The stereospecific synthesis of methyl α-*C*-mannobioside: a potential inhibitor of *M. tuberculosis* binding to human macrophages

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The synthesis of the *C*-glycoside analogue of the mycobacteria capping disaccharide, Manα1-2Man, employing a glycosyl organosamarium is described.

The recent outbreaks of drug-resistant strains of *Mycobacterium tuberculosis* worldwide has renewed interest in this life-threatening pathogen.[1] Early in infection, *M. tuberculosis* is phagocytized by mononuclear phagocytes, resisting destruction and multiplying within these cells. It has been reported that macrophage mannose receptors, in addition to complement, mediate phagocytosis of virulent strains of MT, but not of avirulent ones.[2] Recently, several reports have shown that extensive capping of a major cell-surface lipopolysaccharide, lipoarabinomannan, with mannobiose residues occurs in virulent strains of MT (Fig. 1),[3] but is absent in avirulent strains, and is in part responsible for the recognition and uptake of these pathogenic strains by macrophages.[4]

As part of our overall goal in preparing new and potentially stable inhibitors *in vivo* of this cellular interaction, as well as potential inhibitors of the bacterial mannosyl transferase, we present here the synthesis of the *C*-glycoside analogue† of the major capping disaccharide, methyl α-*C*-mannobioside **1**, whose retrosynthetic sequence is outlined in Scheme 1.[6] The key feature of this highly convergent synthesis includes a stereospecific and direct coupling of the anomeric organosamarium **2** with the appropriately functionalised aldehyde **3**, according to our previously published stereoselective synthesis of 1,2-*trans*-*C*-glycosides.[7] In addition, a modified version of the Jung procedure[8] for the preparation of aldehyde **3** is disclosed employing a stereospecific formyl group transfer from C-3 of the iodo compound **4** promoted by a 5-*exo* radical cyclisation, fragmentation sequence.

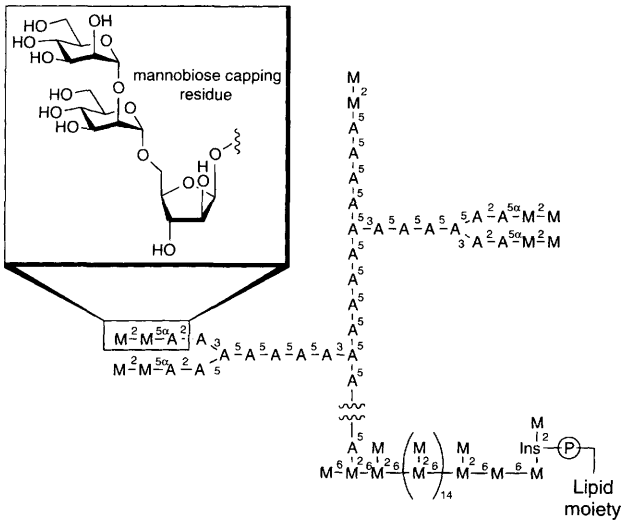
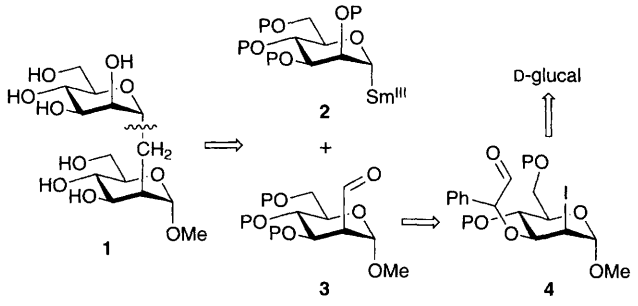
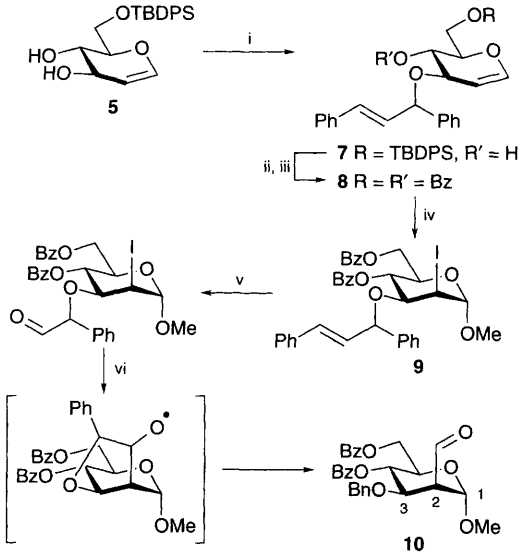


Fig. 1 Proposed partial structure of ManLipoarabinomannan from *M. tuberculosis* (Erdman strain)

Preparation of aldehyde **3** commenced with the regioselective functionalisation of the readily available glucal **5**[9] at C-3 as illustrated in Scheme 2. Thus, prior formation of the stannylene with dibutyltin oxide in refluxing toluene was followed by the addition of the racemic allylic chloride **6**[10] at 0 °C to give a diastereoisomeric mixture of allylic ethers **7** in a 68% yield. Next, the silyl protecting group was removed and the obtained diol was benzoylated to give glycal **8**. Iodoglycosylation with methanol proceeded well in acetonitrile in the presence of *N*-iodosuccinimide,[11] leading to the iodo-compound **9** in good yield. With the stage set for the formyl group transfer, **9** was first subjected to ozonolysis to give the corresponding aldehyde which was treated with 2 equiv. of tributyltin hydride in refluxing benzene.[8] This afforded the C-2 carbon-branched



Scheme 1 Retrosynthetic scheme for the methyl *C*-mannobioside **1**



Scheme 2 *Reagents and conditions*: i, 1.3 equiv. Bu_2SnO, toluene, reflux, then 1.5 equiv. NBu_4Br, 1.2 equiv. (*E*)-1,3-diphenyl-3-chloropropene **6**, 0 °C, 68%; ii, 1.5 equiv. NBu_4F, THF, 0 °C, 100%; iii, 4 equiv. BzCl, pyridine, 0 °C, 100%; iv, 5 equiv. MeOH, 2.2 equiv. NIS, MeCN, 4 Å MS, 0–20 °C, 78%; v, O_3, CH_2Cl_2, −78 °C, then 2.5 equiv. PPh_3; vi, 2 equiv. Bu_3SnH, 0.2 equiv. AIBN, benzene, reflux, 2 h, 63% from **9**

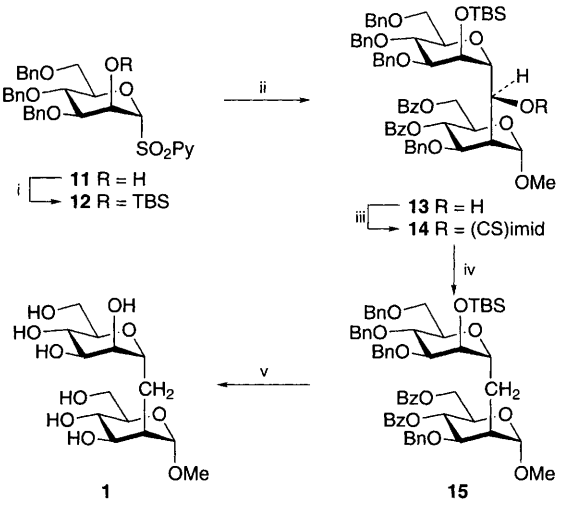
sugar **10** possessing the desired *manno*-configuration in combined yields of 63% for the two steps. That an axially-oriented substituent at the C-2 position was indeed obtained and that no epimerization had occurred was confirmed by the small $J_{H\text{-}1,H\text{-}2}$ and $J_{H\text{-}2,H\text{-}3}$ coupling constants of 5.4 and 2.6 Hz observed for **10** in the ^{1}H NMR spectrum.

Access to the glycosyl donor was obtained by silylation of the easily available and previously described pyridylsulfone **11**.[12] Preliminary experiments have shown that the samarium diiodide promoted coupling of the mannosyl pyridylsulfone **12** with simple carbonyl compounds efficiently afforded the α-*C*-mannosides in good yields. Unlike its predecessors containing other C(2)–OH protecting groups, such as $SiMe_3$, Bn, MEM or Ac,[7] the product of elimination, tribenzylglucal, could not be detected in these reactions.

With the two components in hand, the next step included the important coupling (Scheme 3). Treatment of a THF solution of aldehyde **10** and pyridylsulfone **12** (1.5 equiv.) with 2 equiv. of the blue samarium diiodide in THF led to an instantaneous decolouration indicating completion of the reaction.[7] After chromatographic purification, disaccharide **13** was secured in a good 73% yield. Again, none of the elimination product was detected. Unlike the coupling of **12** with simpler carbonyl substrates, only one diastereoisomer was obtained with aldehyde **10**. The newly created exocyclic stereogenic centre was assigned to possess the (*S*)-configuration in analogy to the assignment of the major diastereoisomer produced in the simpler cases.[13]

Deoxygenation in turn proved to be somewhat troublesome owing to the sterically encumbered environment surrounding the unwanted secondary alcohol. After much experimentation, the best conditions found were by first transforming **13** to its imidazolylthiocarbonyl derivative **14** which proceeded well only when performed with 1,1′-thiocarbonyldiimidazole (20 equiv.) in refluxing acetonitrile. In this way an 89% yield of **14** was furnished. Deoxygenation proved effective when **14** was treated with the three component triphenyltin hydride, AIBN and 1 equiv. of pentafluorophenol in hot toluene affording a 70% yield of the protected *C*-disaccharide **15**. The addition of the phenol was essential for the obtention of good yields of the reduction product **15**. In the absence of this additive, the reduction did not proceed cleanly and considerable amounts of the alcohol **13** were produced. We assume that prior to the reduction of **15**, the imidazolylthiocarbonate derivative **14** was transformed *in situ* to the corresponding pentafluorophenylthiocarbonate, and the greater radicophilicity of this derivative subsequently led to better reduction yields.[14]

Finally, sequential deprotection led to the methyl α-*C*-mannobioside **1**, characterised as its peracetylated derivative. Preliminary analysis of the ^{1}H NMR spectrum of either **1** or its acetylated derivative revealed that in both cases normal $^4C_1$-chair conformations were seen for the two sugar units.§ A more detailed conformational analysis of **1** in comparison with its parent *O*-glycoside, as well as its biological evaluation, is currently being pursued and will be reported elsewhere.



Scheme 3 *Reagents and conditions*: i, 3 equiv. TBSOTf, 4.5 equiv. TEA, DMAP (cat.), CH_2Cl_2, 0 °C, 78%; ii, 0.7 equiv. **10**, 2.2 equiv. SmI_2, THF, 20 °C, 73%; iii, 20 equiv. $(Imid)_2CS$, MeCN, reflux, 89%; iv, 1 equiv. F_5C_6OH, 2.6 equiv. Ph_3SnH, 0.06 equiv. AIBN, toluene, 95 °C, 70%; v, 4 equiv. NBu_4F, THF, 20 °C, then NaOMe, MeOH, then H_2, 5% Pd/C, AcOH/MeOH, 75%

Footnotes

† The choice of a *C*-glycoside analogue is based on the findings that such mimics possess similar conformational preferences as their parent *O*-glycosides as well as being hydrolytically stable (see ref. 5).

‡ Attempted derivatisation of **13** with the pentafluorophenoxythiocarbonyl chloride led to an approximately 2 : 1 mixture of the corresponding thio- and thiono-carbonates, respectively in a modest yield.

§ *Selected data* for peracetylated **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (dd, 1 H, *J* 3.4, 3.4 Hz, H-2′), 4.88 (d, 1 H, *J* 1.8 Hz, H-1), 4.00 (ddd, 1 H, *J* 8.5, 5.0, 3.4 Hz, H-1′).

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