Synthesis of Higher Monosaccharides using Nitrile Oxide–Isoxazoline Chemistry

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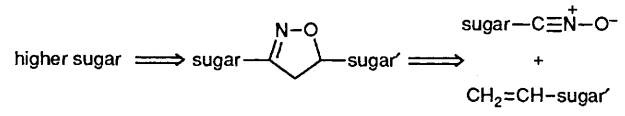
Octose, nonose and decose derivatives **1**, **2**, **11**, **12** and **18–21** have been synthesised by a sequence involving cycloaddition of sugar nitrile oxides to sugar alkenes, and reductive hydrolytic cleavage of the resulting 2-isoxazolines.

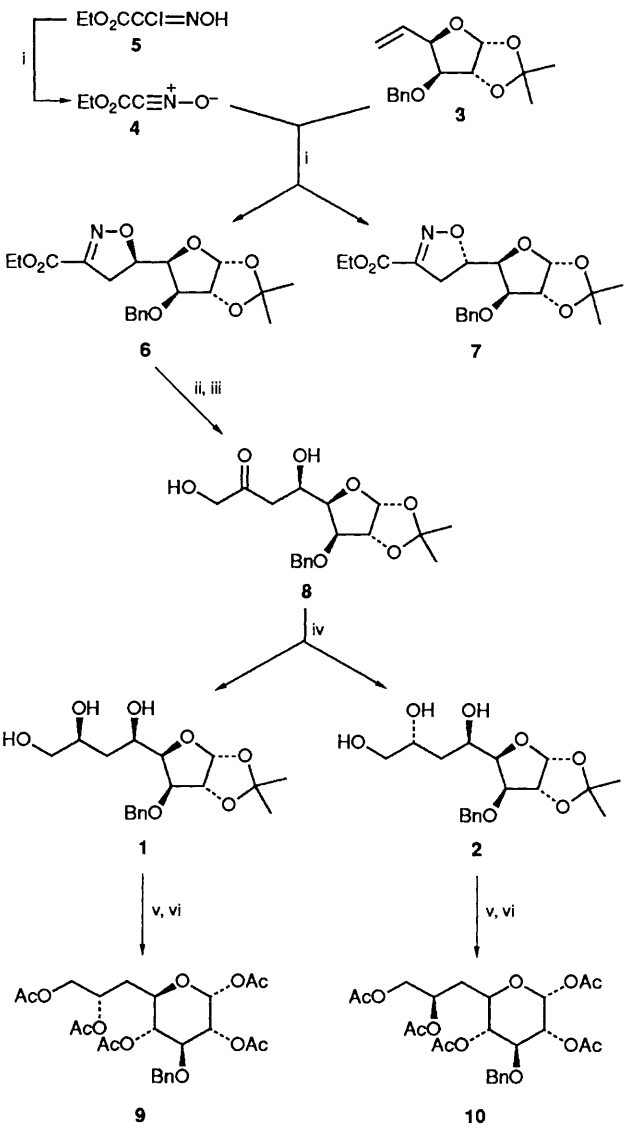
The biological activity associated with higher-carbon sugars (monosaccharides with more than six carbons) makes them an attractive target for synthesis.[1] In order to develop a general route to these long-chain polyhydroxylated aldehydes allowing control of stereochemistry, we have utilised nitrile oxide–dihydroisoxazole chemistry.[2]

Our synthetic approach (Scheme 1) is based on chain extension from the non-reducing end of simple readily available ω-unsaturated monosaccharides by cycloaddition with sugar nitrile oxides, and reductive hydrolytic cleavage of the resulting 2-isoxazolines (4,5-dihydroisoxazoles).

The method is illustrated by the synthesis of 6-deoxyoctoses



Scheme 1



Scheme 2 *Reagents and conditions*: i, **5** (24 mmol) in Et_2O (45 ml) added over 14 h to **3** (36 mmol) and Et_3N (26 mmol) in Et_2O (150 ml); ii, $NaBH_4$, THF, EtOH; iii, Pd/C, H_2, $B(OH)_3$, H_2O, MeOH, 20 °C, 18 h; iv, $NaBH_4$, EtOH, H_2O; v, CF_3CO_2H, H_2O; vi, Ac_2O, $ZnCl_2$, pyridine

1 and **2** from D-glucose-derived alkene **3** and ethoxycarbonylformonitrile oxide **4**. To avoid formation of unwanted furoxan dimer,[3] the nitrile oxide was generated *in situ* in the presence of an excess of the alkene (1 : 1.5) by dehydrochlorination of the corresponding hydroximoyl chloride **5**. From the reaction mixture was isolated a diastereoisomeric mixture of isoxazolines **6** and **7** in a combined yield of 75%. The product ratio was measured by ^1H NMR spectroscopy as 86 : 14 and the individual isomers were separated by chromatography and/or crystallisation. The new asymmetric centre at C(5) in the major adduct has the *R*-configuration, corresponding to an *erythro*-relationship for C(4)–C(5). Such π-facial selectivity has been observed[4–6] for various cycloadditions of nitrile oxides to allyl ethers and has been rationalised[7] in terms of the so-called 'inside alkoxy effects.'

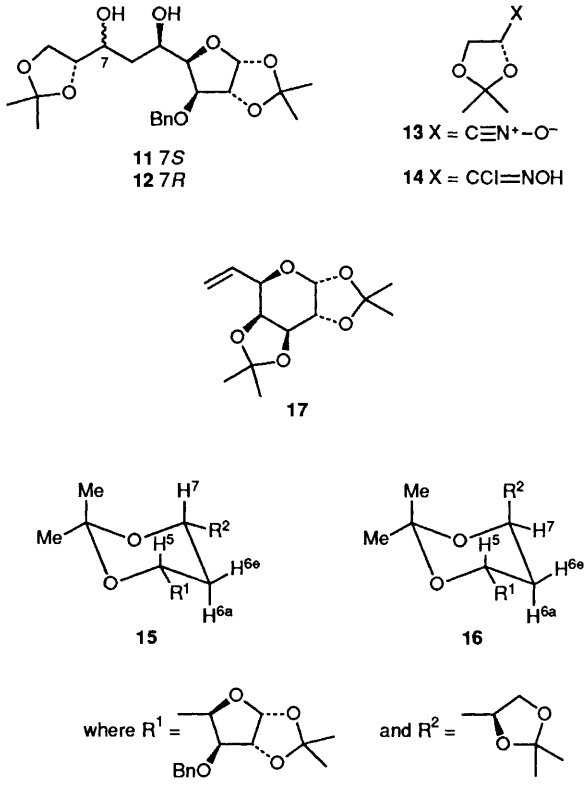


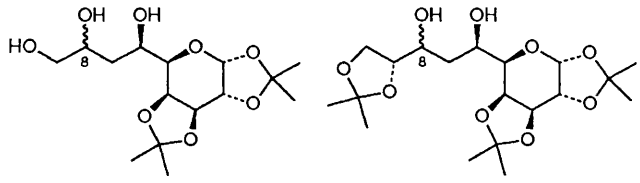
Table 1 Selected ^1H–^1H couplings for compounds **15** and **16**

J/Hz	H_5–H_{6a}	H_5–H_{6e}	H_{6a}–H_{6e}	H_{6a}–H_7	H_{6e}–H_7
15	11.5	2.5	13.1	11.5	2.5
16	8.9	6.3	13.1	6.5	9.4

The isoxazoline **6** was converted in 78% overall yield to 5,8-dihydroxy-7-keto derivative **8** by borohydride reduction of the ethoxycarbonyl substituent to hydroxymethyl, followed by reductive hydrolytic cleavage of the isoxazoline ring using Pd/C, H_2 and boric acid in methanol–water.

In the final step keto sugar **8** was reduced with sodium borohydride in ethanol–water to yield a mixture of 6-deoxy-D- and L-*glycero*-D-*gluco*-octofuranoses **1** (22%) and **2** (43%), which were separated by chromatography. For each isomer acid-catalysed hydrolysis followed by acetylation afforded the corresponding 1,2,4,7,8-pentaacetyl-D-*gluco*-octopyranose derivatives **9** and **10**. The observed couplings (Hz) for compound **9** of $J_{1,2}$ 3.8, $J_{2,3}$ 9.8, $J_{3,4}$ 9.8, and $J_{4,5}$ 9.8 confirmed the D-*gluco* stereochemistry for the pyranose ring.

6-Deoxy-D-*erythro*- and -D-*threo*-D-*gluco*-nonofuranoses **11** and **12** were prepared by a similar reaction sequence from alkene **3** and D-glyceronitrile oxide **13**, generated by dehydrochlorination of hydroximoyl chloride **14**.[8] The proportions of diols **11** and **12** were dependent on the reducing conditions used in the final step. The ratio varied from 39 : 61 using borane in tetrahydrofuran (THF) to 28 : 72 for $NaBH_4$ in EtOH–H_2O and 5 : 95 for L-Selectride in THF. For each isomer the configuration at the new asymmetric centre C(7), formed on reduction of the carbonyl group, was established by examination of the ^1H NMR spectra of their 5,7-*O*-isopropylidene derivatives **15** and **16**. For isomer **15** with the *S*-configuration at C(7) the ^1H–^1H couplings for the 1,3-dioxane ring are wholly consistent with a chair conformation (Table 1), in which the bulky substituents R^1 at C(5) and R^2 at C(7) are arranged equatorially. Protons H(5) and H(7) both show typical axial–axial couplings (11.6 Hz) to H(6a) and axial–equatorial coupling (1.5 Hz) to H(6e). In contrast, for isomer **16** the 1,3-dioxolane substituent at C(7) occupies the less favourable axial position and, as expected, the chair is



18 8*S*
19 8*R*

20 8*S*
21 8*R*

significantly distorted, as evidenced by the corresponding *J*-values; the *R*-configuration is therefore assigned to C(7).

Use of D-galactose-derived alkene **17** as dipolarophile provided a seven-carbon component which, combined with nitrile oxides **4** and **13**, enabled nine- and ten-carbon sugars to be prepared. The cycloaddition reactions occurred with comparable regio- and stereo-selectivity,[4] and subsequent reductive hydrolytic ring opening of the resulting isoxazolines followed by reduction afforded 7-deoxynonopyranoses **18** and **19** and 7-deoxydecopyranoses **20** and **21**. The assignment of configuration at C(6) and C(8) in compounds **18** and **19** is based on X-ray crystal structure analysis[4] of the initial isoxazoline cycloadduct from which they were derived, and from the ^{1}H NMR spectra for their 1,3-dioxane derivatives as described above for compounds **15** and **16**.

These results demonstrate that long-chain monosaccharides can be synthesised stereoselectively from readily accessible precursors using nitrile oxide–isoxazoline methodology. By choosing appropriate four-, five- or six-carbon sugar nitrile oxides this approach is capable of extension to undecose to tridecose analogues and, by alternative non-hydrolytic reduction[6] of the isoxazolines, to a range of amino sugar analogues. These reactions are currently under investigation.

Received, 11th October 1990; Com. 0/04582I

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