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α-Glucosaminide synthesis: exercising stereocontrol at C1 or C2 via torsional effects or DeShong nucleophiles

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Abstract

The synthesis of α-glucosaminides may be carried out by installing synthons for the *cis*-related C1 and C2 functionalities in either order. When the C2 azide is installed first, α-glycosidation can be induced by using a 4,6-*O*-benzylidene ring to provide torsional control of anomeric selectivity. In the alternative option, the C1 linkage can be established by use of an *n*-pentenyl-*manno*-1,2-orthoester, the C2–oxygen of the resulting α-mannoside being replaced with inversion by use of DeShong's hypervalent silicon azide.

Keywords: hypervalent silicon azido nucleophiles; *n*-pentenyl glycosides; *n*-pentenyl orthoesters.

The laboratory synthesis of *cis*-1,2-glucosaminides, **2**, presents problems with respect to both the C1 and C2 stereocenters.[1,2] Option A of Scheme 1 relates to C1, and in this connection, Paulsen and co-workers introduced a C2 azido group as the 2-amino precursor, e.g. **1**, in the expectation that being a non-participating entity, it would facilitate α-glycosidation.[3] This seminal contribution has inspired novel synthetic approaches to C2 azido sugars,[4] one of the most recent being Vasella's facile procedure for diazo transfer to amines.[5] That development enabled us to employ pent-4-enoyl[6] and tetrachlorophthaloyl (TCP)[7] as protecting groups for preparing a variety of C2 azido sugars including **4a** and **7**.[8]

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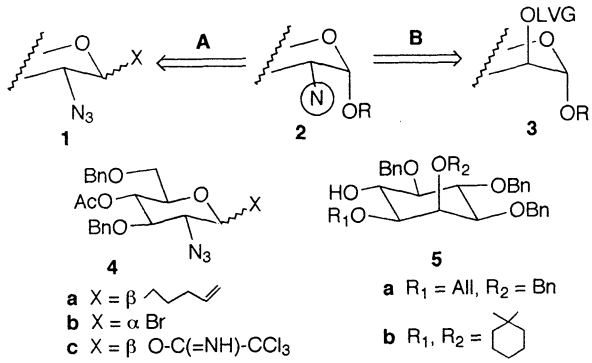
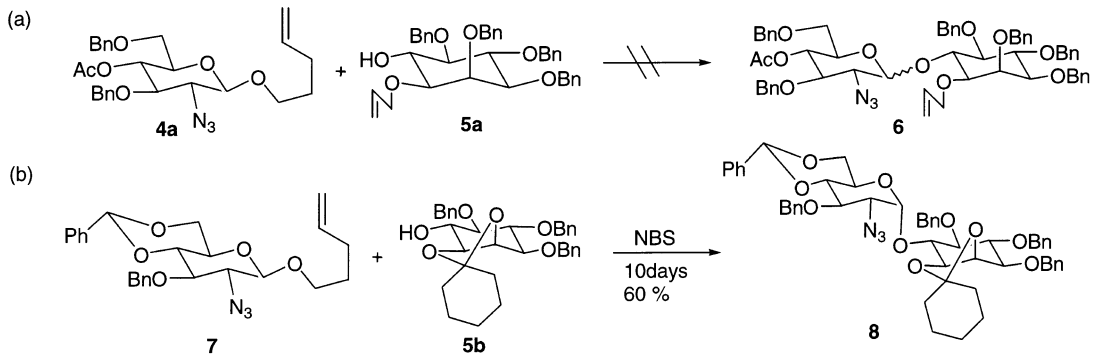


Scheme 1.

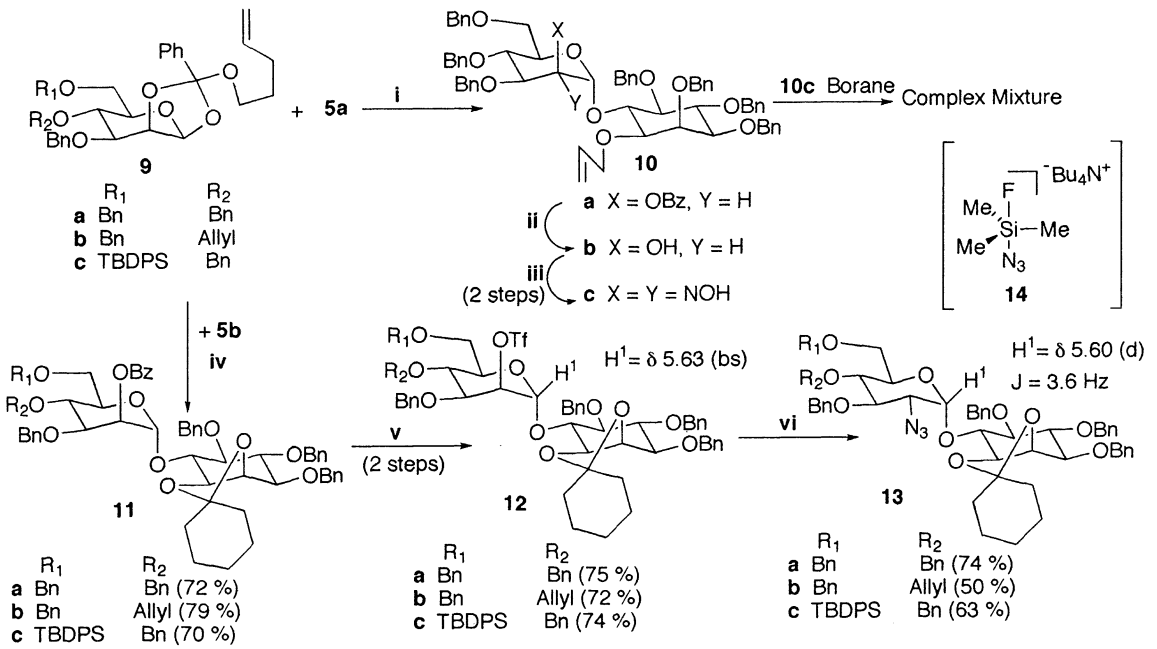
We were interested to determine the best donor-partner for the partially protected inositols **5**(**a**[9] or **b**)[10] to obtain an α-product with good yield and selectivity. As indicated in Scheme 2a, the NPG **4a** failed to undergo appreciable coupling with **5a**; the material was therefore converted into glycosyl bromide, **4b**, and trichloroacetimidate, **4c** (Scheme 1), by standard procedures.[11,12] With **4b**, excellent α-selectivity was achieved by the Lemieux-halide assisted protocol,[13] although the yield was disappointing.[14] On the other hand, the yield of coupled products with the trichloroacetimidate **4c** was very good; but the anomeric selectivity was problematic.[15]



Scheme 2.

Theoretical[16] and experimental[17] studies have shown that torsional factors strongly influence reactions at the anomeric center, and Crich and co-workers have applied this chemistry elegantly for controlling anomeric selectivities.[18] In light of the abject failure with **4a** (Scheme 2a) the torsionally constrained benzylidene analog **7** was tested with acceptor **5b** and, in contrast to **4a**, was found to give a satisfactory yield of **8** with complete α-selectivity (Scheme 2b). Notably, *N*-bromosuccinimide had to be used as promoter, since the more potent combination (NIS/TESOTf)[11] caused cleavage of the benzylidene ring.

The routes in Scheme 2 are based upon the retrosynthetic strategy, option A, Scheme 1. The alternative, option B, could (a) take advantage of the ready formation of α-mannosides, e.g. **3**, if (b) the resulting C2–OR could be replaced by an amino group with inversion of configuration. In order to explore option B, the *n*-pentenyl orthoester **9a**[19] was coupled with the inositol **5a** to provide the α-mannoside **10a** (Scheme 3). The strategy of Lemieux and Gunner for stereocontrolled reduction of C2-oximo glycosides[20] was investigated with the derived oxime **10c**, but the borane reduction step proved too drastic for the substrate.



Scheme 3. Reaction conditions: i. **9a** (1.3 equiv.), NIS (1.3 equiv.), TBDMSOTf (0.3 equiv.), rt, 20 min, 78%; ii. NaOMe, MEOH/CH_2Cl_2, 14 h, 94%; iii. (a) DMSO/Ac_2O, rt, 24 h. (b) NH_2OH, HCl, NaOAc·$3H_2O$, H_2O/EtOH, rt, 14 h; iv. **9** (1.3 equiv.), NIS (1.3 equiv.), $BF_3{\cdot}OEt_2$ (0.3 equiv.), 0°C, 20–30 min; v. (a) Tf_2O, DMAP, Pyr, CH_2Cl_2, –75°C–rt, 3 h; vi. $TMSN_3$ (1.5 equiv.), TBAF (1.5 equiv.), THF, 65°C, 14–24 h.

Nucleophilic displacement at C2 of α-mannosides is traditionally difficult,[21] and so the complete failure of Mitsunobu displacement[22] on alcohol **10b** was not surprising.

Binkley's triflate displacement procedure[23] has been successful elsewhere,[2] and in order to test this, the orthoesters **9a–c** were coupled with inositol **5b** to give **11a–c** in excellent yields, and without detectable contamination of β anomers (Scheme 3). Unfortunately, treatment of compound **12a** with sodium azide in DMF at room temperature gave only elimination products.

The recent report on the use of hypervalent silicon nucleophiles by DeShong and co-workers[24] was therefore timely. Particularly impressive were the quantitative displacements with β-phenethyl bromide, without β-elimination to give styrene. The triflates, **12a–c** were subjected to the hypervalent silicon azide as described by DeShong and co-workers. The $TMSN_3$/tetrabutylammonium triphenyldifluorosilicate (TBAT) reagent combination was problematic in that the product was contaminated with aromatic impurities. This outcome was avoided by use of the $TMSN_3$/TBAF combination, **14**, leading to the displacement products **13a–c** in good yields. These transformations could be easily monitored by analyzing the appropriate signals in the ^1H NMR spectra, (the parameters shown in Scheme 3 for **12a** and **13a** being typical) and the IR spectra, which showed the required absorption for the azido group at 2104 cm^{-1}.

In light of the widespread use of silicon protecting groups in carbohydrate transformations, success in obtaining the *tert*-butyl diphenylsilyl (TBDPS)[25] protected analogue **13c** is noteworthy.

In summary, the C2 and C1 stereocenters of α-glucosaminides can be cleanly established either by retrosynthetic option A or B (Scheme 1). For the former, the restraining effect of a 4,6-*O*-benzylidene ring can be used to induce α-coupling. For the latter, a *manno* NPOE ensures (a) clean α-coupling and (b) a convenient C2–ester ready to be replaced with a triflate leaving group for displacement with DeShong's hypervalent silicon azide.

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