ChemComm

Synthesis of aza-*C*-disaccharides using cycloaddition reactions of a functionalized cyclic nitrone

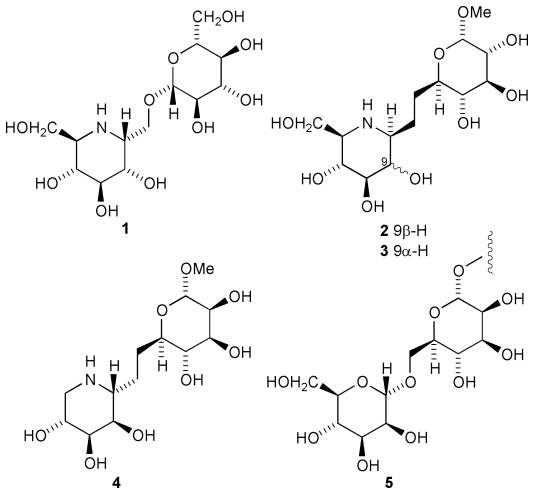
Fraser J. Duff, Vincent Vivien and Richard H. Wightman*

Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, UK EH14 4AS. E-mail: cherhw@hw.ac.uk

Received (in Liverpool, UK) 18th July 2000, Accepted 14th September 2000
First published as an Advance Article on the web

Cycloaddition reactions of a functionalized nitrone with sugar alkenes gives stereoselective access to aza-*C*-disaccharide analogues of α-D-Lyx(1→6)-α-D-Man and α-D-Lyx(1→6)-D-Gal.

Iminosugars have attracted much attention in recent years[1] due to their ability to act as inhibitors of glycosidases, and hence to have potential application in the treatment of a number of disparate disease states such as viral infections,[2] diabetes[3] and tumour metastasis.[4] It has been theorised that glycosidase inhibitors which permit interaction with the aglycon binding site should be more potent than those which lack this ability,[5] and the validity of this concept has been demonstrated.[6] The attachment of a second aglycone-mimicking sugar unit to an iminosugar has been done in a number of ways, as for example in the α,β-trehalose analogue **1**[6a] or by attachment *via*



nitrogen,[6c,7] but the aza-analogues of disaccharides which can be regarded as being closest in structure to the natural sequences are those with an all-carbon link, namely the aza-*C*-disaccharides prepared in the laboratories of Johnson[8] and of Vogel and van Boom,[9] such as **2**[8a,9] and **3**.[8c,9]

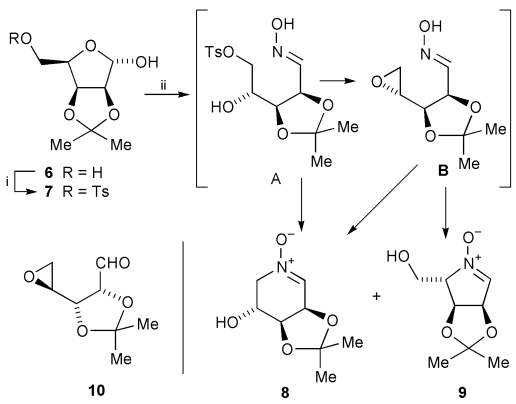
In this communication we describe our preliminary results on the synthesis of aza-*C*-disaccharides by a different synthetic approach to those previously employed,[8,9] and in which stereoselective cycloaddition reactions between functionalized cyclic nitrones and sugar alkenes are employed to establish the disaccharide analogue; our approach is illustrated by the synthesis of **4**, related to the sequence α-D-Man(1→6)-α-D-Man **5**, which is hydrolysed by Golgi α-mannosidase II during the processing of *N*-linked glycans of glycoproteins,[10] and of a related aza-*C*-disaccharide **20**.[11]

Treatment of 2,3-*O*-isopropylidene-D-lyxose **6**[12] with TsCl-pyridine (Scheme 1) gave in high yield the solid but somewhat unstable tosylate **7**, which was directly treated with excess hydroxylamine to give predominantly (44–47%) the nitrone **8**,† together with smaller amounts (3–8%) of the nitrone **9** with a five-membered ring. We consider that **9** is formed *via* intermediates **A** and **B** (Scheme 1), whilst **8** is derived predominantly by direct cyclisation of **A**,[13] but also to a lesser extent by 6-*endo*- ring closure of **B**.‡ In support of this, we have shown that epoxide **10**, on treatment with hydroxylamine, gives (54%) a mixture of the enantiomers of **8** and **9** in a 1 : 1 ratio.

Methyl α-D-mannopyranoside was converted routinely (66% overall) into **11** (see Scheme 2), which was oxidised and converted to alkene **12**. Reaction of **12** and nitrone **8** in toluene at reflux led to the isolation of a crystalline cycloadduct **13** in 84% yield. The stereostructure of **13**, which corresponds to reaction on the face of **8** *anti*- to the isopropylidenedioxy group, and *via* an *exo*-transition state,§ was indicated by NOESY data, which were obtained at high temperature (120 °C) since at lower temperatures signal-broadening was found, presumably due to slow inversion at nitrogen. Strong interactions were observed between 6-H and 7β-H, and between 7α-H and both 5-H and 8-H. The structure of **13** was subsequently confirmed by X-ray crystallography.¶ The stereoselectivity of this cycloaddition is enhanced (double stereodifferentiation) by the known facial preference of chiral allylic ethers in cycloadditions, such that an *erythro*-relationship between the stereocentres at C-5′ and C-8 will be preferred.[14]

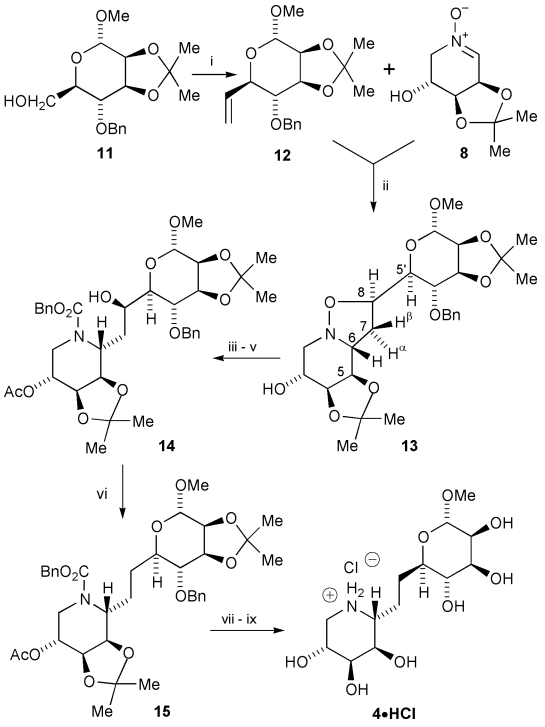
The cycloadduct **13** was acetylated, whereupon reductive cleavage of the N–O bond was carried out using $Mo(CO)_6$ in aqueous acetonitrile,[15] to give after protection of the amine the benzyloxycarbonyl derivative **14**. Deoxygenation to give **15** was carried out through the intermediacy of the imidazolyl-thiocarbonyl derivative, but we observed that it was necessary to carry out the reaction of **14** with thiocarbonyldiimidazole at high concentrations and with excess of reagent in order to obtain a high yield, an observation recently reported by others during the synthesis of *C*-disaccharides.[16] Routine deprotection of **15** then led to the aza-*C*-disaccharide **4**, isolated as its hydrochloride (44% overall from **13**).†

As a further example of this approach to aza-*C*-disaccharides, reaction of nitrone **8** with the D-galactopyranosyl alkene **16**[17] gave in 88% yield the *anti*-, *exo*-cycloadduct **17**† (Scheme 3), together with 1% of the *syn*-, *exo*-isomer. The stereochemistry of **17** again followed from NOESY spectra run at elevated temperatures, with strong interactions being observed between

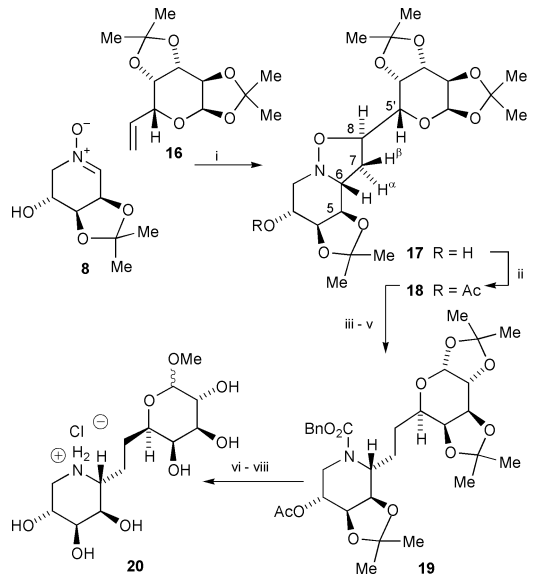


Scheme 1 *Reagents and conditions*: i, TsCl, pyridine–$CHCl_3$, 5 h (76%); ii, $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH–H_2O, rt, 20h (44–47% **8**, 3–8% **9**).

DOI: 10.1039/b005984f



Scheme 2 *Reagents and conditions*: i, PCC, DCM, then $Ph_3PMe{\cdot}Br$, KHMDS, −78 °C to rt; ii, toluene, reflux (84%); iii, Ac_2O, DMAP, pyridine; iv, $Mo(CO)_6$, MeCN–H_2O, reflux; v, BnOCOCl, Na_2CO_3, acetone (67% from **13**); vi, excess $(Im)_2C{=}S$, $(CH_2Cl)_2$, reflux, 2 h, then Bu_3SnH, AIBN, toluene, reflux (81% from **14**); vii, NaOMe, MeOH; viii, H_2, Degussa Pd/C, MeOH; ix, HCl, MeOH (80% from **15**).



Scheme 3 *Reagents and conditions*: i, toluene, reflux (88%); ii, Ac_2O, DMAP, pyridine (82%); iii, $Mo(CO)_6$, MeCN–H_2O, reflux; iv, BnOCOCl, Na_2CO_3, acetone; v, excess $(Im)_2C{=}S$, $(CH_2Cl)_2$, reflux, then Bu_3SnH, AIBN, toluene, reflux; vi, NaOMe, MeOH, rt, 1.5 h; vii, H_2, Pd/C, MeOH; viii, HCl, MeOH, rt, 24h (48% overall from **18**).

6-H and 7β-H, between 7α-H and both 5-H and 8-H, and between 5′-H and both 6-H and 7β-H; these last interactions, and the observed value of 7.4 Hz for $J_{5',8}$ imply a preferred rotamer about the C-8–C-5′ bond as indicated in **17** (for **13**, $J_{5',8}$ = 2.4 Hz). This, and the configuration of **17**, was confirmed by X-ray crystallography of the crystalline *O*-acetyl derivative **18**. Reduction of **18**, followed by *N*-protection and deoxygenation under conditions of high concentration, gave **19**, deprotected as indicated in Scheme 3 to give the aza-*C*-disaccharide **20**, as an anomeric mixture (α:β, 5:2), in 48% overall yield from **18**.

We thank EPSRC for financial support (GR/K97301) and for access to facilities at the National Mass Spectrometry Service Centre, and Dr Georgina Rosair for X-ray crystallography.

Notes and references

† Selected data (*J* values in Hz): **8**: mp 162–164 °C; $[\alpha]_D$ +235.2 (*c* 1.05, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (6H, s, C*Me*$_2$), 3.90 (1H, dd, J_{gem} 15.2, *J* 0.9, 6_a-H), 4.07 (1H, dd, J_{gem} 15.2, *J* 1.1, 6_b-H), 4.34 (1H, m, 4-H), 4.39 (1H, m, 5-H), 4.87 (1H, dd, *J* 5.1, 3.8, 3-H), 7.12 (1H, t, *J* 2.9, 2-H); **4·HCl**: $[\alpha]_D$ +52.2 (*c* 0.67, MeOH); δ_H (400 MHz, CD_3OD) 1.74–1.82 (1H, m, 6_a-H), 1.89–2.13 (3H, m, 6_b-H and 7-H_2), 3.06 (1H, dd, J_{gem} 12.8, $J_{12a,11}$ 2.4, 12_a-H), 3.26 (1H, br ddd, *J* ~ 10, ~ 8, 2.9, 8-H), 3.31 (1H, dd, J_{gem} 12.8, $J_{12b,11}$ 1.8, 12_b-H), 3.36 (3H, s, OMe), 3.44–3.54 (2H, m, 4-H, 5-H), 3.64 (1H, dd, $J_{3,4}$ 9.1, $J_{3,2}$ 3.2, 3-H), 3.80 (1H, dd, $J_{2,3}$ 3.2, *J* 1.8, 2-H), 3.86–3.93 (2H, m, 9-H, 10-H), 4.00 (1H, m, 11-H), 4.62 (1H, d, $J_{1,2}$ 1.8, 1-H). **17**: $[\alpha]_D$ −53.5 (*c* 0.99, $CHCl_3$); δ_H [400 MHz, $(CDCl_2)_2$, 120 °C] 2.10 (1H, dt, J_{gem} 12.6, $J_{7\alpha,6}$ ~ $J_{7\alpha,8}$ ~ 9.0, 7α-H), 2.20 (1H, br s, OH), 2.45 (1H, ddd, J_{gem} 12.6, $J_{7\beta,6}$ 7.0, $J_{7\beta,8}$ 3.8, 7β-H), 2.93–3.00 (1H, m, H-6), 2.96 (1H, dd, J_{gem} 11.0, $J_{2\beta,3}$ 3.5, 2β-H), 3.03 (1H, dd, J_{gem} 11.0, $J_{2\alpha,3}$ 6.0, 2α-H), 3.57 (1H, dd, $J_{5',8}$ 7.4, $J_{5',4'}$ 1.75, 5′-H), 3.92 (1H, br q, *J* ~ 4.4, 3-H), 4.00 (1H, t, *J* ~ 5.0, 4-H), 4.15 (1H, t, *J* ~ 5.7, 5-H), 4.17 (1H, dd, $J_{2',1'}$ 4.95, $J_{2',3'}$ 2.3, 2′-H), 4.20 (1H, dd, $J_{4',3'}$ 7.9, $J_{4',5'}$ 1.8, 4′-H), 4.22 (1H, ddd, $J_{8,7\alpha}$ 8.65, $J_{8,5'}$ 7.5, $J_{8,7\beta}$ 3.8, 8-H), 4.48 (1H, dd, $J_{3',4'}$ 7.9, $J_{3',2'}$ 2.3, 3′-H), 5.38 (1H, d, $J_{1',2'}$ 4.95, 1′-H).

‡ It is possible that the cyclisations of **A** and/or **B** occur through the intermediacy of geminal bis(hydroxylamine)s (see ref. 13). In a similar cyclisation to form a stereoisomer of **8**, we have also isolated and fully characterised an *N*-hydroxy-2-hydroxylaminopiperidine as a byproduct (V. Vivien, unpublished results).

§ *endo*-Transition states are disfavoured for cyclic nitrones on steric grounds; see, *e.g.* J. J. Tufariello in *1,3-Dipolar Cycloaddition Reactions*, Vol 2, ed. A. Padwa, Academic Press, New York, 1983, p. 83.

¶ CCDC 182/1789. See http://www.rsc.org/suppdata/cc/b0/b005984f/ for crystallographic files in .cif format.

1 *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, ed. A. E. Stütz, Wiley–VCH, Weinheim, 1999.
2 *e.g.* A. Karpas, G. W. J. Fleet, R. A. Dwek, S. Petursson, S. K. Namgoong, N. G. Ramsden, G. S. Jacob and T. W. Rademacher, *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 9229.
3 G. D. Dimitriadis, P. Tessari, V. L. W. Go and J. E. Gerich, *Metabolism*, 1985, **34**, 261.
4 M. J. Humphries, K. Matsumoto, S. L. White and K. Olden, *Cancer Res.*, 1986, **46**, 5215; P. E. Goss, M. A. Baker, J. P. Carver and J. W. Dennis, *Clin. Cancer Res.*, 1995, **1**, 935.
5 *e.g.* G. Legler, in *Carbohydrate Mimics*, ed. Y. Chapleur, Wiley–VCH, Weinheim, 1998, p. 463.
6 *e.g.* (*a*) P. B. Anzeveno, L. J. Creemer, J. K. Daniel, C.-H. R. King and P. S. Liu, *J. Org. Chem.*, 1989, **54**, 2539; (*b*) M. Horsch, L. Hoesch, A. Vasella and D. M. Rast, *Eur. J. Biochem.*, 1991, **197**, 815; (*c*) W. Dong, T. Jespersen, M. Bols, T. Skrydstrup and M. R. Sierks, *Biochemistry*, 1996, **35**, 2788.
7 L. Sun, P. Li, N. Amankulor, W. Tang, D. W. Landry and K. Zhao, *J. Org. Chem.*, 1998, **63**, 6472.
8 (*a*) B. A. Johns, Y. T. Pan, A. D. Elbein and C. R. Johnson, *J. Am. Chem. Soc.*, 1997, **119**, 4856; (*b*) C. R. Johnson and B. A. Johns, *Tetrahedron Lett.*, 1997, **38**, 7977; (*c*) J. L. Asensio, F. J. Cañada, A. García-Herrero, M. T. Murillo, A. Fernández-Mayoralas, B. A. Johns, J. Kozak, Z. Zhu, C. R. Johnson and J. Jiménez-Barbero, *J. Am. Chem. Soc.*, 1999, **121**, 11 318.
9 M. A. Leewenburgh, S. Picasso, H. S. Overkleeft, G. A. van der Marel, P. Vogel and J. H. van Boom, *Eur. J. Org. Chem.*, 1999, 1185.
10 For a review, see: K. W. Moremen, R. B. Trimble and A. Herscovics, *Glycobiology*, 1994, **4**, 113.
11 For the synthesis by a different approach of another aza-*C*-disaccharide involving the same iminoalditol see: C. Marquis, S. Picasso and P. Vogel, *Synthesis*, 1999, 1441.
12 M. Morita, E. Sawa, K. Yamaji, T. Sakai, T. Natori, Y. Kuezuka, H. Fukushima and K. Akimoto, *Biosci. Biotech. Biochem.*, 1996, **60**, 288.
13 For a similar cyclisation to give a nitrone related to L-fucose, see A. Peer and A. Vasella, *Helv. Chim. Acta*, 1999, **82**, 1044.
14 M. Ito, M. Maeda and C. Kibayashi, *Tetrahedron Lett.*, 1992, **33**, 3765, and references therein.
15 S. Cicchi, A. Goti, A. Brandi, A. Guarna and F. De Sarlo, *Tetrahedron Lett.*, 1990, **31**, 3351.
16 O. Jarreton, T. Skrydstrup, J.-F. Espinosa, J. Jiménez-Barbero and J.-M. Beau, *Chem. Eur. J.*, 1999, **5**, 430.
17 A. J. Blake, R. O. Gould, R. M. Paton and A. A. Young, *J. Chem. Res.*, 1993, (*S*) 482, (*M*) 3173, and refs. therein.