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Synthesis of (1→6)-Linked *C*-Disaccharide Derivatives using Nitrile Oxide/Isoxazoline Chemistry[1]

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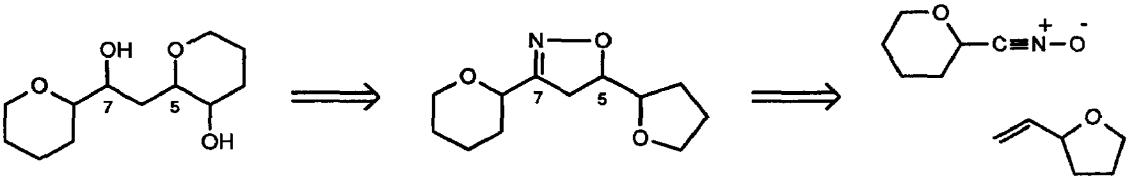
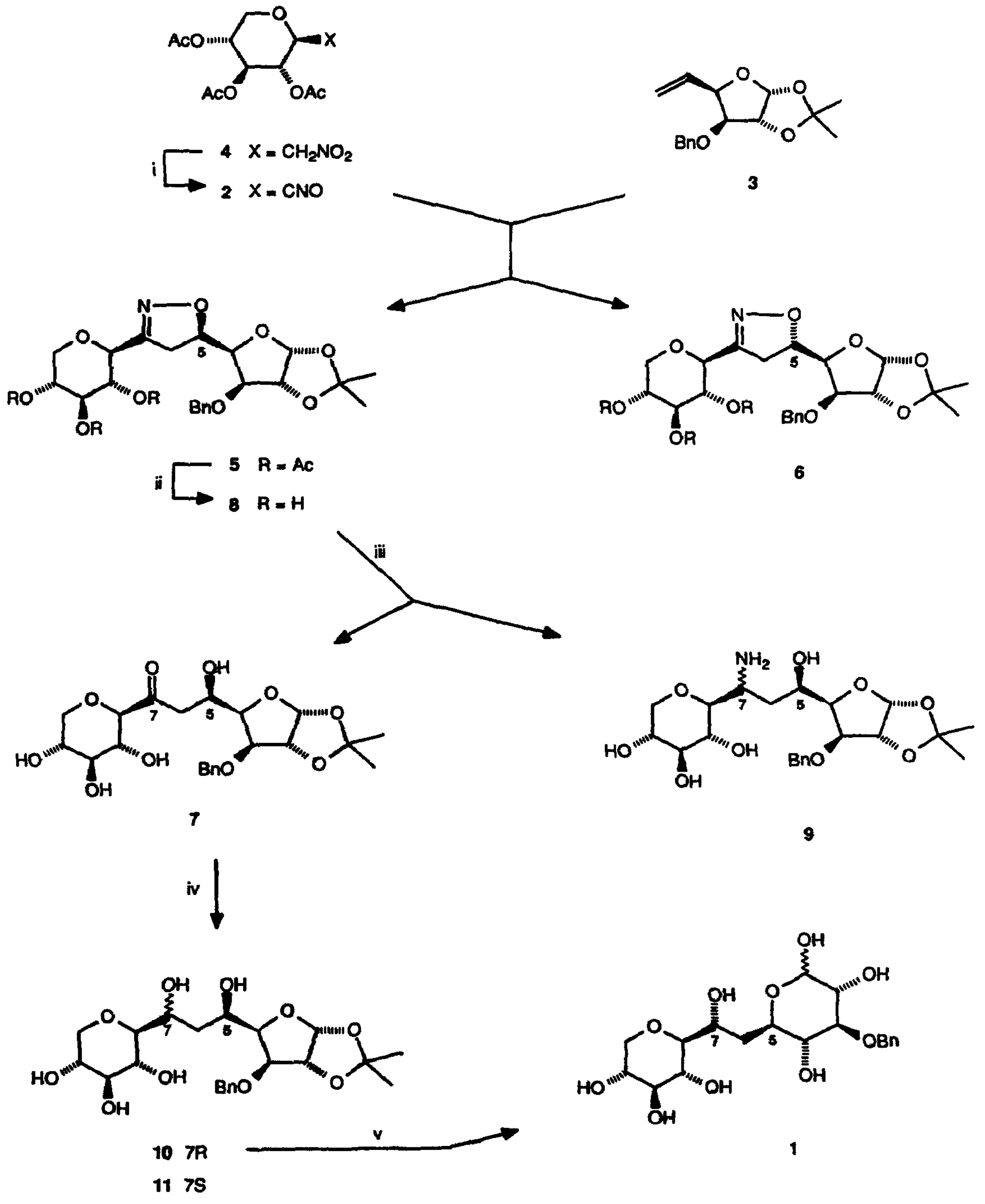
Abstract: A stereocontrolled route to (1→6)-hydroxymethylene-linked *C*-disaccharide derivatives has been developed based on cycloaddition of pyranose 1-carbonitrile oxides to 5,6-dideoxyhex-5-enofuranoses and reductive hydrolytic cleavage of the resulting 2-isoxazolines.

Disaccharide analogues in which the glycosidic oxygen is replaced by carbon (*C*-disaccharides) are the subject of intensive investigation in view of their potential as glycosidase inhibitors.[2,3] (1→6)-Linked *C*-disaccharides are of particular interest and several methods for the preparation of methylene-bridged derivatives have been reported.[3] We now describe a route from readily accessible precursors to (1→6)-hydroxymethylene-linked *C*-disaccharides which is based on nitrile oxide-isoxazoline chemistry.[4] The approach (Scheme 1) is based on cycloaddition of pyranose-1-carbonitrile oxides to ω-unsaturated hexofuranoses and subsequent manipulation of the resulting 2-isoxazolines.



Scheme 1

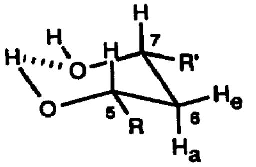
The method is illustrated (Scheme 2) by the synthesis of (1→6)-hydroxymethylene-linked xylose-glucose derivative **1** by combination of D-xylose-derived nitrile oxide **2** and alkene **3**[5] prepared from D-glucose. In order to minimise formation of furazan *N*-oxide dimer[6] the nitrile oxide was generated *in situ* in the presence of the alkene using a modified Mukaiyama procedure[7,8] involving dehydration of nitromethylxylose derivative **4**[9] using tolylene di-isocyanate. Chromatography of the reaction mixture afforded unreacted alkene followed by a pair of diastereomeric isoxazolines **5** and **6** in a combined yield of 93%. The individual isomers were separated by further chromatography and their structures assigned by comparison of their ^1H- and ^{13}C-NMR parameters with those of previously reported isoxazolines prepared from the same alkene.[10] The major adduct **5** has *R*-configuration[11] at the new asymmetric centre C(5). The product ratio **5**:**6** was determined by ^1H-NMR spectroscopy as 78:22 and neither of the other two possible regioisomeric cycloadducts were detected. The reaction is therefore regiospecific and diastereoselective in favour of adducts in which there is an *erythro* relationship between C(4) and C(5). Similar π–facial selectivity



Scheme 2 *Reagents:* (i) 4 (3 mmol) in PhMe (50 ml) added over 48 h to 3 (12 mmol), TDI (9 mmol), Et$_3$N (1.5 mmol) in PhMe (50 ml) under reflux; after 10 h quenched at 0°C with $H_2NCH_2CH_2NH_2$; (ii) KCN, MeOH; (iii) H_2/Raney Ni, H_3BO_3, MeOH-THF-H_2O; (iv) $NaBH_4$ or L-Selectride; (v) CF_3CO_2H, H_2O

has been reported for cycloaddition of nitrile oxides to a wide variety of chiral allyl ethers and is attributed[12] to the so called "inside alkoxy effect".

Isoxazoline **5** was converted in 55% yield to β-hydroxyketone **7** by deacetylation to **8** followed by reductive hydrolytic cleavage of the heterocyclic ring using Raney-Ni, hydrogen and boric acid in methanol-THF-water. The presence of the carbonyl group in the product is confirmed by an IR absorption at 1718 cm^{-1} and a characteristic ^{13}C-NMR peak at 207 ppm. Although **7** was the major product it was accompanied by 18% of γ-amino alcohol **9** which presumably results from hydrogenation of the imine intermediate competing with its hydrolysis.[13] Compound **7** was reduced with sodium borohydride in ethanol-water to give in 76% yield a 17:83 mixture of 6-deoxy-D-*glycero*-L-*talo*-D-*gluco*- and 6-deoxy-D-*glycero*-L-*galacto*-D-*gluco*-8,12-anhydro-dodecose derivatives **10** and **11** which were separated by chromatography. Reduction with L-Selectride occurred with reversed selectivity affording a 65:35 mixture of 1,3-diols **10** and **11** in 79% combined yield. The configuration at the newly created asymmetric centre C(7) in the individual 1,3-diols was assigned from their ^1H-NMR spectra by comparison with similar 6-deoxynonose, decose and undecose derivatives.[14,15] In each case the *5R,7S* compound adopts a hydrogen-bonded chair-like conformation. For isomer **11** the ^1H-^1H couplings (Table) are as expected for such a chair conformation with both bulky substituents furanosyl (R) at C(5) and pyranosyl (R') at C(7) in equatorial positions; protons H(5) and H(7) both show typical axial-axial couplings (10.0 Hz) to H(6a) and axial-equatorial couplings (2.4 Hz) to H(6e). In contrast for isomer **10** the substituent at C(7) would be in the less favoured axial position and there is significant distortion towards a skew arrangement. In the final stage treatment with aqueous trifluoroacetic acid resulted in deacetalisation followed by furanose to pyranose conversion to afford dipyranose *C*-disaccharide **1**[16] as a 38:62 mixture of α- and β-isomers in 92% yield.

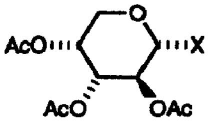


11

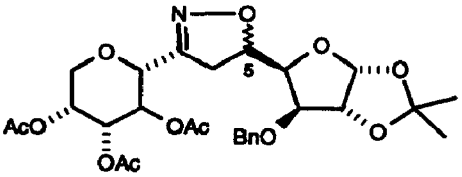
Table Selected ^1H-^1H couplings for **10** and **11**

J/Hz	H_5-H_{6a}	H_5-H_{6e}	H_{6a}-H_{6e}	H_{6a}-H_7	H_{6e}-H_7
10	2.1	10.1	13.8	2.1	11.3
11	2.4	10.0	14.4	10.0	2.4

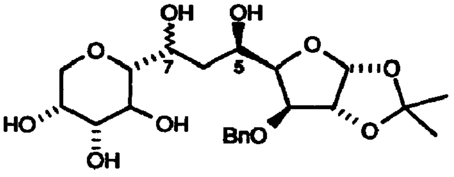
The method is capable of linking various combinations of pyranose units. For example, cycloaddition to alkene **3** of D-arabinose-derived nitrile oxide **12**, which was generated similarly by dehydration of nitromethyl compound **13**, afforded in 89% yield an 80:20 diastereomeric mixture of adducts **14** and **15**. The major adduct **14** also has *R*-configuration at the new chiral centre C(5), *ie* both nitrile oxides **3** and **12** show a similar preference for formation of *erythro* adducts. These observations provide further evidence that the configuration of the α-carbon in the nitrile oxide component has negligible influence on stereoselectivity.[15,17] Deacetylation and hydrogenolysis of isoxazoline **14**, followed by reduction of the resulting β-hydroxyketone with sodium borohydride or L-Selectride, afforded 6-deoxy-D-*glycero*-D-*galacto*-D-*gluco*- and 6-deoxy-D-*glycero*-D-*talo*-D-*gluco*-8,12-anhydrododecose derivatives **16** and **17**. In conclusion, the nitrile oxide/isoxazoline route provides access, not only to carbonyl-bridged disaccharides,[8] but also hydroxymethylene- and aminomethylene-linked analogues.



12 X = CNO
13 X = CH_2NO_2



14 5R
15 5S



16 7R
17 7S

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16. New compounds were characterised by their IR and NMR spectra and their elemental compositions established by high resolution mass spectrometry and/or combustion analysis. Selected ^{1}H-NMR data (D_2O, 600 MHz) for compound **1**α(β): δ_H H(1) 5.11 (4.56), H(2) 3.55 (3.26), H(3) 3.63 (3.42), H(4) 3.22 (3.44*), H(5) 3.88 (3.46*), H(6a) 1.46 (1.46), H(6b) 2.16 (2.14), H(7) 4.01 (4.05), H(8) 3.07 (3.09), H(9) 3.45* (3.45*), H(10) 3.34 (3.34), H(11) 3.50 (3.50), H(12a) 3.88 (3.88), H(12b) 3.15 (3.15), PhCH_2 4.79 (4.79), Ph 7.31-7.40 (7.31-7.40); $J_{X\text{-}Y}$ (Hz) 1-2 3.9 (8.7), 2-3 9.8 (9.3), 3-4 9.2 (9.3), 4-5 9.8, 6a-7 3.4 (3.4), 6b-7 9.8 (9.8), 7-8 0 (0), 8-9 9.8 (9.3), 9-10 9.3 (9.3), 10-11 9.3 (9.3), 11-12a 5.9 (5.9), 11-12b 10.2 (10.2), 12a-12b 10.9 (10.7).
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