

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

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Received (in Cambridge, UK) 29th November 2004, Accepted 20th January 2005

First published as an Advance Article on the web 2nd February 2005

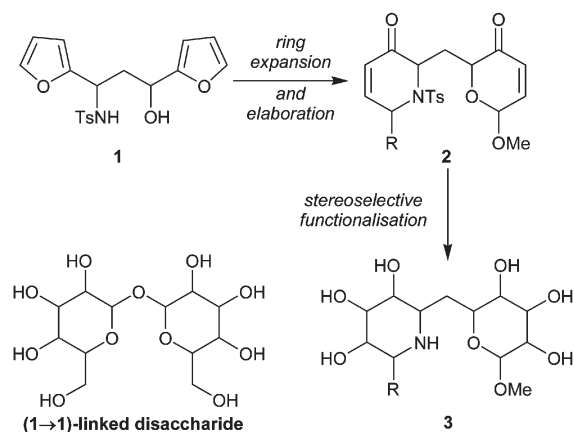
DOI: 10.1039/b417899h

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.<sup>1</sup> Previously, oxocarbenium ion cyclisations<sup>1c</sup> and the samarium Barbier,<sup>1d</sup> aldol,<sup>1e</sup> Michael,<sup>1f</sup> and Suzuki<sup>1g</sup> 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

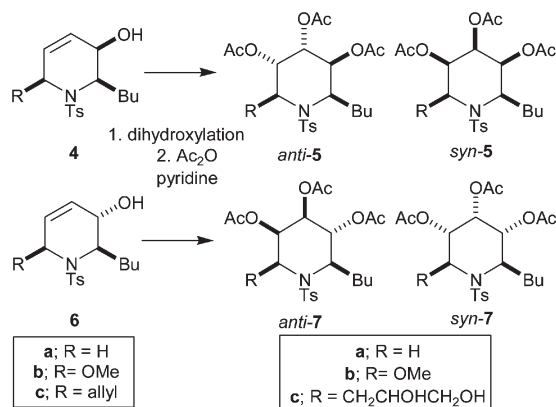
functionalisation was expected to give a range of aza-C-linked disaccharide mimetics **3**.



Scheme 1

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



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

<sup>a</sup> A: (i) cat. OsO<sub>4</sub>, NMO, acetone-H<sub>2</sub>O; (ii) Ac<sub>2</sub>O, pyridine; B: (i) OsO<sub>4</sub>, TMEDA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (ii) Ac<sub>2</sub>O, pyridine. <sup>b</sup> Determined by analysis of the 500 MHz <sup>1</sup>H NMR spectrum of the crude product; configurations determined by analysis of <sup>3</sup>J values and NOEs. <sup>c</sup> Dihydroxylation of the cyclic alkene was slow. <sup>d</sup> ca. 50:50 mixture of side chain epimers. <sup>e</sup> Plus 26% of a side product. <sup>f</sup> Plus 8% yield of *anti-7c*.

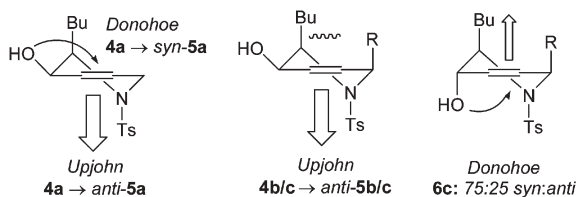


Fig. 1 Stereoselective dihydroxylation of the allylic alcohols **4a–c**.

To assess the viability of the approach, we investigated the dihydroxylation of the allylic alcohols **4** and **6** (Table 1), prepared<sup>2</sup> from the corresponding 2-furyl sulfonamide. The Upjohn<sup>3</sup> and Donohoe<sup>4</sup> 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.  $\text{OsO}_4$ , NMO, acetone- $\text{H}_2\text{O}$ ) and Donohoe's ( $\text{OsO}_4$ , TMEDA,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ) 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.<sup>3,4</sup>

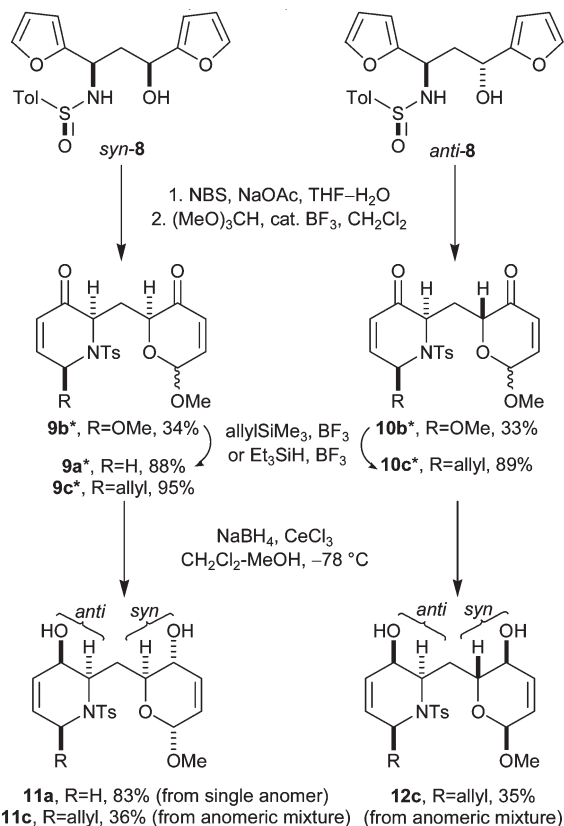
The introduction of an  $R$  substituent had a profound effect on the complementarity of the Upjohn and the Donohoe methods (see Fig. 1). Although high ( $>95:<5$ ) levels of *syn* selectivity were still observed using the Upjohn protocol (entries 2a and 3), efficient direction of  $\text{OsO}_4$ ·TMEDA by the hydroxyl group was precluded: with **4b** ( $R = \text{OMe}$ ), 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  $\text{OsO}_4$ ·TMEDA.

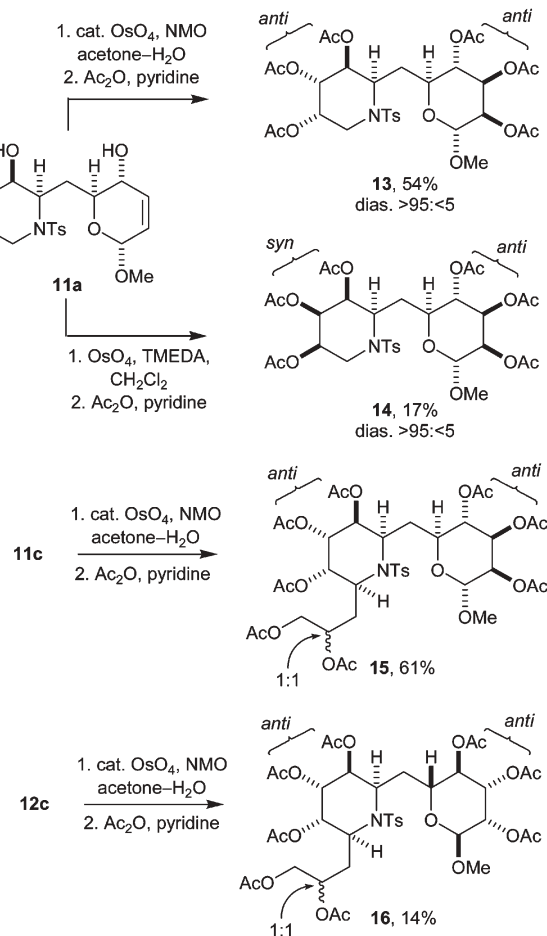
With scope of the dihydroxylation protocols determined, we turned to the synthesis of aza-*C*-(1  $\rightarrow$  1)-linked disaccharide derivatives. At each stage, configurations were determined by comparison with monocyclic model compounds. The starting materials were synthesised from the known<sup>5</sup> 1,3-amino alcohol derivatives *syn*- and *anti*-**8**. Two-directional<sup>6</sup> 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<sup>7</sup> ( $\rightarrow$ **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 ( $\rightarrow$ **14**): the *pseudoaxial* methoxy group in the pyran ring prevented more usual *syn*-selective dihydroxylation.

In summary, the asymmetric, stereoselective synthesis of aza-C-(1  $\rightarrow$  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.

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