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Stereospecific mannosylations of *myo*-inositol: Synthesis of manno-*myo*-inositol fragment of *Mycobacterium tuberculosis*[+]

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Abstract. Methyl iodide activated stereospecific α-mannosylations utilising 2-pyridyl-1-thio-mannopyranoside derivatives (2,3,4) as donors and suitably protected *myo*-inositol derivatives (1,25,27,29) as acceptors to prepare 2-O-α-D-mannopyranosyl-6-[O-α-D-mannopyranosyl-(1–6)-O-α-D-mannopyranosyl-(1–6)-O-α-D-mannopyranosyl]-D-*myo*-inositol derivative (31) is described.

Keywords. Stereospecific mannosylations; *myo*-inositol; *Mycobacterium tuberculosis.*

The phospholipid component of mycobacteria is unique in that it consists mainly of phosphatidyl-*myo*-inositol mannosides. Glycolipids of *Mycobacterium tuberculosis* and *Mycobacterium phlei* have been shown to contain 1-glyceryl phosphoryl-D-*myo*-inositol pentamannosides in which mannosides are axially (α-linkage) attached to position 2 and 6 of the inositol ring (Lee and Ballou 1965). On the basis of structural studies, pentamannosides have been assigned L-phosphatidyl-2-O-α-D-mannopyranosyl-6-[O-α-D-mannopyranosyl(1-2)-O-α-D-mannopyranosyl-(1–6)-O-α-D-mannopyranosyl (1-6)-O-α-D-mannopyranosyl]-D-*myo*-inositol structure (I) (Lee and Ballou 1965).

In earlier work from our group, we have developed a highly stereospecific α-glycosylation methodology making use of 2-pyridyl 1-thiohexapyrano- and furanosides and also their corresponding 2-deoxysaccharides as glycosyl donors and methyl iodide as an activator for the synthesis of several axially linked oligosaccharides (Mereyala and Reddy 1991; Mereyala *et al* 1992). The main advantages of this methodology are (i) mild reaction conditions, (ii) use of highly stable glycosyl donors in any form (pyrano-, furano-, 2-deoxy pyrano- and furanosides) and as anomeric mixture (α and β anomers), (iii) most of the common protecting groups remain intact including the sensitive interglycosidic linkages.

We report here an application of this methodology to synthesize axially linked mannosides of *myo*-inositol. In known work involving the use of Koenigs–Knorr reaction (Angyal and Schelton 1966) and the ortho ester method (Klyashchitskii *et al* 1970) the yield of 2-O-mannosyl-*myo*-inositol was not greater than 16%. Iodonium ion-mediated mannosylations of *n*-pentenylmannosides proved to be better, however anomeric selectivity was still a problem and always required a C-2 participating group; however this is not the case while using 2-pyridyl-1-thiomannopyranosides

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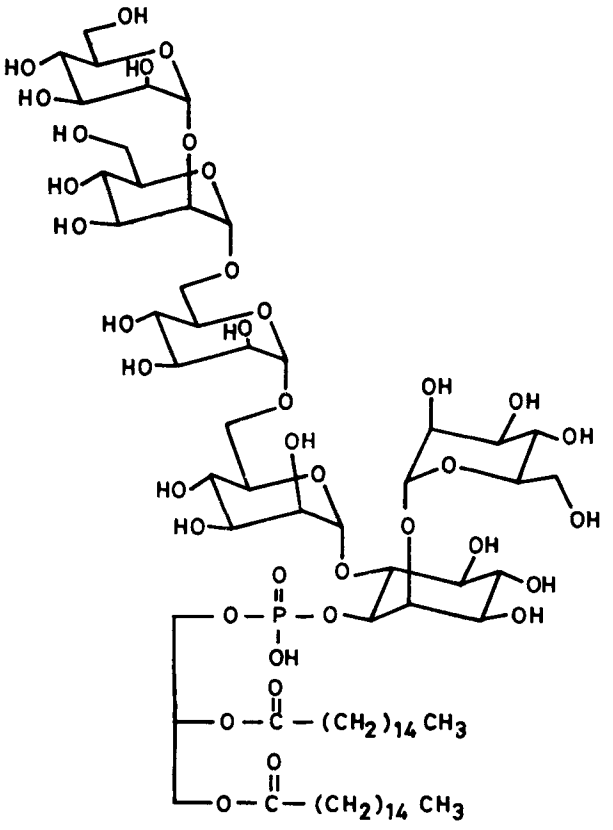

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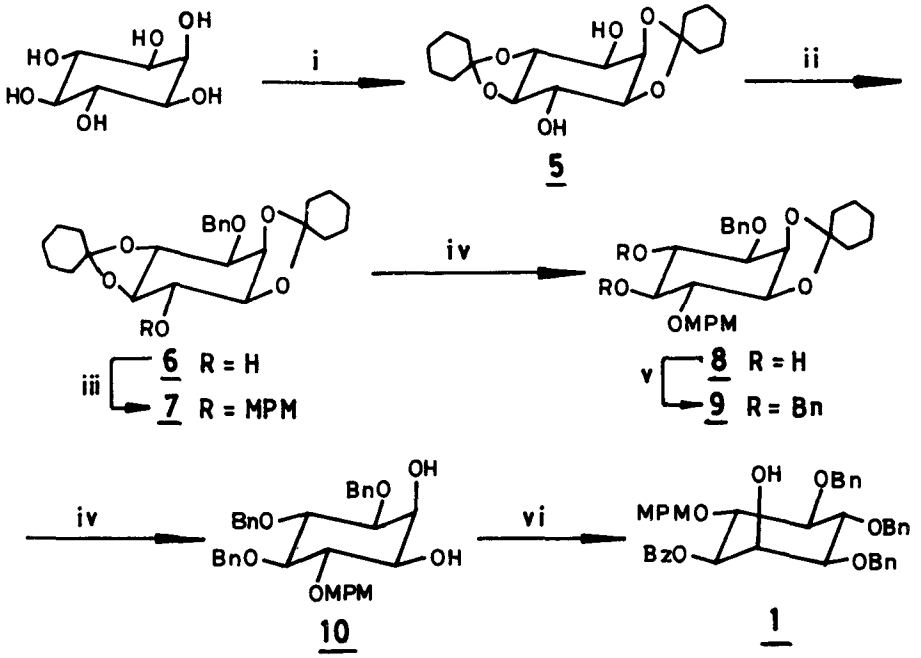
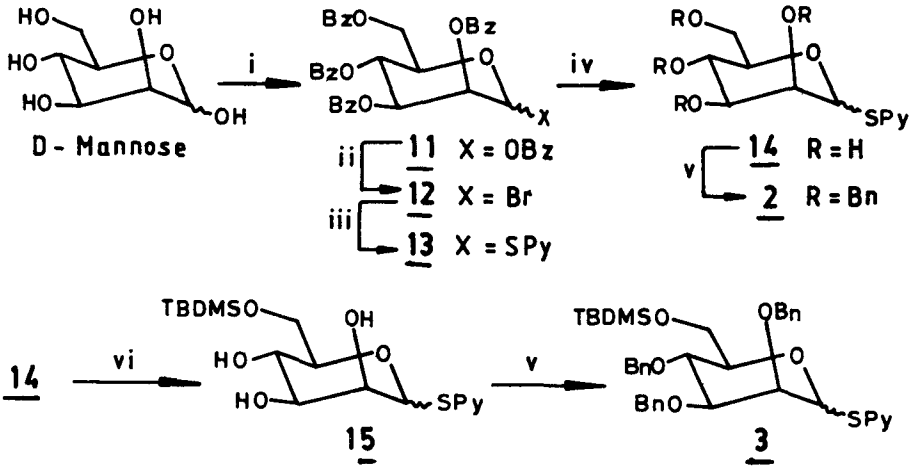
as donors. Hence, choice of per-O-benzylated 1-thiomannopyranosides as mannosyl donors was considered to synthesize pentamannoinositides in preparative quantities.

Myo-inositol was converted by known methods (Elie *et al* 1992) to 1-O-benzoyl-3,4,5-tri-O-benzyl-6-O-*p*-methoxybenzyl-*myo*-inositol (1).

1 was reacted with per-O-benzylated 2-pyridyl-1-thiomannopyranoside 2 in dichloromethane having 3% methyl iodide, molecular sieves (4A) at 50°C for 40h to obtain axially linked D and L mannosylated inositol derivatives 24D and 24L in 72% yield (1:1 ratio). 24D and 24L were separated by flash chromatography on silica gel and were well characterised by ^1H, ^{13}C NMR spectra and optical rotation values. [24D, ^1H, δ 5·31 (*brs*); ^{13}C; δ 98·9, $J_{C-1-H} = 156{\cdot}7$ Hz, $[\alpha]_D - 4{\cdot}1°$ (*c* 1·4, $CHCl_3$)] [24L, ^1H, δ 5·42 (*brs*), ^{13}C, δ 97·8, $J_{C-1-H} = 156{\cdot}9$ Hz, $[\alpha]_D$ 18·6° (*c* 1·7, $CHCl_3$)]. 24D was processed further by reacting with DDQ in chloroform-H_2O (18/1) at room temperature for 1 h to obtain the MPM deprotected inositol-saccharide 25 as a syrup. 25 was again mannosylated on reaction with 2-pyridyl 6-O-*t*-butyldimethylsilyl-2,3,4-tri-O-benzyl-1-thio-α/β-D-mannopyranoside (3) (CH_2Cl_2, CH_3I, 4A molecular sieves, 50°, 58h) to obtain axially linked dimannosyl-*myo*-inositol 26 in 75% yield as a syrup. 26 was characterised from ^{13}C NMR data [26, ^{13}C, δ C-1,1′ = 98·9, 99·4; $[\alpha]_D$ 8·2° (*c* 1·0, $CHCl_3$)]. 2 and 3 were prepared from D-mannose via the known

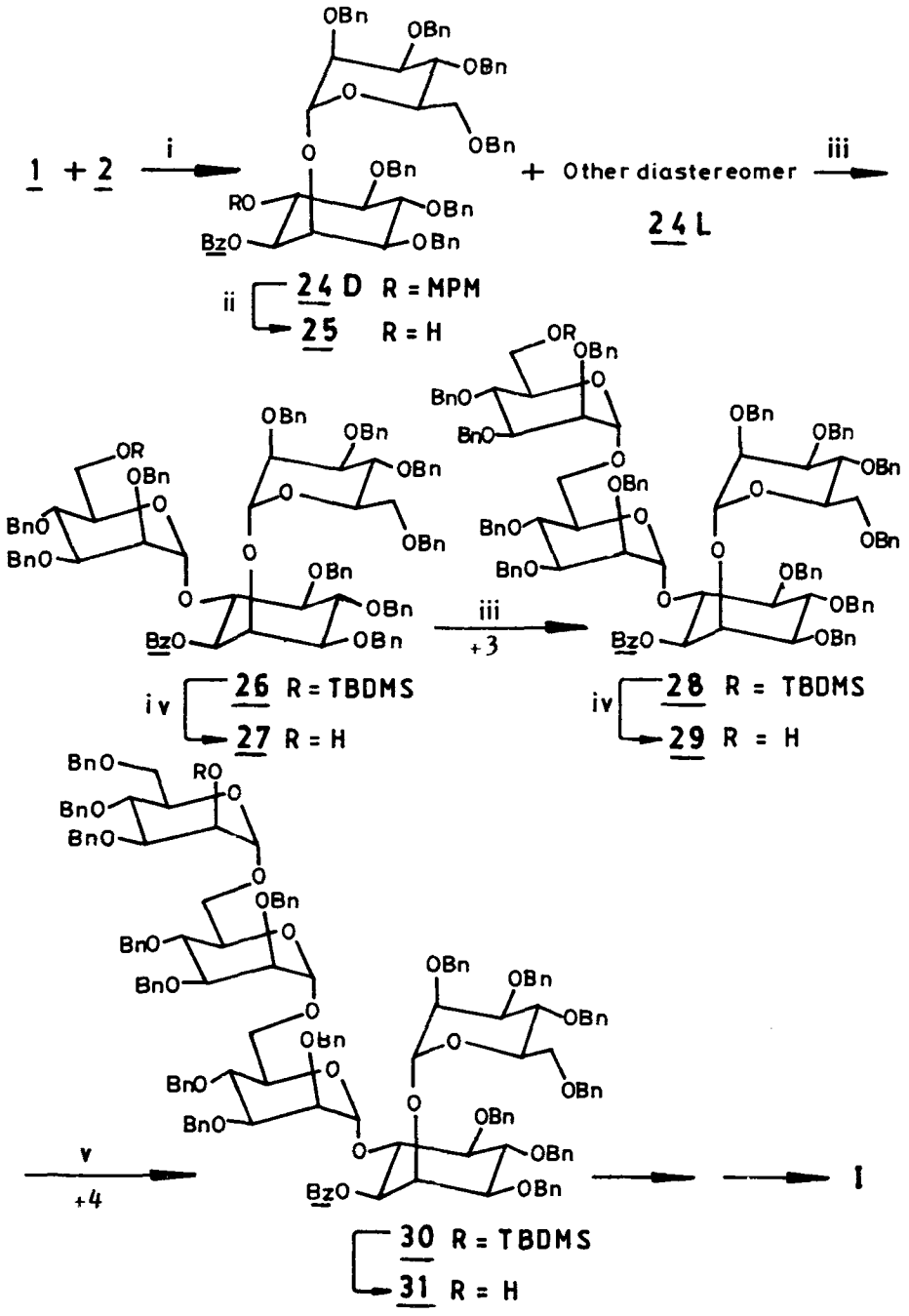


Scheme 1. *Reagents and conditions*: (i) Cyclohexanone, DMF, toluene, 150°C, 9h; (ii) BnBr, NaH, toluene, reflux, 14h, (iii) MPM-Br, NaH, DMF, RT, 2h; (iv) ethylene glycol, *p*-TsOH, CH_2Cl_2, 4h; (v) BnBr, NaH, DMF, RT, 15 min; (vi) BzCl, imidazole, CH_2Cl_2, 1h.



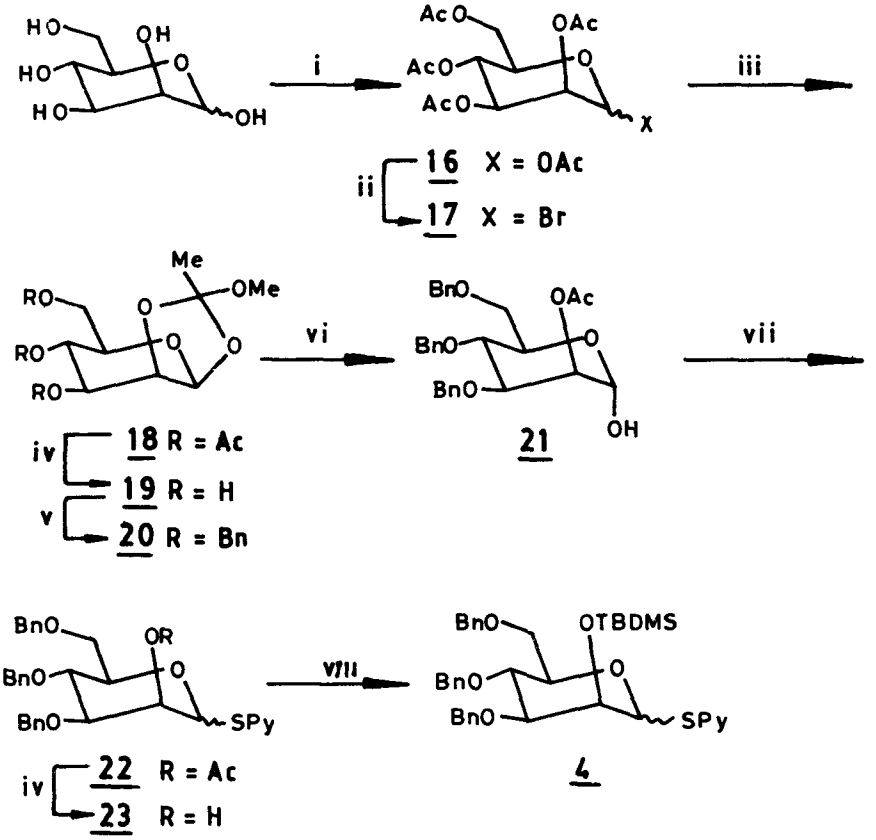
Scheme 2. *Reagents and conditions*: (i) BzCl, pyridine, 0°C–RT; (ii) HBr, AcOH, CH_2Cl_2, RT; (iii) 2-mercaptopyridine, K_2CO_3, acetone, toluene (1/1), 60°C, 4h; (iv) Cat. NaOMe, MeOH, RT; (v) BnBr, NaH, DMF, 0°C–RT, 30 min; (vi) TBDMSCl, pyridine, RT, 4h.

penta-O-benzoyl-D-mannopyranoside 11 (Ness *et al* 1950). 11 on reaction with HBr/CH_3CO_2H at room temperature gave tetra-O-benzoyl-α-D-mannopyranosyl bromide (12), which on further reaction with 2-mercaptopyridine in acetone/toluene/K_2CO_3 (1/1) at 60° for 4h gave the 2-pyridyl 2,3,4,6-tetra-O-benzoyl-1-thio-α/β-D-



Scheme 3. *Reagents and conditions*: (i) MeI, 4A molecular sieves, CH_2Cl_2, 40h; (ii) DDQ, DCM-water (18/1), RT, 1 h; (iii) MeI, 4A molecular sieves, CH_2Cl_2, 58 h; (iv) *p*-TsOH, MeOH, DCM (1/20), 5h, (v) MeI, 4A molecular sieves, CH_2Cl_2, 3 days.

mannopyranoside (13) as a solid, m.p. 73–75°C in 85% yield. 13 on reaction with a catalytic amount of $NaOCH_3$ in MeOH at 60° for 2h gave 14 as a syrup. Reaction of 14 with BnBr/NaH in dimethyl formamide at room temperature gave 2 as a syrup in 88% yield. 14 on reaction with TBDMSCl in pyridine at room temperature for 1h gave the regioselectively protected 2-pyridyl 6-O-*t*-butyldimethylsilyl-1-thio-α/β-D-mannopyranoside in 92% yield as a thick syrup which without isolation was benzylated (BnBr/NaH/DMF) to obtain 3 as a syrup in 89% yield. Reaction of 26 with a catalytic amount of *p*-toluenesulphonic acid in $MeOH/CH_2Cl_2$ (1/20) at room temperature for 3h gave the alcohol 27 as a syrup in quantitative yield. 27 was mannosylated with 3 (CH_2Cl_2, MeI, 4A, 50°, 48h) to obtain 28 as a syrup in 71% yield. 28 on reaction with a catalytic amount of *p*-toluenesulphonic acid in $MeOH/CH_2Cl_2$ (1/20) at room temperature for 5h gave 29 in quantitative yield as a syrup. [29, ^{13}C–NMR; δ C–1,1′, 1″ = 98·81, 99·78, 100·5, $[\alpha]_D$ 14·7° (*c* 1·0, $CHCl_3$)]. 29 was mannosylated with the mannosyl donor 2-pyridyl 2-O-*t*-butyldimethylsilyl-3,4,6-tri-O-benzyl-1-thio-α/β-D-mannopyranoside (4) in CH_2Cl_2/MeI/4A at 50°C for 3 days to obtain the tetramannosyl inositol derivative 30 in 21% yield as a syrup. (^{1}H NMR, H-1,1′, 1″,1‴ = δ 5·45, 5·31 × 2, 5·16). Mannosyl donor 4 was prepared



Scheme 4. *Reagents and conditions*: (i) Ac_2O, NaOAc, 80°C, 2h; (ii) HBr-AcOH, CH_2Cl_2, RT, 2h; (iii) MeOH, collidine, CH_2Cl_2, RT, 14h; (iv) cat. NaOMe, MeOH, RT, 30 min; (v) BnBr, NaH, DMF, 0°C–RT, 30 min; (vi) *p*-TsOH, diethyl ether, RT, 10 min; (vii) 2,2′-dipyridyldisulphide, *n*-Bu_3P, CH_2Cl_2, 15 min; (viii) TBDMSCl, pyridine, RT, 2h.

from the known 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranose (21) (Frankes and Montgomery 1968) by reacting with 2,2′-dipyridyldisulphide/*n*-Bu_3P/CH_2Cl_2 at room temperature for 15 min to obtain 22 as a crystalline solid m.p. 128°C in 81% yield. 22 was deacetylated (catalytic amount of $NaOCH_3$ in MeOH) and reacted with TBDMSCI/pyridine at room temperature for 2h to obtain 4 in 98% yield.

Desilylation of 30 to liberate the alcohol 31 and further mannosylations would form the subject for future work to complete the total synthesis of PIMs.

In summary, synthesis of major core of α-linked PIMs has been achieved by methyl iodide promoted activation procedure of 2-pyridyl per O-benzylated-1-thio-mannopyranoside.

Acknowledgements

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