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First synthesis of methyl α-*C*-D-arabinofuranosyl-(1→5)-α-D-arabinofuranoside: the *C*-disaccharide segment of motif C of *Mycobacterium tuberculosis*

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Abstract—The synthesis of *C*-analogue of the disaccharide **2** α-ara*f*-(1→5)-ara*f*, present in motif C of the arabino-galactan portion of *Mycobacterium tuberculosis*, has been described. The critical C–C bond formation reaction to couple both the furanosyl residues has been accomplished through nitro-aldol condensation.

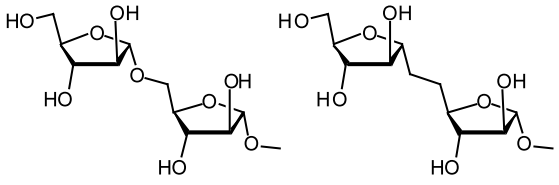
The mycolic arabino-galactan (AG) complex present on the cell wall surface of *Mycobacterium tuberculosis* has unique structural features unknown in actinomycetes.[1] The furanoside rings of AG complex are conformationally more mobile (than pyranosides) and are largely linked through primary hydroxyl groups.[2] These characteristics enable the crowded AG complex to adopt a structure in which mycolic acids are closely arranged in parallel arrays.[3] The AG complex is critical for the survival of *M. tuberculosis*. The hydrophobic AG complex acts as a strong barrier for the passage of antibiotics into the cell and therefore, play an important role in developing resistance of *Mycobacteria* to many antibiotics.

The drug ethambutol blocks the biosynthetic pathway of arabinose.[4] The inhibition of biosynthetic pathway, involved in development of *M. tuberculosis* cells, is considered as an attractive strategy for drug development against *M. tuberculosis*. The oligosaccharides present on various motifs of AG complex are structurally elucidated and their synthesis from our group[5] as well as from others[6] have dominated the area in recent years.

The *C*-linked glycosides[7] of glycosyl compounds are stable to both chemical and metabolic degradation. The conformational features of *C*-glycosides to a large extent resemble those of naturally occurring *O*-glycosides. The *C*-glycosides serve as glycosyl regulators and as synthetic ligands for probing cellular interactions. To our knowledge, no attempts have yet been made to synthesize *C*-analogues of any oligosaccharide present in AG complex of *M. tuberculosis*. In continuation of our interest in AG complex, we undertook the first synthesis of α-*C*-D-ara*f*-(1→5)-α-D-ara*f* as a methyl glycoside **2** which constitutes the *C*-analogue of motif C oligosaccharide (Fig. 1).

The retrosynthetic scheme for **2** was based on the C–C coupling reaction between two partners **4** and **5** via the nitro-aldol condensation reaction (Scheme 1).

The synthesis of **4** was initiated from methyl 2,3-di-*O*-benzyl-α-D-arabinofuranoside[8] **6** which was converted into the 5-deoxy-5-*iodo* derivative **7**. Replacement[9] of the iodine with a nitro group was accomplished with $NaNO_2$, phloroglucinol.monohydrate in DMSO (Scheme 2). In the ^1H NMR spectrum of **4**, the distinc-



Motif C (1) **2**

Figure 1.

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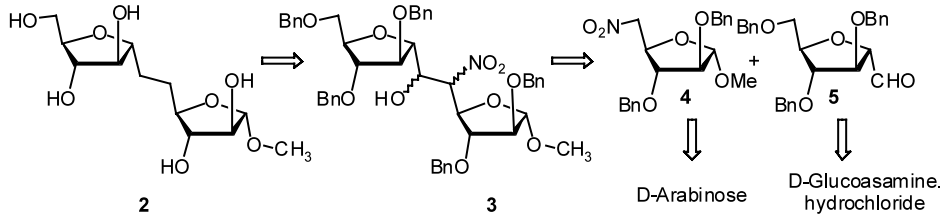
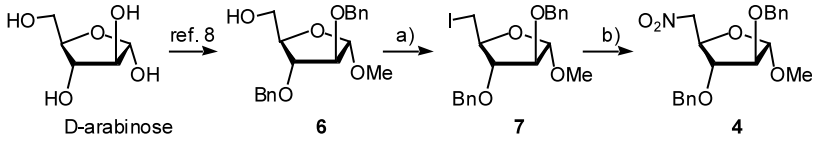


Scheme 1. Retrosynthetic analysis for the disaccharide **2**.



Scheme 2. *Reagents and conditions*: (a) I_2, imidazole, PPh_3, $C_6H_5CH_3$, Δ, 1.5 h (81%); (b) $NaNO_2$, phoroglucinol.H_2O, DMSO, rt, 72 h (68%).

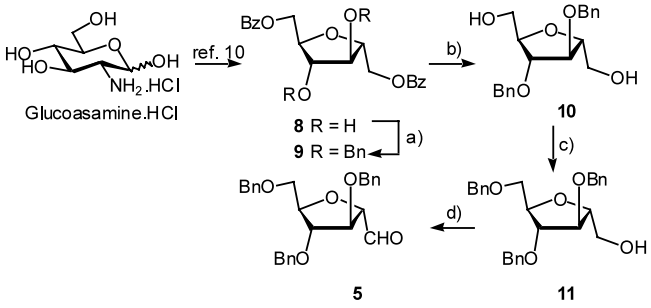
tive down-field shift of resonances due to methylene protons at C-5 were observed. The ^{13}C NMR spectrum was consistent with the assigned structure.

The second component **5** was obtained from D-glucosamine-hydrochloride which was subjected to a diazotization-mediated ring contraction reaction, subsequent reduction and selective benzoylation to afford the known[10] dibenzoate derivative **8**. The free hydroxyl group of **8** was protected as benzyl ethers by treatment with BnBr/Ag_2O in CH_2Cl_2 followed by debenzoylation with NaOMe in methanol to give the dibenzyl derivative **10**.

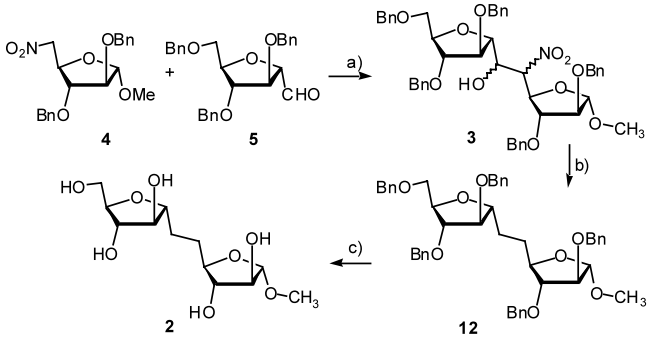
The selective protection of one of the hydroxymethyl groups was performed with 1 equiv. of each NaH and BnBr in DMF. Compound **10** being C_2-symmetric, afforded only one diastereomer **11**. The free hydroxymethyl functionality in **11** was oxidized under Swern conditions and the resulting aldehyde **5**, being unstable, was utilized for the next step without any delay (Scheme 3).

The coupling reaction[11] between **4** and **5** occurred in the presence of catalytic KF in CH_3CN to give a diastereomeric mixture of **3** which was subjected to three successive steps, i.e. dehydration, selective reduction of conjugated olefin and denitration with *n*-Bu_3SnH to give the penta-*O*-benzyl *C*-disaccharide **12**.

The structure of **12** was fully scrutinized by spectroscopic and analytical examination.[12] For example, the ^1H NMR spectrum of **12** showed characteristic signals due to two methylene groups, which serve as a linker between two sugar moieties, between 2.57 (t) and 3.61 (m) ppm. The anomeric protons were located at δ 3.77 (H-1′, dd) and δ 4.89 (H-1, s). The ^{13}C NMR spectrum and elemental analysis of compound **12** were consistent with the assigned structure. Finally hydrogenolysis of **12** in presence of $Pd(OH)_2$ at normal temperature and pressure gave the *C*-disaccharide **2** (Scheme 4), the



Scheme 3. *Reagents and conditions*: (a) BnBr, Ag_2O, CH_2Cl_2, rt, 10 h (86%); (b) NaOMe, MeOH, rt, 0.5 h (88%); (c) NaH (1 equiv.), BnBr (1 equiv.), DMF, 0°C, 1.5 h (84%); (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, Et_3N, 0.5 h (95%).



Scheme 4. *Reagents and conditions*: (a) KF, 18-C-6, MeCN, rt, 3.5 h (48%); (b) (i) Ac_2O, Py., $CHCl_3$, 12 h; (ii) $NaBH_4$, EtOH, CH_2Cl_2, rt, 2.5 h; (iii) Bu_3SnH, AIBN, $C_6H_5CH_3$, Δ, 1 h (44% in three steps); (c) $Pd(OH)_2$, H_2, rt, 1 atm, 24 h (74%).

spectroscopic and elemental data for which was consistent with the assigned structure.[12]

In summary, this report describes the first successful synthesis of the *C*-oligosaccharide of motif C of *M. tuberculosis*. The biological and structural implications of this *C*-analogue will not be only interesting but significant from a drug development point of view.

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12. Spectroscopic and elemental data for some selected compounds: **Compound 12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.57 (t, 2H, $J=5.9$ Hz), 3.33 (s, 3H), 3.61 (m, 2H), 3.77 (dd, 1H, $J=2.9$, 5.9 Hz), 3.94 (m, 1H), 4.01 (t, 1H, $J=2.9$ Hz), 4.11 (q, 1H, $J=5.9$ Hz), 4.27 (brs, 1H), 4.35–4.70 (m, 14H), 4.89 (s, 1H), 7.30 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 28.8, 54.4, 70.1, 71.2, 71.8, 71.9, 73.1, 73.6, 80.8, 81.2, 82.3, 83.7, 86.1, 88.5, 91.2, 107.0, 127.6–128.2, 134.1–135.0. Anal. calcd for $C_{47}H_{52}O_8$: C, 75.78; H, 7.04. Found: C, 75.43; H, 6.97. **Compound 2**: ^{1}H NMR (200 MHz, D_2O) δ 1.80 (m, 4H), 3.70 (s, 3H), 3.66–4.25 (m, 9H), 4.81 (s, 1H); ^{13}C NMR (125 MHz, D_2O) δ 27.3, 29.1, 53.2, 62.5, 77.4, 77.5, 78.9, 81.8, 83.2, 84.2, 84.7, 107.1. Anal. calcd for $C_{12}H_{22}O_8$: C, 48.97; H, 7.53. Found: C, 48.93; H, 7.92.