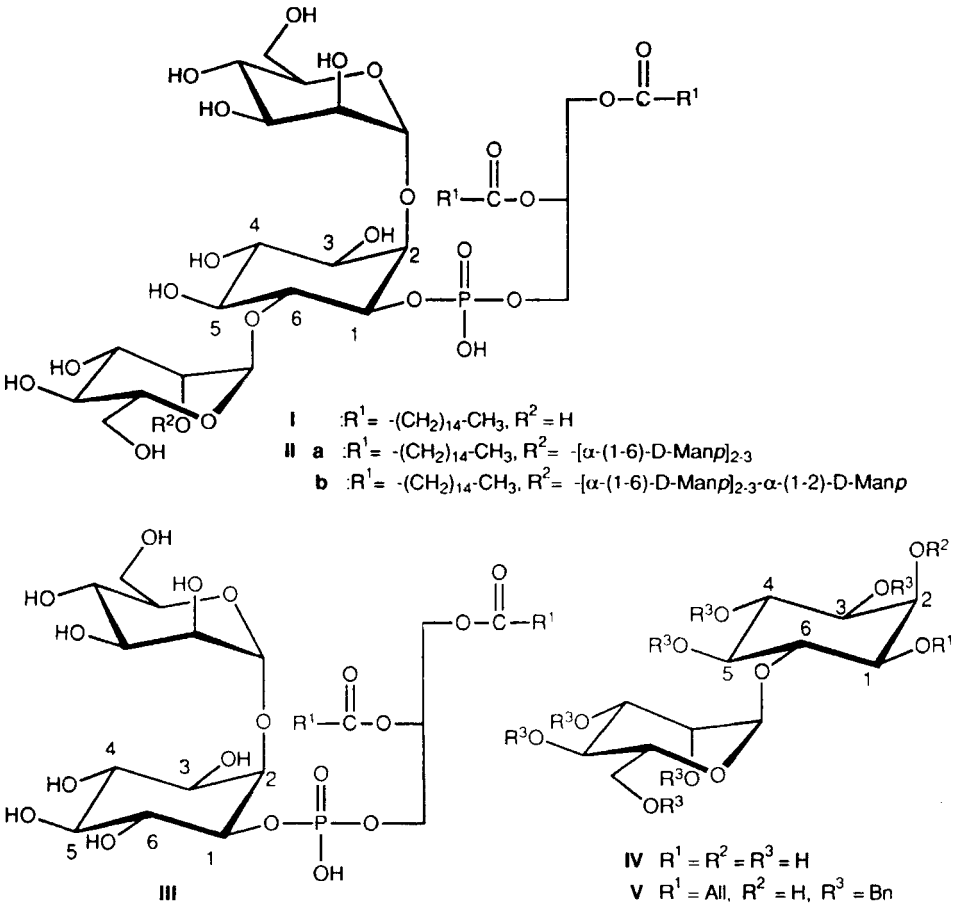


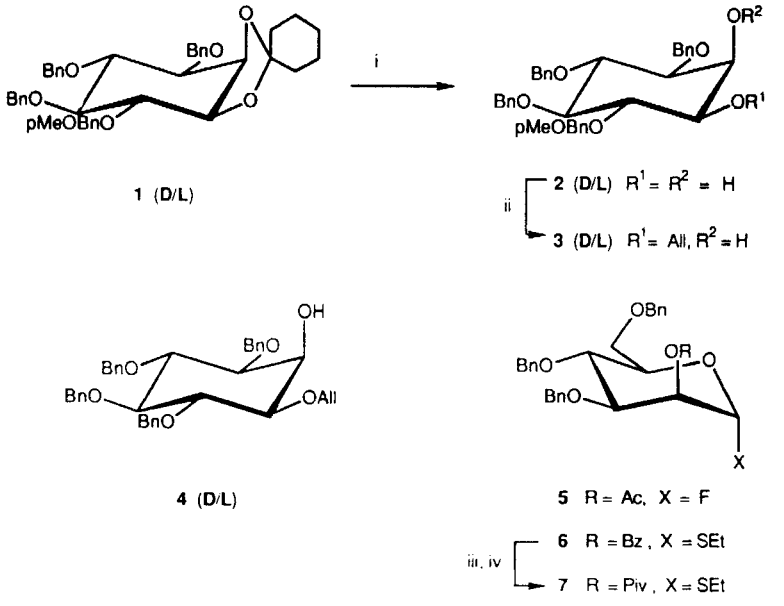
Figure 1

subsequent mannosylation of the hydroxyl at C-2 of the partially protected *myo*-inositol mono-mannoside V (*i.e.* a precursor of IV) was abortive.[3]

We report here that the synthesis of the trisubstituted D-*myo*-inositol I can be concluded successfully, if the sequential introduction of the two mannosyl substituents commences with the mannosylation of the hydroxyl at C-2.

RESULTS AND DISCUSSION

On the basis of the insight gathered so far during the synthesis of the *Mycobacteria* fragments III and IV, it was to be expected that the availability of the racemic 1-*O*-

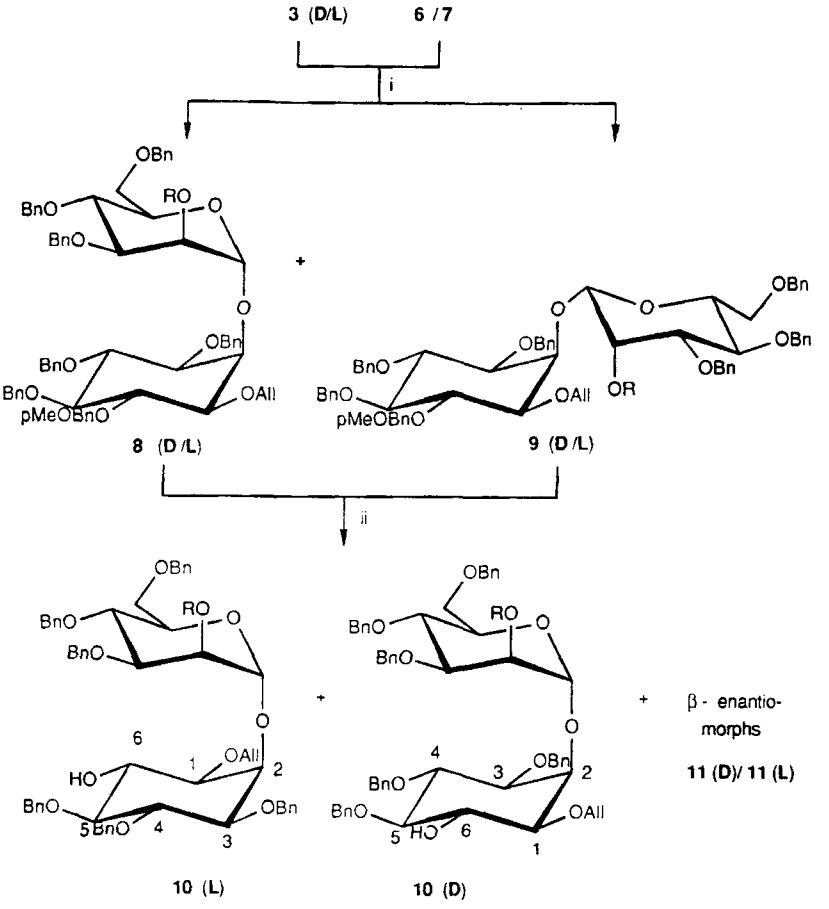


Reagents : i) 0.5N HCl/MeOH, MeOH:dioxane (1/1, v/v), 3h, 20 °C; ii) Bu_2SnO, MeOH, reflux; CsF, allyl bromide, DMF, 18h, 20 °C; iii) KOtBu, MeOH:dioxane (1/1, v/v), 12h, 45 °C; iv) pivaloyl chloride, pyridine, 18h, 20 °C.

Scheme 1

allyl-3,4,5-tri-*O*-benzyl-6-*O*-*para*-methoxybenzyl-(D/L)-*myo*-inositol (**3**)[4] would in principle meet the demands for a successful assembly of the target molecule **I**. Thus the presence of the free axial hydroxyl in **3** is in accordance with the prerequisite that mannosylation of this position has to be executed first. On the other hand, the second mannosylation step can be performed after selective removal of the *p*-methoxybenzyl (*p*-MeOBn) group. Finally, deblocking of the allyl (All) group from the C-1 position will allow the introduction of the phosphatidic acid moiety.

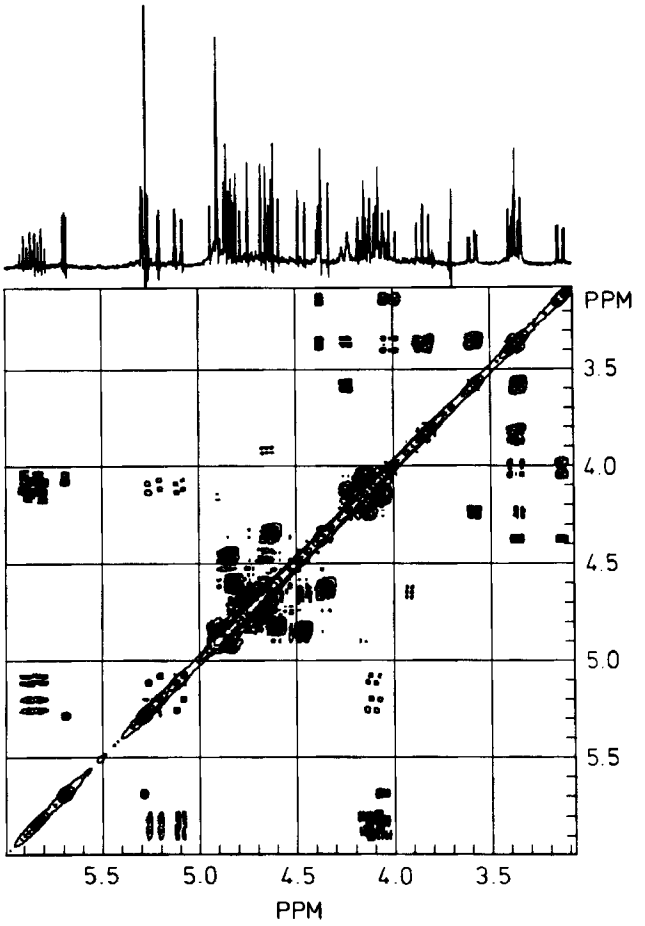
The synthesis of **3** is outlined in Scheme 1 and commences with the acidolysis[5] of the 1,2-*cis*-cyclohexylidene acetal function from the known 3,4,5-tri-*O*-benzyl-1,2-*O*-cyclohexylidene-6-*O*-*para*-methoxybenzyl-(D/L)-*myo*-inositol (**1**)[3] to give the diol **2** in 71% yield. Regioselective allylation of the stannylidene complex[6] of **2** with allyl bromide in the presence of cesium fluoride[7] gave, after purification by silica gel chromatography, key intermediate **3** in 72% yield.



Reagents : i) NIS-TfOH (cat.), 1,2-dichloroethane:diethyl ether (3/1, v/v), -10 °C, 5 min; iia) DDQ, CH_2Cl_2:H_2O (9/1, v/v), 2.5h, 20 °C, iib) column chromatography.

Scheme 2

In the next stage, we turned our attention to the sequential glycosylation of **3**. It was shown earlier[2] that glycosylation of the axially orientated hydroxyl group in the *myo*-inositol derivative **4** by the D-mannosyl fluoride **5** (anomeric mixture), *via* the agency of BF_3·OEt_2,[8] proceeded with a high degree of stereoselectivity (*i.e.* solely formation of the required 1,2-*trans* bond). However, it was anticipated that BF_3·OEt_2-assisted coupling of **5** with **3** would be incompatible with the presence of the *p*-



Part of the ^{1}H-^{1}H correlated (COSY) NMR-spectrum of derivative **10** (D)

Figure 2

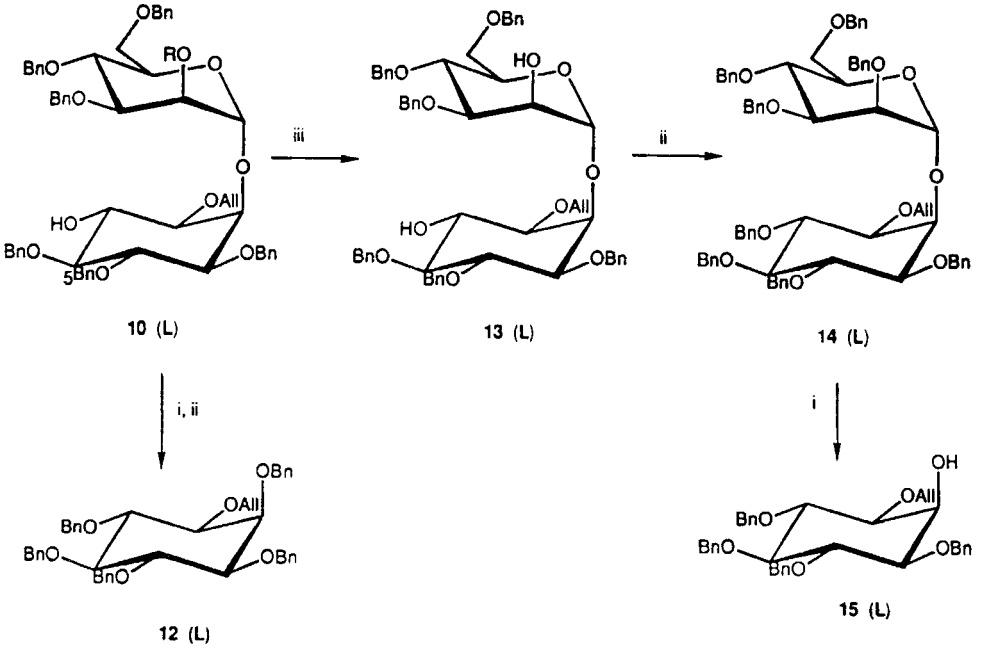
MeOBn protecting group in **3**. Indeed, short treatment (5 min. at 20 °C) of **3** with the Lewis acid catalyst led to the complete removal of *p*-MeOBn group.

In order to circumvent this problem, it was decided to glycosylate **3** by ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**6**)[3] using the promoter *N*-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH).[9]

However, iodonium ion-mediated condensation of **3** with **6** (Scheme 2) gave, after work-up and purification, an intractable mixture of coupling products in a yield of 77%. Surprisingly, ^{13}C NMR analysis indicated that the mixture contained not only

the expected 1,2-*trans* but also the 1,2-*cis* linked diastereoisomeric dimers [*i.e.* **8** (D/L) and **9** (D/L) {R=Bz}, respectively]. In order to substantiate this finding further, the mixture was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[10] TLC-analysis of the thus obtained mixture revealed the presence of four products, which could be separated by silica gel column chromatography, to give the individual compounds in a yield of 10-30% [*i.e.* 30% (Rf 0.68), 30% (Rf 0.65), 10% (Rf 0.43) and 10% (Rf 0.41)]. ^{13}C NMR spectroscopy (gated coupling) showed that the structures of the relatively faster running products were in accordance[11] with the α-linked diastereoisomers **10** (D/L) [R=Bz, $J_{C\text{-}1,H\text{-}1}$ = 168.5 and 169.9 Hz], and the slower running enantiomorphs with the β-linked stereoisomers **11** (D/L) [R=Bz, $J_{C\text{-}1,H\text{-}1}$ = 161.6 and 162.2 Hz]. The concomitant formation of the 1,2-*cis* linked stereoisomers **11** (D/L) in the condensation of **6** (R=Bz) with **3** goaded us to find out whether the recently proposed stereocontrolling auxiliary effect of a pivaloyl group[12] at C-2 in the donor would on the one hand enhance the coupling efficiency, and possibly prevent *cis*-glycosylation of acceptor **3** on the other. However, the yield of the NIS/TfOH (cat.) promoted condensation of **3** with **7**, prepared by debenzoylation of **6** followed by treatment with pivaloyl chloride, was of the same order (*i.e.* 78%). In addition, analysis of the resulting coupling products by ^{13}C NMR spectroscopy revealed the presence of four distinct anomeric C-1 resonances (*i.e.* at δ 98.8, 98.5, 98.1 and 98.0 ppm): thus indicating the formation of α- and β-linked monomannosylated *myo*-inositol derivatives [*i.e.* **8** and **9** (D/L), {R=Piv}].

Determination of the D- or L-configuration of the *myo*-inositol unit in the required α-linked diastereoisomers **10** was corroborated by selecting[3] the stereoisomer with the highest Rf-value to be degraded and further processed (or *vice versa*) to furnish a chirally pure *myo*-inositol derivative with known specific optical rotation. Accordingly, elaboration of **10** (Rf 0.68) gave, as illustrated in Scheme 3, the L-*myo*-inositol derivatives **12** and **15**. Thus, acid hydrolysis of the glycosidic linkage in **10**,[13] followed by benzylation of the purified *myo*-inositol moiety, furnished the fully protected *myo*-inositol **12**, the specific optical rotation of which was the same as reported[14] for 1-*O*-allyl-2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol ($[\alpha]_D^{20}$ -2.1°). Furthermore, two-step conversion of **10** into **14** [debenzoylation (**10**→**13**) followed by benzylation (**13**→**14**)] resulted, after acid hydrolysis of **14**, in the isolation of the *myo*-inositol derivative **15**. The specific optical rotation of **15** ($[\alpha]_D^{20}$ +2.1°) was in good

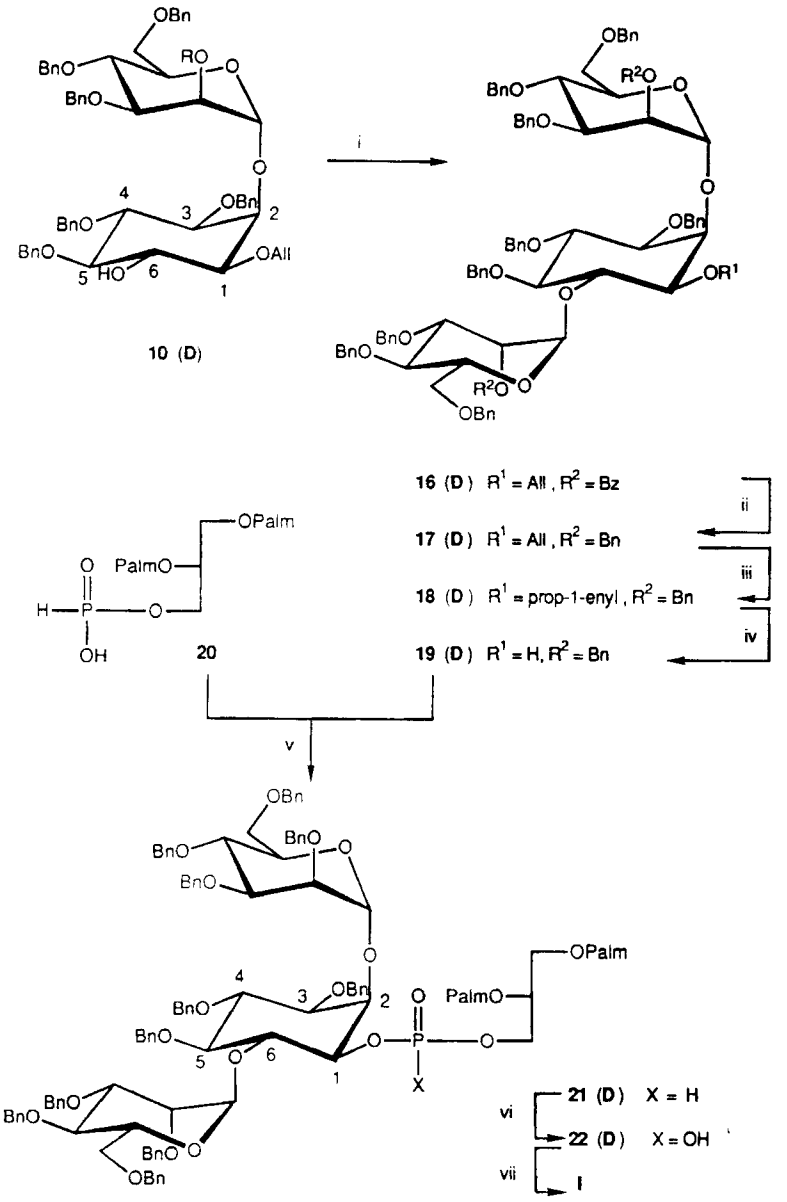


Reagents : i) 3% aq. HCl:HOAc (1/9, v/v), reflux, 8h; ii) benzyl bromide, NaH, DMF, 8h, 20 °C; iii) KOtBu, MeOH:dioxane (1/1, v/v), 1h, 20 °C.

Scheme 3

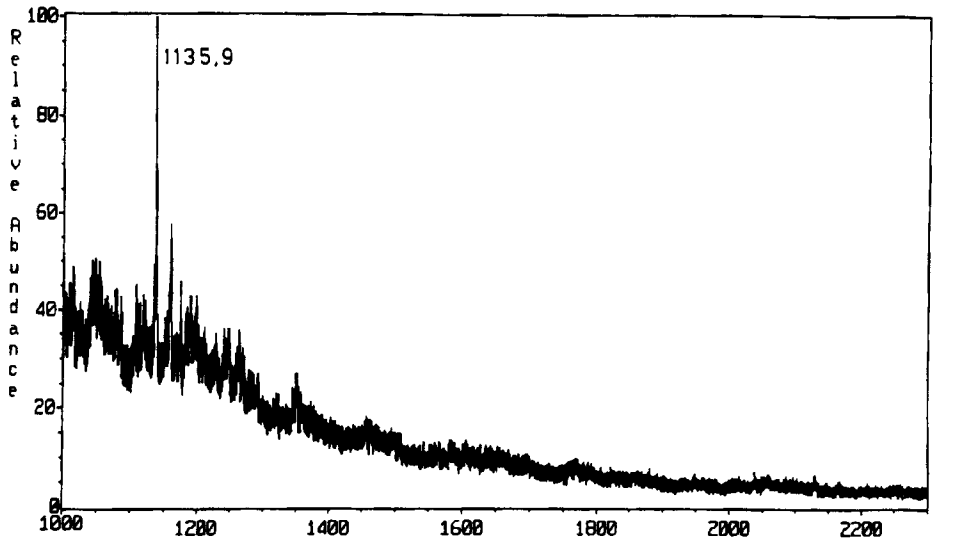
accord with the reported[15] value of 1-*O*-allyl-3,4,5,6-tetra-*O*-benzyl-L-*myo*-inositol. It may therefore be concluded that the lower-running α-linked manninositose **10** contains the required D-*myo*-inositol unit.

The introduction of the second mannopyranosyl unit could, in contrast with the first one, be realized in a stereospecific manner by glycosylation of **10** (D) [a part of the COSY spectrum of **10** (D) is shown in Figure 2] by the thioglycoside donor **6**, as depicted in Scheme 4. Thus, condensation of **10** (D) with **6** (D) in the presence of NIS/TfOH (cat.) gave, after purification, the α-linked di-mannosylated D-*myo*-inositol **16** (D) in 84% yield. Conversion of **16** (D) into **19** (D), having a free hydroxyl at C-1 of the D-*myo*-inositol unit necessary for the introduction of the phosphatidic acid moiety, was executed as follows. Debenzoylation and benzylation [**16** (D) → **17** (D)] followed by isomerization of the allyl group in **17** (D) with the



Reagents : i) NIS-TfOH (cat.), 1,2-dichloroethane:diethyl ether (3/1, v/v), 6, -10 °C, 5 min; ii) a] KOtBu, MeOH:dioxane (1/1, v/v), 1h, 20 °C; b] benzyl bromide, NaH, DMF, 8h, 20 °C; iii) 1,2-dichloroethane, $Ir(COD)[PMe(Ph)_2]_2^+PF_6^-/H_2$, 24h, 20 °C ; iv) 0.5N HCl/MeOH, MeOH:dioxane (1/1, v/v), 8h, 45 °C; v) 0.15N pivaloyl chloride/THF, pyridine, 20 min, 20 °C; vi) iodine, pyridine:H_2O (49:1, v/v), 0 °C, 5 min; vii) Pd/C, H_2, *iso*-propyl alcohol:ethyl acetate:H_2O (5/3/2, v/v/v), 24h.

Scheme 4



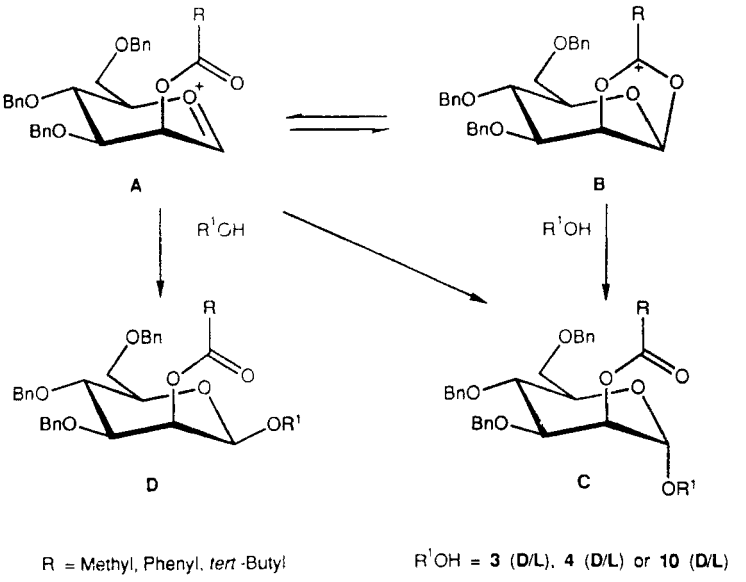
Part of the FAB (+) mass spectrum of compound **I**

Figure 3

catalyst 1,5-cyclooctadiene-*bis* [methyldiphenylphosphine]iridium hexafluorophosphate[16] into the *trans* prop-1-enyl derivative **18** (D), and acidolysis of the *trans* prop-1-enyl group,[17] afforded alcohol **19** (D) in 72% yield for the four steps.

Apart from this, we also prepared, in an analogous fashion as mentioned for the synthesis of **19** (D), the stereoisomer **19** (L) by condensing **10** (L) with **6** (D) followed by protecting group manipulations on **16** (L). Catalytic hydrogenolysis of **19** (L) furnished the fully deprotected dimannosylated *myo*-inositol derivative, the identity of which was unambiguously ascertained by ^{1}H and ^{13}C NMR spectroscopy.

Phosphorylation of the secondary hydroxyl in derivative **19** (D) could be realized using the 1-*H*-phosphonate **20**.[18] Thus phosphonylation of **19** (D) with **20**, prepared by the phosphitylation of 1,2-dipalmitoyl-*sn*-glycerol with 2-chloro-5,6-benzo-1,3,2-dioxaphosphin-4-one[19] in the presence of a stoichiometric amount of pivaloyl chloride resulted in the formation of the *H*-phosphonate diester **21** (D) [^{31}P NMR ($CDCl_3$ δ 8.82; J_{PH} = 706 Hz]. Oxidation of **21** (D) with iodine in a mixture of pyridine and water afforded, after purification and ion-exchange chromatography, the phosphate diester **22** (D) in 51% overall yield [based on **19** (D)].



Scheme 5

Finally, removal of the benzyl protecting groups by catalytic hydrogenolysis of **22** (D) with palladium on charcoal furnished the target compound **I**, the identity and homogeneity of which was ascertained by ^{31}P and ^{1}H NMR, as well as FAB-mass spectroscopy. The FAB(+) mass spectrum (see Figure 3) showed signals at m/z 1135.9 and 1158.1, corresponding with $[M+H]^+$ and $[M+Na]^+$, respectively.

The unexpected stereochemical outcome of the iodonium-ion promoted glycosylation of the axial hydroxyl group in acceptor **3** (D/L) by the thioglycoside **6** (D), and previously observed phenomena related to the synthesis of the target molecule **I**, can be rationalized by the following line of reasoning. First of all, it has to be noted that the α/β ratio of the products obtained by the coupling reaction of the D- and L- *myo*-inositol acceptors **3** with donor **6** (D) is the same (*i.e.* 3:1) : thus excluding the possibility that the stereochemistry of the glycosylation reaction is under the influence of double stereodifferentiation.[20]

Secondly, condensation of the same donor **6** (D) with the individual D- or L-acceptors **10** proceeded in a stereospecific manner. The latter result can be explained (Scheme 5) by α-face attack of the equatorial hydroxyl in the acceptor R'OH [*i.e.* **10** (D/L)] on the more stable dioxocarbenium ion **B** (R=Phenyl) generated in the

iodonium-ion promoted activation of **6** (D). On the other hand, it may be assumed that a similar attack of the relatively less reactive axial hydroxyl group in the acceptor R'OH [*i.e.* **3** (D/L)] on the same ion **B** would be less favourable. Consequently, acceptor R'OH will have a higher tendency to react with the more reactive oxocarbenium ion **A** (R = Phenyl), to give the β- and α-linked products **D** and **C**, respectively [*i.e.* **8** and **9** (D/L), R = Bz]. It is also conceivable that the relatively less crowded ion **A** (R = *tert*-Butyl) plays a similar role in the stereochemical outcome of the glycosylation of **3** (D/L) by donor **7** (D). On the other hand, it is reasonable to assume that the more pronounced activity of the dioxocarbenium ion **B** (R = Me), in comparison with the corresponding ion **B** (R = Phenyl), may account for the earlier observed α-glycosylation of the axial hydroxyl group in acceptor **4** (D/L), which closely resembles acceptor **3** (D/L), by donor **5** (R = Ac). Furthermore, it is evident now that the earlier reported failure to glycosylate **V** has to be ascribed to an even more decreased reactivity of the axial hydroxyl group in the equatorially glycosylated *myo*-inositol moiety.

In conclusion, the heuristic approach described in this and preceding papers[2,3] towards the synthesis of *Mycobacteria* phospholipid fragment **I** led to a better understanding of the factors which govern the stereochemistry and effectiveness of the glycosylation of *myo*-inositol derivatives. For example, it may be postulated that 1,2-*trans* glycosylation of rather inert hydroxyl groups can be achieved most effectively when using the sterically less demanding acetyl as a participating group at the C-2 position of the donor molecule.

EXPERIMENTAL

General Methods and Materials. Tetrahydrofuran, triethylamine, dichloromethane, *N,N*-dimethylformamide and 1,2-dichloroethane were dried by refluxing with calcium hydride (5 gram per litre) for 16 h and distilled. Tetrahydrofuran was stored over molecular sieves 0.5 nm and the other solvents over molecular sieves 0.4 nm. Tetrahydrofuran and 1,2-dichloroethane were redistilled from lithium aluminum 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 phosphorus pentoxide and stored over sodium wire. Benzyl

alcohol was distilled under reduced pressure. Triethylammonium bicarbonate buffer (TEAB, 2M) was prepared by passing a stream of carbon dioxide gas through a cooled (ice-water bath) mixture of triethylamine (825 mL) and de ionized water (2175 mL) until pH 7. 1*H*-tetrazole was purchased from Janssen Chimica, cesium fluoride from Fluka and *p*-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% sulfuric 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 sulfate (10 g) in 10% aqueous sulfuric acid, followed by charring at 140 °C. Short column chromatography was performed on Kieselgel 60 (230-400 mesh ASTM, Merck). ^{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. ^{31}P and ^{13}C NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer on line with a JEC 980B computer at 50.1 and 80.7 MHz, respectively. ^{13}C and ^{1}H chemical shifts are given in ppm (δ), relative to tetramethylsilane (TMS) as internal standard and ^{31}P chemical shifts in ppm (δ) to 85% H_3PO_4 as external standard. Optical rotations were measured at 20 °C using a Perkin Elmer 241 Polarimeter. The FAB (+) mass spectrum of compound **I** was recorded on a JEOL HX110/HX110 mass spectrometer, equipped with a standard JEOL FAB source operated at 3 kV. The spectrum was obtained using a magnet scan rate of 40 s from m/z 1000 to 2300.

Procedures

3,4,5-Tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-D/L-*myo*-inositol (2). A mixture of acetyl chloride in methanol (0.5M, 8 mL) was added to a solution of compound **1**[3] (2.6 g, 4.0 mmol) in methanol and dioxane (50 mL, 1/1, v/v). TLC analysis (ethyl acetate/toluene, 1/5, v/v) showed, after stirring for 3 h at 20 °C, complete conversion of **1** (Rf 0.67) into **2** (Rf 0.28). The solution was neutralized with triethylamine (2 mL) and concentrated to dryness. The syrup was purified by silica gel column (6 x 4 cm) chromatography. Elution was effected with dichloromethane to give **2** (1.72 g, 3.0 mmol) as an oil; ^{13}C NMR ($CDCl_3$) δ 159.2 (C_{arom}, *p*-MeOBn), 138.7 and 137.8 (C_{arom}, Bn), 130.7 (C_{arom}, *p*-MeOBn), 130.0-127.6 (CH_{arom}, Bn and *p*-MeOBn), 113.9

(CH_{arom}, *p*-MeOBn), 83.2, 81.6, 81.1, 80.0, 71.8 and 69.3 (CH *myo*-inositol), 75.9, 75.6, 75.2 and 72.6 (3 x CH_2, Bn and CH_2, *p*-MeOBn), 55.2 (OCH_3, *p*-MeOBn); ^1H NMR ($CDCl_3$) δ 7.45-6.80 (m, 19 H, H_{arom}, Bn and *p*-MeOBn), 4.94-4.64 (m, 8 H, CH_2, Bn and *p*-MeOBn), 4.21 (t, 1 H), 3.96 (t, 1 H), 3.82 (m, 4 H, OCH_3), 3.49-3.42 (m, 3 H), 2.48 (s, 1 H, 2-OH), 2.35 (d, 1 H, 1-OH).

Anal. Calcd for $C_{35}H_{38}O_7$: C, 73.66; H, 6.71. Found : C, 73.21; H, 6.43.

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-D/L-*myo*-inositol (3). A solution of **2** (2.4 g, 4.21 mmol) and dibutyltin oxide (1.16 g, 4.63 mmol) in dry methanol was refluxed for 4 h and subsequently concentrated *in vacuo*. The residue was coevaporated with toluene (2 x 40 mL), dissolved in *N,N*-dimethylformamide (40 mL) and cesium fluoride (0.83 g, 5.47 mmol) and allyl bromide (0.56 g, 4.63 mmol) were added. After stirring for 18 h at 20 °C, TLC analysis (*n*-hexane/ethyl acetate, 2:3, v/v) indicated complete conversion of **2** (Rf 0.32) into **3** (Rf 0.68). The solution was concentrated and the obtained oil was taken up in dichloromethane (100 mL). The organic layer was washed with water (50 mL), aqueous sodium bicarbonate (50 mL, 10%, w/v) and water (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. The oily residue was purified by silica gel column (4 x 6 cm) chromatography (*n*-hexane/ethyl acetate, 3/1, v/v, 500 mL) to afford **7** (2.50 g, 3.31 mmol) as an oil; ^{13}C NMR ($CDCl_3$) δ 154.6 (C_{arom}, *p*-MeOBn), 138.6, 138.4 and 137.7 (C_{arom}, Bn), 133.0 (CH=, All), 129.9-125.2 (CH_{arom}, Bn), 116.8 (CH_2=, All), 97.7 (CH_{arom}, *p*-MeOBn), 82.0, 80.0, 77.5, 74.1, 71.6 and 68.6 (CH *myo*-inositol), 75.0, 73.3, 71.2 and 68.8 (CH_2, Bn, *p*-MeOBn and All), 55.0 (OCH_3).

Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found : C, 74.52; H, 7.04.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-pivaloyl-1-thio-α-D-mannopyranoside (7). Potassium *tert*-butoxide was added to a solution of **6** (0.5 g, 0.84 mmol) in a methanol-dioxane mixture (10 mL, 1/1, v/v). The reaction mixture was stirred for 20 h at 45 °C, after which TLC analysis (*n*-hexane/ethyl acetate, 4/1, v/v) indicated conversion of **6** (Rf 0.7) into the corresponding HO-2 derivative (Rf 0.22). The reaction mixture was neutralized with Dowex 50 WX4 (100-200 mesh, H^+-form) filtered and concentrated *in vacuo*. The oily residue was coevaporated with toluene (2 x 5 mL), dissolved in pyridine (20 mL), and pivaloyl chloride (2 eq.) was added. The reaction mixture was stirred for 16 h at 20 °C and TLC analysis (*n*-hexane/ ethyl acetate, 4:1, v/v) showed the complete conversion of the alcohol (Rf 0.22) into **7** (Rf 0.65). The reaction was

stopped by the addition of water (1 mL). The mixture was diluted with dichloromethane (50 mL) and the organic layer was washed with water, aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered and concentrated to dryness. The crude oil was purified by silica gel column (2 x 2 cm) chromatography (*n*-hexane/ ethyl acetate, 100 mL, 6/1, v/v), to give **5** (0.35 g, 0.62 mmol, 74% overall yield) as an oil; ^{13}C NMR ($CDCl_3$) δ 177.4 (C_{carb}, Piv), 138.2 and 137.8 (C_{arom}, Bn), 82.4, 78.7, 74.3, 71.6 and 69.8 (CH mannopyranoside), 75.0, 73.1, 71.3 and 68.8 (CH_2, Bn, C-6), 27.0 (CH_3, Piv), 25.5 (C_q, Piv), 25.4 (CH_2 SEt), 14.9 (CH_3, SEt).

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-D/L-*myo*-inositol (8 D/L) and 1-*O*-Allyl-3,4,5-tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-mannopyranosyl)-D/L-*myo*-inositol (9 D/L). A mixture of compound **3** (2.2 g, 3.5 mmol) and **6**[3] (2.3 g, 3.84 mmol) was dried by coevaporation with toluene (2 x 40 mL) and dissolved in 1,2-dichloroethane (70 mL). Subsequently, a 0.1M stock solution (42 mL) of *N*-iodosuccinimide (1.58 g) and trifluoromethanesulphonic acid (126 µL) in 1,2-dichloroethane/diethyl ether (1/1, v/v, 70 mL) was added to the cooled (-10 °C) reaction mixture containing activated molecular sieves 0.4 nm (2.0 g) under argon atmosphere. After 5 minutes, TLC analysis (ethyl acetate/toluene, 1/5, v/v) showed the formation of an intractable mixture of compounds (**8 D/L** and **9 D/L**; Rf 0.7). The reaction was stopped by the addition of triethylamine, the solids were removed by filtration and the filtrate was washed with aqueous sodium thiosulfate (10%, w/v). The organic layer was dried, filtered and concentrated to dryness. The residual oil was purified by silica gel column (4 x 6 cm) chromatography which was eluted with ethyl acetate/*n*-hexane (500 mL, 1/4, v/v), to give **8 D/L** and **9 D/L** as an oil in 77% yield (3.1 g, 2.70 mmol); ^{13}C NMR ($CDCl_3$) δ 165.2 (C_{carb}, Bz), 159.0 (C_{carb}, *p*-MeOBn), 138.9, 138.6, 138.5, 138.0 and 137.7 (C_{arom}, Bn and *p*-MeOBn), 135.3 (CH=, All), 132.7-126.9 (CH_{arom}, Bn, Bz and *p*-MeOBn), 113.6 (CH_2, All), 98.8 and 98.2 (C-1), 83.1, 81.1, 80.9, 80.4, 78.7, 77.3, 74.1, 72.7 and 68.8 (CH *myo*-inositol and C-2, C-3, C-4 and C-5), 75.9, 75.1, 73.1, 72.1, 71.4, 71.1 68.5 and 53.3 (C-6, CH_2, Bn, *p*-MeOBn and All), 54.9 (CH_3, *p*-MeOBn).

Anal. Calcd for $C_{72}H_{74}O_{13}$: C, 75.37; H, 6.50. Found : C, 75.21; H, 6.38.

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-pivaloyl-α-D-mannopyranosyl)-D/L-*myo*-inositol (8 D/L) and 1-*O*-Allyl-3,4,5-tri-*O*-

benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-pivaloyl-β-D-mannopyranosyl)-D/L-*myo*-inositol (9 D/L). Glycosylation of **3** (0.22 g, 0.35 mmol) by **7** (0.22 g, 0.38 mmol) was realized according to the same procedure as described for the glycosylation of **3** by **6**. TLC analysis (ethyl acetate/toluene, 1/5, v/v) showed, after 5 minutes at -10 °C, complete formation of an intractable mixture of diastereoisomers (**8 D/L** and **9 D/L**; Rf 0.7). The reaction was stopped by the addition of triethylamine, worked up and subsequently the crude product was purified in the same manner as described for **8** and **9** (R = Bz). Yield : 0.3 g, 0.28 mmol; ^{13}C NMR ($CDCl_3$) δ 177.0 (C_{carb}, Bz), 159.0 (C_{carb}, *p*-MeOBn), 139.0, 138.6, 138.4, 138.0 and 137.9 (C_{arom}, Bn and *p*-MeOBn), 134.7 and 134.3 (CH=, All), 132.7-126.9 (CH_{arom}, Bn, Bz and *p*-MeOBn), 117.3, 116.6 and 116.0 (CH_2, All), 98.8, 98.5, 98.1 and 98.0 (C-1), 83.2, 82.9, 81.3, 80.9, 80.7, 80.5, 80.2, 79.4, 78.7, 78.4, 78.3, 78.2, 77.7, 77.6, 77.3, 76.7, 73.9, 72.3, 72.1, 67.9 and 67.3 (CH *myo*-inositol and C-2, C-3, C-4 and C-5), 75.9, 75.6, 75.5, 74.9, 73.1, 72.6, 72.0, 71.3, 71.0, 70.9, 70.8, 69.7, 69.0, 68.4 and 53.3 (C-6, CH_2, Bn, *p*-MeOBn and All), 54.9 (CH_3, *p*-MeOBn).

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-L-*myo*-inositol (10 L), 1-*O*-allyl-3,4,5-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-D-*myo*-inositol (10 D), 1-*O*-allyl-3,4,5-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-mannopyranosyl)-L-*myo*-inositol (11 L) and 1-*O*-allyl-3,4,5-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-mannopyranosyl)-D-*myo*-inositol (11 D). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (4.5 mmol) was added to a solution of **8 D/L** and **9 D/L** [(R = Bz), 3.5 g, 3.06 mmol] in dichloromethane/water (50 mL, 9/1, v/v) within 2.5 h at ambient temperature. TLC analysis (dichloromethane/acetone, 99/1, v/v) showed, after 5 h, conversion of the starting compounds **8 D/L** and **9 D/L** into two pairs of diastereoisomers **10 D/L** and **11 D/L**. The organic layer was diluted with dichloromethane (200 mL), washed with water, aqueous sodium bicarbonate (100 mL, 10%, w/v) and water, dried over magnesium sulfate, filtered and concentrated to dryness. The four individual derivatives **10 D/L** and **11 D/L** were obtained after silica gel column (2 x 15 cm) chromatography (dichloromethane/acetone, 3000 mL, 99/1, v/v); **10 L** (1.0 g, 0.98 mmol) : Rf 0.68 (dichloromethane/acetone, 99/1, v/v); $[\alpha]_D^{20}$ - 8.3° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 165.3 (C_{carb}, Bz), 138.5 and 137.8 (C_{arom}, Bn), 134.3 (CH=, All), 132.9-127.1 (CH_{arom}, Bn), 117.4 (CH_2, All), 99.1 (C-1, $J_{C-1,H-}$

$_1$ = 168.5 Hz), 83.0, 81.0, 80.6, 77.8, 77.6, 74.1, 72.4, 71.5 and 68.9 (CH *myo*-inositol and mannopyranosyl), 75.8, 75.5, 75.1, 73.4, 72.8, 71.7 and 70.8 (CH_2, Bn, All and C-6 mannopyranosyl); **10 D** (1.0 g, 0.98 mmol) : Rf 0.65; $[\alpha]_D^{20}$ -0.8° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 165.1 (C_{carb}, Bz), 138.4, 138.2, 137.9 and 137.7 (C_{arom}, Bn), 133.9 (CH=, All), 132.7-127.0 (CH_{arom}, Bn and Bz), 117.2 ($CH_{2=}$, All), 98.7 (C-1, $J_{C-1,H-1}$ = 169.9 Hz), 82.7, 80.6, 79.4, 78.7, 77.4, 73.9, 72.7, 71.4 and 68.8 (CH *myo*-inositol and mannopyranosyl), 75.5, 74.9, 73.1, 72.0, 71.3 and 71.1 (CH_2, Bn and All, C-6 mannopyranosyl); ^1H NMR ($CDCl_3$) δ 8.18-7.92 (m, 5 H, H_{arom}, Bz), 7.62-6.98 (m, 30 H, H_{arom}, Bn), 5.91-5.78 (m, 1 H, CH=, All), 5.68 (t, 1 H, H-2 mannopyranosyl, $J_{2,3}$ = 2.40 Hz), 5.28 (d, 1 H, H-1 mannopyranosyl, $J_{1,2}$ = 2.0 Hz), 5.26-5.07 (m, 2 H, CH_2=, All), 4.93-4.58 (m, 10 H, CH_2, Bn), 4.47-4.32 (m, 3 H, CH_2, Bn, H-2 *myo*-inositol, $J_{2,3}$ = 2.40 Hz), 4.22 (dt, 1 H, H-5 mannopyranosyl), 4.17-3.98 (m, 5 H, H-3/4 mannopyranosyl, CH_2, All and H-6 *myo*-inositol, $J_{1,6}$ = 9.50 Hz), 3.84 (t, 1 H, H-6 mannopyranosyl, $J_{5,6}$ = 2.90 Hz, $J_{6,6'}$ = 10.79 Hz), 3.39-3.32 (m, 3 H, H-6' mannopyranosyl, H-3/4 *myo*-inositol), 3.15-3.11 (dd, 1 H, H-1, $J_{1,2}$ = 2.18 Hz), 2.55 (bs, 1 H, OH).

Anal. Calcd for $C_{64}H_{66}O_{12}$: C, 74.83; H, 6.48. Found : C, 74.65; H, 6.35.

11 L (0.34 g, 0.33 mmol) : Rf 0.43; ^{13}C NMR ($CDCl_3$) δ 166.3 (C_{carb}, Bz), 138.9, 138.8, 138.4, 138.3, 137.8 and 137.6 (C_{arom}, Bn), 134.4 (CH=, All), 132.3-126.4 (CH_{arom}, Bn and Bz), 116.8 (CH_2=, All), 98.9 (C-1, $J_{C-1,H-1}$ = 161.6 Hz), 83.0, 80.9, 78.8, 77.7, 77.5, 77.4, 72.8, 72.2, 71.4 and 68.8 (CH *myo*-inositol and mannopyranosyl), 75.5, 74.9, 73.1, 72.6, 71.3, 71.1 and 70.7 (CH_2, Bn and All), 68.5 (C-6, mannopyranosyl); **11 D** (0.33 g, 0.32 mmol) : Rf 0.42; ^{13}C NMR ($CDCl_3$) δ 166.4 (C_{carb}, Bz), 138.8, 138.7, 138.5, 138.1 and 137.5 (C_{arom}, Bn), 134.4 (CH=, All), 132.4-127.0 (CH_{arom}, Bn and Bz), 116.9 (CH_2=, All), 98.7 (C-1, $J_{C-1,H-1}$ = 162.2 Hz), 82.5, 80.2, 80.0, 78.7, 75.1, 74.6, 72.1, 69.3 and 68.6 (CH *myo*-inositol and mannopyranosyl), 75.0, 74.3, 73.1, 71.4, 70.9 and 70.6 (CH_2, Bn and All), 69.7 (C-6 mannopyranosyl); ^1H NMR ($CDCl_3$) δ 8.10-7.91 (m, 5 H, H_{arom}, Bz), 7.71-6.98 (m, 30 H, H_{arom}, Bn), 5.95-5.82 (m, 2 H, CH=, All and H-2 mannopyranosyl, $J_{2,3}$ = 3.10 Hz), 5.28-5.11 (m, 2 H, CH_2=, All), 4.93-4.81 (m, 5 H, CH_2, Bn and H-1, $J_{1,2}$ = 3.53 Hz), 4.67-4.32 (m, 8 H, CH_2, Bn), 4.24-3.78 (m, 10 H), 3.60-3.10 (m, 5 H), 2.36 (s, 1 H, OH).

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (13 L). Potassium *tert*-butoxide (0.1 g) was added to a solution of **10 L** (0.3

g, 0.29 mmol) in methanol/dioxane (20 mL, 1/1, v/v). TLC analysis (*n*-hexane/ethyl acetate, 5/1, v/v) indicated conversion of **10 L** (Rf 0.67) into **13 L** (Rf 0.34) after 5 h at 20 °C. The solution was neutralized with Dowex 50 WX4 [100-200 mesh (H^+-form)], filtered and concentrated *in vacuo* to give **13 L** in a quantitative yield. ^{13}C NMR ($CDCl_3$) δ 138.5, 138.1 and 137.7 (C_{arom}, Bn), 134.3 (CH=, All), 130.3-124.8 (C_{arom}, Bn), 117.2 (CH_2=, All), 99.9 (C-1), 83.0, 81.1, 80.7, 79.5, 77.8, 74.1, 72.4, 71.1, 70.9 and 68.4 (CH *myo*-inositol and mannopyranosyl), 75.6, 75.4, 74.8, 73.4, 72.8, 72.0, 70.8 and 68.9 (CH_2, Bn and All, C-6 mannopyranosyl); ^1H NMR ($CDCl_3$) δ 7.21-7.04 (m, 30 H, H_{arom}, Bn), 5.82-5.69 (m, 1 H, CH=, All), 5.27 (d, 1 H, H-1 mannopyranosyl, $J_{1,2}$ = 1.46 Hz), 5.15-5.02 (m, 2 H, CH_2=, All), 4.84-4.38 (m,12 H, CH_2, Bn), 4.23 (t, 1 H, H-2 *myo*-inositol, $J_{2,3}$ = 2.22 Hz), 4.14-3.96 (m, 4 H), 3.88-3.53 (m, 7 H), 3.28 (t, 1 H), 2.98-2.94 (dd, 1 H, H-1, $J_{1,2}$ = 2.45 Hz).

1-O-Allyl-3,4,5,6-tetra-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (14 L). Benzyl bromide (0.01 mL, 0.5 mmol) was added to a suspension of **13 L** (0.25 g, 0.27 mmol) and sodium hydride (30 mg, 1.0 mmol) in *N,N*-dimethylformamide (20 mL). TLC analysis (toluene/ethyl acetate, 5/1, v/v) showed, after stirring for 18 h at 20 °C, complete conversion of **13 L** (Rf 0.34) into **14 L** (Rf 0.65). Excess sodium hydride was quenched with methanol, the reaction mixture was diluted with diethyl ether (50 mL) and the organic layer was washed with water, aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered and concentrated to dryness. The crude oil was purified by silica gel column (2 x 3 cm) chromatography and elution was effected with *n*-hexane/ethyl acetate (200 mL, 10/1, v/v). Concentration of the appropriate fractions furnished **14 L** (0.23 g, 0.21 mmol, 78% yield) $[\alpha]_D^{20}$ +7.0° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.6, 138.4, 138.1, 137.7 (C_{arom}, Bn), 134.8 (CH=, All), 128.3-127.5 (CH_{arom}, Bn), 116.6 (CH_2, All), 98.1 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 171.6 Hz), 83.2, 81.3, 81.1, 80.9, 79.0, 78.6, 74.8, 74.1 and 71.6 (CH *myo*-inositol and mannopyranosyl), 76.1, 75.7, 75.6, 75.0, 73.4, 72.0, 71.2 and 69.3 (CH_2, Bn and All, C-6 mannopyranosyl); ^1H NMR ($CDCl_3$) δ 7.42-7.16 (m, 40 H, H_{arom}, Bn), 5.93-5.80 (m, 1 H, CH=, All), 5.43 (d, 1 H, H-1 mannopyranosyl, $J_{1,2}$ = 1.62 Hz), 5.13-5.08 (m, 2 H, CH_2=, All), 4.93-4.37 (m, 17 H, CH_2, Bn and H-2 *myo*-inositol), 4.25-3.98 (m, 4 H), 3.87-3.67 (m, 6 H), 3.46-3.35 (dd, 1 H), 3.25-3.21 (dd, 1 H, H-2 *myo*-inositol, $J_{2,3}$ = 2.66 Hz).

1-*O*-Allyl-3,4,5,6-tetra-*O*-benzyl-L-*myo*-inositol (15 L). A solution of **14 L** (0.2 g, 0.18 mmol) in 3% hydrochloric acid/acetic acid (15 mL, 1/9, v/v) was heated for

8 h at 100 °C, followed by cooling to 20 °C and neutralization with triethylamine. After coevaporation of the reaction mixture with toluene (3 x 50 mL), the oily residue was taken up into dichloromethane (50 mL), washed with water, aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered and concentrated to dryness. Purification of the crude product by silica gel column (2 x 1 cm) chromatography (elution : *n*-hexane/ethyl acetate, 70 mL, 4/1, v/v) furnished pure **15 L** (70 mg, 0.12 mmol, 67% yield) as an oil; $[\alpha]_D^{20}$ +2.1° (*c* 1 $CHCl_3$), lit.[15] $[\alpha]_D^{20}$ +2.9° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.7 (C_{arom}, Bn), 134.6 (CH=, All), 128.4-127.5 (CH_{arom}, Bn), 117.4 (CH_2=, All), 83.1, 81.1, 79.8, 67.2 (CH *myo*-inositol), 75.9, 72.8, 71.9 (CH_2, Bn and All).

Anal. Calcd for $C_{37}H_{40}O_6$: C, 76.53; H, 6.94. Found : C, 76.83; H, 7.09.

1-*O*-Allyl-2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol (12 L). A solution of **10 L** (0.2 g, 0.19 mmol) in 3% hydrochloric acid/acetic acid (10 mL, 1/9, v/v) was heated for 8 h at 100 °C. After cooling to room temperature, the solution was neutralized with triethylamine and coevaporated with toluene (2 x 50 mL) to a syrup, which was dissolved in *N,N*-dimethylformamide (10 mL). The solution was cooled to 0 °C, followed by the addition of excess sodium hydride and benzyl bromide. TLC analysis showed, after stirring for 6 h, conversion of the two alcohols into two main products. After addition of methanol, the reaction mixture was diluted with diethyl ether and the organic layer was washed with water, aqueous sodium bicarbonate and water, dried over magnesium sulfate, filtered and concentrated to an oil. The crude product was purified by silica gel column (2 x 1 cm) chromatography, which was eluted with *n*-hexane/ethyl acetate (70 mL, 5/1, v/v) to afford **12 L** (80 mg, 0.12 mmol, 63% yield) as a pure oil; $[\alpha]_D^{20}$ -2.1° (*c* 1 $CHCl_3$) lit.[14] $[\alpha]_D^{27}$ -2.2° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.9 (C_{arom}, Bn), 134.9 (CH=, All), 129.0-125.3 (CH_{arom}, Bn), 116.6 (CH_2=, All), 83.7, 81.7, 80.9, 80.7 and 74.2 (CH *myo*-inositol), 75.8, 74.1, 72.8, 72.1 and 71.7 (CH_2, Bn and All).

1-*O*-Allyl-3,4,5,-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-D-*myo*-inositol (16 D). Glycosylation of **10 D** (0.4 g, 0.4 mmol) by **6** (0.29 g, 0.48 mmol) was realized according to the same procedure as described for the glycosylation of **3** by **6**. TLC analysis (toluene/ethyl acetate, 5/1, v/v) showed, after 5 minutes, conversion of starting compounds **6** (Rf 0.79) and **10 D** (Rf 0.52) into **16 D** (Rf

0.76). After the addition of triethylamine, the solids were removed by filtration and the filtrate was worked-up in the same manner as for the synthesis of **8 D/L** and **9 D/L**. The crude product was purified by silica gel column (3 x 3 cm) chromatography, which was eluted with ethyl acetate/*n*-hexane (200 mL, 6/1, v/v) and Sephadex LH20 (methanol/dichloromethane, 1/2, v/v). The appropriate fractions were pooled and concentrated to afford homogeneous **16 D** (0.52 g, 0.33 mmol, 80% yield); $[\alpha]_D^{20}$ +1.0° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 165.4 and 164.9 (C_{carb}, Bz), 138.8, 138.6, 138.5, 138.2, 138.1, 137.9 and 137.8 (C_{arom}, Bn), 133.6 (CH=, All), 132.7-127.1 (CH_{arom}, Bn and Bz), 117.9 (CH_2 =, All), 99.1 and 98.3 (C-1 and C-1', $J_{C\text{-}1,H\text{-}1}$ = 172.9 Hz, $J_{C\text{-}1',H\text{-}1'}$ = 167.8 Hz), 81.2, 81.1, 80.7, 78.6, 78.0, 77.2, 76.0, 74.2, 73.9, 72.2, 71.7 and 68.7 (CH *myo*-inositol and mannopyranosyl), 75.8, 75.5, 75.0, 73.1, 72.1 and 71.2 (CH_2, Bn and All), 68.6 and 68.4 (C-6 mannopyranosyl).

Anal. Calcd for $C_{98}H_{98}O_{18}$: C, 75.27; H, 6.32. Found : C, 75.58, H, 6.18.

1-*O*-Allyl-3,4,5-*O*-tri-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-α-D-mannopyranosyl)-L-*myo*-inositol (16 L). Derivative **16 L** (0.45 g, 0.28 mmol) was obtained in 90% yield according to the same procedure as described for the synthesis of **16 D**; $[\alpha]_D^{20}$ -13.8° (*c* 1 $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 165.3 and 165.1 (C_{carb}, Bz), 138.9, 138.8, 138.3, 138.3, 138.1, 137.9, 137.8, 137.7 and 137.6 (C_{arom}, Bn), 134.3 (CH=, All), 132.8-127.0 (CH_{arom}, Bn and Bz), 117.9 (CH_2=, All), 98.9 and 97.7 (C-1 and C-1', $J_{C\text{-}1,H\text{-}1}$ = 175.8 Hz, $J_{C\text{-}1',H\text{-}1'}$ = 173.4 Hz), 83.7, 81.4, 80.8, 80.3, 78.2, 78.0, 77.2, 76.9, 74.2, 73.9, 71.6, 69.1, 68.7 and 68.3 (CH *myo*-inositol and mannopyranosyl), 75.9, 75.6, 75.0, 74.6, 73.4, 72.7, 72.5, 72.0 and 71.2 (CH_2, Bn and All, C-6 and C-6' mannopyranosyl).

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (17 D). Potassium *tert*-butoxide (0.1 g) was added to a solution of derivative **16 D** (0.4 g, 0.24 mmol) in dioxane/methanol (20 mL, 1:1, v/v). The mixture was stirred for 1 h at ambient temperature when TLC analysis (ethyl acetate/*n*-hexane, 2/3, v/v) showed complete conversion of compound **16 D** (Rf 0.87) into the corresponding alcohol (Rf 0.23). After neutralization of the reaction mixture with Dowex 50 WX4 [100-200 mesh (H^+-form)], the solution was filtered, concentrated to dryness and the resulting oil was coevaporated with toluene (2 x 25 mL). The residue was dissolved in *N,N*-dimethylformamide (15 mL) and sodium hydride (50 mg) and benzyl bromide (0.15

mL) were added. The suspension was stirred for 8 h when TLC analysis (ethyl acetate/*n*-hexane, 1/4, v/v) showed the conversion of the intermediate (Rf 0.15) into compound **17 D** (Rf 0.55). The reaction was stopped by the addition of methanol, the solvents removed by evaporation and the residue was diluted with diethyl ether (20 mL). The organic layer was washed with water (10 mL), aqueous sodium bicarbonate (15 mL, 10%, w/v) and water, dried over magnesium sulfate and concentrated *in vacuo*. The syrup thus obtained, was purified by silica gel column (3 x 4 cm) chromatography (ethyl acetate/*n*-hexane, 250 mL, 1:5, v/v) to furnish **17 D** (0.25 g, 0.15 mmol, 65% yield) as a homogeneous oil; ^{13}C NMR ($CDCl_3$) δ 139.0, 138.8, 138.7, 138.6, 138.5, 138.4, 138.3 and 138.0 (C_{arom}, Bn), 133.9 (CH=, All), 129.7-126.6 (CH_{arom}, Bn), 117.7 (CH_2, All), 98.6 (C-1 and C-1'), 81.7, 81.4, 81.3, 80.1, 78.8, 78.7, 75.9, 75.5, 74.7, 74.4, 71.8, 71.7 and 70.7 (CH mannopyranosyl and *myo*-inositol), 75.9, 75.6, 74.9, 73.3, 73.1, 72.3, 72.2, 71.9, 71.5 and 71.0 (CH_2, Bn and All), 68.8 and 68.5 (C-6, mannopyranosyl).

Anal. Calcd for $C_{98}H_{102}O_{16}$: C, 76.64; H, 6.69. Found : C, 75.98; H, 6.22.

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (17 L). Derivative **17 L** was obtained in the same manner as described for the synthesis of **17 D**. ^{13}C NMR ($CDCl_3$) δ 139.0, 138.8, 138.4, 138.3 and 137.6 (C_{arom}, Bn), 134.6 (CH=, All), 128.3-126.5 (CH_{arom}, Bn), 117.8 (CH_2, All), 98.3 and 98.0 (C-1 and C-1'), 84.1, 81.3, 81.1, 80.8, 80.1, 79.9, 79.4, 74.7, 74.5, 74.1, 73.7 and 71.6 (CH mannopyranosyl and *myo*-inositol), 75.2, 73.4, 73.2, 72.8, 72.6, 71.8 (CH_2, Bn and All), 69.3 and 68.9 (C-6 mannopyranosyl).

1-*O*-Prop-1-enyl-3,4,5-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (18 D). Derivative **17 D** (0.1 g, 0.06 mmol) was dissolved in 1,2-dichloroethane (10 mL). The solution was alternatingly degassed and placed under argon (3x). 1,5-Cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate (20 mg) was added and the solution was degassed again and placed under argon (3x). The catalyst was activated by passing over a stream of hydrogen for 1.5 min. Once again the reaction mixture was degassed and thereafter, left under a gentle stream of argon for 24 h. TLC analysis (ethyl acetate/*n*-hexane, 1/4, v/v) showed conversion of the starting compound **17 D** (Rf 0.47) into **18 D** (Rf 0.45). The solution was evaporated and the

catalyst was removed by short column (2 x 1 cm) chromatography (ethyl acetate/*n*-hexane, 1/5, v/v, 100 mL), to give pure **18 D** (90 mg, 0.055 mmol) as an oil in 90% yield; ^{13}C NMR ($CDCl_3$) δ 145.1 (*O*-CH=), 139.0, 138.7, 138.6, 138.3 and 137.9 (C_{arom}, Bn), 129.6-126.3 (CH_{arom}, Bn), 102.5 (=CH-), 98.9 and 98.3 (C-1'), 84.7, 83.0, 81.1, 79.7, 79.2, 78.8, 78.3, 75.8, 75.4, 74.5, 72.5 and 71.8 (CH *myo*-inositol and mannopyranosyl), 76.0, 75.6, 74.9, 73.3, 72.3, 72.0, 71.9 and 71.5 (CH_2, Bn), 68.7 and 68.5 (C-6 mannopyranosyl), 12.4 (CH_3).

3,4,5-Tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-D-*myo*-inositol (19 D). Acetyl chloride in methanol (0.5 M, 0.4 mL) was added to a solution of **18 D** (90 mg, 0.055 mmol) in dichloromethane/methanol (10 mL, 1/1, v/v) and the reaction mixture was stirred for 8 h at 45 °C. TLC analysis (ethyl acetate/*n*-hexane, 2/3, v/v) indicated complete conversion of **18 D** (Rf 0.76) into **19 D** (Rf 0.56). After cooling of the reaction mixture to room temperature triethylamine was added. The solution was diluted with dichloromethane and washed with water and aqueous sodium bicarbonate (20 mL, 10%, w/v). The organic layer was dried with magnesium sulfate, filtered and concentrated to dryness. Purification of the crude product was accomplished by silica gel column (2 x 2 cm) chromatography (ethyl acetate/*n*-hexane (100 mL, 1/3, v/v) to afford homogeneous **19 D** (72 mg, 0.044 mmol, 80% yield); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.6, 138.4, 138.3, 138.1, 138.0 and 137.7 (C_{arom}, Bn), 128.4-127.3 (CH_{arom}, Bn), 99.0 and 95.6 (C-1'), 81.1, 80.1, 80.0, 79.3, 78.9, 78.4, 75.4, 75.0, 74.6, 74.3 and 72.0 (CH *myo*-inositol and mannopyranosyl), 75.5, 75.2, 75.0,74.5, 73.4, 72.5, 72.0, 71.7 and 71.5 (CH_2, Bn), 69.4 and 68.9 (C-6' mannopyranosyl); ^1H NMR ($CDCl_3$) δ 7.43-6.92 (m, 55 H, H_{arom}, Bn), 5.45 (s, 1 H, H-1', $J_{1',2'}$ = 1.9 Hz), 5.23 (d, 1 H, H-1'', $J_{1'',2''}$ = 2.3 Hz), 4.91-4.33 (m, 22 H, CH_2, Bn), 4.21 (t, 1 H, H-2 *myo*-inositol, $J_{1,2}$ = 2.41 Hz), 4.12-4.08 (m, 4 H), 3.93-3.69 (m, 7 H), 3.59-3.55 (m, 3 H), 3.46-3.22 (m, 5 H), 2.92 (bs, 1 H, HO-1).

Anal. Calcd for $C_{95}H_{98}O_{16}$: C, 76.28; H, 6.60. Found : C, 75.77, H, 6.99.

3,4,5-Tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-L-*myo*-inositol (19 L). Compound **19 L** was prepared in a similar way as described for the synthesis of derivative **19 D**; ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 138.2 and 137.7 (C_{arom}, Bn), 128.4-127.0 (CH_{arom}, Bn), 99.8 and 98.4 (C-1'), 84.8, 82.8, 81.0, 80.8, 79.6, 74.9, 74.5, 72.5, 71.7 and 70.3 (CH

mannopyranosyl and *myo*-inositol) 75.9, 73.2, 72.4, 72.2, 71.9 and 69.1 (CH_2, Bn and C-6 mannopyranosyl).

1,2-Dipalmitoyl-*sn*-glycero-3-*H*-phosphonate triethylammonium salt (20). A solution of 1,2-dipalmitoyl-*sn*-glycerol (1.0 g, 1.76 mmol) in dioxane/pyridine (15 mL, 2/1, v/v) was added dropwise to a stirred solution of salicylchlorophosphite (0.6 g, 3.0 mmol) in dioxane (5 mL). TLC analysis showed, after 15 minutes at 0 °C, complete conversion of the alcohol (Rf 0.82) into the *H*-phosphonate **20** (Rf 0.10). The reaction mixture was quenched by the addition of water/pyridine. After 15 minutes the reaction mixture was diluted with dichloromethane (50 mL) and the organic layer was washed with TEAB (0.1 M, 50 mL) and water, dried over magnesium sulfate, filtered and concentrated to dryness. After coevaporation of the oily residue with toluene (40 mL), the crude product was purified by silica gel column (3 x 4 cm) chromatography. Elution was effected with ethyl acetate/dichloromethane/methanol (500 mL, 95/100/5 → 60/100/40, v/v/v) to furnish **20** as a white powder (1.15 g, 1.52 mmol) in 86% yield; ^{31}P NMR ($CDCl_3$) δ 3.69 ($J_{P,H}$ = 635 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4 and 173.0 (C_{carb}, Palm), 70.0 (C-2, glycerol), 62.0 and 61.4 (C-1 and C-3, glycerol), 29.2-22.1 (CH_2, Palm), 13.3 (CH_3, Palm).

3,4,5-Tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-1-*O*-(1,2-dipalmitoyl-*sn*-glycero)-D-*myo*-inositol *H*-phosphonate (21 D). A mixture of derivative **19 D** (53 mg, 0.07 mmol) and **20** (46 mg, 0.032 mmol) was dried by coevaporation with pyridine (4 mL) and redissolved in pyridine (2 mL). Subsequently, a stock solution of pivaloyl chloride in THF (0.5 mL, 0.15 M) was added at ambient temperature. TLC analysis (*n*-hexane/ethyl acetate, 3/2, v/v) showed, after 20 minutes, the formation of **21 D** (Rf 0.56). The reaction was quenched by addition of TEAB (0.1 M, 2 mL) and the solution was stirred for another 10 minutes. The mixture was diluted with dichloromethane (35 mL) and washed with TEAB (0.1 M, 15 mL) and water (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. The residue was coevaporated with toluene (2 x 10 mL) *in vacuo* and used without further purification. ^{31}P NMR ($CDCl_3$) δ 8.82 ($J_{P,H}$ = 706 Hz).

3,4,5-Tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-1-*O*-(1,2-dipalmitoyl-*sn*-glycero)-D-*myo*-inositol phosphate (22 D). To a solution of crude **21 D** in pyridine/water (10 mL, 49/1, v/v)

was added iodine (20 mg) at 0 °C. TLC analysis indicated, after 3 minutes at 0 °C, complete conversion of the *H*-phosphonate **19 D** (Rf 0.56) into the phosphodiester **22 D** (Rf 0.04). The reaction mixture was diluted with dichloromethane (30 mL) and the organic layer was washed with sodium thiosulfate (10 mL, 10%, w/v) and water (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue thus obtained was purified by Sephadex gel filtration (dichloromethane/methanol, 2/1, v/v). The appropriate fractions were pooled and concentrated to dryness. The product was subsequently applied to an ion-exchange column [Dowex 50 WX4, 100-200 mesh, (Na^+-form)] to furnish the phosphate **22 D** in the sodium form. Yield : 50 mg ; Rf 0.37 (MeOH/dichloromethane, 9:1, v/v); ^{31}P NMR ($CDCl_3$) δ - 0.22; ^{13}C NMR ($CDCl_3$) δ 173.3 and 173.0 (C_{carb}, Palm), 138.9-137.6 (C_{arom}, Bn), 132.8-127.1 (CH_{arom}, Bn), 98.3 and 97.6 (C-1'), 82.3-73.1 (CH *myo*-inositol, mannopyranoside and C-2 glycerol), 72.9-65.8 (CH_2, Bn, C-1 and C-3 glycerol), 31.7-28.9 (CH_2, Palm), 13.9 (CH_3, Palm).

1-*O*-(1,2-Dipalmitoyl-*sn*-glycero-3-phosphoryl)-2,6-di-*O*-α-D-mannopyranosyl-D-*myo*-inositol (I). Derivative **22 D** (30 mg) was dissolved in *iso*-propyl alcohol/water/ethyl acetate (25 mL, 5/3/2, v/v/v) and hydrogenated in the presence of 10% palladium on charcoal (200 mg) for 24 h at ambient temperature. The catalyst was removed by filtration and washed with *iso*-propyl alcohol/water/ethyl acetate (50 mL, 1/1/1, v/v/v). The combined filtrates were concentrated to dryness to give **IV** (5 mg) as a solid. The crude product was purified by gel filtration (HiLoad Sephadex S100, HR26/60). Elution was effected with 0.15M TEAB, containing 30% methanol. The appropriate fractions were pooled and concentrated *in vacuo*. Excess TEAB-salts were removed by repeated lyophilization with de-ionized water to afford compound **I**. Yield : 4 mg; ^1H NMR (DMSO/D_2O, 49/1, v/v) δ 5.39 (s, 1 H, H-1), 5.06 (d, 1 H, H-1', $J_{H\text{-}1',H\text{-}2'}$ = 1.80 Hz), 4.11-3.31 (m, 18 H, *myo*-inositol and mannopyranosyl), 1.63-1.14 (m, 56 H, Palm), 0.84 (s, 6 H, 2 x CH_3 Palm); ^{31}P NMR (DMSO/D_2O, 49/1, v/v) δ -0.74; FAB (+) mass spectrum *m/z* 1135.9, $[M + H]^+$ for $C_{53}H_{100}O_{23}P$ 1135.6

2,6-Di-*O*-α-D-mannopyranosyl-L-*myo*-inositol. A solution of **19 L** (100 mg) in a mixture of *iso*-propyl alcohol, water and ethyl acetate (25 mL, 2/3/5, v/v/v) was hydrogenated in the presence of 10% palladium on charcoal (200 mg) for 24 h at room temperature. The catalyst was removed by filtration and washed with *iso*-propyl alcohol/water/ethyl acetate (25 mL, 1/1/1, v/v/v). The combined filtrates were

concentrated to dryness to give the title compound; the crude product was purified by gel filtration (HiLoad Sephadex S100, HR26/60). Elution was effected with 0.15M TEAB. The appropriate fractions were pooled and concentrated *in vacuo*. Excess TEAB-salts were removed by repeated lyophilization of the title compound with de-ionized water. ^{1}H NMR ($CDCl_3$) δ 5.22 (s, 1 H, H-1), 5.12 (s, 1 H, H-1'), 4.13 (m, 2 H, H-2 and H-2'), 4.06-3.26 (m, 16 H, *myo*-inositol and mannopyranosyl); ^{13}C NMR ($CDCl_3$) δ 102.3 and 101.6 (C-1 and C-1'), 81.1, 80.5, 75.8, 73.6, 73.5, 73.4, 72.1, 71.2, 71.1, 71.0, 69.8, 67.5 and 67.4 (CH mannopyranosyl and *myo*-inositol), 61.7 and 61.5 (C-6 and C-6').

Anal. Calcd for $C_{18}H_{32}O_{16}$: C, 42.86; H, 6.39. Found : C, 43.09; H, 6.48.

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