ORGANIC LETTERS

2013
Vol. 15, No. 10
2466–2469

Facile Synthesis of β- and α-Arabinofuranosides and Application to Cell Wall Motifs of *M. tuberculosis*

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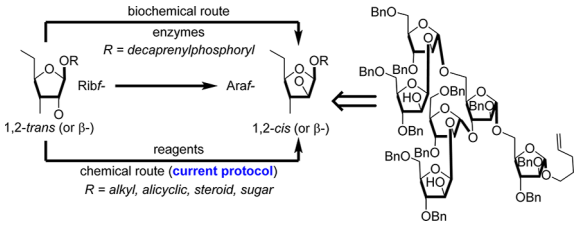
Received April 4, 2013

ABSTRACT



Propargyl 1,2-orthoesters of arabinose are exploited for the synthesis of 1,2-*trans* furanosides; easily accessible 1,2-trans ribofuranosides are converted to challenging 1,2-*cis*-arabinofuranosides by oxidoreduction. Utility of these protocols was demonstrated by the successful synthesis of major structural motifs present in the cell surface of *Mycobacterium tuberculosis*. Key furanosylations were carried out under gold-catalyzed glycosidation conditions.

Tuberculosis (TB) has plagued mankind for centuries and still continues to kill more than two million lives every year globally.[1,2] *Mycobacterium tuberculosis* (Mtb) is the etiological agent, and pioneering efforts from the Brennan group highlighted two major carbohydrate epitopes viz. lipoarabinomannan (LAM) and arabinogalactan (AG) in the cell surface of Mtb.[3] Both LAM and AG have an oligoarabinofuranoside which is highly characteristic to the Mtb cell wall. The xenobiotic nature of arabinofuranose is noteworthy since inhibitors of biosynthetic pathways for oligomerization of arabinofuranoses could offer opportunities for the development of novel therapeutics. Indeed, ethambutol, an antitubercular drug, has been shown to arrest the biosynthesis of arabinan.[4] Specificity and the xenobiotic nature of arabinofuranosides coupled with the challenge in synthesizing 1,2-*trans* (or α-) and 1,2-*cis* (or β-) arabinofuranosides has attracted many to develop strategies.[5,6] Motifs A−C are the structural constituents present in the arabinan part of Mtb (Figure 1); arabinan is ligated to the oligomeric chain of galactofuranoses through a 1→5 *trans* linkage.[3] Among the host of

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10.1021/ol400931p
Published on Web 05/09/2013

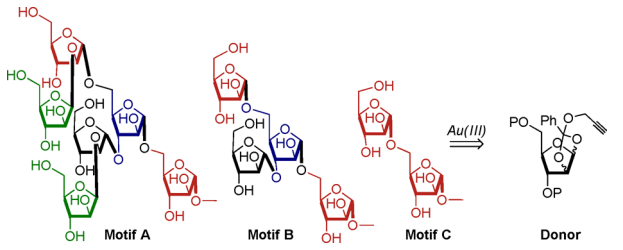


Figure 1. Mtb cell wall motifs A–C and the strategy.

glycosyl donors,[5a] thio-,[5b–e] *n*-pentenyl,[5a,f] trichloroacetamidates,[5g,6] 1,2,5-orthoester,[5h] and *n*-pentenyl orthoesters[6d] are investigated for the synthesis of arabinofuranosides.

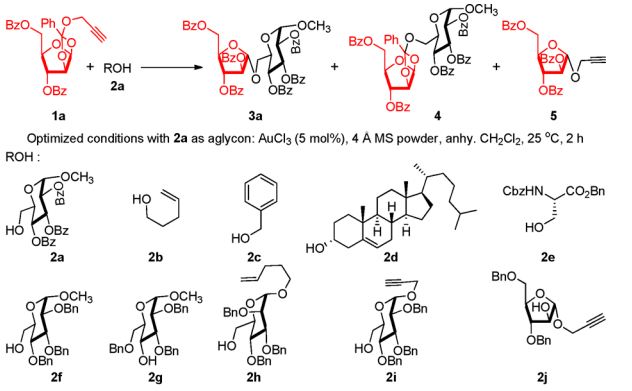
Recent independent synthetic efforts from the Lowary[6a] and Ito[6b] groups culminated in the synthesis of docosaarabinofuranoside (22-mer) with 4 1,2-*cis* and 18 1,2-*trans* glycosidic linkages. An octadodecamer fragment of LAM in the protected form has been synthesized by Fraser-Reid's group.[6c,d] However, among the two linkages, stereoselective synthesis of 1,2-*cis* furanosides is still a formidable task and notoriously difficult.

From our laboratory, a gold-catalyzed transglycosidation by the activation of propargyl (or methyl) glycosides was identified;[7a–c] subsequently, propargyl 1,2-orthoesters were observed to give 1,2-*trans* glycopyranosides at room temperature.[7d,e] Gold-catalyzed glycosidation was tested on many substrates and noticed to facilitate synthesis of biomimitics and glycopolypeptides in an advantageous manner.[7] Thus, 1,2-*trans* arabinofuranosides can also be envisaged in a facile manner through a propargyl 1,2-orthoester strategy (Figure 1).

Accordingly, the propargyl 1,2-orthoester of arabinofuranose **1a** was synthesized[8] and subjected to standard gold-catalyzed glycosidation conditions[7c] ($AuCl_3$/4 Å MS powder/CH_2Cl_2/25 °C) with model aglycon **2a** to observe 1,2-*trans* furanoside **3a**, orthoester **4**, and the propargyl arabinofuranoside (**5**) in 1 h (Scheme 1).[8] Interestingly, orthoester **4** got converted into the required furanoside **3a** in 2 h. Further studies with other alkyne activators ($RuCl_3$, $PdCl_2$) and Lewis acids (AgOTf, TMSOTf) illustrated the importance of $AuCl_3$ since $RuCl_3$ and $PdCl_2$ failed to activate the orthoester (Table S1, Supporting Information). Addition of Et_3N arrested the furanosylation indicating in situ generation of Brønsted acid. Propargyl glycoside **5** was the only identified product when the reaction was carried out in anhydrous CH_2Cl_2.HCl which indicated that Brønsted acid alone is not sufficient.[8] AuCl gave the product in diminished yield, whereas $HAuCl_4$ and $AuBr_3$ showed the required 1,2-*trans* disaccharide in almost comparative yield to that of $AuCl_3$; however, $HAuCl_4$ is found to be more hygroscopic, and thus, $AuCl_3$ was chosen for further reactions.[8] Optimized reaction conditions were then applied on variety of aglycons comprising aliphatic (**2b**), aromatic (**2c**), steroidal (**2d**), amino acid (**2e**), and carbohydrate derived aglycons (**2f–j**), and gratifyingly, the corresponding 1,2-*trans* arabinofuranosides (**3b–j**) were obtained in high yields (Scheme 1).[8]

Identification of a practical procedure for 1,2-*trans* arabinofuranosides prompted us to look at the utility of our gold catalysis repertoire to 1,2-*cis* furanosides which are renowned for their synthetic difficulty. For a long time, biochemists thought that β-arabinofuranosides are obtained from β-ribofuranosides by epimerization at the *C*-2 position.[9]

Scheme 1. Propargyl 1,2-Orthoesters for α-Arabinofuranosides



Aglycon	Product	% Yield	Aglycon	Product	% Yield
2a	**3a**	78	**2f**	**3f**	82
2b	**3b**	92	**2g**	**3g**	80
2c	**3c**	83	**2h**	**3h**	77
2d	**3d**	82	**2i**	**3i**	81
2e	**3e**	90	**2j**	**3j**	72

In addition, chemistry of pyranosides[10a,b] has a long precedence of oxidoreduction strategy for the conversion of 1,2-*trans* to 1,2-*cis* pyranosides; however, a parallel approach in furanosides is rare except for a report of oxidoreduction strategy on a more substituted L-arabinofuranosyl system by de Oliviera et al.[10c] The biochemical approach of Mtb and many examples in pyranosides is sufficiently enticing to investigate the chemical conversion

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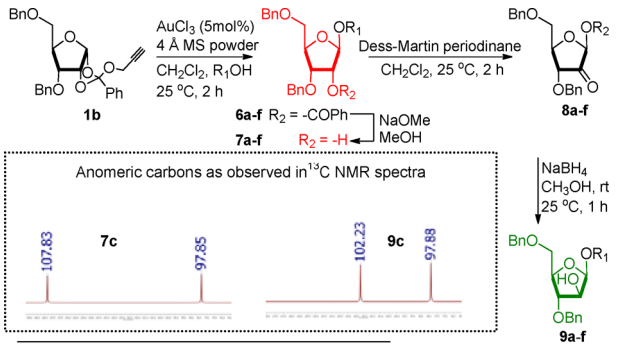
Scheme 2. Conversion of β-Ribofuranosides to β-Arabinofuranosides



R_1OH	Glycosides			
	β-Ribf (**7**)	% Yield from **1b**	β-Araf (**9**)	% Yield from **7**
2b	**7a**	85	**9a**	94
2d	**7b**	75	**9b**	90
2f	**7c**	80	**9c**	93
2k	**7d**	81	**9d**	92
2l	**7e**	78	**9e**	92
2m	**7f**	85	**9f**	93

R_1OH: **2k** **2l** **2m**

of 1,2-*trans* (or β-) ribofuranosides to 1,2-*cis* (or β-) arabinofuranosides. β-Ribofuranosides shall be easily accessed by the above delineated propargyl 1,2-orthoester strategy. To evaluate, a suitably protected propargyl 1,2-orthoester of ribofuranose was required. Accordingly, ribofuranosyl donor **1b** was synthesized from D-ribose and subjected to the aforementioned gold catalyzed glycosidation with a panel of aglycons (**2b**,**d**,**f**,**k**−**m**) to obtain corresponding β-ribofuranosides (**6a**−**f**) in very good yields (Scheme 2).[8] Subsequently, all ribofuranosides **6a**−**f** in parallel were saponified under Zemplén conditions (NaOMe, MeOH) to **7a**−**f** and oxidized with Dess−Martin periodinane in CH_2Cl_2 at 25 °C to the respective 2-ribulofuranoses (**8a**−**f**) in greater than 90% yields. Crude residues of 2-ribulofuranoses **8a**−**f** were subsequently subjected to $NaBH_4$ reduction in CH_3OH to observe complete conversion to 1,2-*cis*-arabinofuranosides **9a**−**f** (Scheme 2).[8]

Conversion of β-ribofuranoside to β-arabinofuranoside was monitored by UPLC−MS using a model β-ribofuranoside **7c**. Initially, standards of β-rib*f* (**7c**) and β-ara*f* (**9c**) were injected to find two well-separated peaks at t_R 8.48 min for β-rib*f* and t_R 9.93 min for β-ara*f* (Figure 2). Crude residue of oxidation reaction was noticed to contain hydrated *gem*-diol (t_R = 6.30 min) in addition to the required ketone (t_R = 17.45 min) and the remaining starting material (8%).

Fortunately, $NaBH_4$ reduction gave an 8:92 ratio of **7c**:**9c** which clearly showed that the reduction took place in a diastereoselective manner. Conversion of ribofuranose to arabinofuranose was confirmed as anomeric carbons of disaccharides **7c** were noticed at δ 97.9, 107.8 ppm whereas

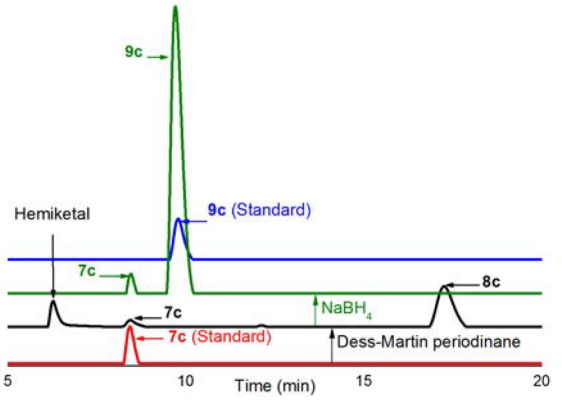


Figure 2. Representative UPLC trace for the conversion of β-Rib*f* substrate **7c** to β-Ara*f* product **9c**.

those of **9c** were found at δ 98.0, 102.4 ppm in the ^{13}C NMR spectrum (Scheme 2).[11] In addition, $^1J_{C-H}$ values further confirmed as anomeric linkages of **7c** were observed at 171, 176 Hz whereas $^1J_{C-H}$ values of both 1,2-*cis* linkages of **9c** were noticed at 174 and 183 Hz.[8]

Identification of facile protocols for 1,2-*cis* and 1,2-*trans* arabinofuranosides inspired to synthesize major arabinan structural motifs A-C of Mtb. *n*-Pentenyl group was selected at the reducing end among many other possibilities since propargyl orthoesters can be orthogonally activated in the presence of aglycons containing *n*-pentenyl moiety.[7e] In addition, *n*-pentenyl group serves as a protecting group at the anomeric postion and acts as a leaving group when required.

Accordingly, *n*-pentenyl glycoside (**3b**) was saponified under Zemplén conditions and the primary hydroxyl group was protected as silyl ether using TBDPSCl to obtain compound **10**. Per-*O*-benzylation with NaH/BnBr in DMF followed by deprotection of a silyl group using TBAF in THF gave the required aglycon **11** in good yield. The key 1,2-*trans* arabinofuranosylation with propargyl 1,2-orthoester **1a** under $AuCl_3$/4 Å MS powder/CH_2Cl_2/25 °C for 2 h gave the disaccharide **12**, which is also the protected form of motif C present in the Mtb cell wall. Conversion of disaccharide **12** to tetrasaccharide demands free hydroxyl groups at the *C*-3 and *C*-5 postions on the nonreducing furanoside. Accordingly, disaccharide **12** was converted to aglycon **13** in three steps. Protection of *C*-3, *C*-5 hydroxyl groups with $Cl(i\text{-}Pr)_2SiOSi(i\text{-}Pr)_2Cl$ in pyridine and conversion of *C*-2 OH to benzyl ether under standard conditions afforded a fully protected disaccharide which was further subjected to desilylation reaction with TBAF to obtain the aglycon **13** in good yields. In parallel, glycosyl donor **1c** was synthesized from propargyl 1,2-orthoester **1a** by saponification and benzylation (Scheme 3). Gold-catalyzed furanosylation between aglycon **13** and 2 equiv of propargyl 1,2-orthoester **1c** as furanosyl donor resulted in the isolation of a fully protected tetrasaccharide (which is a fully protected form of motif B) that was converted to diol **14** using NaOMe in MeOH.

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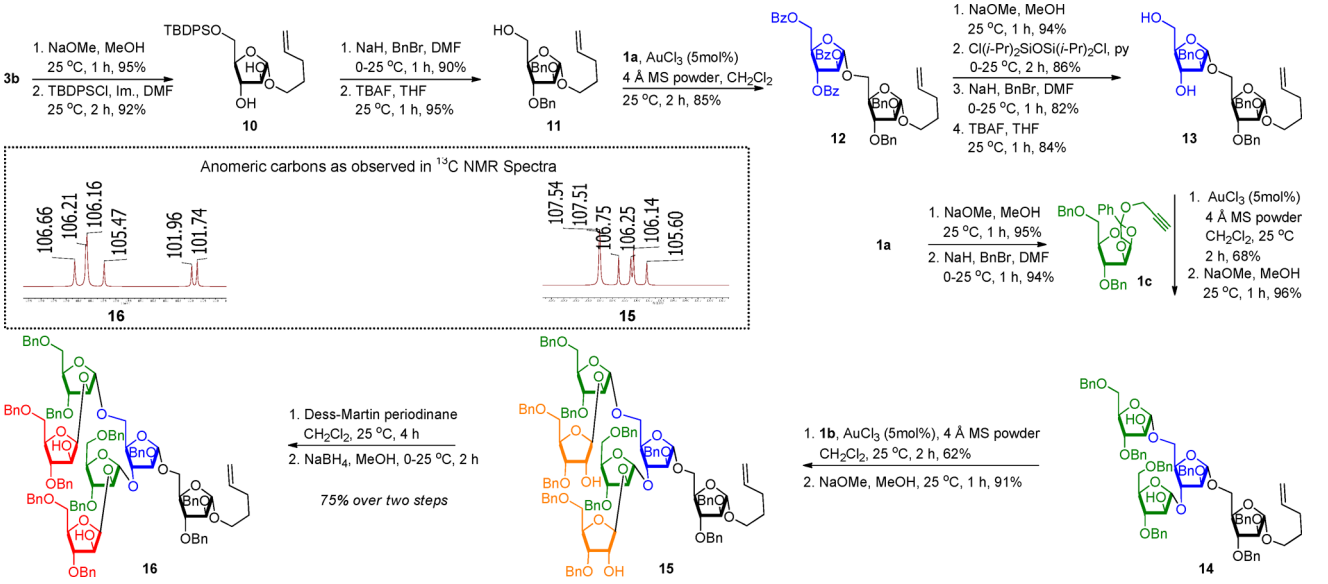
Scheme 3. Synthesis of Arabinan Motifs of *M. tuberculosis*



The next challenge was to convert the tetrasaccharide **14** to the hexaarabinofuranosyl motif A for which the above identified chemical method for β-arabinofuranosylation can be employed. Thus, the gold-catalyzed furanosylation between aglycon **14** and 2 molar equiv ribofuranosyl donor **1b** was carried out to obtain the hexafuranoside in 62% yield. Subsequent saponification under Zemplén conditions resulted in aglycon **15** that was oxidized with Dess–Martin periodinane to give the 2-ulose derivative. $NaBH_4$-mediated stereoselective reduction of the 2-ulose derivative gave the hexaarabinofuranoside **16** with two 1,2-*cis* and four 1,2-*trans* linkages (Scheme 3).

Conversion of ribofuranose-containing hexasaccharide to hexasaccharide with all arabinofuranosyl residues is confirmed by its anomeric ^{13}C NMR spectral signatures. The six anomeric carbons of compound **15** are observed as a single set between δ 105.6–107.5 ppm, whereas those carbons were noticed as two sets in the hexaarabonofuransyl compound **16**. The two carbons linked in 1,2-*cis* fashion are identified at δ 101.7 and 102.0 ppm, and the remaining four 1,2-*trans* anomeric carbons were observed between δ 105.5 and 106.7 ppm (Scheme 3).[11] Furthermore, $^1J_{C-H}$ values for four 1,2-*trans* linkages were noticed around 173–177 Hz, and that of the other two 1,2-*cis* linkages were found around 183 Hz of hexasaccharide **16**, whereas all $^1J_{C-H}$ values of compound **15** were noticed between 173 and 176 Hz only (Scheme 3).[8]

In conclusion, propargyl 1,2-orthesters were exploited to synthesize 1,2-*trans* and 1,2-*cis* furanosides in a stereoselective fashion. Utility of thus-identified arabinofuranosylation protocols was demonstrated by the successful synthesis of major structural motifs present in the cell wall of *Mycobacterium tuberculosis*. Essentially, key furanosylations for 1,2-*trans* and 1,2-*cis* glycosides were achieved by exploiting salient features of gold catalysis and propargyl 1,2-orthoesters.

Acknowledgment. S.H. thanks the DST, New Delhi, for a SwarnaJayanthi Fellowship, and S.A.T. thanks CSIR and B.M. thanks UGC for financial support.

Supporting Information Available. Experimental procedures, spectroscopic data, and spectral charts. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.