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Synthesis of furanoid sugar amino acids†

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Abstract

A novel cycloetherification process involving a facile 5-*exo* S_N2-type ring closure by intramolecular opening of a terminal aziridine ring by a γ-hydroxyl group, with concomitant debenzylation, during the deprotection of a dithioacetal moiety following a method developed by Mehta and Uma (*Tetrahedron Lett.*, 1996, **37**, 1897–1898) using nitrogen oxides, served as the key step in the stereoselective syntheses of furanoid sugar amino acids.

Keywords: Oligomers, sugar amino acids.

1. Introduction

Emulating the basic principles followed by nature to build its vast repertoire of biomolecules, organic chemists are developing many novel multifunctional building blocks to construct oligomers that mimic the ordered secondary structures displayed by the biopolymers and their functions.[1–4] Rationally chosen monomeric units from the large number of structurally diverse designed building blocks are woven together in specific sequences by iterative synthetic methods leading to the development of novel homo- and heteropolymers with architecturally beautiful 3D structures and desirable properties. Sugar amino acids constitute an important class of such polyfunctional scaffolds where the carboxyl, amino and hydroxyl termini provide an excellent opportunity to organic chemists to create structural diversities akin to nature's molecular arsenal.[5–19] The rigid furan or pyran rings of these molecules make them ideal candidates as nonpeptide scaffolds in peptidomimetic studies where they can be easily incorporated by using their carboxyl and amino termini utilizing well-developed solid-phase or solution-phase peptide synthesis methods.[20–27] At the same time, it allows an efficient exploitation of the structural diversities of carbohydrate molecules to create combinatorial library of sugar amino acid-based molecular frameworks predisposed to fold into architecturally beautiful ordered structures which may also have interesting properties. The protected/unprotected hydroxyl groups of sugar rings can also influence the hydrophobic/hydrophilic nature of such molecular assemblies.

Recently, we have reported the synthesis of furanoid sugar amino acids (**1**), used them as conformationally constrained scaffolds in peptidomimetic studies (**2**),[28,29] synthesized their oligomers (**3**) and studied their structures and properties.[30] In this paper, we communicate the

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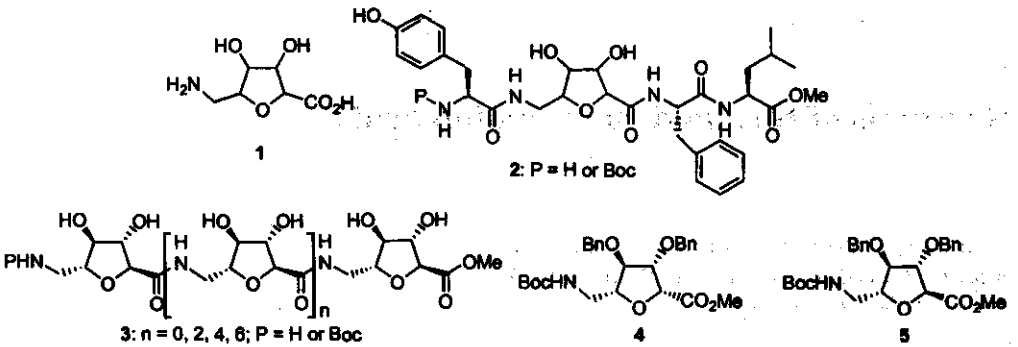


syntheses of two furanoid sugar amino acids[31,32] in protected forms, methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-gluconate (**4**) and methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-mannonate (**5**), following an alternate strategy, which can be used for large-scale preparations. The salient feature of the synthesis is a facile cycloetherification step in which a terminal aziridine ring was opened regio- and stereoselectively by a γ-hydroxy group, with concomitant debenzylation, during the deprotection of a dithioacetal moiety leading to the targeted tetrahydrofuran ring of **4**.

Scheme 1 delineates the actual synthesis of methyl gluconate (**4**). D-glucose (**6**) was transformed into its trimethylene dithioacetal derivative (**7**) in 70% yield on treatment with propane-1,3-dithiol under acid-catalyzed conditions.[33–36] Acetonide protection of **7** under standard conditions gave the 5,6-isopropylidene derivative (**8**) as the major product in 40% isolated yield. The remaining free hydroxyl groups in **8** were protected next as the benzyl ethers to obtain the fully protected intermediate (**9**) in 82% yield. Cleavage of the acetonide ring gave the diol **10** in 85% yield. The primary hydroxyl group of **10** was converted to an azide (**11**) in two steps in 80% overall yield. Next, the azido alcohol (**11**) was treated with Ph_3P in refluxing toluene leading to the formation of aziridinyl intermediate, which was protected *in situ* with Boc_2O to give Boc-protected terminal aziridinyl intermediate (**12**) in 91% yield. The aziridine formation followed an S_N2 mechanism executing inversion at the C5 position.

Most of the methods known for the deprotection of the dithioacetal moiety failed to carry out the desired deprotection in **12**. The only method that executed the deprotection successfully was the one developed recently by Mehta *et al.* using nitrogen oxides.[37] Treatment of **12** with nitrogen oxides in CH_2Cl_2, according to the reported procedure,[37] gave a reasonably clean reaction as observed by TLC. However, during the process, it also underwent a facile and spontaneous intramolecular ring closure by 5-*exo* S_N2-type opening of the aziridine ring by the γ-OH group with concomitant debenzylation giving the desired 2,5-anhydro-D-glucose framework. However, the product obtained did not show the characteristic N*H* signal in its ^1H NMR spectrum and was assumed to be the *N*-nitroso derivative (**13**). Ni-catalyzed sodium borohydride reduction of **13** removed the nitroso group and reduced the aldehyde function as well furnishing the glucitol intermediate (**14**) with the N*H*Boc moiety in 40% overall yield from **12**. Thus, the dethioacetalization step with nitrogen oxides carried out three transformations in one pot—deprotection, a facile cycloetherification and *N*-nitrosation. The cycloetherification reaction can be explained on the basis of the known susceptibility of linear molecules having S_N2

active sites to undergo spontaneous ring-closure, induced by a heteroatom at the γ-position, to produce thermodynamically favourable 5-membered cyclic products, a phenomenon observed earlier by us[28–30] and others.[38]

Finally, oxidation of the primary hydroxyl group in **14** to the carboxylic function using an excess of pyridinium dichromate (PDC) in DMF followed by esterification with CH_2N_2 gave the methyl gluconate (**4**) in 70% yield.

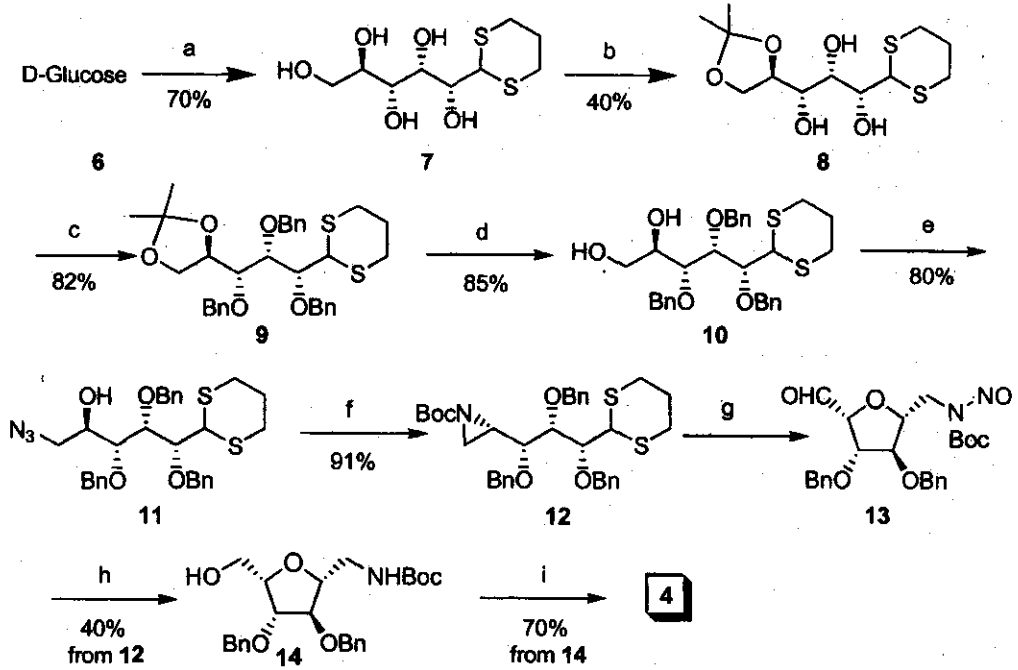
The same strategy was followed for the synthesis of mannonate congener (**5**). Starting with D-mannose and following the same chemistry described in Scheme 1, the methyl mannonate (**5**) was prepared. The physical data of compounds **4** and **5** were identical with those reported by us earlier.[29]

The route described here will allow large-scale preparations of sugar amino acids required for various structural and biological studies.

2. Experimental

2.1. *General procedures*

NMR spectra were recorded on Varian Gemini 200 or Unity 400 instruments with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on Shimadzu IR-470 and Perkin-



Reagents and conditions: (a) 1,3-Propanedithiol, conc. HCl, $CHCl_3$, r.t., 24 h; (b) $Me_2C(OMe)_2$, *p*-TsOH (cat.), DMF, r.t., 2 h; (c) BnBr, NaH, THF, TBAI, 0°C-r.t., 6 h; (d) Conc. HCl, MeOH, r.t., 12 h; (e) i. TsCl, Et_3N, DMAP (cat.) CH_2Cl_2, 0°C, r.t.; ii. NaN_3, DMF, 80°C; (f) i.Ph_3P, toluene, reflux; ii. Boc_2O; (g) Nitrogen oxides, CH_2Cl_2, 0°C; (h) $NaBH_4$, $NiCl_2.6H_2O$, THF; (i) i. PDC, DMF, r.t., 12 h; ii. CH_2N_2.

Scheme 1. Stereoselective synthesis of methyl *N*-Boc-6-amino-2,5-anhydro-3,4-di-*O*-benzyl-6-deoxy-D-gluconate (**4**).

Elmer 283B instruments. MS were recorded on VG Micromass 70–70H and VG Auti Spec M spectrometers under electron impact (EI), chemical ionization (CI) or liquid secondary ion mass spectrometric (LSIMS) techniques. All reactions were monitored by TLC and were carried out on 0.25 mm E. Merck silica gel plates (60F-254). The spots were visualized using either UV light or I_2 or 7% ethanolic phosphomolybdic acid or 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4) as developing agents. Silica gel (finer than 200 mesh) (Acme, India), was used for flash column chromatography. All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

2.2. *N-Boc-6-amino-2,5-anhydro-3,4-di-O-benzyl-6-deoxy-D-glucitol (14)*

To a stirred solution of the aziridine (**12**) (1.3 g, 2.09 mmol) in dry CH_2Cl_2 (10 ml), cooled in an ice bath, a solution of nitrogen oxides in CH_2Cl_2 was added dropwise until all the starting material disappeared (monitored by TLC). After completion of the reaction, the reaction mixture was quenched with ice-cold aq. $NaHCO_3$ solution (30 ml) and extracted with CH_2Cl_2 (50 ml). The organic layer was separated, dried (Na_2SO_4), and the residue, obtained after the removal of the solvent, was used for the next step without purification. A solution of the resulting crude nitrosamine (**13**) (750 mg, 1.59 mmol) in THF (10 ml) was gradually added to a stirred suspension of nickel(II) chloride hexahydrate (756 mg, 3.18 mmol) and sodium borohydride (361 mg, 9.54 mmol) in THF (20 ml). Stirring was continued for 4 h at room temperature. The reaction mixture was then poured into ice-cold water (30 ml) and the resultant mixture was extracted with ethyl acetate (2 × 40 ml). The combined organic extracts were washed with water (40 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (SiO_2, 25–30% EtOAc in petroleum ether eluant) gave pure Boc-protected amino alcohol (**14**) (370 mg, 40% from **12**) as a syrupy liquid. $R_f = 0.5$ (silica gel, 40% EtOAc in petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.4–7.2 (m, 10 H, Ar*H*), 5.08 (m, 1 H, N*H*Boc), 4.6 and 4.38; 4.6 and 4.5 (two ABq, 4 H, PhCH_2O-), 4.1–3.75 (m, 6 H, C1-C5-*H*), 3.5–3.3 (m, 2 H, C6-H_2), 2.3 (broad, 1 H, O*H*), 1.45 (s, 9 H, Boc).

2.3. *Methyl N-Boc-6-amino-2,5-anhydro-3,4-di-O-benzyl-6-deoxy-D-gluconate (4)*

To a solution of **14** (301 mg, 0.68 mmol) in dry DMF (5 ml), PDC (1.023 g, 2.72 mmol) was added at 0°C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 12 h. It was then diluted with EtOAc (30 ml), washed with saturated $CuSO_4$ (20 ml), brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was dissolved in ether (4 ml) and an ethereal solution of diazomethane was added dropwise at 0°C till the esterification was complete as shown by TLC. The reaction mixture was then concentrated *in vacuo* and chromatographed (SiO_2, 5–25% EtOAc in petroleum ether eluant) to get pure ester (**4**) (191 mg) and a bicyclic side product.[29] A solution of the bicyclic product (40 mg, 0.091 mmol) in dry MeOH (1 ml) was treated with anhydrous K_2CO_3 (25 mg, 0.182 mmol) at 0°C and the reaction mixture was stirred for 1 h at the same temperature. It was then diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5–25% EtOAc in petroleum ether eluant) afforded the ester (**4**) (32 mg), as a syrupy liquid, leading to an overall yield of 70% from **14**. Data for **4**: $R_f = 0.4$ (silica gel, 30% EtOAc in

petroleum ether); $[\alpha]_D^{20}$ 9.4 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1765, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.4–7.2 (m, 10H, aromatic), 5.3 (m, 1H, N*H*Boc), 4.68 (d, $J = 5$ Hz, 1H, C2-*H*), 4.48 (ABq, 4H, PhCH_2O-), 4.22 (dd, $J = 5$ and 2 Hz, 1H, C3-*H*), 4.13 (m, 1H, C5-*H*), 3.88 (dd, $J = 3$ and 2 Hz, 1H, C4-*H*), 3.72 (s, 3H, CO_2CH_3), 3.4 (m, 2H, C6-*H*), 1.42 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.6, 156.1, 137.3, 137.1, 128.5, 128.4, 128, 127.8, 127.7, 83.6, 83.2, 82.7, 80, 79.1, 72.4, 72.1, 52, 42.2, 28.4; Mass: (*m/z*) (%): 494 (25) [M^++Na], 472 (20) [M^++H], 372 (100) [M^++H–100]. HRMS (LSIMS): Calc. for $C_{26}H_{34}NO_7$ [M^++H]: 472.2335, Found: 472.2363.

2.4. *Methyl N-Boc-6-amino-2,5-anhydro-3,4-di-O-benzyl-6-deoxy-D-gluconate (5)*

Compound **5** was prepared from D-mannose in the same way as described above for the synthesis of **4**. Data for **5**: $R_f = 0.45$ (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}$ 14.3 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1770, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.4–7.2 (m, 10H, Ar*H*), 5.0 (m, 1H, N*H*), 4.6 and 4.47 (two ABq, 4H, PhCH_2O-), 4.65 (s, 1H, C2-*H*), 4.33 (s, 1H, C3-*H*), 4.3 (m, 1H, C5-*H*), 3.88 (d, $J = 1.8$ Hz, 1H, C4-*H*), 3.72 (s, 3H, CO_2CH_3), 3.48 and 3.38 (two m, 2H, C6-H_2), 1.42 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169, 156.1, 138.25, 128.37, 127.88, 127.68, 82.68, 78.65, 75.91, 75.41, 72.68, 71.68, 71.28, 66.93, 41.62, 28.4; Mass: (*m/z*) (%): 494 (16) [M^++Na], 472 (10) [M^++H], 372 (100) [M^++H–100].

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