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Synthesis of aza-*C*-galacto disaccharides from C1-substituted galactals

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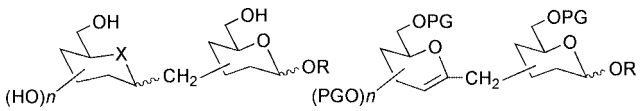
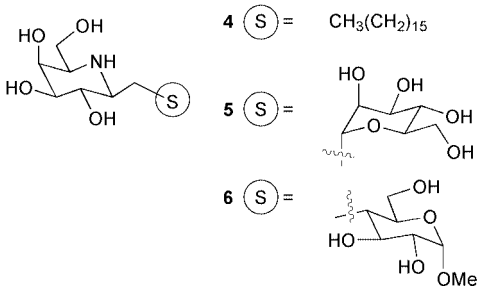
C1-substituted galactals are transformed *via* the double reductive amination on their 1,5-diketone derivatives, to aza-β-*C*-galacto-disaccharides.

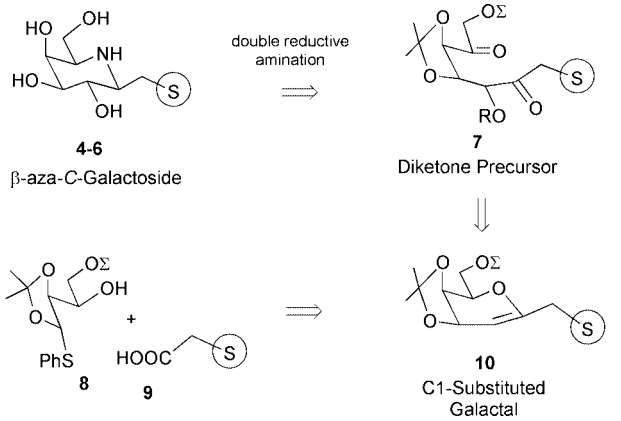
Interest in polyhydroxylated azaheterocycles as biochemical tools and therapeutic agents has been extensively documented.[1] Attention has focused on their potent activity as glycosidase inhibitors.[1,2] Guidelines for the design of glycone specific glycosidase inhibitors are well known, but models for aglycone specific inhibitors,[2] or for mimetics associated with other carbohydrate mechanisms are not as well developed.[3] Structures with a high degree of structural complexity, for example as found in disaccharide analogues, are of interest as probes of recognition specificity.[2a,b] Of these, *C*-disaccharides (*e.g.* **1**, **2**) have the added benefit of stability towards chemical and enzymic hydrolysis. We and others have shown that C1-substituted glycals **3** are attractive precursors to *C*-disaccharides **1**.[4–6] Herein, we illustrate the versatility of such C1 substituted glycals, by the synthesis of the novel, biologically interesting aza-β-*C*-galactosides **4**–**6**. N-linked lipid iminocyclitols related to **4** have recently shown potential as inhibitors of gp-120/galactosylceramide binding.[3c] Azasugar **5** is an analog of the ubiquitous lactose subunit and **6** is a potential mimetic of a recently discovered selectin antagonist.[7]



1 X = O *C*-Disaccharide
2 X = NH Aza-*C*-Disaccharide
3



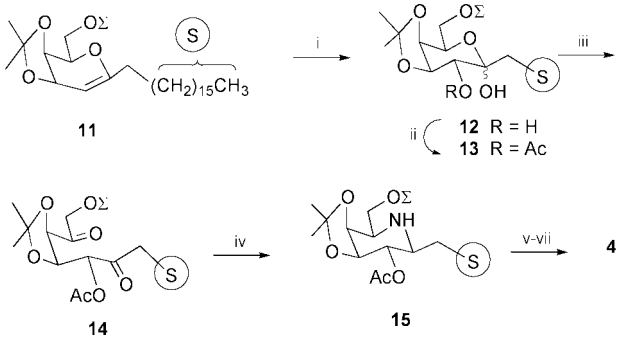
We envisaged a route to aza-*C*-disaccharides which is based on the stereoselective double reductive amination on a complex diketone **7** (Scheme 1).[8] Our optimism was guided by several examples of highly stereoselective double reductive aminations in polyhydroxylated dicarbonyl substrates.[9] An attractive aspect of this approach is the introduction of the amine in a single operation at a relatively late stage in the synthesis, thereby reducing protecting group inefficiencies. In addition the synthetic precursors are C1-substituted glycals which may be assembled *via* convergent syntheses, and therefore appropriate for complex disaccharide structures. Prompted by a recent report of a similar double reductive amination strategy to aza-β-(1 → 6)-*C*-disaccharides,[10] we describe a preliminary account of our results. In the former case, the diketone substrates were prepared from 'disaccharide' ketal precursors, obtained *via* the



Scheme 1

addition of monosaccharide lithio acetylides to pyranolactones. While applicable to 1 → 6 type disaccharide systems, this type of organometallic coupling strategy is not generally applicable to methylene linked structures (*e.g.* 1 → 2, 1 → 3 and 1 → 4 linked disaccharide analogues). By comparison, the diketones in our approach are obtained through dihydroxylation of C1-substituted glycals (*e.g.* **10**). Such glycals may be obtained through our oxocarbenium ion cyclization methodology, starting from the ester derived from the 1-thio-1,2-isopropylidene acetal (TIA)-alcohol **8** and the acid partner **9**,[4] or *via* other protocols.[6] The esterification reaction used for the 'glycone'–'aglycone' coupling is experimentally straightforward and allows access to C1-pyrano substituted glycals (and hence *C*-disaccharide derivatives) with intersaccharide linkers of any length.

The methodology was first applied to the galactal **11** (Scheme 2). Dihydroxylation of **11** with osmium tetroxide–NMNO proceeded with complete α-selectivity to provide lactol **12** in 80% yield. Selective acetylation of **12** and PCC oxidation of the monoacetate **13** led to the diketone **14** in 78% overall yield from **12**. Treatment of **14** with 1.5 equiv. of $NaCNBH_3$, 1.2 equiv. of ammonium formate in anhydrous methanol in the presence of freshly activated 4 Å molecular sieves afforded the



Scheme 2 (i) OsO_4, NMNO, acetone, 80%; (ii) Ac_2O, DMAP, EtOAc, 95%; (iii) PCC, CH_2Cl_2, NaOAc; Celite, 4 Å MS, 82%; (iv) $NaCNBH_3$, NH_4HCO_2, 4 Å MS, anhyd. MeOH, 72%; (v) NaOMe, MeOH; (vi) Bu_4NF, THF; (vii) HCl, MeOH, 58% over three steps.

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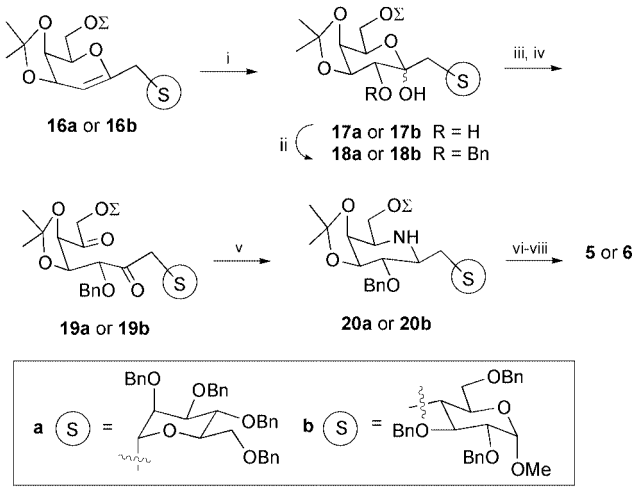
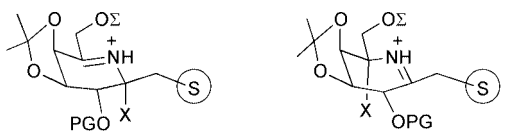


Scheme 3 (i) OsO_4, NMNO, acetone, **17a** (81%), or K_3FeCN_6, DBU, acetone, **17b** (83%); (ii) BnBr, AgOTf, CH_2Cl_2, **18a** (87%), **18b** (62%); (iii) $NaBH_4$, EtOH; (iv) Swern's Ox. **19a** (60%), **19b** (64%), over two steps; (v) $NaCNBH_3$, NH_4HCO_2, 4 Å MS, anhyd. MeOH, **20a** (72%), **20b** (68%); (vi) Bu_4NF, THF; (vii) HCl, MeOH; (viii) H_2, Pd/C, EtOH, HCOOH, **5** (67%), **6** (60%) over three steps.

aza-β-*C*-galactoside **15** as a single stereoisomer in 72% yield.[11] The stereochemistry of **15** was assigned on the basis of *J* values ($J_{1,2}$ = 9.9, $J_{2,3}$ = 7.7, $J_{3,4}$ = 5.1, $J_{4,5}$ = 2.2 Hz) and observation of 1% NOE effects between H1, and H3 and H5 respectively.[12] Removal of protecting groups in **15** under standard conditions provided the desired aza-β-*C*-galactoside **4** in 58% overall yield from **15**.[13]

Dihydroxylation of galactal **16a** (Scheme 3) under the aforementioned conditions produced a single ketal **17a** in 80% yield. These conditions led to lower yields for the reaction of the gluco linked galactal **16b**. However use of potassium ferricyanide instead of NMNO as co-oxidant in the presence of DBU led to high yield of the desired hydroxy ketal **17b**.[14] Although the secondary alcohols in **17a,b** could be selectively converted to their acetate derivatives, this protecting group proved to be incompatible with subsequent steps. Compounds **17a,b** were therefore converted to the respective benzyl ethers **18a,b**. Unlike the case for ketal **12**, direct oxidation of **18a,b** to the requisite diketones was not successful. Diketones **19a,b** were eventually obtained *via* a two step reduction–oxidation procedure on **18a,b**. Treatment of **19a,b** under reductive amination conditions provided the *C*-aza derivatives **20a,b** in 72 and 64% yields respectively. The stereochemistry in **20a,b** was assigned from NOESY experiments in a similar fashion as described for **15**. Standard deprotection procedures on **20a** and **20b** provided the desired β-aza-*C*-disaccharides **5** and **6** respectively.[15]

The high stereoselectivity of these double reductive aminations is consistent with the model developed by Stevens for the hydride reduction of six membered cyclic iminium ions.[16] Thus preferred α-face reduction on imium ions like **21** and **22** would



lead to the observed β-aza-*C*-galacto motif. The observation of the same sense of stereochemical bias in gluco and manno type diketones, supports this stereochemical model.[8c,10] Therefore, given the availability of C1-substituted glucals and galactals, and the amenability of such compounds to conversion to different C2 substituted ketals, the methodology described herein is expected to provide access to a wide variety of aza-β-*C*-glycosides. These directions are currently being explored.

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13 For **4**: clear oil; ^{1}H NMR (500 MHz, CD_3OD) δ0.90 (t, J = 7.0 Hz, 3H), 1.30 (m, 28H), 1.50 (m, 2H), 1.62 (m, 1H), 1.94 (m, 1H), 2.78 (m, 1H), 3.15 (t, J = 6.5 Hz, 1H), 3.42 (dd, J = 3.0, 8.5 Hz, 1H), 3.62 (t, J = 10.0 Hz, 1H), 3.78 (m, 2H), 4.00 (br s, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 14.6, 23.9, 26.8, 30.6, 30.7, 30.9, 31.1, 32.0, 32.2, 60.9, 61.2, 61.5, 68.9, 71.7, 75.6. FAB HRMS calcd for $C_{23}H_{48}NO_4$ (M + H) 402.3583, found 402.3584.

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15 For **5**: white powder; ^{1}H NMR (500 MHz, D_2O) δ2.05 (m, 1H), 2.32 (br d, J = 15.5 Hz, 1H), 3.29 (br t, J = 9.5 Hz, 1H), 3.45 (t, J = 6.5 Hz, 1H), 3.63 (dd, J = 3.0, 9.5 Hz, 1H), 3.68–3.90 (m, 9H), 4.15 (br s, 1H), 4.20 (m, 1H). ^{13}C NMR (90 MHz, D_2O) δ 28.7, 59.0, 59.7, 60.1, 66.8, 68.0, 69.5, 70.4, 70.5, 73.2, 74.9, 76.0. FAB HRMS calcd for $C_{13}H_{26}NO_9$ (M + H) 340.1608, found 340.1608. For **6**: ^{1}H NMR (500 MHz, D_2O) δ1.29 (m, 1H), 1.67 (m, 1H), 2.09 (br d, J = 16.0 Hz, 1H), 2.44 (t, J = 10.0 Hz, 1H), 2.83 (t, J = 6.5 Hz, 1H), 3.36 (t, J = 10.0 Hz, 1H), 3.41 (s, 3H), 3.50–3.70 (m, 6H), 3.83 (m, 2H), 4.01 (d, J = 3.0 Hz, 1H), 4.83 (d, J = 3.5 Hz, 1H). ^{13}C NMR (90 MHz, D_2O) δ 31.6, 42.6, 55.1, 58.2, 59.3, 61.6, 61.9, 69.5, 71.9, 72.1, 72.3, 72.6, 75.0, 99.6. ESMS: 354.2 (M + H).

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