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The stereoselective synthesis of *C*-linked 4′-deoxy aza-disaccharides from *C*-linked carbo-β-amino acids☆

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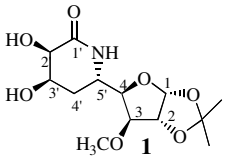
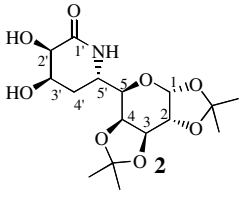
Abstract—The stereoselective synthesis of 4′-deoxy aza-disaccharides in a concise and practical approach is described from *C*-linked carbo-β-amino acid esters and this protocol utilizes an intramolecular amide bond formation and *cis*-dihydroxylation for the construction of the new sugar ring.

In recent years, the chemistry of aza-saccharides has attracted much attention, since they are powerful inhibitors of glycosidases or glycosyl transferases, thus having enormously interesting potential applications for the treatment of diabetes,[1] cancer,[2] and viral infections.[3] The 'iminosugars' (aza-sugars) are monosaccharide analogs having a nitrogen atom instead of the oxygen atom in the furan/pyran ring. Johnson et al.[4] first reported the synthesis of an aza-disaccharide by applying the Suzuki reaction. Recently Dhavale et al.[5] reported aza-sugars from monosaccharides, while Le Merrer et al.[6] reported aza-disaccharides from C_2-symmetrical bis-epoxides derived from D-mannitol. In continuation of our efforts[7] on the synthesis of new glyco-substances from monosaccharides, herein, we report a new and efficient approach for the stereoselective synthesis of C(4)–C(5′)/C(5)–C(5′)-linked 4′-deoxy aza-D-disaccharides **1** and **2** from from *C*-linked carbo-β-amino acid esters (Caa).

From the retrosynthetic analysis of **1** and **2** (Scheme 1), it was envisaged that cyclic amides **3** and **4** would be the late stage intermediates which could in turn be made from the corresponding *C*-linked carbo-β-amino acid esters **5** and **6**, respectively.



1



2

Accordingly, for the synthesis of furano-pyranose C(4)–C(5′)-linked 4′-deoxy aza-D-disaccharide **1**, the known ester **5**[8] was subjected to hydrogenolysis (Scheme 2) with 10% Pd–C in methanol under hydrogen to give free amine **7** (96%), which on reduction with $LiAlH_4$ in THF gave **8** (96%). Treatment of **8** with $(Boc)_2O$ and Et_3N in THF gave **9** (60%), which on oxidation with IBX in DMSO gave aldehyde **10** (93%). Wittig olefination of aldehyde **10** in methanol at 0 °C gave α,β-unsaturated ester **11** (*cis*/*trans*, 1.5:1) in 83% yield. From esters **11** on Boc deprotection with trifluoroacetic acid in CH_2Cl_2 followed by further treatment with DMAP in toluene, only the *cis* isomer was converted into the cyclic amide **3**, while the *trans* isomer remained as amino ester **11a**. The crude reaction mixture was treated with Boc_2O and purified to give **3** (51%) and **11b**. Finally, hydroxylation of amide **3** with OsO_4 and NMO in acetone:H_2O (4:1) furnished C(4)–C(5′)-linked 4′-deoxy aza-disaccharide **1** in 54% yield as the exclusive product, whose structure was unambiguously assigned from NMR spectroscopic studies.[9]

A twist conformation of the six-membered ring (Fig. 1) was confirmed by the $^3J_{H4'a-H5'} = 11.4$ Hz,

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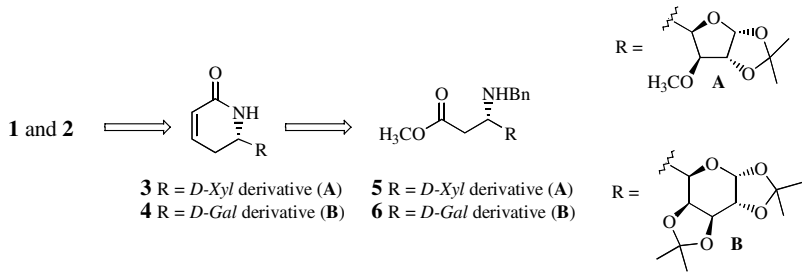
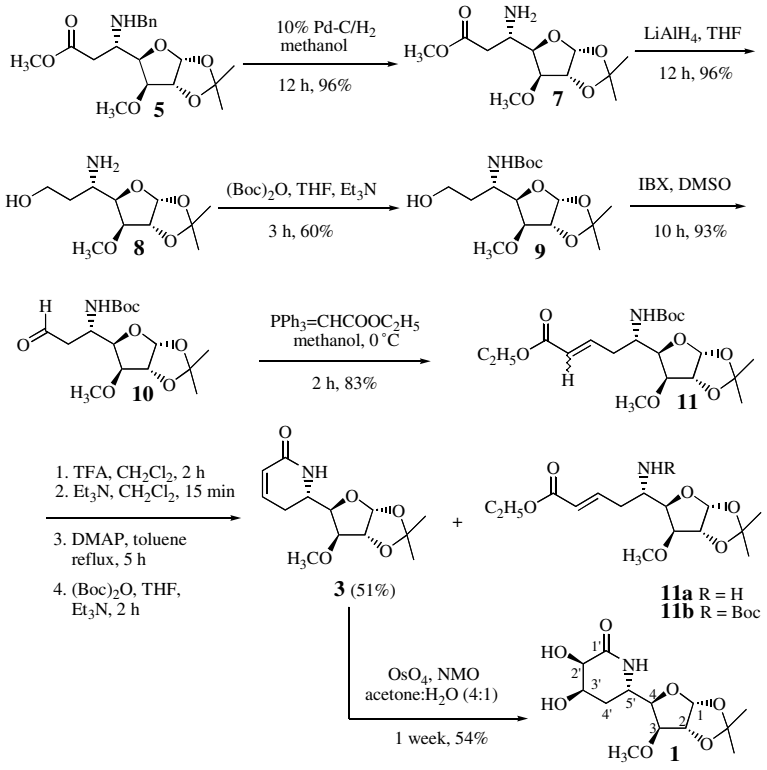


Scheme 1.



Scheme 2.

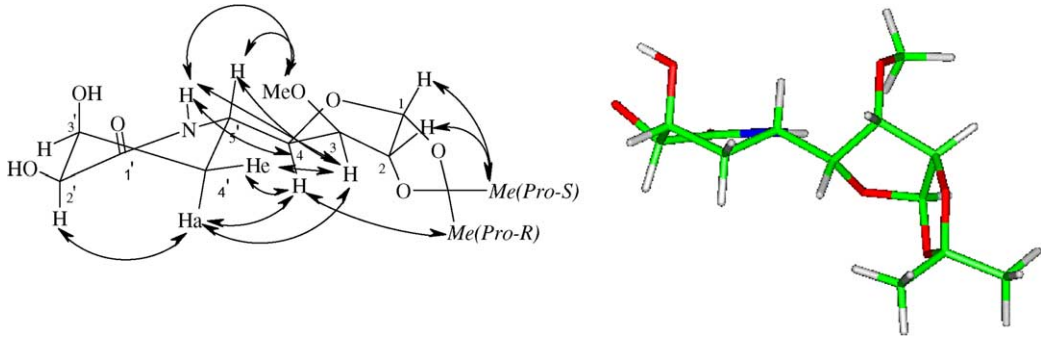
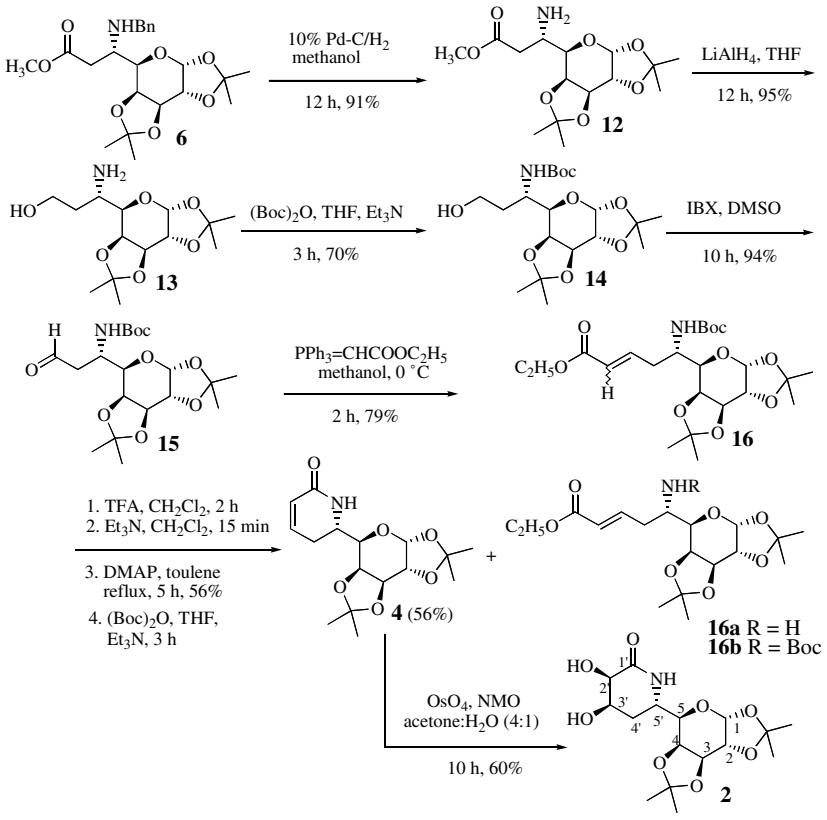


Figure 1. Characteristic NOEs and minimum energy structures for **1**. The numbering shown in the NOE diagram was used for the NMR data.

$^{3}J_{H4'e-H5'} = 1.9$ Hz, $^{3}J_{H3'-H4'e} = 4.7$ Hz, $^{3}J_{H3'-H4'a} = 1.9$ Hz, $^{3}J_{H2'a-H3'} = 3.1$ Hz coupling and long-range ω-coupling $^{4}J_{NH-H4'e} = 1.9$ Hz. This was further supported by the NOE between H2′–H4′a. The $^{3}J_{H1-H2} = 3.8$ Hz, $^{3}J_{H2-H3} = 0$ Hz, and $^{3}J_{H3-H4} = 3.6$ Hz couplings present in the sugar ring correspond to a sugar pucker of $^{3}T_{2}$, in agreement with earlier observations.[7] NOEs between H1–Me(*pro-S*), H2–Me(*pro-S*) and H4–Me(*pro-R*)



Scheme 3.

further support the proposed structure for the furanose ring. The $^{3}J_{H4-H5'} = 5.5\,Hz$ coupling and NOEs between NH–H3, NH–OCH_3, NH–H4, H3–H5′, H5′–OMe, H4–H4′a and H3–H4′e suggests averaging of NMR parameters due to the presence of several orientations about C(4)–C(5′). Further, the structure was confirmed by energy minimization calculations (Fig. 1) obtained from the MOPAC programme (Insight II (97.0)/Discover programme).[10]

In continuation of our study on the synthesis of furanopyranose C(4)–C(5′)-linked 4′-deoxy aza-disaccharide **1**, the synthesis of pyranose–pyranose C(5)–C(5′)-linked aza-disaccharide **2** was initiated from *C*-linked carbo-β-amino acid **6**.[8] Accordingly, ester **6** (Scheme 3) on hydrogenolysis (Pd–C) and subsequent reduction ($LiAlH_4$, THF) of **12** followed by protection of the amine **13** with $(Boc)_2O$ furnished **14** (70%). Oxidation of **14** with IBX and subsequent Wittig olefination of **15** gave **16** (79%) as a mixture of *cis*/*trans* (1.5:1) isomers. Deprotection of **16** with trifluoroacetic acid followed by cyclization with DMAP in toluene and subsequent Boc protection of the crude mixture furnished cyclic amide **4** (56%), while uncyclised **16a** was converted only into **16b**. Amide **4** on *cis*-dihydroxylation (OsO_4, NMO in acetone:H_2O 4:1) gave C(5)–C(5′)-linked 4′-deoxy aza-disaccharide **2** (60%), whose structure was extensively characterized by NMR and other spectral studies.[9]

The dihydroxy containing six-membered ring of **2** adopts a twisted structure similar to that shown by **1**

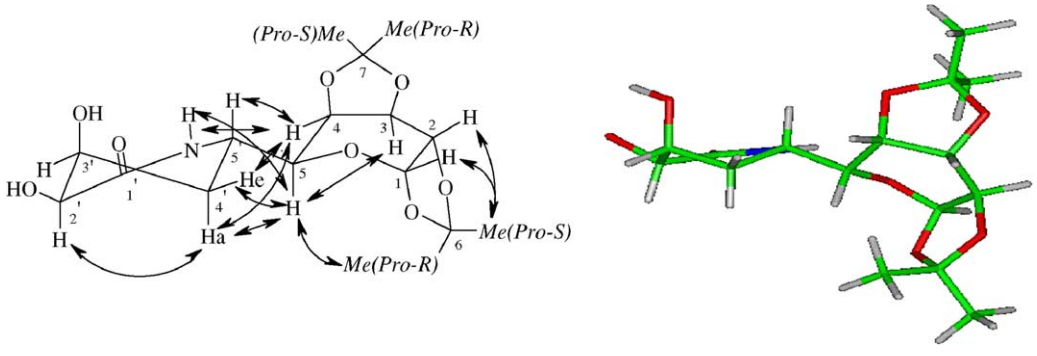


Figure 2. Characteristic NOEs and the minimum energy structures for **2**. The numbering shown in the NOE diagram was used for the NMR data.

(Fig. 1). The couplings $^{3}J_{H4'a-H5'} = 11.2\,Hz$, $^{3}J_{H4'e-H5'} = 1.7\,Hz$, $^{3}J_{H3'-H4'e} = 4.7\,Hz$, $^{3}J_{H3'-H4'a} = 1.7\,Hz$, and $^{3}J_{H2'-H3'} = 3.0\,Hz$ and long range ω-coupling $^{4}J_{NH-H4'e} = 1.7\,Hz$, as well as NOE the H2′–H4′a NOE confirm this fact. The galactose ring exists in a slightly distorted boat form supported by the $^{3}J_{H1-H2} = 5.0\,Hz$, $^{3}J_{H2-H3} = 2.5\,Hz$, $^{3}J_{H3-H4} = 7.8\,Hz$ and $^{3}J_{H4-H5} = 1.7\,Hz$ couplings in addition to the H3–H5 NOE. The structure was further supported by H5–Me(*pro-R*) NOE. The $^{3}J_{H5-H5'} = 5.8\,Hz$ coupling and NOEs between NH–H4, NH–H5, H4–H5′, H4′a–H5, H4′e–H5, H4–H4′a, and H4–H4′e suggest averaging of NMR parameters due to the presence of several orientations about the C(5)–C(5′) junction. The structure was further confirmed from the energy minimization calculations (Fig. 2) obtained from the MOPAC programme (Insight II (97.0)/Discover programme).[10]

In conclusion, a concise and efficient approach for the stereoselective synthesis of furano-pyranose C(4)-C(5′)-linked 4′-deoxy aza-disaccharide **1** and pyrano-pyranose C(5)–C(5′)-linked 4′-deoxy aza-disaccharide **2** from the corresponding *C*-linked carbo-β-amino acid monomers has been demonstrated. Making use of the *cis*-double bond in cyclic amides, a 4-deoxy-D-*gulo* aza-saccharide moiety has been very effectively installed at the C-4 and C-5 positions of Caas **5** and **6**, respectively.

Acknowledgements

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9. Selected spectroscopic and physical data: **1**: white solid; mp 161–163 °C; $[\alpha]_D^{25}$ −14.3 (*c* 0.5, $CHCl_3$); IR (KBr): 3464, 3346, 2924, 1671, 1382, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 6.39 (brs, 1H, NH), 5.91 (d, 1H, $J_{H1-H2} = 3.8\,Hz$, H-1), 4.59 (d, 1H, $J_{H1-H2} = 3.8\,Hz$, H-2), 4.33 (ddd, 1H, $J_{H3'-H4'a} = 1.9\,Hz$, $J_{H2'-H3'} = 3.1\,Hz$, $J_{H3'-H4'e} = 4.7\,Hz$, H-3′), 4.09 (m, 1H, H-5), 4.00 (d, 1H, $J_{H2'-H3'} = 3.1\,Hz$, H-2′), 3.98 (dd, 1H, $J_{H3-H4} = 3.6\,Hz$, $J_{H4-H5'} = 5.5\,Hz$, H-4), 3.85 (s, 1H, –OH-7), 3.75 (d, 1H, $J_{H3-H4} = 3.6\,Hz$, H-3), 3.43 (s, 3H, –OMe), 2.79 (s, 1H, –OH-2′), 2.19 (tdd, 1H, $J_{H4'e-H5'} = 1.9\,Hz$, $J_{H3'-H4'e} = 4.7\,Hz$, $J_{H4'a-H4'e} = 14.1\,Hz$, H-4′e), 1.87 (ddd, 1H, $J_{H3'-H4'a} = 1.9\,Hz$, $J_{H4'a-H5'} = 11.4\,Hz$, $J_{H4'a-H4'e} = 14.1\,Hz$, H-4′a), 1.49 (s, 3H, $Me_{(pro-R)}$), 1.33 (s, 3H, $Me_{(pro-S)}$); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.33, 111.90, 104.85, 84.87, 81.67, 81.30, 69.59, 65.78, 57.69, 48.91, 29.52, 26.79, 26.18; FABMS: 304 $(M + H)^+$; **2**: white solid; mp 256–258 °C; $[\alpha]_D^{25}$ −49.2 (*c* 1.0, $CHCl_3$); IR (KBr): 3492, 3315, 2984, 1668, 1384, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): 6.51 (brs, 1H, NH), 5.54 (d, 1H, $J_{H1-H2} = 5.0\,Hz$, H-1), 4.61 (dd, 1H, $J_{H2-H3} = 2.5$, $J_{H3-H4} = 7.8\,Hz$, H-3), 4.34 (m, 1H, H-3′), 4.33 (dd, 1H, $J_{H2-H3} = 2.5\,Hz$, $J_{H1-H2} = 5.0\,Hz$, H-2), 4.26 (dd, 1H, $J_{H4-H5} = 1.7\,Hz$, $J_{H3-H4} = 7.8\,Hz$, H-4), 4.04 (m, 1H, H-5′), 4.00 (d,1H, $J_{H2'-H3'} = 3.0\,Hz$, H-2′), 3.85 (s, 1H, –OH-2′), 3.53 (dd, 1H, $J_{H4-H5} = 1.7\,Hz$, $J_{H5-H5'} = 5.8\,Hz$, H-5), 2.81 (s, 1H, –OH-3′), 2.28 (tdd, 1H, $J_{H4'e-H5'} = 1.9\,Hz$, $J_{H3'-H4'e} = 4.7\,Hz$, $J_{H4'a-H4'e} = 13.9\,Hz$, H-4′e), 1.83 (ddd, 1H, $J_{H3'-H4'a} = 1.9\,Hz$, $J_{H4'a-H5'} = 11.2\,Hz$, $J_{H4'a-H4'e} = 13.9\,Hz$, H-4′a), 1.49 (s, 3H, $Me_{(pro-R)}$), 1.47 (s, 3H, $Me_{(pro-S)}$), 1.33 (s, 3H, $Me_{(pro-S)}$), 1.33 (s, 3H, $Me_{(pro-R)}$); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.31, 109.91, 108.82, 96.35, 71.62, 70.80, 70.56, 69.63, 65.78, 50.07, 29.66, 29.09, 26.09, 25.86, 24.86, 24.24; FABMS: 360, $(M + H)^+$.
10. Discover Version 2.98, Biosyn Molecular Simulations, San Diego, CA, 1995.