

The Synthesis of 4-amino-4-deoxy-D-mannose and Glucosamine: A New Methodology for the Design of Homochiral Amino Sugars from non-Carbohydrate Precursors

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Abstract: A new methodology for the synthesis of amino sugars from non-carbohydrate precursors (derived from chlorobenzene) is described. The key step involves the ozonolysis of vinyl halides of type **1** and subsequent reductive regio- and stereo controlled cyclization to form amino pyranose derivatives.

Ubiquitous in nature, amino sugars occur in plants, microorganisms, invertebrates, and mammals.^{1,2} Amino sugars are found as constituents of blood and antigenic determinants,³ glycoproteins,⁴ and glycolipids.⁵ Other amino sugars are constituents of aminoglycoside antibiotics,^{6,7} nucleoside antibiotics,⁸ and heparin.⁹ We have devoted considerable effort to the development of a general synthetic methodology that would permit access to many members of this vital class of compounds and other carbohydrates. To this end, we have developed methods for the efficient synthesis of cyclitols,¹⁰ aminocyclitols,¹¹ monosaccharides,¹² aza sugars¹³ and, most recently, pseudo-sugars.¹⁴ In this paper, we address the systematic approach to the synthesis of amino sugars.

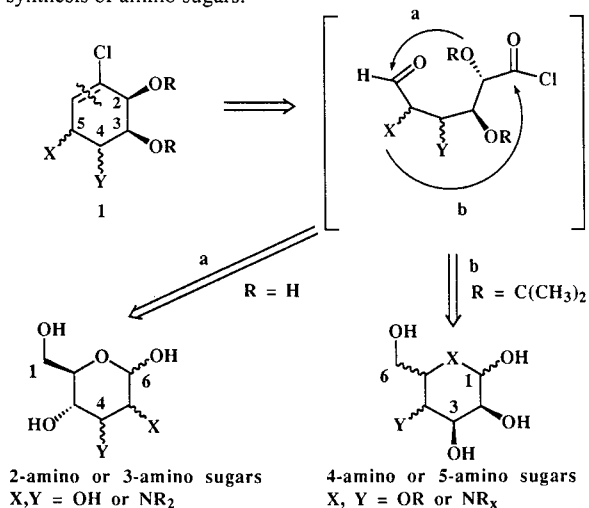
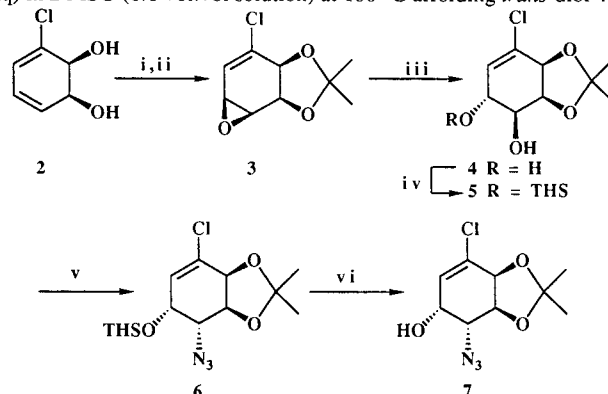


Figure 1

The key feature of our approach is the ozonolysis of compounds of type **1**^{15a,b} (originally developed in our laboratories in 1987 in connection with the synthesis of PGE₂)^{15b,c} in which the peripheral substitution patterns are already set (Figure 1). The C1 and C6 of compound **1** represent a latent acid chloride and a latent aldehyde, respectively. These latent functionalities become fully expressed during the oxidative cleavage and subsequent reductive work-up, permitting annulation by either a C2–C6 or a C5–C1 ring closure generating either 2-amino (3-amino) sugar derivatives (depending on the functionalities X and Y) or 4-amino (5-amino) sugar derivatives. The functional topography would be delivered by a *a priori* placement of nitrogenous functionality at either C4 or C5. There are a total of eight possible isomers of azido alcohols at C4 and C5. This number of possibilities multiplied by the number of types of recyclizations provides the basis for a viable approach to any possible isomer of an amino pyranose. Herein we wish to report the synthesis of protected 4-amino-4-deoxymannose and a formal synthesis of glucosamine by means of the above methodology.

Exposure of chlorocyclohexadiene-*cis*-diol **2** to 2,2-dimethoxypropane and *p*-toluene sulfonic acid (catalytic amount) gave an acetonide, which was immediately treated with *N*-bromosuccinimide followed by sodium hydroxide in methylene chloride (with tetrapropylammoniumhydrogensulfate as a phase-transfer catalyst) to yield

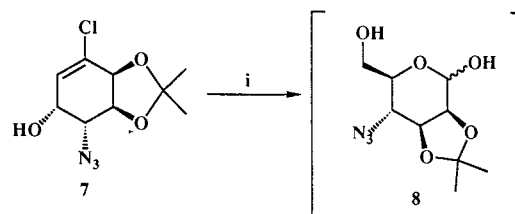
epoxide **3** as a white solid (57% from diol **2**), Scheme 1. Hydrolysis of oxirane **3** was accomplished by means of potassium hydroxide (10% aq) in DMSO (1:1 vol:vol solution) at 100 °C affording *trans*-diol **4**



Reagents: (i)(a) DMP, *p*TSA, CH₂Cl₂ (b) NBS, DME/H₂O (4:1) (ii) NaOH, nBu₄NHSO₄, CH₂Cl₂ (iii) KOH (10%), DMSO, 90 °C (iv) THS, imidazole, CH₂Cl₂ (v)(a) Tf₂O, pyridine, CH₂Cl₂, 0 °C (b) NaN₃, DMF, 53 °C (vi) TBAF·H₂O, THF, 0 °C.

Scheme 1

(59%), which was protected with dimethylthexylsilyl chloride in methylene chloride to give thexyl alcohol **5** in 65% yield. Azide displacement of the triflate derived from alcohol **5** furnished thexyl azide **6** (70%), which was deprotected with tetrabutylammonium fluoride in THF to yield azido alcohol **7** in 89% yield.



Reagents: (i)(a) O₃, MeOH, NaHCO₃, -78 °C (b) NaBH₄, 0 °C - r.t. (ii) Ac₂O, pyridine, DMAP, CH₂Cl₂ (iii) H₂, Pd/C (10%), EtOH

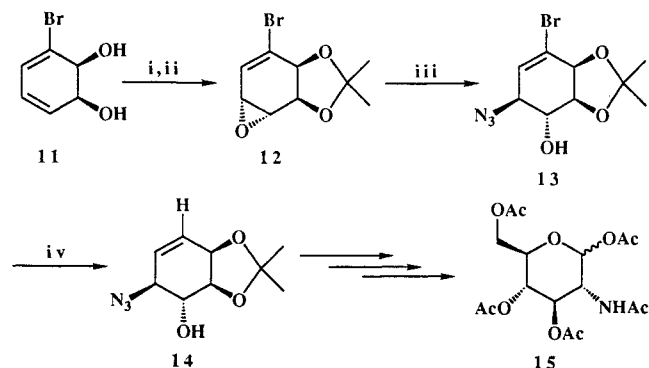
Scheme 2

The oxidative cleavage of the olefin of azido alcohol **7** (Figure 1) permits annulation via a C5–C1 functionality closure and leads to a mannosyl-lactone-aldehyde, which requires only subsequent reductions to yield 4-aminomannose. Thus standard ozonolysis conditions (Scheme 2) followed by reductive work-up and acetate protection gave diacetate **9** in an overall isolated yield of 28% from azido alcohol **7**.¹⁶ Hydrogenation of **9** (H₂, Pd/C 10%) followed by acetamide formation (Ac₂O, pyridine) gave the final product, 4-acetamido-4,6-diacetoxymannose.

2,3-*O*-isopropylidene-4-deoxy-D-mannose **10**¹⁷ in a 76% yield, which, to the best of our knowledge, constitutes the first synthesis of this compound.

Fleet¹⁸ has used the benzyl aglycone of azido-mannose **8** to synthesize swainsonine, 1,4-dideoxy-1,4-imino-D-mannitol, and the α -galactosidase inhibitor 1,4-dideoxy-1,4-imino-D-lyxitol. Therefore the synthesis of 4-amino-4-deoxymannose also constitutes a formal synthesis of these compounds.

A formal synthesis of glucosamine has also been achieved by means of the above methodology. Following known procedures,^{13b} bromocyclohexadiene-*cis*-diol **11** was protected as its acetonide (DMP, *p*TSA, CH₂Cl₂) and subjected to *m*CPBA epoxidation to yield α -oxirane **12** (Scheme 3). *Trans*-azido alcohol **13** was obtained as a white solid by the treatment of α -oxirane **12** with sodium azide in DMF (73% overall yield from diol **11**). Removal of bromine from azido alcohol **13** was achieved *via* halogen-metal exchange (*t*BuLi, THF -78 °C) to give azido alcohol **14** as a white solid (40%) (mp = 59–61 °C, $[\alpha]_D^{25} = -59.3^\circ$, $c = 1.58$, CHCl₃). This material, synthesized in its racemic form, has previously been converted through ozonolysis and further derivatization to 2-amino-2-deoxyglucose.¹⁹



Reagents: (i) DMP, *p*TSA, CH₂Cl₂ (ii) *m*CPBA, CH₂Cl₂ (iii) NaN₃, DMF (iv) (a) *t*BuLi, THF (b) H₂O, -78 °C - r.t.

Scheme 3

The attainment of protected 4-amino-4-deoxymannose **10** and the formal synthesis of protected glucosamine **15**, representative examples of two of four biologically important carbohydrate groups, bodes well for a methodology that can be adapted for the synthesis of other amino sugars. Stereo- and regioisomers of compounds **7** and **14** will provide access to such amino sugars as: 2-amino-2-deoxymannose; 3-amino-3-deoxymannose; 2-amino-2-deoxyaltrose; 3-amino-2-deoxyaltrose; 2-amino-2-deoxyallose; 3-amino-3-deoxyallose; and 4-amino-4-deoxytalose to name a few. All of these amino sugars can be stereo specifically synthesized from single enantiomers of either compound **2** or compound **11**. Further applications of this new procedure and confirmation of its generality in enantiospecific synthesis will be reported in due course.

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- (16) *Trans* azido alcohol **7** (40.9 mg, 0.166 mmol) was dissolved in a methanol/water (8%) solution (10 mL) containing sodium hydrogen carbonate (66.8 mg, 5 eq). The solution was cooled to -78 °C and a stream of oxygen containing ozone was passed through the reaction until a dark blue color persisted for approximately five minutes. The temperature was raised to 0 °C whereupon sodium borohydride was added in 5-mg portions until only one spot main spot was observed by TLC (Note: the reaction was brought to ambient temperature after the first sodium borohydride addition). The mixture was brought to pH ~5 with HCl (10%, aq.). Once the the correct pH was achieved, the reaction was concentrated on a rotary evaporator and diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (5X). The combined organic layers were then washed with brine, dried (MgSO₄), filtered, and concentrated. The crude product was dissolved in acetic anhydride and pyridine. After 24 hrs, the reaction was diluted with methylene chloride and transferred to a separatory funnel and washed with water (2X). The combined aqueous layers were extracted with CH₂Cl₂ (5X). The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated onto silica gel. Flash chromatography (4:1 hexane:ethyl acetate) provided aceto 6-aceto-4-azido-2,3-*O*-isopropylidene-4-deoxy-D-mannose **9** as a colorless oil (28%).
Rf = 0.18 (4:1 hexane:ethyl acetate); $[\alpha]_D^{23} = +30.3^\circ$ ($c = 1.34$, CHCl₃); IR (neat) cm⁻¹ 2990, 2940, 2115, 1747, 1456, 1373, 1219; ¹H-NMR (CDCl₃) δ 6.32 (s, 1H), 4.33 (dd, 1H, $J = 12.2$ Hz, 2.27 Hz), 4.26 (dd, 1H, $J = 8.0$ Hz, 5.4 Hz), 4.17 (dd, 1H, $J = 12.3$ Hz, 4.8 Hz), 4.06 (d, 1H, $J = 5.43$), 3.70 (ddd, 1H, $J = 10.7$ Hz, 4.8 Hz, 2.7 Hz), 3.54 (dd, 1H, $J = 10.7$ Hz, 8.0 Hz), 2.09 (s, 3H), 2.08 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H); ¹³C-NMR: (CDCl₃) δ 170.4 (C), 168.2 (C), 110.7 (C), 91.04 (CH), 76.6 (CH), 74.2 (CH), 68.8 (CH), 63.1 (CH₂), 60.8 (CH), 28.1 (CH₃), 26.2 (CH₃), 20.8 (CH₃), 20.7 (CH₃); MS: (CI, 10 eV) m/z (rel. intensity) 314 (M⁺ - 15) (10), 270 (100), 212 (31), 184 (10), 142 (28); HRMS calcd. for C₁₃H₂₀N₃O₇: 330.1301 Found: 330.1333, error 9.6 ppm.; Calcd. for C₁₃H₁₉N₃O₇: C 47.41%, H 5.82% Found: C 47.62%, H 5.83%.
(17) Rf: 0.32 (9:1 ethyl acetate:acetone); $[\alpha]_D^{24} = 7.15^\circ$ ($c = 1.51$,

CHCl₃); **IR**: cm⁻¹ 3285, 3072, 2989, 2937, 1745, 1659, 1548, 1435; **¹H-NMR**: (CDCl₃) δ 6.34 (s, 1H), 5.68 (d, 1H, J = 8.4 Hz), 4.38 (dd, 1H, J = 8.4 Hz, 5.2 Hz), 4.18 (m, 3H), 4.12 (d, 1H, J = 5.6 Hz), 3.83 (q, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.56 (s, 3H), 1.36 (s, 3H); **¹³C-NMR**: (CDCl₃) δ 171 (C), 170.4 (C), 168.4 (C), 110.2 (C), 91.1 (CH), 74.5 (CH), 74.1 (CH), 69.5 (CH), 63.2 (CH₂), 50.0 (CH), 27.8 (CH₃), 26.2 (CH₃), 23.5 (CH₃), 20.9 (CH₃), 20.8 (CH₃); **MS**: (CI, 10 eV)

m/z (rel. intensity) 346 (M⁺ + 1) (8), 330 (15), 286 (100), 228 (20); **HRMS** calcd. for C₁₅H₂₄NO₈: 346.1502 **Found**: 346.1486, error 4.7 ppm; **Calcd. for C₁₅H₂₃NO₈**: C 52.17% H 6.71% N 4.06% **Found**: C 52.44% H 6.83% N 3.88%.

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