A general, two-directional approach to aza-*C*-(1 → 1)-linked disaccharide mimetics

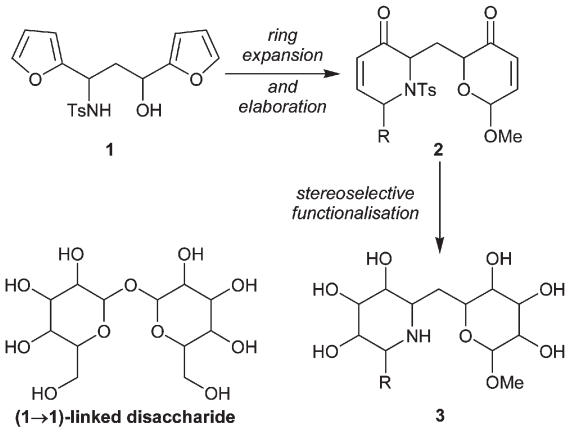
Andrew Kennedy,[a] Adam Nelson*[b] and Alexis Perry[b]

Received (in Cambridge, UK) 29th November 2004, Accepted 20th January 2005
First published as an Advance Article on the web 2nd February 2005
DOI: 10.1039/b417899h

The Upjohn and Donohoe dihydroxylations were exploited in divergent syntheses of aza-*C*-(1 → 1)-linked disaccharides.

Aza-*C*-linked disaccharides are stable sugar mimetics in which the oxygen in one of the sugar rings is replaced by a nitrogen atom, and the inter-ring oxygen by a methylene group. These compounds, whose nitrogen atom may be protonated at physiological pH, can be potent glycosidase inhibitors: the transition state for glycoside hydrolysis, including the departing sugar, is effectively mimicked.[1] Previously, oxocarbenium ion cyclisations[1c] and the samarium Barbier,[1d] aldol,[1e] Michael,[1f] and Suzuki[1g] reactions have been used to prepare aza-*C*-linked disaccharides from the corresponding monosaccharides.

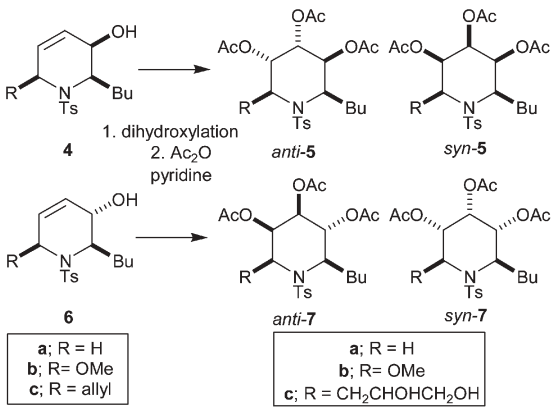
We envisaged a two-directional approach for the synthesis of aza-*C*-linked analogues, **3**, of (1 → 1)-linked disaccharides (Scheme 1). Oxidative ring expansion of the di(2-furyl) amino alcohol derivatives **1** was expected to give, after further elaboration, diketones of general structure **2**. Stereoselective functionalisation was expected to give a range of aza-*C*-linked disaccharide mimetics **3**.



Scheme 1

*adamn@chem.leeds.ac.uk

Table 1 Stereoselectivity of the dihydroxylation of the allylic alcohols **4** and **6** under Upjohn and Donohoe's conditions



Entry	Starting material	R	Conditions[a]	*anti*:*syn*[b]	Product	Yield (%)
1a	**4a**	H	A	>95:<5	*anti*-**5a**	65
1b			B	<5:>95	*syn*-**5a**	74
2a	**4b**	OMe	A	>95:<5	*anti*-**5b**	77
2b			B	>95:<5	*anti*-**5b**	4[c]
3	**4c**	allyl	A	>95:<5	*anti*-**5c**	36[d,e]
4a	**6c**	allyl	A	—	—	—[c]
4b			B	25:75	*syn*-**7c**	26[d,f]

[a] A: (i) cat. OsO_4, NMO, acetone–H_2O; (ii) Ac_2O, pyridine; B: (i) OsO_4, TMEDA, CH_2Cl_2, −78 °C; (ii) Ac_2O, pyridine. [b] Determined by analysis of the 500 MHz ^1H NMR spectrum of the crude product; configurations determined by analysis of ^3J values and NOEs. [c] Dihydroxylation of the cyclic alkene was slow. [d] *ca.* 50:50 mixture of side chain epimers. [e] Plus 26% of a side product. [f] Plus 8% yield of *anti*-**7c**.

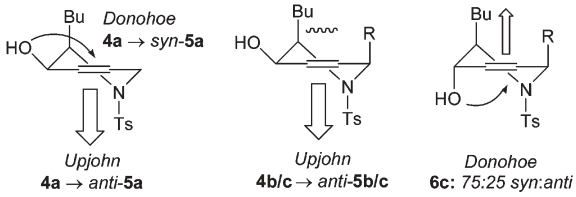


Fig. 1 Stereoselective dihydroxylation of the allylic alcohols **4a–c**.

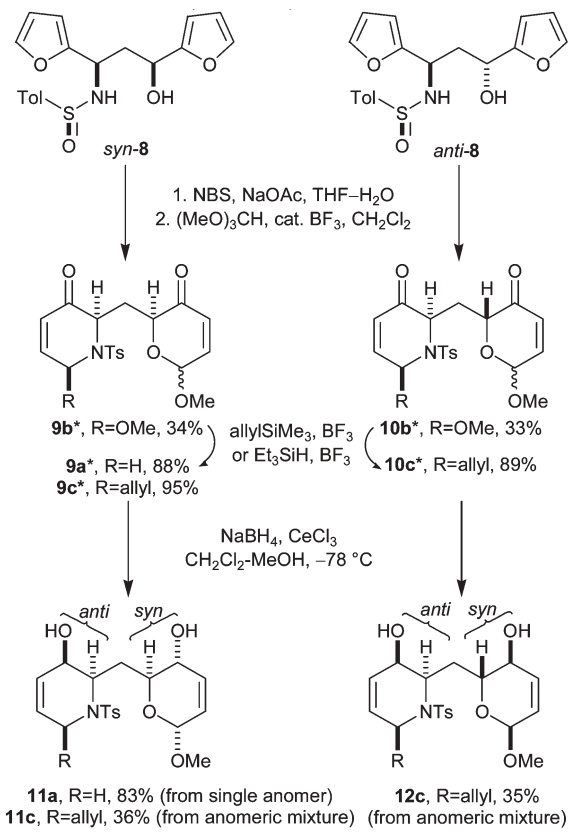
To assess the viability of the approach, we investigated the dihydroxylation of the allylic alcohols **4** and **6** (Table 1), prepared[2] from the corresponding 2-furyl sulfonamide. The Upjohn[3] and Donohoe[4] protocols were studied to assess their potential in the divergent synthesis of stereoisomeric aza-*C*-linked disaccharide mimetics **3**. With **4a** (R = H), a high level of complementarity was observed: dihydroxylation under Upjohn (cat. OsO_4, NMO, acetone–H_2O) and Donohoe's (OsO_4, TMEDA, CH_2Cl_2, −78 °C) conditions gave, after acetylation, the triacetates *anti*-**5a** and *syn*-**5a**, respectively, as >95:<5 mixtures of diastereoisomers (compare entries 1a and 1b). This general pattern of stereoselectivity, Fig. 1, has been rationalised elsewhere.[3,4]

The introduction of an R substituent had a profound effect on the complementarity of the Upjohn and the Donohoe methods (see Fig. 1). Although high (>95:<5) levels of *syn* selectivity were still observed using the Upjohn protocol (entries 2a and 3), efficient direction of OsO_4·TMEDA by the hydroxyl group was precluded: with **4b** (R = OMe), a very low yield of the *anti* product was obtained (entry 2b). The epimeric series of substrates, **6**, fared even less well: **6c** reacted sluggishly under Upjohn conditions, and low *syn* stereoselectivity was observed with OsO_4·TMEDA.

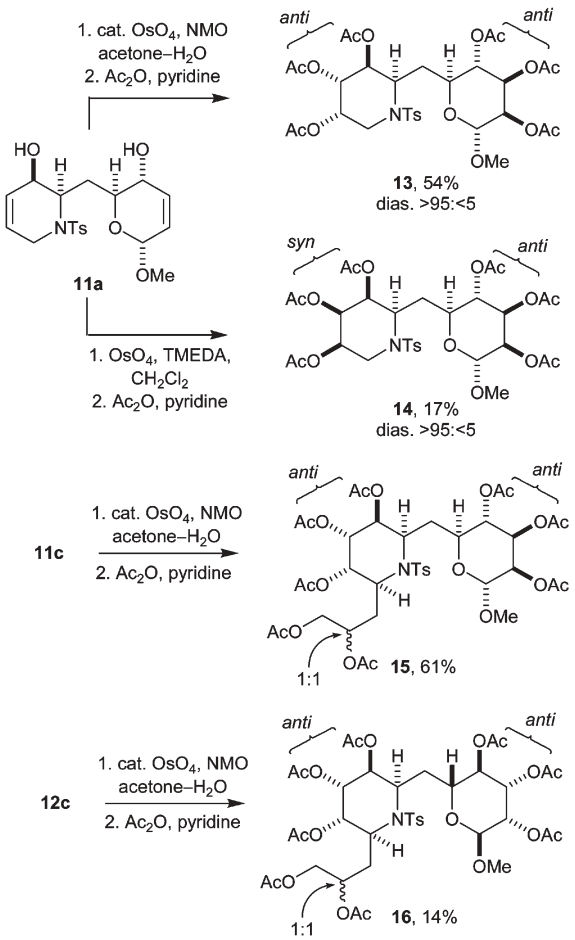
With scope of the dihydroxylation protocols determined, we turned to the synthesis of aza-*C*-(1 → 1)-linked disaccharide derivatives. At each stage, configurations were determined by comparison with monocyclic model compounds. The starting materials were synthesised from the known[5] 1,3-amino alcohol derivatives *syn*- and *anti*-**8**. Two-directional[6] oxidative ring expansion and concomitant sulfur oxidation was followed by acetalisation: the corresponding heterocycles were obtained as 70:30 mixtures of pyran anomers **9b/10b** (Scheme 2).

The differential reactivity of the pyran and piperidine rings allowed one- and two-directional synthetic approaches to be freely interchanged. Most simply, selective substitution of the piperidinyl methoxy group was possible with high stereoselectivity, and gave **9a**, **9c** and **10c**. Furthermore, conformational differences between the pyran and the *N*-tosyl piperidine rings could also be exploited synthetically. Luche reduction[7] (→**11a**, **11c** and **12c**) was uniformly highly stereoselective, and resulted in different outcomes (*syn* and *anti*) in the two heterocyclic rings (see Scheme 2).

Dihydroxylation of **11a**, **11c** and **12c**, and peracetylation, gave the protected aza-*C*-linked disaccharide derivatives **13–16**



Scheme 2 A 70:30 anomeric mixture is denoted by an asterisk (*).



Scheme 3

(Scheme 3); in the cases where yields were disappointing, no starting materials were recovered. Using the Upjohn protocol, dihydroxylation occurred *anti* to the allylic hydroxyl group in both rings. Unfortunately the remote stereogenic centre in the side chains of **15** and **16** was not controlled. However, the outcome of the dihydroxylation of **11a** could be controlled by careful choice of reagent. Indeed, using Donohoe's conditions, different stereochemical outcomes were observed in the two rings (→**14**): the *pseudo*axial methoxy group in the pyran ring prevented more usual *syn*-selective dihydroxylation.

In summary, the asymmetric, stereoselective synthesis of aza-*C*-(1 → 1)-linked disaccharide derivatives was possible in a rather divergent manner. The divergency stemmed from (1) the ability to switch between one- and two-directional modes by exploiting the differential reactivity of the heterocyclic rings; and (2) the complementary substrate-controlled stereoselectivity often possible with the Upjohn and Donohoe dihydroxylation reagents.

We thank EPSRC and GlaxoSmithKline for funding and Jacqueline Colley and James Titchmarsh for HPLC analysis and purification.

Andrew Kennedy,[a] **Adam Nelson***[b] **and Alexis Perry**[b]
[a]*Synthetic Chemistry, Chemical Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
[b]*School of Chemistry and the Astbury Centre, University of Leeds, Leeds, UK LS2 9JT. E-mail: adamn@chem.leeds.ac.uk; Fax: +44 (0)113 343 6565; Tel: +44 (0)113 343 6502*

Notes and references

1 (*a*) C. S. Rye and S. G. Withers, *Curr. Opin. Chem. Biol.*, 2000, **4**, 573; (*b*) P. Sears and C.-H. Wong, *Angew. Chem. Int. Ed.*, 1999, **38**, 2300; (*c*) X. Cheng, G. Kumaran and D. R. Mootoo, *Chem. Commun.*, 2001, 811; (*d*) O. R. Martin, L. Liu and F. Yang, *Tetrahedron Lett.*, 1996, **37**, 1991; (*e*) A. Baudat and P. Vogel, *Tetrahedron Lett.*, 1996, **37**, 483; (*f*) E. Frérot, C. Marquis and P. Vogel, *Tetrahedron Lett.*, 1996, **37**, 2023; (*g*) B. A. Johns, Y. T. Pan, A. D. Elbein and C. R. Johnson, *J. Am. Chem. Soc.*, 1997, **119**, 4856.
2 J. C. P. Hopman, E. van den Berg, L. O. Ollero, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1995, **36**, 4315.
3 J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.
4 T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe and G. Stemp, *J. Org. Chem.*, 2002, **67**, 7946.
5 A. Kennedy, A. Nelson and A. Perry, *Synlett*, 2004, **6**, 967.
6 C. Poss and S. L. Schreiber, *Acc. Chem. Res.*, 1994, **27**, 9.
7 J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226.

