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Synthesis of Carbohydrate Mimics: α-1-*C*-Substituted-deoxymannojirimycins†

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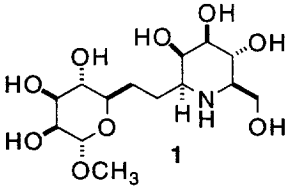
Abstract: Methodology for the construction of diverse α-1-*C*-substituted-deoxymannojirimycin analogues is reported. The pseudoanomeric carbon-carbon bond was formed using a Suzuki cross-coupling between vinyl bromide **5**, derived biocatalytically from bromobenzene, and an aryl, alkyl, or carbohydrate boron coupling partner. Ozonolysis and stereoselective reduction followed by an intramolecular nucleophilic ring closing served to form the polyhydroxylated piperidine ring.

The study of carbohydrate mimics (glycomimetics) has become an area of intense interest due to the realization that carbohydrates serve as information centers for many cellular phenomena.[1] The regulation of the biological machinery (glycosidase enzymes) responsible for manipulation of glycoconjugates associated with cellular processes has huge implications in controlling many diseases from diabetes to HIV.[2] At the center of the selective inhibition of these glycosidase enzymes is the family of *N*-containing carbohydrate mimics commonly referred to as azasugars. We have recently described the synthesis of several polyhydroxylated piperidine derivatives containing the β-1-*C*-deoxymannojirimycin (DMJ) azasugar core such as D-azaMan-β-(1→6)-D-Man (**1**), and β-1-*C*-phenyl-deoxymannojirimycin (**2**).[3] Our previous methodology provided selectively the β oriented substituent at the C[1] position of the DMJ ring *via* an intramolecular reductive amination. We desired to access the α series of compounds to test the effects of the pseudoanomeric configuration on the biological activity of the DMJ core structure.[4] We now wish to report novel complementary methodology for the selective formation of the α-1-*C*-substituted DMJ derivatives **3**.



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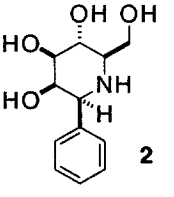

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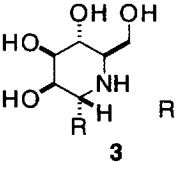
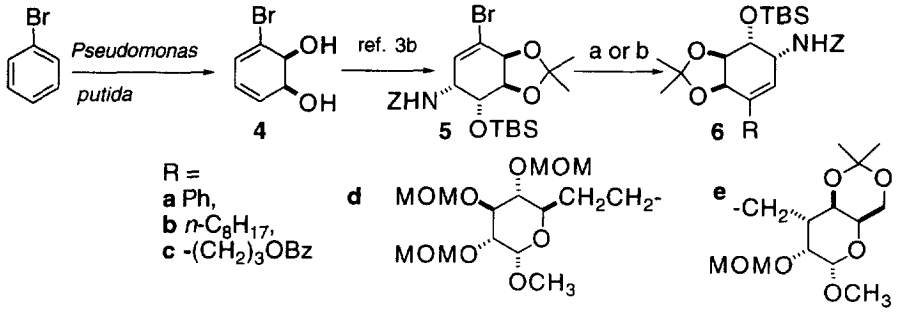


3

R = Alkyl, Aryl, Carbohydrate

The microbial oxidation metabolite **4** derived from bromobenzene can be converted into vinyl bromide **5** in 55-60% overall yield on a multigram scale as reported previously.[3b,5] Vinyl bromide **5** can be coupled efficiently with arylboronic acids as well as alkyl 9-BBN derived boranes using the mild conditions of the Suzuki cross coupling[3,6] protocol (Scheme 1).

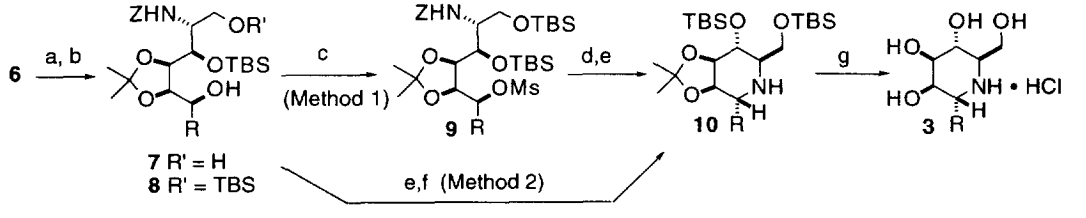
Scheme 1[a]



[a](a) for **a**: $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, THF, Δ (89%); (b) for **b-e**: corresponding olefin,[7] 9-BBN-H, THF, Δ; then $PdCl_2(dppf)$, K_3PO_4, **5**, DMF, rt. **b** (93%), **c** (60%), **d** (93%), **e** (73%)

Azasugar ring construction was accomplished as shown in Scheme 2. Ozonolysis of the trisubstituted olefins **6** followed by a quench of the ozonide with $NaBH_4$ led in each case to a single diastereomer of diol **7**. The resultant stereochemistry of the 2° alcohol **7b** was proven by conversion to the piperidine ring and comparison of the ^1H NMR and NOE data to the previously synthesized β epimer **11**[7] (Figure 1a). A deshielding of the equatorial proton H_A in **10b** (δ 3.10 ppm), with respect to the axial proton H_A of **11** (δ 2.85ppm) is consistent with the assigned stereochemistry. The stereochemistry was unambiguously assigned based on NOE results for **10a** where a positive enhancement was observed between the ortho proton on the phenyl ring and the axial protons H_C, and H_E (Figure 1b). The stereochemistry of **10c-e** were determined in a similar manner or assigned by analogy.[7] A protection of the 1° alcohol as its corresponding silyl ether **8** proceeded smoothly. Two ring closing strategies were examined for the construction of the piperidine ring. Method 1 consisted of mesylation of the 2° alcohol **8** leading to mesylate **9** which was stable for all cases including the benzylic mesylate **9a**. None of the potentially reactive mesylates underwent ring closing during the mesylation reaction.[8] Subjection of **9** to basic conditions facilitated the desired S_N2 ring closing cleanly. Reductive removal of the Cbz led to protected α-1-*C*-DMJ derivative **10**. An alternative more direct strategy (Method 2) for the ring closing involved removal of the *N*-protecting CBz group *via* catalytic hydrogenation and cyclization using modified Mitsunobu type of conditions[9] whereby a phosphonium leaving group is displaced intramolecularly by the tethered nitrogen. Overall the mesylate route provided better results, but the activated phosphine methodology was satisfactory in most cases and was one step shorter.

Scheme 2[a]



[a](a) i. O_3, CH_2Cl_2/CH_3OH, -78 °C, 10 min; ii. O_2, 3 min; iii. $NaBH_4$ (5 eq) -78 °C to rt 3-5 h (57-97%); (b) TBSCl (1.1 eq), Imidazole, DMF (90-99%); (c) Ms_2O, pyridine, CH_2Cl_2 (70-99%); (d) *t*-BuO⁻K⁺, THF (91-99%); e) Pd/C, H_2 EtOAc/CH_3OH (77-99%); f) PPh_3, I_2, Imidazole, Toluene, Δ (47-99%); (g) 6 *N* HCl, THF (80-99%)

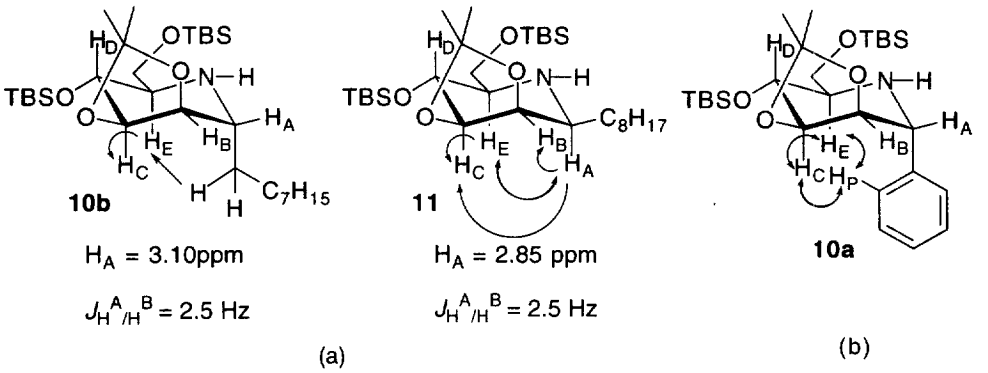
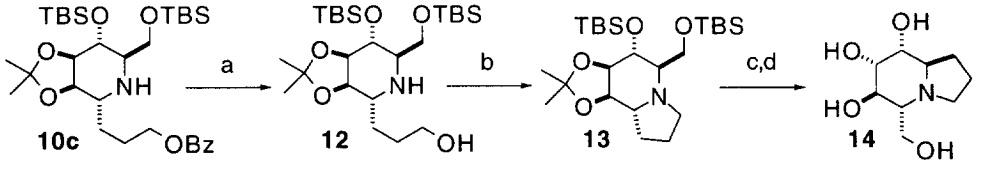


Figure 1 (a) Comparison of ^{1}H NMR and NOE data for α-1-*C*-DMJ (**10b**) and the previously synthesized β-1-*C*-DMJ (**11**)[7] (b) NOE results for **10a**.

Azasugar derivative **10c** was not subjected to the acidic deprotection conditions as depicted in Scheme 2, but rather the benzoyl protecting group was removed providing indolizidine precursor **12** (Scheme 3). Treatment of amino-alcohol **12** with the Mitsunobu cyclization conditions as described above led to the indolizidine skeleton **13** in high yield. Acidic deprotection of **13** followed by formation of the free base led to indolizidine **14**.

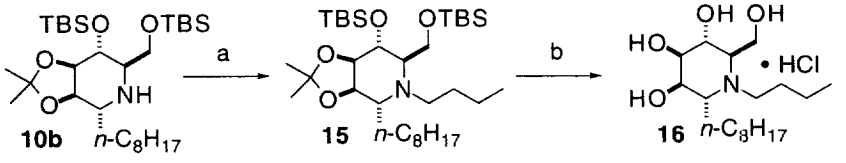
Scheme 3[a]



[a](a) 1% NaOH, CH_3OH (77%); (b) PPh_3, I_2, Imid., Tol, Δ (99%); (c) 6 *N* HCl, THF; (d) Amberlite IRA 400 (OH), CH_3OH (80%)

Protected azasugar **10b** was converted to its corresponding *N*-butyl derivative **15** *via* reductive amination[10] with butyraldehyde taking advantage of the otherwise fully protected polyhydroxylated piperidine framework (Scheme 4). Acidic deprotection of **15** gave *N*-butyl-α-1-*C*-octyl-deoxymannojirimycin (**16**) as its hydrochloride salt.

Scheme 4[a]



[a](a) Butyraldehyde, DCE, $NaBH(OAc)_3$, AcOH (75%); (b) 6 *N* HCl, THF (99%)

In summary, we have described additional methodology for our program of azasugar synthesis providing access to the series of α-1-*C*-DMJ derivatives which complements the already established methods for the

synthesis of the β-1-*C*-DMJ derivatives. Biological examination of the reported compounds will be disclosed in due course.

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