1,2,5-ortho esters of D-arabinose as versatile arabinofuranosidic building blocks. Concise synthesis of the tetrasaccharidic cap of the lipoarabinomannan of *Mycobacterium tuberculosis*

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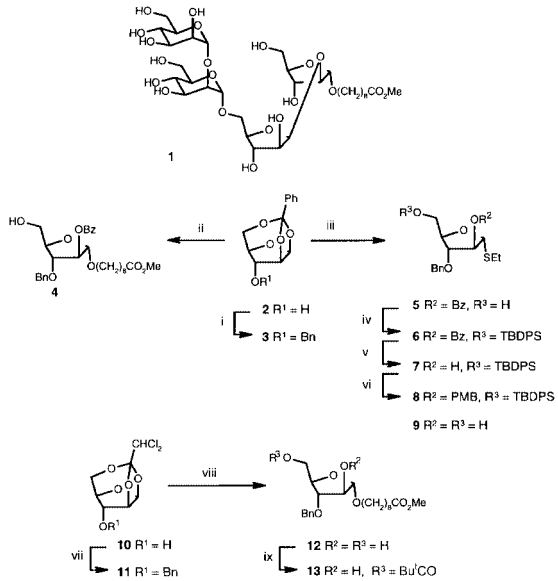
1,2,5-ortho esters of D-arabinose were found to be ideally suited building blocks for the stereoselective formation of α and β arabinofuranosidic linkages after nucleophilic opening of the orthoester with oxygen and sulfur nucleophiles; the tetrasaccharidic cap of the lipoarabinomannan of *Mycobacterium tuberculosis* was then synthesized in a highly convergent manner.

Lipoarabinomannans (LAMs) are highly antigenic polysaccharidic compounds isolated from the cell wall of various species of mycobacteria.[1] They share common structural features, a phosphatidyl *myo*-inositol anchor and a mannan core substituted by an arabinan domain, exclusively composed of D-arabinofuranosidic units.[1] At the ends of this arabinan domain, are found β-D-arabinofuranosides substituted on position 5 by small motifs, called caps, variable on the mycobacterial species.[2–5] Strong modulations of the biological properties of the LAMs were observed for LAMs isolated from different species of mycobacteria and these variations have been tentatively correlated to the structure of these caps.[2,4–8]

In light of the importance of these motifs for the biological properties of the LAMs in relation with the immunopathogenicity of *M. tuberculosis*, we now report the expeditious synthesis of **1** (Scheme 1) the major tetrasaccharide found at the ends of the LAMs of *M. tuberculosis* and *M. bovis* BCG in a form suitable for further conjugation with a protein.[9] Orthoesters **3** and **11** were found to be highly versatile precursors for the elaboration of the two different arabinofuranosidic rings and the construction of the crucial β-arabinofuranosidic linkage. The result is a rapid and convergent synthesis of **1**.

3-*O*-benzyl 1,2,5-benzylidene D-arabinofuranose **3** was readily obtained in 82% yield from the 1,2,5-benzylidene D-arabinofuranose **2** {$[\alpha]_D^{25}$ −28 (*c* 0.94, $CHCl_3$) lit.[10] +28 for the enantiomer} after treatment with benzyl bromide and sodium hydride in dimethylformamide (Scheme 1). $SnCl_4$ catalyzed opening of orthoester **3** with 5 equiv. of methyl 9-hydroxynonanoate[9] in CH_2Cl_2 gave the 2-*O*-benzoyl-α-D-arabinofuranoside **4** as the only isolated product in 76% yield. Complete regio- and stereo-selectivity were observed for the double orthoester opening[11] and none of the isomeric 5-*O*-benzoyl arabinofuranosidic compound was observed with this catalyst. In an analogous manner, ethyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-α-D-arabinofuranoside **5** was obtained in 80% yield from the opening of **3** with 1.1 equiv. of ethanethiol under $SnCl_4$ catalysis, once again with complete stereocontrol of the orthoester opening.[12,13] Unmasking of the hydroxy group on the 2-position of the arabinofuranosidic ring of thioglycoside **5** for later attachment of the *p*-methoxybenzyl tether[14] was carried out in two steps and gave alcohol **7** in 73% overall yield (Scheme 1).

We also looked at the reactions of 3-*O*-benzyl 1,2,5-dichloroethylidene D-arabinofuranose **11**, available in 90% yield (BnBr, NaH, DMF) from known compound **10**, prepared in only two steps from D-arabinose.[15] As was expected from electronic factors, nucleophilic opening of the orthoester function of **11**



Scheme 1 *Reagents and conditions*: i, NaH, BnBr, DMF, room temp., 1 h, 82%; ii, 5 equiv. methyl 9-hydroxynonanoate, 0.1 equiv. $SnCl_4$, MS 4 Å, CH_2Cl_2, room temp., 15 min, 76%; iii, 1.1 equiv. EtSH, 0.1 equiv. $SnCl_4$, MS 4 Å, CH_2Cl_2, −18 °C, 30 min, 80%; iv, 1.5 equiv. Bu^tPh_2SiCl, 1.5 equiv. imidazole, DMF, room temp., 1 h, 92%; v, 0.1 equiv. MeONa, MeOH, room temp., 79%; vi, 2.5 equiv. BEMP, 2.5 equiv. *p*-MeOBnBr, MeCN, 0 °C to room temp., 1 h, 70%. vii, NaH, BnBr, DMF, room temp., 1 h, 90%; viii, 5 equiv. $HOCH_2(CH_2)_7C(O)OMe$, 2 equiv. $SnCl_4$, MS 4 Å, CH_2Cl_2, room temp., 3 h, then MeONa, MeOH, room temp., 1 h, 60%; ix, 1.5 equiv. Bu^tCOCl, 0.1 equiv. DMAP, pyridine, 0 °C, 1.5 h, 80%.

proved to be more difficult than for **3**. 2 Equiv. of $SnCl_4$ at room temperature were necessary to bring the reaction of **11** with methyl 9-hydroxynonanoate to completion and a mixture of 2-*O*- and 5-*O*-dichloroacetyl α-arabinofuranosides was obtained. α-Arabinofuranoside **12** was isolated in 60% yield after deacylation with sodium methoxide. Selective pivaloylation of the primary hydroxy group of **12** (0 °C, Bu^tCOCl, DMAP, pyridine) gave alcohol **13** ready for glycosylation (80%). Opening of **11** with ethanethiol was also obtained with 1.2 equiv. of EtSH and 0.2 equiv. $SnCl_4$ at 0 °C, deacylation of the mixture of dichloroacetates as above gave **9** in 64% overall yield from **11**. Selective silylation of the primary position of **9** with TBDPSCl and imidazole afforded 73% of the previously prepared **7**. Finally, the 4-methoxybenzyl group was introduced on the 2-position of **7** with 2.5 equiv. of 4-methoxybenzyl bromide[16] and 2.5 equiv. of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine[17] (BEMP) in acetonitrile to give thioarabinofuranoside **8** in 70% yield.

Coupling of the arabinofuranosidic units and elaboration of the β-arabinofuranosidic linkage were accomplished according to Ogawa's internal aglycon delivery approach.[14,18] Reaction of 1.1 equiv. of **8** with **13** and 1.5 equiv. of 2,3-dichloro-

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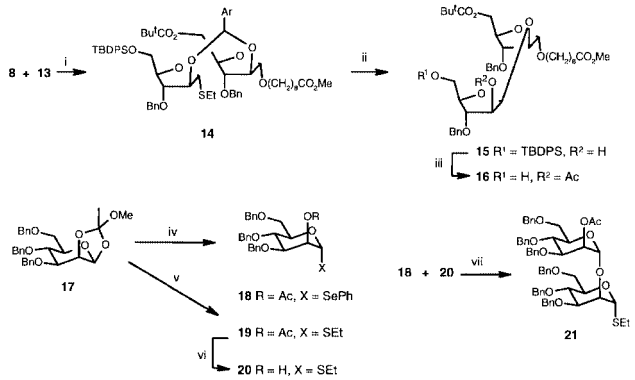
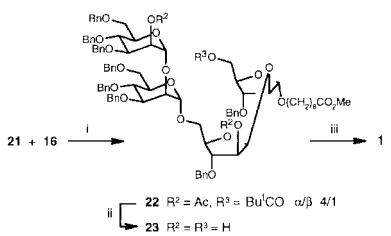


Scheme 2 *Reagents and conditions*: i, 1.1 equiv. **8**, 1 equiv. **13**, 1.5 equiv. DDQ, MS 4 Å, CH_2Cl_2, 0 °C to room temp., 2.5 h, 84%; ii, 1.2 equiv. IDCP, MS 4 Å, CH_2Cl_2, room temp., 1.5 h, 73%; iii, Ac_2O, pyridine, room temp., then 1.2 equiv. Bu^n_4NF, THF, room temp., 0.5 h, 75%, 2 steps; iv, 1.5 equiv. PhSeH, MS 4 Å, cat. $HgBr_2$, MeCN, room temp., 2 h, 75% ; v, 5.5 equiv. EtSH, MS 4 Å, cat. $HgBr_2$, MeCN, room temp., 48 h, 79% ; vi, MeONa, MeOH, room temp., 16 h, 91% ; vii, 1 equiv. **18**, 1.1 equiv. **20**, 1.1 equiv. NIS, 0.1 equiv. TMSOTf, MS 4 Å, CH_2Cl_2, −18 °C to room temp., 71%.

5,6-dicyano-1,4-benzoquinone in CH_2Cl_2 gave the mixed acetal **14** in 84% isolated yield after chromatography (Scheme 2). Intramolecular glycosylation was promoted with 1.2 equiv. of iodonium dicollidine perchlorate (IDCP)[19] in CH_2Cl_2 and gave a rewarding 73% yield of the β-linked disaccharide **15** as the only isolated product. The β-(D) configuration of the new anomeric center was firmly established from the ^1H and ^{13}C NMR data ($\delta_{H\text{-}1'}$ 5.15, $J_{H\text{-}1',H\text{-}2'}$ 4.5 Hz; $\delta_{C\text{-}1'}$ 101.48).[20] Acetylation (acetic anhydride, pyridine) and silyl ether deprotection with tetrabutylammonium fluoride in tetrahydrofuran gave the diarabinofuranoside **16** ready for further elongation (75% from **15**).

The dimannosidic glycosyl donor **21** was efficiently obtained from orthoester **17**[21] taking advantage of the higher reactivity of selenoglycosides over thioglycosides towards activation.[22,23] **17** was first opened with 1.5 equiv. of selenophenol[24] under $HgBr_2$ catalysis and gave (α-selenoglycoside **18** in 75% yield (Scheme 2). The known thioglycoside **19**,[25] obtained in 79% from **17** after $HgBr_2$-promoted ethanethiol opening, was deacetylated (MeONa, MeOH) to give glycosyl acceptor **20** in 91% yield. Selective activation of selenoglycoside **18** with 1.1 equiv. of *N*-iodosuccinimide (NIS) and 10% trimethylsilyl trifluoromethanesulfonate (TMSOTf),[26] and coupling with 1.1 equiv. of thioglycoside **20** in CH_2Cl_2 at −18 °C gave the expected α-linked dimannosidic compound **21** in 71% yield with complete control of the new anomeric center. **21** was isolated in slightly lower yield (64%) when the original silver trifluoromethanesulfonate/potassium carbonate combination[22] was used as promoter for the glycosylation of **20** with **18**.

Final coupling was done by glycosylation of disaccharide **16** with 1.5 equiv. of thiodisaccharide **21** under NIS/catalytic TMSOTf activation (Scheme 3). A 70% yield of tetrasaccharidic compounds **22** was obtained as a 4 : 1 α,β anomeric



Scheme 3 *Reagents and conditions*: i, 1 equiv. **16**, 1.5 equiv. **21**, 1.7 equiv. NIS, 0.15 equiv. TMSOTf, MS 4 Å, CH_2Cl_2, −15 °C, 1 h, 70%; ii, 0.5 M MeONa, MeOH, room temp., 5 h, 75%; iii, H_2, $Pd(OH)_2$/C, MeOH, room temp., 1 h, 65%.

mixture on the H-1″ anomeric center. This mixture could not be separated at this stage, so the ester groups were removed with 0.5 M sodium methoxide solution in methanol (75%) and the mixture of triols was chromatographed to give pure **23**. Hydrogenolysis of the benzyl groups [H_2, $Pd(OH)_2$/C, MeOH] gave the target compound **1**[27] in 65% yield.

In conclusion, orthoester derivatives of arabinose and mannose were used for the efficient synthesis of **1**, the tetrasaccharidic cap of the lipoarabinomannan of *M. tuberculosis*, *via* a convergent route using minimal protecting groups manipulation and selective anomeric activation. Both α- and β-arabinofuranosides were obtained with complete stereocontrol from 3-*O*-benzyl-1,2,5-orthoesters of D-arabinose. Extension of this methodology to the elaboration of other complex polyarabinofuranosidic structures and synthesis of neoantigens from **1** for biological evaluation are currently under way.

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27 *Selected data* for **1**. $[\alpha]_D^{25}$ +18 (*c* 0.44, water); ^1H NMR (500 MHz, D_2O, 293 K): δ 5.16 (d, 1H, *J* 1.7 Hz, H-1″), 5.11 (d, 1H, *J* 4.5 Hz, H-1′), 5.10 (d, 1H, *J* 2 Hz, H-1), 5.02 (d, 1H, *J* 2 Hz, H-1‴). ^{13}C NMR (125.72 MHz, D_2O, 293 K) δ 106.09 (C-1), 103.01 (C-1‴), 101.05 (C-1′), 98.86 (C-1″), 87.48 (C-2), 80.40 (C-2″), 76.67 (C-2′).