## 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- $\beta$ -C-galacto-disaccharides.

Interest in polyhydroxylated azaheterocycles as biochemical tools and therapeutic agents has been extensively documented.<sup>1</sup> Attention has focused on their potent activity as glycosidase inhibitors.<sup>1,2</sup> Guidelines for the design of glycone specific glycosidase inhibitors are well known, but models for aglycone specific inhibitors,<sup>2</sup> or for mimetics associated with other carbohydrate mechanisms are not as well developed.<sup>3</sup> Structures with a high degree of structural complexity, for example as found in disaccharide analogues, are of interest as probes of recognition specificity.<sup>2a,b</sup> 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 C1substituted 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- $\beta$ -C-galactosides 4–6. N-linked lipid iminocyclitols related to 4 have recently shown potential as inhibitors of gp-120/galactosylceramide binding.<sup>3c</sup> Azasugar 5 is an analog of the ubiquitous lactose subunit and 6 is a potential mimetic of a recently discovered selectin antagonist.7



We envisaged a route to aza-*C*-disaccharides which is based on the stereoselective double reductive amination on a complex diketone 7 (Scheme 1).<sup>8</sup> Our optimism was guided by several examples of highly stereoselective double reductive aminations in polyhydroxylated dicarbonyl substrates.<sup>9</sup> 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- $\beta$ -(1  $\rightarrow$  6)-*C*-disaccharides,<sup>10</sup> we describe a preliminary account of our results. In the former case, the diketone substrates were prepared from 'disaccharide' ketal precursors, obtained *via* the



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munication

Scheme 1

addition of monosaccharide lithio acetylides to pyranolactones. While applicable to  $1 \rightarrow 6$  type disaccharide systems, this type of organometallic coupling strategy is not generally applicable to methylene linked structures (*e.g.*  $1 \rightarrow 2$ ,  $1 \rightarrow 3$  and  $1 \rightarrow 4$  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**,<sup>4</sup> or *via* other protocols.<sup>6</sup> 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  $\alpha$ -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<sub>3</sub>, 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<sub>3</sub>, NH<sub>4</sub>HCO<sub>2</sub>, 4 Å MS, anhyd. MeOH, 72\%; (v) NaOMe, MeOH; (vi) Bu<sub>4</sub>NF, THF; (vii) HCl, MeOH, 58% over three steps.



Scheme 3 (i) OsO<sub>4</sub>, NMNO, acetone, **17a** (81%), or  $K_3FeCN_6$ , DBU, acetone, **17b** (83%); (ii) BnBr, AgOTf, CH<sub>2</sub>Cl<sub>2</sub>, **18a** (87%), **18b** (62%); (iii) NaBH<sub>4</sub>, EtOH; (iv) Swern's Ox. **19a** (60%), **19b** (64%), over two steps; (v) NaCNBH<sub>3</sub>, NH<sub>4</sub>HCO<sub>2</sub>, 4 Å MS, anhyd. MeOH, **20a** (72%), **20b** (68%); (vi) Bu<sub>4</sub>NF, THF; (vii) HCl, MeOH; (viii) H<sub>2</sub>, Pd/C, EtOH, HCOOH, **5** (67%), **6** (60%) over three steps.

aza-β-*C*-galactoside **15** as a single stereoisomer in 72% yield.<sup>11</sup> 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.<sup>12</sup> Removal of protecting groups in **15** under standard conditions provided the desired aza-β-*C*-galactoside **4** in 58% overall yield from **15**.<sup>13</sup>

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  $\beta$ -aza-C-disaccharides **5** and **6** respectively.<sup>15</sup>

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.<sup>16</sup> Thus preferred  $\alpha$ -face reduction on imium ions like **21** and **22** would



lead to the observed  $\beta$ -aza-*C*-galacto motif. The observation of the same sense of stereochemical bias in gluco and manno type diketones, supports this stereochemical model.<sup>8c,10</sup> 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  $aza-\beta$ -C-glycosides. These directions are currently being explored.

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- 15 For **5**: white powder; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O)  $\delta$ 2.05 (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). <sup>13</sup>C NMR (90 MHz, D<sub>2</sub>O)  $\delta$ 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<sub>13</sub>H<sub>26</sub>NO<sub>9</sub> (M + H) 340.1608, found 340.1608. For **6**: <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O)  $\delta$  1.29 (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), 1.43 (d, J = 3.5 Hz, 1H). <sup>13</sup>C NMR (90 MHz, D<sub>2</sub>O)  $\delta$  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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