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A New, Stereocontrolled Approach to Iminosugar *C*-Glycosides from L-Sorbose

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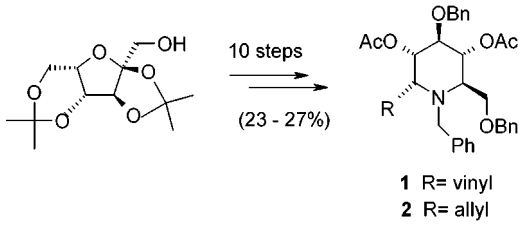
ABSTRACT



The efficient synthesis of the iminoalditols derivatives 1 and 2 (nojirimycin α-*C*-glycosides) has been achieved in 10 steps from commercially available 2,3;4,6-di-*O*-isopropylidene-α-L-sorbofuranose in an overall yield of 23–27%.

Owing to their remarkable biological activities, iminosugars form undoubtedly the most important and attractive class of carbohydrate mimics reported so far. As potent glycosidase[1] and glycosyltransferase[2] inhibitors, they promise a new generation of carbohydrate-based therapeutics for the control of various diseases including diabetes, cancer, and viral infection.[1] The main drawback associated with the use of such "azasugars" is their lack of selectivity as α- or β-glycosidase inhibitors, which may lead to detrimental side effects in therapeutic applications. Therefore, despite a large amount of synthetic effort in this area,[3] there is still a need for an efficient methodology to iminosugar *C*-glycosides of predictable configuration from simple precursors to facilitate the discovery of more selective inhibitors. To achieve this challenging goal and as part of our continuing studies on azaglycoside mimics,[4] we have designed a flexible synthetic strategy for the preparation of various types of piperidinoses *C*-substituted at C-1.

In this paper, we wish to report our preliminary results concerning the stereocontrolled synthesis of the α-1-*C*-

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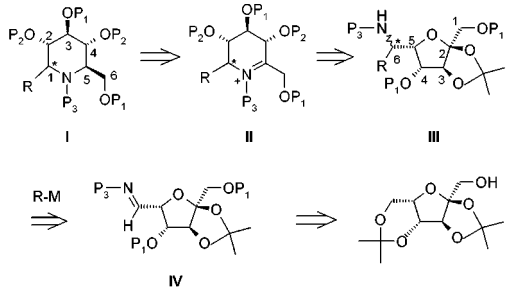
substituted-1-deoxynojirimycin **1** and **2** and analogues. As outlined in Scheme 1, our retrosynthetic analysis takes

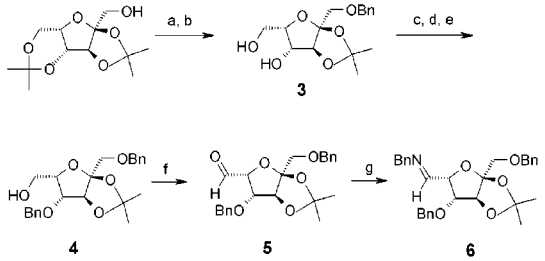
Scheme 1



advantage of the chirality of L-sorbose, which provides the three stereogenic centers (C-2, C-3, and C-4) of our target **I** and acts as an internal chiral auxiliary. It is noteworthy that L-sorbose has been used as the starting material for the first synthesis, as well as for some of the shortest syntheses, of 1-deoxynojirimycin[5] but not for the preparation of chain-extended analogues. The diastereoselective chain extension of imine **IV** is the key step of our synthetic strategy for the following two reasons: first, the careful choice of reaction conditions can give access selectively to the two possible epimers at C-6 in **III**, i.e., the precursors of the α- or *β*-epimers of imino-*C*-glycoside **I**. Second, at this stage, structural diversity may be introduced at the "anomeric" position by using the wide library of organometallic nucleophiles available. This point is particularly significant if one wants to explore the affinity of the aglycon binding site within a range of glycosidases to increase the selectivity of potential inhibitors.[6] The last steps of the synthetic plan consisted in generating the final imino-sugar *C*-glycosidic structure (**I**) by way of the intramolecular reductive amination of the latent keto function of the chain-extended amino-sorbofuranose derivative, a reaction that was expected to be highly stereoselective and to give the desired epimer in the D-series.[7] Finally, an orthogonal protecting group strategy was designed to facilitate the differentiation of the sugar hydroxyl groups, notably at C-3 (structure **I**), thus opening the way to oligosaccharide analogues or to other iminosugars by controlled epimerisation of one of the OH group (see Scheme 1).

This approach required an efficient and easy access to multigram quantities of imine **6**. This key intermediate was prepared from commercially available 2,3;4,6-di-*O*-isopropylidene-α-L-sorbofuranose in seven steps and 69% overall yield (Scheme 2). Quantitative benzylation of the primary alcohol, followed by selective deprotection of the six-membered isopropylidene acetal under aqueous acidic conditions, in the presence of acetone, gave the diol **3** in 97% yield.[8] Benzylation of the secondary hydroxyl group was performed by the following three-step procedure: selective protection of the primary alcohol function of **3** as a trityl ether, benzylation of the secondary OH, and cleavage of the trityl group using a solution of HBr in glacial acetic acid.[9]

Scheme 2[a]

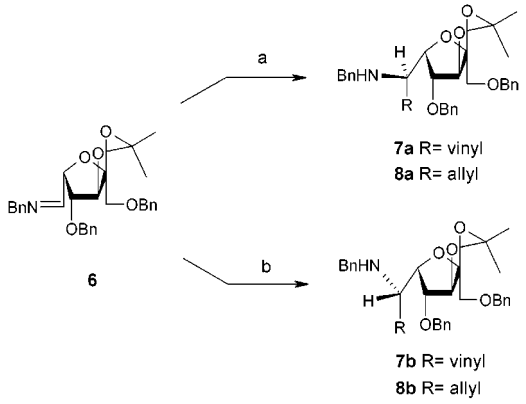


[a]Reagents and conditions: (a) NaH (2 eq.), BnBr (1.8 eq.), THF, quant. (b) acetone, H_2SO_4 / H_2O, 96%. (c) TrCl (1.4 eq.), pyridine, 40°C, 93%. (d) NaH (2 eq.), BnBr (1.8 eq.), THF, 95%. (e) HBr/AcOH, 10°C, 96%. (f) PCC (1.8 eq.), molecular sieves, CH_2Cl_2, 85%. (g) $BnNH_2$ (1.1 eq.), molecular sieves, 0°C, quant.

The aldehyde **5** was obtained from **4** in 85% yield by standard PCC oxidation.[10] Finally, condensation of **5** with 1.1 equiv of benzylamine in dichloromethane in the presence of molecular sieves (4 Å)[11] afforded quantitatively the imine **6**, as judged by proton NMR spectroscopy.

Having in hand the key intermediate **6**, we first studied the diastereoselectivity of the addition of vinylmagnesium bromide to the C=N bond (Scheme 3).[12] The resulting allylic

Scheme 3[a]



[a]Reagents and conditions: (a) RMgBr (4 or 5 equiv.), Et_2O, 0°C to r. t., de >98%, 74% (R=vinyl), 87% (R=allyl). (b) RMgBr (4 equiv.), $BF_3.Et_2O$ (5 equiv.), Et_2O, -78°C to -10°C, de > 98%, 65% (R=vinyl) de = 20%, 90% (R=allyl).

amine was of particular interest owing to the various synthetic possibilities offered by the transformation of the C=C double bond at different stages of the synthesis. A solution of the *N*-benzylimine **6** in Et_2O was added dropwise to a cooled solution of 5 equiv of the Grignard reagent in Et_2O at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. Proton NMR analysis

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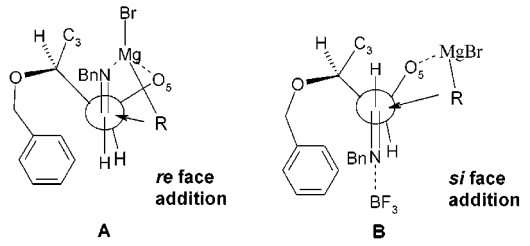
of the crude product after workup revealed the presence of a single diastereomer. The pure amine **7a** was obtained in 74% yield after purification by flash chromatography. The addition of allylmagnesium bromide (4 equiv) to **6** was also found to be highly diastereoselective and proceeded to give **8a** in a yield of 87%. The absolute configuration of the newly created stereocenter was unambiguously established to be *R* at the stage of the cyclic product **9**.

The high stereoselectivity of the addition of the organomagnesium species to imine **6** can be best rationalized by the chelated intermediate **A**[12] involving as ligands the ring oxygen atom of the sorbofuranose moiety and the nitrogen atom of the *N*-benzylimine (Scheme 4). The propensity of

Scheme 4

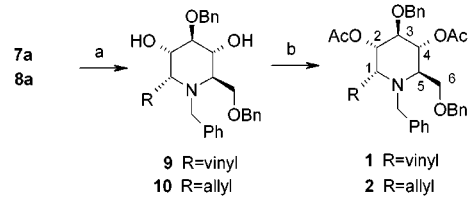


the ring oxygen in furanose derivatives to act as a coordinating Lewis base in additions of organometallic species to 5-*aldehydo*-pentofuranose derivatives is well documented.[13] To modifiy the stereoselectivity of the reaction, we performed the addition in the presence of a monodentate Lewis acid [BF_3·Et_2O (5 equiv)[14] at −78 °C] with the goal of precomplexing the imine and suppressing chelation effects. Addition of vinylmagnesium bromide (4 equiv) at −50 °C to **6** thus preactivated and warming up the reaction mixture to −10 °C afforded, after purification, the epimeric amine **7b** with the opposite configuration at C-6, as expected according to the open transition state model **B**[12] depicted in Scheme 4. The addition of allylmagnesium bromide to the imine **6** under the same conditions gave, however, the expected product with a very low degree of stereoselectivity.

The intramolecular reductive amination of the amino-sorbose hemiketal liberated upon acidic hydrolysis of the isopropylidene group was then investigated.

The best experimental conditions consisted in using 90% aqueous CF_3COOH at room temperature for 24 h[15] for the hydrolysis step, followed by evaporation of the reaction mixture and treatment of the crude intermediates with $NaBH_3CN$ (4 equiv) in glacial acetic acid for the reduction step. This sequence of reactions gave, after purification of the final product by flash chromatography, the expected diastereomerically pure piperidinols **9** and **10** in moderate yield (48−49%) from the 6(*R*) amino-sorbose derivatives **7a** and **8a**, respectively (Scheme 5).

Scheme 5[a]



[a]Reagents and conditions: (a) CF_3COOH / H_2O (9/1), 24h, then $NaBH_3CN$ (4 equiv.), CH_3COOH, 3h, 48-49%. (b) Ac_2O, pyridine, 40°C, 18h, 92-93%.

The relative configuration of the substituents in the piperidine ring system was unambiguously established by the ^1H NMR spectra (COSY and NOESY) of **9** and **10** and of their respective acetates **1** and **2**,[16] obtained in excellent yield by acetylation using Ac_2O in pyridine at 40 °C. As shown by the data,[16,17] both compounds have a pseudo-α-D-*gluco* configuration and adopt predominantly a chair conformation in which all substituents are in equatorial position except the allyl/vinyl group.

The intramolecular reductive amination of the alternate 6-benzylamino-6-deoxy-L-sorbose derivative **7b** gave a labile product, the configuration of which could not yet be

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(16) **Data for 9:** ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.02 (dt, 1H, $J_{5,6}$ = 4.4, $J_{5,4}$ = 8.8 Hz, H-5), 3.39 (dd, 1H, $J_{1,2}$ = 4.9, $J_{1,1'}$ = 9.8 Hz, H-1), 3.47 (t, 1H, $J_{3,2} = J_{3,4} \approx$ 8.5 Hz, H-3), 3.55 (d, 1H, J = 14.2 Hz, NCH_AH$_B$Ph), 3.75 (t, 1H, $J_{4,5} = J_{4,3} \approx$ 8.5 Hz, H-4), 3.75 (dd, 1H, $J_{2,3}$ = 9.2, $J_{2,1} \approx$ 5 Hz, H-2), 3.77 (dd, 1H, $J_{6a,6b} \approx$ 10, $J_{6a,5}$ = 3.9 Hz, H-6a), 3.82 (dd, 1H, $J_{6b,6a}$ = 10.3, $J_{6b,5}$ = 4.9 Hz, H-6b), 4.00 (d, 1H, J = 14.2 Hz, NCH$_A$$H_B$Ph), 4.46 (AB, 2H, J = 11.7 Hz, OCH_2Ph), 4.83 (AB, 2H, J = 11.7 Hz, OCH_2Ph), 5.19 (dd, 1H, J_{gem} = 1.9, J_{trans} = 17.1 Hz, CH=CH_AH$_B$), 5.45 (dd, 1H, J_{gem} = 1.9, J_{cis} = 10.5 Hz, CH=CH$_A$$H_B$), 5.99 (dt, 1H, $J_{1,1'}$ = 10, J_{trans} = 17.0, J_{cis} = 10.5 Hz, C$H_{1'}$=CH$_2$), 7.05−7.50 (m, 15H, 3 C$_6H_5$); ^{13}C NMR (62.9 MHz, $CDCl_3$, δ $CDCl_3$ = 77.16) δ (ppm) 52.98 (NCH$_2$Ph), 59.78, 63.40 (C-1, 5), 70.14 (C-6), 71.59, 72.67 (C-2, 4), 73.44 and 74.49 (2 OCH$_2$C$_6$H$_5$), 83.53 (C-4), 122.39 (CH=CH$_2$), 126.9−128.6 (C$_{ArH}$), 131.19 (CH=CH$_2$), 137.95, 138.85, 139.94 (3 C$_{Ar}$); MS *m*/*z* 460.0 [(M + H)$^+$]. **Data for 1:** ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.86 (s, 3H, OAc), 1.90 (s, 3H, OAc), 3.16 (dt, 1H, $J_{5,6}$ = 3.9, $J_{5,4}$ = 9.8 Hz, H-5), 3.51 (d, 2H, $J_{6,5}$ = 3.9 Hz, 2 H-6), 3.59 (dd, 1H, $J_{1,2}$ = 5.4, $J_{1,1'}$ = 8.8 Hz, H-1), 3.68 (d, 1H, J = 14.2 Hz) and 4.08 (d, 1H, J = 14.2 Hz) (AB, NCH_2Ph), 3.76 (t, 1H, $J_{3,4} = J_{3,2}$ = 9.5 Hz, H-3), 4.33 (d, 1H, J = 11.7 Hz) and 4.38 (d, 1H, J = 11.7 Hz) (AB, OCH_2Ph), 4.58 (d, 1H, J = 11.7 Hz) and 4.67 (d, 1H, J =11.7 Hz) (AB, OCH_2Ph), 5.05 (dd, 1H, $J_{2,3}$ = 9.8, $J_{2,1}$ = 5.4 Hz, H-2), 5.12 (br d, 1H, J_{trans} = 17.1 Hz, CH=CH_AH$_B$), 5.14 (t, 1H, $J_{4,3} = J_{4,5}$ = 9.8 Hz, H-4), 5.36 (br d, 1H, J_{cis} = 10.2 Hz, CH=CH$_A$$H_B$), 5.92 (ddd, 1H, $J_{1,1'}$ = 8.8, J_{trans} = 17.1, J_{cis} = 10.2 Hz, C$H_{1'}$=CH$_2$), 7.15−7.35 (m, 15H, 3 C$_6H_5$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 21.05, 21.07 (2 OAc), 52.66 (NCH$_2$Ph), 57.91, 59.85 (C-1, 5), 69.04 (C-6), 72.07, 72.84 (C-2, 4), 73.19, 74.22 (2 OCH$_2$Ph), 79.09 (C-3), 121.45 (CH=CH$_2$), 126.0−128.67 (C$_{ArH}$), 130.66 (CH=CH$_2$), 137.93, 138.54, 139.72 (3 C$_{Ar}$), 169.79, 170.07 (2 OAc); MS *m*/*z* 544.5 [(M + H)$^+$]; $[\alpha]^{20}_D$ +18.5 (*c* 1.2, $CHCl_3$). **Data for 2**: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.89 (s, 3H, OAc), 1.95 (s, 3H, OAc), 2.24 (m, 1H) and 2.37 (m, 1H) (CH$_2$CH=CH$_2$), 3.19 (m, 2H, H-5 and H-1), 3.58 (m, 2H, H-6), 3.80 (t, 1H, $J_{3,4} = J_{3,2}$ = 8.3 Hz, H-3), 3.96 (AB, 1H, J = 14.2 Hz, NCH_2Ph), 4.33 (near s, 2H, OCH_2Ph), 4.62 (d, 1H, J = 11.7 Hz) and 4.66 (d, 1H, J = 11.7 Hz) (OCH_2Ph), 4.96 (br d, 1H, J_{cis} = 10.3, J_{gem} = 1.5 Hz, CH=CH_AH$_B$), 4.99 (dd, 1H, J_{gem} = 1.5, J_{trans} = 17.1 Hz, CH=CH$_A$$H_B$), 5.15 (dd, 1H, $J_{2,1}$ = 5.4, $J_{2,3}$ = 8.8 Hz, H-2), 5.23 (t, 1H, $J_{4,5} \approx$ 8.5, $J_{4,3} \approx$ 8.5 Hz, H-4), 5.62 (m, 1H, J = 6.8, 6.8, 10.3, 17.1 Hz, C$H_{2'}$=CH$_2$), 7.10−7.45 (m, 15H, 3 C$_6H_5$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) 21.17 (2 OAc), 30.71 (CH$_2$CH=CH$_2$), 52.64 (NCH$_2$Ph), 55.85, 56.03 (C-1, 5), 69.59 (C-6), 71.44, 71.84 (C-2, 4), 73.18, 74.22 (2 OCH$_2$Ph), 78.65 (C-3), 116.11 (CH=CH$_2$), 126.00−128.5 (C$_{ArH}$), 136.10 (CH=CH$_2$), 138.05, 138.44, 140.12 (3 C$_{Ar}$), 169.97, 170.08 (2 OAc); MS: *m*/*z* 558.5 [(M + H)$^+$]; $[\alpha]^{20}_D$ +26 (*c* 1, $CHCl_3$).

(17) For example, in the case of the piperidinol **9**, crucial NOE effects were observed between H-1′ and H-5 and between H-1′ and H-3.

established. Further work on the epimers **7b** and **8b**, which should give access to β-configured imino-*C*-glycosyl compounds is currently in progress.

In conclusion, the diastereoselective addition of organometallic reagents onto the L-sorbose-derived imine **6**, followed by an internal reductive amination, provides a stereocontrolled approach to nojirimycin α-*C*-glycosides and related compounds; this is a very useful procedure since α-substituted piperidinose-*C*-glycosides are generally of more difficult access than the β-epimers. For example, double internal reductive amination procedures yielded exclusively 1,5-*cis*-disubstituted piperidinose derivatives.[7b] The 10-step reaction sequence proceeds in an overall yield of 23−27%. This strategy is currently being extended to other types of organometallic nucleophiles, and the piperidinose moiety is being modified with the goal of generating new types of glycosyltransferase inhibitors.

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