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Total Synthesis of Both Methyl 4a-Carba-D-arabinofuranosides

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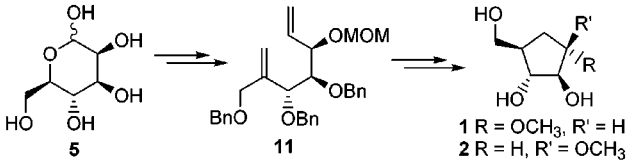
ABSTRACT



The total synthesis of methyl 4a-carba-α-D-arabinofuranoside (1) and methyl 4a-carba-β-D-arabinofuranoside (2) has been achieved starting from D-mannose (5). Key transformations included a ring-closing metathesis of diene 11 employing Schrock's catalyst followed by a stereoselective hydrogenation with Wilkinson's catalyst.

Pseudosugars, or carbasugars, are analogues of monosaccharides in which the ring oxygen has been replaced by a methylene group. In recent years, there has been increasing interest in the synthesis of therapeutic agents containing pseudosugar residues because of their improved acid and metabolic stability relative to their glycoside counterparts. For example, a number of pseudosugar-containing nucleoside analogues have been prepared,[1] and some have shown promise as antiviral agents.[2] Additionally, it has been demonstrated that oligosaccharide analogues containing pseudosugar residues are competent glycosyltransferase substrates, possessing activities essentially the same as the natural glycan parent.[3] It can therefore be expected that metabolically stable glycosyltransferase inhibitors can be prepared by modifying the native oligosaccharide substrate to include both pseudosugar moieties and functionality that will deactivate the enzyme.

We have initiated a research program directed at the identification of inhibitors of cell wall biosynthesis in mycobacteria and, in particular, *Mycobacterium tuberculosis*.[4] Infection by this organism causes tuberculosis, a disease that is a worldwide health threat resulting in over three million deaths each year.[5] We are especially interested in compounds that block the assembly of the arabinan portions of the cell wall, a structure that is critical for the viability of the organism.[6] This arabinan is a polysaccharide comprised of α-D- and β-D-arabinofuranosyl residues, and we have used methyl glycosides **3** and **4** (Figure 1) as model compounds for these residues, respectively.

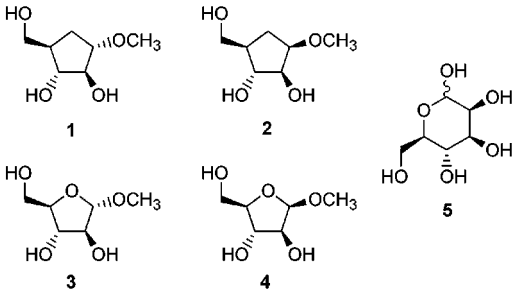


Figure 1.

To prepare inhibitors of mycobacterial arabinosyltransferases containing *pseudo*-arabinofuranosyl residues, we

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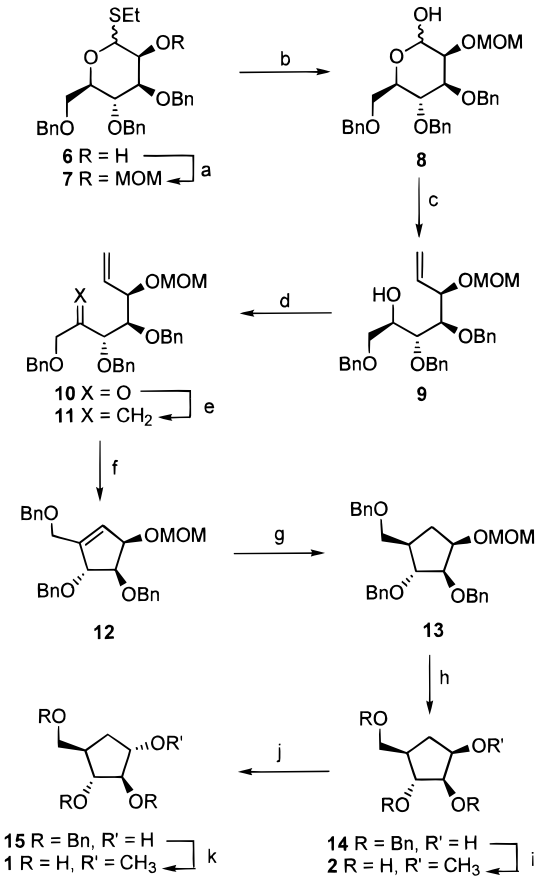
needed to develop an efficient synthetic route to the previously unreported pseudosugar analogues of **3** and **4**, namely, methyl 4a-carba-α-D-arabinofuranoside (**1**) and methyl 4a-carba-β-D-arabinofuranoside (**2**). Polyhydroxylated cyclopentanes and cyclohexanes are common structural features of a large array of natural products, and their preparation has attracted the attention of synthetic chemists. However, most of this work has been focused on the preparation of compounds possessing either a full complement of hydroxyl groups[7] (e.g., inositols) or glycans containing carbapyranose residues.[8] The synthesis of carbafuranoses has been far less investigated.[9]

When evaluating existing methodology which could be applied to the synthesis of **1** and **2**, we were guided not only by our desire to prepare the targets efficiently and in enantiomerically pure form but also by our hope that both could be obtained via a common intermediate. In addition, highly advantageous would be a sequence that would readily enable the synthesis of larger oligomers. Thus, the ability to easily replace the methyl group with other "aglycones", including additional sugar or pseudosugar residues, was important. Unfortunately, none of the reported methods for preparation of carbafuranoses satisfied all these criteria. Therefore, we have developed and report here an alternate route to **1** and **2**. The synthetic sequence involves the conversion of D-mannose (**5**) to diene **11** (Scheme 1), which is cyclized via a ring-closing metathesis (RCM) reaction. The resulting product **12** is, in a subsequent step, reduced stereoselectively to afford the desired cyclopentane framework **13**.[10]

The synthetic route (Scheme 1) began with the known thioglycoside **6**, which can be synthesized in multigram quantities from **5** in five steps.[11] Treatment of **6** with MOMCl and sodium hydride provided **7** in 83% yield. This product was then was hydrolyzed by exposure to *N*-iodosuccinimide and silver triflate in wet dichloromethane, affording **8** in 80% yield.

Scheme 1. Synthesis of **1** and **2**[a]



[a] Legend: (a) MOMCl, NaH, THF, rt, 83%; (b) NIS, AgOTf, CH_2Cl_2, H_2O (5 equiv), rt, 80%; (c) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C → rt, 72%; (d) PCC, NaOAc, 4 Å molecular sieves, CH_2Cl_2, rt, 85%; (e) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C → rt, 76%; (f) **16** (20 mol %), toluene, 60 °C, drybox, 74%; (g) $(Ph_3P)_3RhCl$, (30 mol %), H_2, toluene, rt, 83%; (h) trace concentrated HCl, CH_3OH, rt, 90%; (i) CH_3I, NaH, THF, rt; then Pd/C, H_2, CH_3OH, AcOH, rt, 94%; (j) DEAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, toluene, rt; then $NaOCH_3$, CH_3OH, rt, 83%; (k) CH_3I, NaH, THF, rt; then Pd/C, H_2, CH_3OH, AcOH, rt, 87%.

With gram quantities of **8** in hand, the introduction of the first olefin was achieved by reaction of this substrate with the ylide derived from methyltriphenylphosphonium bromide and *n*-butyllithium. The product, **9**, was obtained in 72% yield. As previously observed with a related mannosyl reducing sugar,[12] in order to prevent elimination during this reaction (leading to diene **18**, Figure 2), pre-exposure of **8** to 1 equiv of *n*-butyllithium for 10 min at 0 °C followed by treatment with the ylide at −78 °C was necessary. Under these conditions, **9** was obtained as the major product and only trace (<5%) amounts of **18** were produced. Alcohol **9**

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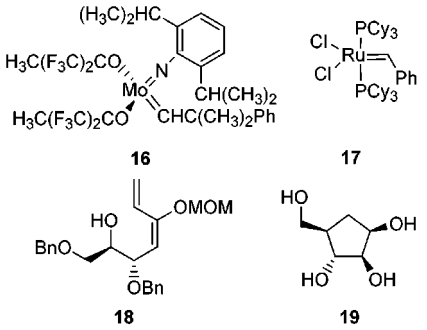

Figure 2.

was subsequently oxidized using pyridinium chlorochromate buffered with sodium acetate[13] in dichloromethane to yield ketone **10** in 85% yield. No epimerization of the C-4 stereocenter was observed under these conditions. The second double bond was then installed in 76% yield by reaction of **10** under conditions similar to those described for the preparation of **9**. However, the synthesis of the diene did not require pre-exposure of the substrate to *n*-butyllithium as in the case of **8**.[14]

Having in place the route to diene **11**, we next investigated its cyclization to **12** via RCM. A series of preliminary experiments using Grubbs' catalyst (**17**)[15] under a variety of reaction conditions produced only poor (12−18%) yields of cyclopentene **12**. This is consistent with previous work which has shown that this catalyst is generally not effective for producing trisubstituted double bonds.[16] Therefore, we investigated Schrock's catalyst (**16**), which is known to be effective for the synthesis of tri- and tetrasubstituted alkenes.[17] In the case of **11**, cyclization with **16** in the drybox (toluene, 60 °C)[18] gave **12** in 74% yield.

The stereoselective reduction of **12** was achieved by reaction with Wilkinson's catalyst ($(Ph_3P)_3RhCl$) under a hydrogen atmosphere, providing **13** in 83% yield. The MOM ether was then removed (trace HCl in CH_3OH) in 90% yield to provide **14**, the core structure for both the α and *β* glycoside analogues. To determine whether the hydrogenation had proceeded to give the correct stereochemistry, **12** was completely deprotected (H_2, Pd/C) to give 4a-carba-*β*-D-arabinofuranose (**19**). The ^1H and ^{13}C NMR spectra of **19** were identical to those previously reported for the racemate,[9g] thus proving the structure of the product. None of the other hydrogenation product, possessing the L-*xylo* stereochemistry, was isolated.

Pseudosugar **2** was straightforwardly obtained via methylation of **14** and subsequent removal of the benzyl groups by hydrogenolysis (94%, two steps). Alternatively, the stereochemistry at C-1 in **14** was inverted via standard Mitsunobu conditions with *p*-nitrobenzoic acid followed by deacylation with sodium methoxide in methanol to yield **15** in 83% yield (two steps). Conversion of **15** to **1**, in 87% yield, was done in a manner identical to the preparation of **2** from **14**.

In summary, we report the total syntheses of methyl 4a-carba-α-D-arabinofuranoside (**1**) and methyl 4a-carba-*β*-D-arabinofuranoside (**2**) from D-mannose. Key transformations include a RCM reaction employing Schrock's catalyst and a stereoselective hydrogenation with Wilkinson's catalyst. The method presented herein should allow access to the entire family of pentocarbafuranoses on the basis of the hexopyranose initially used (e.g., allose → ribocarbafuranose). The route also allows control of the stereochemistry at the pseudo anomeric position, via **14**, leading to either α or *β* glycoside mimetics. Moreover, it will be possible to prepare "glycosides" of these moieties, including oligosaccharide analogues, by alkylation of either **14** or **15** with suitable electrophiles.

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Supporting Information Available: ^1H and ^{13}C spectra of compounds **1**, **2**, and **7**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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