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Synthesis of Eleven-Carbon Monosaccharides using Nitrile Oxide/Isoxazoline Chemistry[1]

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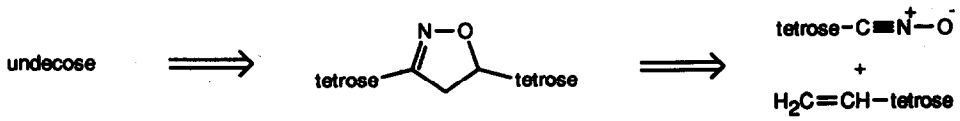
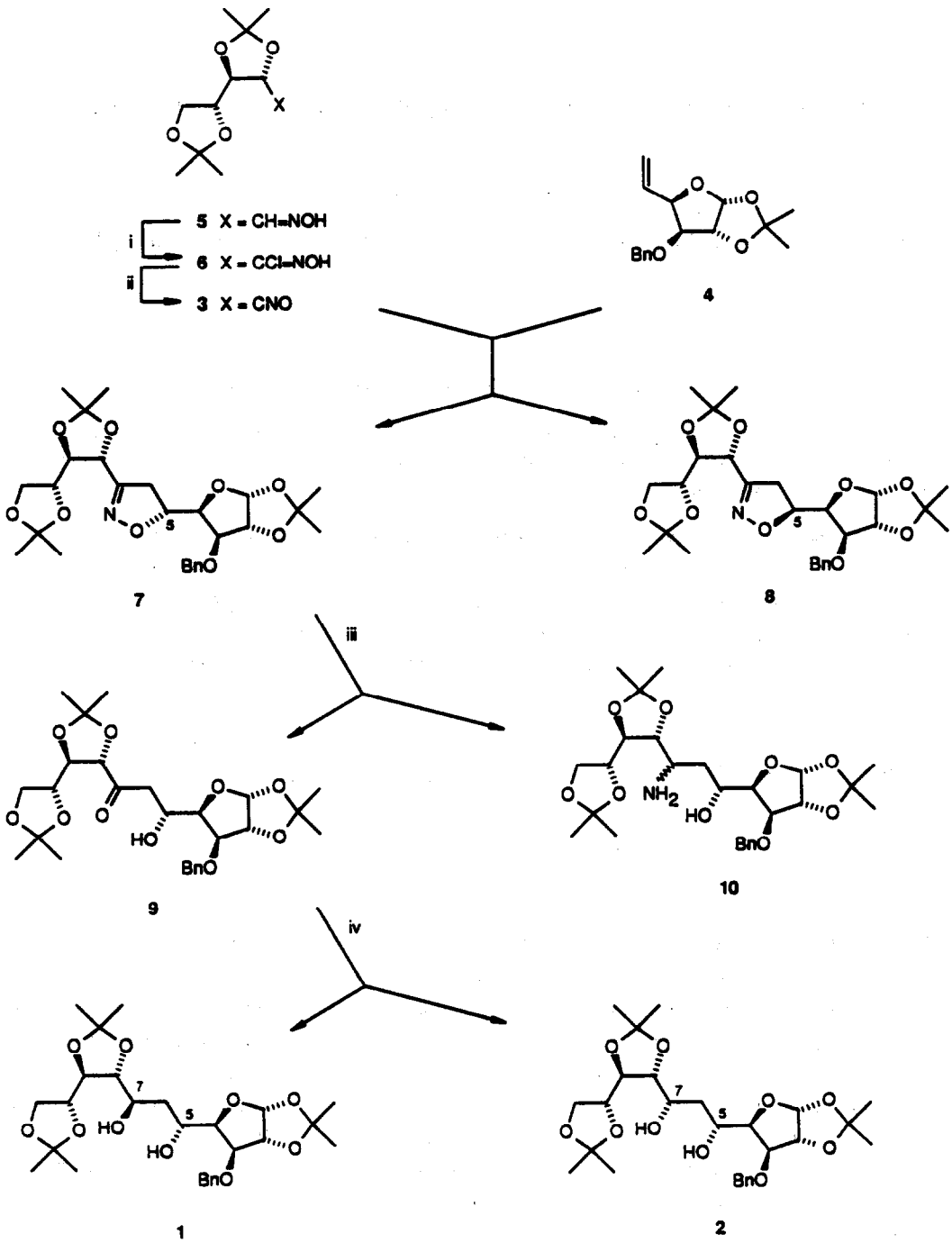
Abstract: A stereocontrolled route to 6-deoxyundecose derivatives has been developed based on cycloaddition of 5-carbon arabinose-derived nitrile oxides to 6-carbon carbohydrate alkenes and reductive hydrolytic cleavage of the resulting isoxazolines.

The discovery of the antibiotics hikizimycin (anthelmycin)[2] and tunicamycin[3] which contain eleven-carbon monosaccharide structural subunits has stimulated interest in the synthesis of such higher sugars.[4] We now describe a route from readily accessible precursors to undecose derivatives which makes use of nitrile oxide-isoxazoline chemistry.[5] The approach (Scheme 1) is based on cycloaddition of 5-carbon pentose-derived nitrile oxides to ω–unsaturated hexoses and subsequent manipulation of the resulting 2-isoxazolines.



Scheme 1

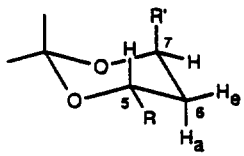
The method is illustrated (Scheme 2) by the synthesis of 6-deoxyundecose derivatives **1** and **2** by combination of D-arabinose-derived nitrile oxide **3** and alkene **4** prepared from D-glucose.[6] The nitrile oxide was generated *in situ* from the corresponding oxime **5** *via* hydroximoyl chloride **6** by initial treatment with *N*-chlorosuccinimide followed by addition of triethylamine. In order to minimise the formation of furazan *N*-oxide dimers[7] the latter dehydrochlorination step was carried out in the presence of an excess of the dipolarophile (1:1.5) by addition of the base over 16 hours thus maintaining a low concentration of the nitrile oxide. Chromatography of the reaction mixture afforded unreacted alkene (58%) followed by a pair of diastereomeric isoxazolines **7** and **8** in a combined yield of 61%. The individual isomers were separated by chromatography and their structures assigned by comparison of their ^{1}H- and ^{13}C-NMR parameters with those of previously reported isoxazolines prepared from the same alkene.[8-10] The major adduct **7** has *R*-configuration at the new asymmetric centre C(5). The product ratio **7**:**8** was determined by ^{1}H-NMR spectroscopy as 89:11 with neither of the other two possible regioisomeric cycloadducts being 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 has been reported for cycloaddition of nitrile oxides to a wide variety of chiral allyl ethers and is attributed[11] to the so called "inside alkoxy effect".



Scheme 2

Reagents: (i) NCS, pyridine; (ii) Et_3N; (iii) H_2/Raney Ni, H_3BO_3, MeOH-H_2O; (iv) $NaBH_4$ or L-Selectride

Isoxazoline **7** was converted in 45% yield to 7-ulose derivative **9** by reductive hydrolytic cleavage of the heterocyclic ring using Raney-Ni, hydrogen and boric acid in methanol-water. The presence of the carbonyl group in the product is confirmed by an infrared absorption at 1724 cm^{-1} and a characteristic ^{13}C NMR peak at 210 ppm. Although the desired β–hydroxyketone **9** was the major product it was accompanied by 33% of γ–amino alcohol **10** as a by-product which presumably results from hydrogenation of the putative imine intermediate competing with its hydrolysis.[12] In the final step compound **9** was reduced with sodium borohydride in ethanol-water to yield a mixture of 6-deoxy-D-*manno*-D-*gluco*- and 6-deoxy-D-*gluco*-D-*gluco*-undecofuranose derivatives **1** (28%) and **2** (51%), which were separated by chromatography. Reduction with L-Selectride proved to be more selective affording a 3:97 mixture of **1** and **2** in 98% combined yield. The configuration at the newly created asymmetric centre C(7) in the individual 1,3-diols was established by treatment with 2,2-dimethoxypropane/acetone/TsOH and examining the ^1H-NMR spectra of the resulting 5,7-*O*-isopropylidene derivatives **11** and **12**. For 5*R*,7*S*-isomer **12** the ^1H-^1H couplings (Table) for the 1,3-dioxane ring are as expected for a chair conformation with both bulky substituents R at C(5) and R' at C(7) in equatorial positions. Protons H(5) and H(7) both show typical axial-axial couplings (11.6 Hz) to H(6a) and axial-equatorial couplings (2.9 Hz) to H(6e). It is therefore deduced that the major isomer **2** has *S*-configuration at C(7). In contrast for the isomeric dioxane **11** the substituent at C(7) is in the less favoured axial position and the chair shows significant distortion.



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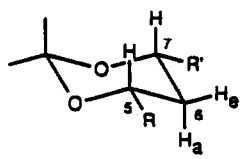

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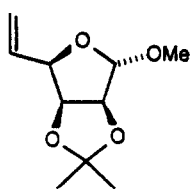
Table Selected ^1H-^1H couplings for **11** and **12**

J/Hz	H_5-H_{6a}	H_5-H_{6e}	H_{6a}-H_{6e}	H_{6a}-H_7	H_{6e}-H_7
11	8.9	5.9	13.2	6.3	9.6
12	11.6	2.9	13.1	11.6	2.9

Nitrile oxide **3** reacted with similar π–facial selectivity with D-mannose-derived alkene **13** to afford an 82:18 diastereomeric mixture of adducts in 61% yield. Hydrogenolysis of isoxazoline **14** followed by reduction with sodium borohydride or L-Selectride, as described above, yielded 6-deoxy-D-*manno*-D-*manno*- and D-*gluco*-D-*manno*-undecose derivatives **15** and **16**.



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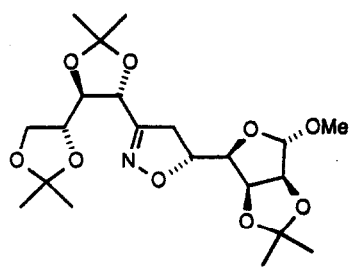

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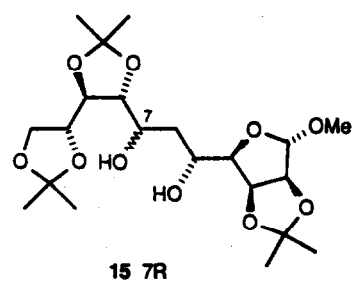
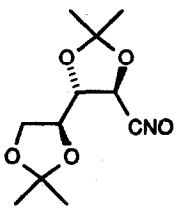


15 7R
16 7S



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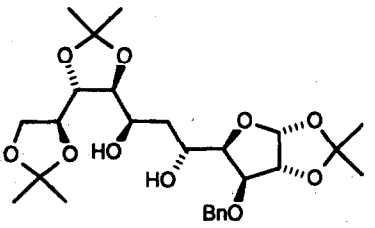

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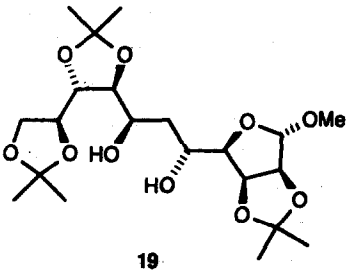

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The cycloaddition reactions of L-arabinose-derived nitrile oxide **17** with alkenes **4** and **13** were also investigated. In each case the major adduct had *R*-configuration at the new chiral centre C(5), *ie* both D- and L-nitrile oxides **3** and **17** show the same preference for formation of *erythro* adducts; furthermore the selectivities (89:11 and 88:12 for **4**, 82:18 and 83:17 for **13**) were also the same within experimental error. It is therefore concluded that, in contrast to the key role played by allylic substituents in the dipolarophile, the configuration of the carbon adjacent to the nitrile oxide has negligible effect on the stereochemical outcome of the reaction. Hydrogenolysis of the resulting isoxazolines, and subsequent reduction with L-Selectride afforded 6-deoxy-L-*gluco*-D-*gluco*-undecose derivative **18** from alkene **4** and the L-*gluco*-D-*manno*- analogue **19** from alkene **13**. When sodium borohydride was used in the final step the reductions were less selective and the isomeric 6-deoxy-L-*manno*-D-*gluco*- and L-*manno*-D-*manno*- undecoses were also formed.[13]

References and Notes

1. We thank ICI plc for financial support and DENI for the award of a studentship (K.E.M.).
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13. New compounds have been characterised by their IR and NMR spectra and their elemental compositions established by high resolution mass spectrometry and/or combustion analysis.

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