

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

Andrew Kennedy,^a Adam Nelson*^b and Alexis Perry^b

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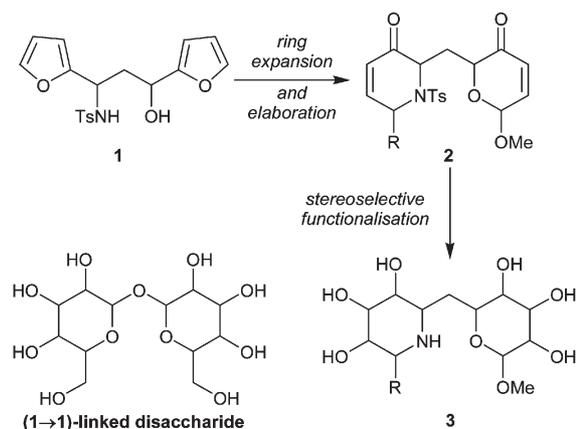
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The Upjohn and Donohoe dihydroxylations were exploited in divergent syntheses of aza-C-(1 → 1)-linked disaccharides.

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

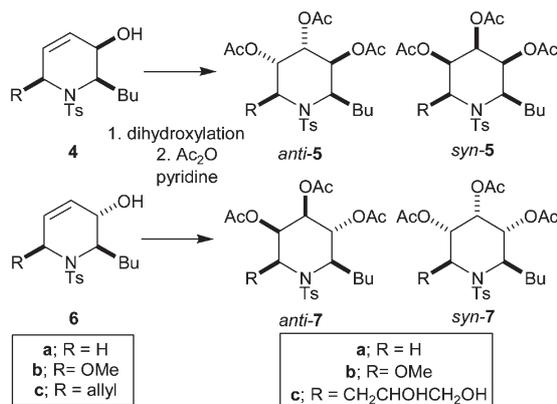
functionalisation was expected to give a range of aza-C-linked disaccharide mimetics **3**.



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	<i>anti</i> - 5a	65
1b	4a	H	B	<5:>95	<i>syn</i> - 5a	74
2a	4b	OMe	A	>95:<5	<i>anti</i> - 5b	77
2b	4b	OMe	B	>95:<5	<i>anti</i> - 5b	4 ^c
3	4c	allyl	A	>95:<5	<i>anti</i> - 5c	36 ^{d,e}
4a	6c	allyl	A	—	—	— ^c
4b	6c	allyl	B	25:75	<i>syn</i> - 7c	26 ^{d,f}

^a A: (i) cat. OsO₄, NMO, acetone-H₂O; (ii) Ac₂O, pyridine; B: (i) OsO₄, TMEDA, CH₂Cl₂, -78 °C; (ii) Ac₂O, 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**.

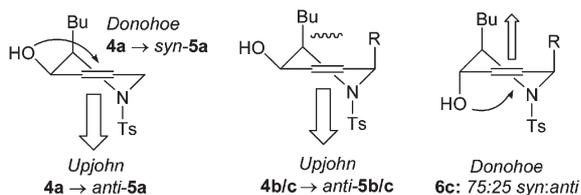


Fig. 1 Stereoselective dihydroxylation of the allylic alcohols 4a–c.

To assess the viability of the approach, we investigated the dihydroxylation of the allylic alcohols **4** and **6** (Table 1), prepared² from the corresponding 2-furyl sulfonamide. The Upjohn³ and Donohoe⁴ 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. OsO₄, NMO, acetone–H₂O) and Donohoe's (OsO₄, TMEDA, CH₂Cl₂, –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}

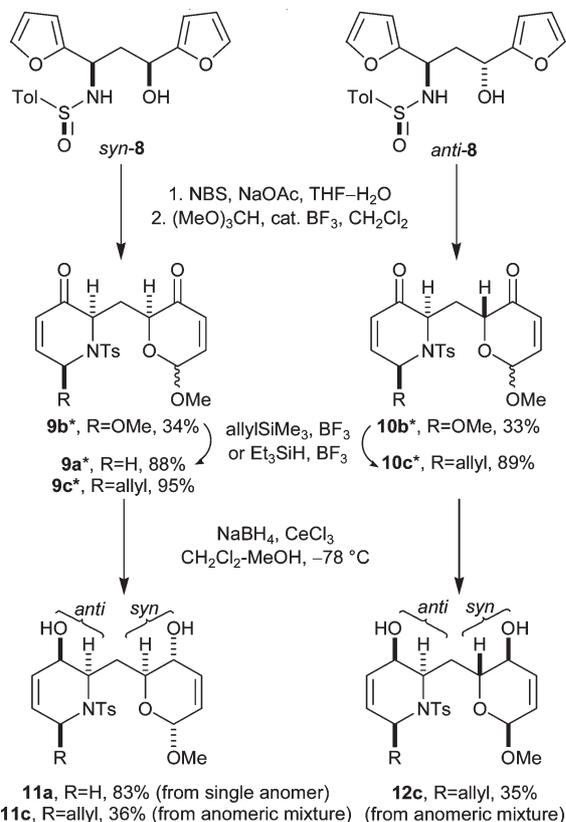
The introduction of an R substituent had a profound effect on the complementarity of the Upjohn and the Donohoe methods (see Fig. 1). Although high (>95:<5) levels of *syn* selectivity were still observed using the Upjohn protocol (entries 2a and 3), efficient direction of OsO₄·TMEDA by the hydroxyl 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 OsO₄·TMEDA.

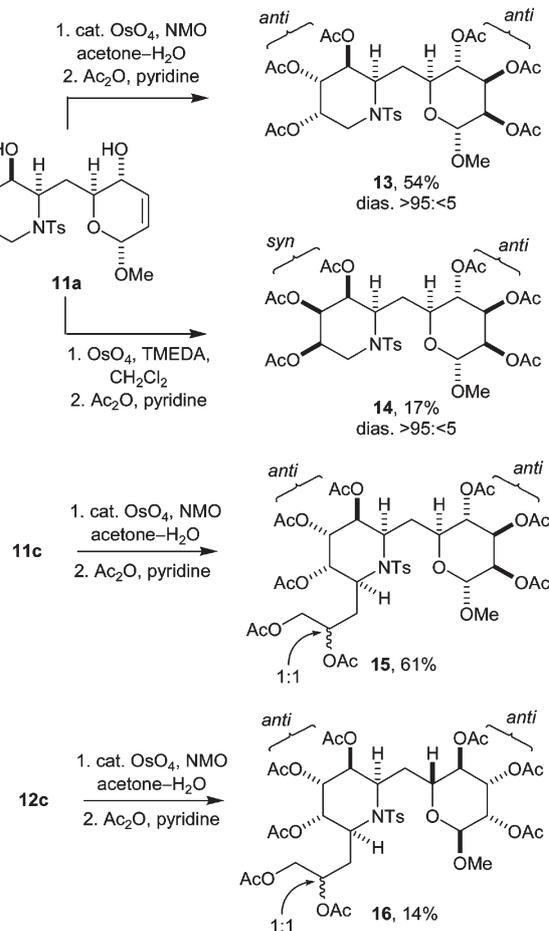
With scope of the dihydroxylation protocols determined, we turned to the synthesis of aza-*C*-(1 → 1)-linked disaccharide derivatives. At each stage, configurations were determined by comparison with monocyclic model compounds. The starting materials were synthesised from the known⁵ 1,3-amino alcohol derivatives *syn*- and *anti*-**8**. Two-directional⁶ 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 reduction⁷ (→**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.

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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*

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