Nitrile oxide/isoxazoline approach to higher monosaccharides: synthesis of 7-deoxy-nonose and -decose derivatives[1]

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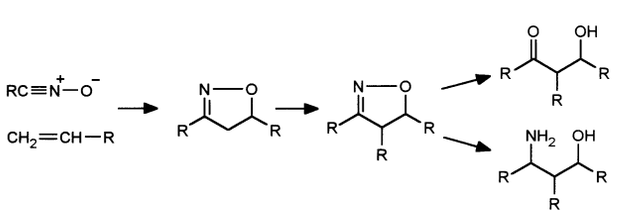
7-Deoxy-D-*ribo*-D-*galacto*- and 7-deoxy-D-*xylo*-D-*galacto*-decopyranoside derivatives 11 and 12 have been prepared by a sequence involving diastereoselective cycloaddition of 2,3-*O*-isopropylidene-D-glyceronitrile oxide to D-galactose-derived alkene 3 to afford the isoxazoline 5 as the major adduct, followed by reductive hydrolytic cleavage of the isoxazoline and reduction of the resulting β-hydroxy ketone. The configuration of the new chiral centre (C-8) in compounds 11 and 12 is established by NMR analysis of their 6,8-*O*-isopropylidene derivatives 13 and 14. 7-Deoxy-L-*threo*-D-*galacto*- and 7-deoxy-D-*erythro*-D-*galacto*-nonopyranosides 15 and 16 are prepared similarly from alkene 3 and ethoxycarbonylformonitrile oxide *via* isoxazolines 8 and 17, and β-hydroxy ketone 18. The 6,7-dideoxynon-6-enos-8-ulose 19 is also prepared from isoxazoline 5.

Introduction

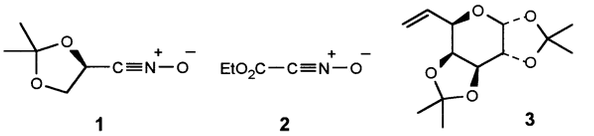
The chemistry of higher monosaccharides containing more than six contiguous carbon atoms has become the subject of widespread interest,[2] with particular attention being focused on developing effective methods for their synthesis. The most attractive routes are based on chain extension of lower-carbon monosaccharides, and therefore require the introduction of new stereocentres in a predictable and controlled manner. A variety of techniques have been adopted for this purpose including radical coupling,[3] enzyme-mediated aldol reactions,[4] nitroaldol additions,[5] four-carbon extensions *via* butenolides,[6] Wittig olefination/osmylation[7] and Wittig olefination/epoxidation[8] protocols and routes based on 2-(trimethylsilyl)-thiazole chemistry.[9] Higher monosaccharides have also been prepared[10–13] from non-carbohydrate precursors using, for example, Wittig osmylation[10] and hetero-Diels–Alder[11] cycloaddition reactions and the so-called 'naked sugar' approach.[12] We now describe the synthesis from readily accessible carbohydrate precursors of a series of nonose and decose derivatives by the application of nitrile oxide/isoxazoline chemistry.[14]

For many years the 1,3-dipolar cycloaddition reactions of nitrile oxides have been used for the construction of five-membered heterocycles incorporating the C=N–O unit,[15] but it is only in the last decade or so that their potential for the synthesis of natural products and analogues has been realised. Their utility stems from their ease of generation under mild conditions, and the regio- and stereo-chemical control of their cycloaddition to alkenes. The well established chemistry of the resulting 2-isoxazoline (4,5-dihydroisoxazole) cycloadducts permits rapid accumulation of polyfunctionality in a small molecular framework, and this methodology[14] has been applied successfully to the preparation of a wide variety of natural products including carbocyclics, alkaloids and carbohydrates. The method involves three basic steps (Scheme 1): first, cycloaddition of the nitrile oxide to the alkene; then modification of the resulting isoxazoline which is usually sufficiently robust as to allow the introduction and/or manipulation of substituents; and finally reductive ring cleavage at the N–O bond of the isoxazoline to afford, for example, β-hydroxy ketones or γ-amino alcohols.



Scheme 1

We considered that this methodology could be well suited for the synthesis of higher-carbon monosaccharides. Our approach, which is summarised in Scheme 2, is based on chain elongation from the non-reducing terminus of simple readily available ω-unsaturated monosaccharides by cycloaddition with the nitrile oxide, followed by hydrogenolysis of the resulting isoxazolines. For initial investigations we selected D-glyceraldehyde-based nitrile oxide **1** and ethoxycarbonylformonitrile oxide **2** as the dipole component, and D-galactose-derived alkene **3** as the dipolarophile.



Scheme 2

1 **2** **3**

Results and discussion

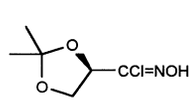
In view of their tendency to dimerise to furoxans (furazan *N*-oxides) the nitrile oxides were generated *in situ* by triethylamine-induced dehydrochlorination of the corresponding hydroximoyl chloride in the presence of an excess of the dipolarophile (1:1.5). 2,3-*O*-Isopropylidene-D-glycerohydroximoyl chloride **4**, the precursor for the glyceronitrile oxide **1**, was prepared by chlorination of 2,3-*O*-isopropylidene-D-glyceraldehyde oxime, which is readily accessible from D-mannitol. The procedure used was a modification of that reported by Jones *et al.*[16] involving addition of chlorine to a solution of the oxime in diethyl ether at −60 °C; the product yields were found to be very sensitive to reaction conditions and work-up. The hydroximoyl chloride ($EtO_2CCCl{=}NOH$) required for the generation of ethoxycarbonylformonitrile oxide **2** was readily prepared in one step by nitrosation of

Table 1 ^{1}H NMR chemical shifts (δ_H/ppm)[a]

	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	Me	OH
5	5.47	4.27	4.58	4.36	3.66	4.76	3.11		4.88	3.95	1.29, 1.33, 1.35	
							3.04			4.17	1.41, 1.42, 1.46	
6	5.53	4.28	4.57	4.27	3.83	4.84	3.14		4.92	3.97	1.28, 1.30, 1.36	
							3.07			4.16	1.42, 1.43, 1.48	
8[b]	5.46	4.27	4.57	4.31	3.73	4.92	3.26				1.27, 1.31	
							3.19				1.40, 1.43	
9[c]	5.56	4.32	4.61	4.25	3.87	4.99	3.24				1.29, 1.32	
							3.24				1.42, 1.49	
10	5.45	4.27	4.58	4.44	3.62	4.21	3.01		4.40	4.03	1.28, 1.33, 1.35	3.15
							2.79			4.15	1.41, 1.44, 1.47	
11	5.51	4.30	4.61	4.47	3.56	*d*	2.09	*d*	*d*	*d*	1.31, 1.34, 1.36	3.18
							e				1.40, 1.46, 1.51	3.50
12	5.49	4.29	4.60	4.48	3.63	4.07	1.84	3.91	3.71	3.99	1.30, 1.33, 1.34	2.69
							1.60			3.99	1.40, 1.42, 1.50	3.18
13	5.47	4.25	4.54	4.35	3.55	4.07	1.16	3.75	3.89	3.85	1.30, 1.32, 1.34	
							2.08			4.04	1.38, 1.42	
14	5.48	4.27	4.55	4.33	3.62	4.07	1.74	3.85	4.10	3.68	1.31, 1.32, 1.35	
							1.60			4.00	1.38, 1.42	
15	5.51	4.31	4.61	4.46	3.55	4.04	1.93	4.00	3.47		1.31, 1.36	1.80, 2.43
							1.56		3.63		1.45, 1.50	3.60
16	5.51	4.31	4.62	4.47	3.64	4.06	1.87	4.06	3.52		1.31, 1.35	1.85
							1.67		3.52		1.44, 1.51	2.51
17	5.48	4.28	4.58	4.35	3.66	4.78	3.09		4.36		1.29, 1.33	2.5
							3.09				1.42, 1.45	
18	5.43	4.25	4.56	4.39	3.53	4.21	2.80		4.23		1.26, 1.30	3.27, 3.36
							2.56				1.38, 1.45	
19	5.58	4.34	4.63	4.59	4.30	6.93	6.78		4.46	4.06	1.29, 1.32, 1.38	
										4.19	1.39, 1.43, 1.49	

[a] Recorded in $CDCl_3$ at 360 MHz. [b] Also δ 4.28 (OCH_2) and 1.30 (CH_3). [c] Also δ 4.33 (OCH_2) and 1.35 (CH_3). [d] Complex multiplet at δ 3.69–4.07. [e] Resonance hidden by Me signals.

glycine ethyl ester hydrochloride.[17] The dipolarophile component, D-*galacto*-hept-6-enopyranose derivative **3**, was synthesized as previously described[18] from 1,2:3,4-di-*O*-isopropylidene-α-D-galactose by pyridinium chlorochromate (PCC) oxidation of the 6-hydroxymethyl group to the aldehyde followed by Wittig olefination with methylenetriphenylphosphorane.



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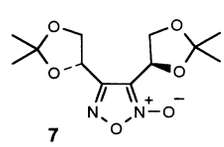

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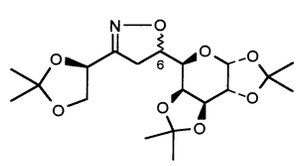
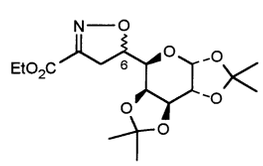


5 6*R*
6 6*S*



8 6*R*
9 6*S*

Cycloaddition reactions

A solution of hydroximoyl chloride **4** in diethyl ether was added during 12 h to a mixture of alkene **3** and triethylamine in diethyl ether. After removal of the precipitated triethylamine hydrochloride by filtration the residue was concentrated and chromatographed to afford, in order of elution, unchanged alkene **3** (48% recovered) and furoxan **7** (14%), followed by a fraction containing two isoxazoline cycloadducts **5** and **6** in a combined yield of 40%. The isomers were separated by further chromatography and compound **6** purified by recrystallisation. The recovered alkene was sufficiently pure to be recycled. The products have characteristic NMR spectra (Tables 1–3). The isoxazoline ring protons appear as an ABX system with 6-H (at the 5- position of the isoxazoline ring) at highest chemical shift; the ^3J values of 7–11 for 6-H/7-H^{a,b} and the geminal coupling of ~18 Hz for 7-H^a/7-H^b are also typical of 3,5-disubstituted isoxazolines.[14f,19–21] The couplings for the pyranose ring protons reflect the conformational constraints imposed by the dioxolane rings fused at C-1/C-2 and C-3/C-4; the ^3J-values for 1-H/2-H, 2-H/3-H, 3-H/4-H and 4-H/5-H of ~5, 2.5, 8 and 2 Hz, respectively, are consistent with the expected distortion from the $^4C_1$ conformation towards a skew arrangement. The isomer ratio (87:13) was measured from the ^{1}H NMR spectrum of the product mixture by comparison of the anomeric proton signals which are well separated. The individual diastereoisomeric isoxazolines **5** and **6** were identified by comparison of their physical and spectroscopic properties with adducts **8** and **9**, obtained from the corresponding reaction of ethoxycarbonylformonitrile oxide **2** with the same alkene, the structures of which had previously been established by X-ray crystallography.[18] The NMR data for isoxazoline moieties are distinctive for each adduct (see Tables 1–3). In particular, the signals for 1-H and 5-H are at lower chemical shift for the major isomers ($\Delta\delta_{1\text{-H}}$ −0.06 for **5**/**6**, −0.10 ppm for **8**/**9**; $\Delta\delta_{5\text{-H}}$ −0.17 for **5**/**6**, −0.14 ppm for **8**/**9**), whereas proton 4-H absorbs at higher frequency ($\Delta\delta_{4\text{-H}}$ +0.06 ppm for both **5**/**6** and **8**/**9**). In the ^{13}C NMR spectra C-6 resonates at lower frequency for the major isomer ($\Delta\delta_{C\text{-}6}$ = −1.7 for **5**/**6**, −1.6 ppm for **8**/**9**), whereas the order is reversed for C-7 ($\Delta\delta_{C\text{-}7}$ +1.5 for **5**/**6**, +0.7 ppm for **8**/**9**). Furthermore the major adduct in each case has the more negative optical rotation (**5** −62.4, **6** +3.4; **8** −181.7, **9** −84.2), and has the greater R_f value for TLC on silica. Similar correlations have been employed on several occasions to assign the stereochemistry of diastereoisomeric pairs of isoxazolines resulting from cycloaddition of nitrile oxides to carbohydrate alkenes.[18–20] The major adduct was therefore assigned structure **5** which, like **8**, has an *R*-configuration at the newly-created asymmetric centre C-6 and an *erythro* relationship between this carbon and the adjacent carbon (C-5). The minor product therefore has 6-*S* structure **6**.

The regiospecificity of the cycloaddition and the diastereoselective preference for *erythro* products is typical for the reactions of nitrile oxides with chiral allyl ethers. The corresponding addition of ethoxycarbonylformonitrile oxide **2** to alkene **3** afforded a 91:9 mixture of isoxazolines **8** and **9** in 62% overall

Table 2 ^{1}H NMR couplings (J_{x-y}/Hz)[a]

	1–2	2–3	3–4	4–5	5–6	6–7	7a–7b	7–8	8–9	9–10	10a–10b
5	4.9	2.4	8.0	1.8	8.0	7.0 9.5	17.6			6.0 6.7	8.7
6	4.9	2.3	7.9	1.7	7.1	8.2 10.8	17.4			6.1 6.8	8.5
8[c]	4.9	2.5	7.9	1.8	7.1	8.1 10.7	18.2				
9[c]	5.0	2.5	7.9	1.9	7.5	10.1 10.1	*b*				
10	5.0	2.4	8.0	1.9	8.7	3.0 8.1	18.2			5.5 7.7	8.7
11	5.0	2.4	8.0	1.9	8.1	2.1 *b*	14.4	*b* 2.1	*b*	*b* *b*	*b*
12	5.1	2.4	8.0	1.8	8.7	3.1 7.3	14.5	9.7 2.6	*b*	*b* *b*	*b*
13	4.9	2.2	8.0	1.7	8.8	11.6 2.5	13.1	11.6 2.5	7.3	5.2 5.9	8.0
14	5.0	2.3	8.0	1.8	9.2	9.2 6.1	13.0	6.3 9.8	7.5	6.5 6.5	8.3
15[d]	5.0	2.4	8.0	1.9	8.2	2.3 10.1	14.5	2.3 10.1	6.6 3.4		
16	5.1	2.4	8.0	2.0	8.3	3.3 7.9	14.5	8.9 3.3	7.8 11.2		
17	5.1	2.4	8.0	1.8	7.7	8.5	8.5				
18	5.0	2.4	7.9	1.9	8.7	3.4 8.1	16.5				
19[e]	5.0	2.6	7.7	5.7	4.0	15.8				5.6 7.5	8.5

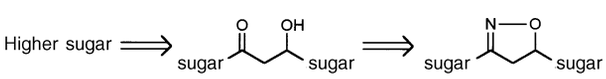
[a] Recorded in $CDCl_3$ at 360 MHz. [b] Not determined. [c] Also CH_2–CH_3 7.2. [d] Also 7a–7b 11.1. [e] Also 5–7 1.8.

Table 3 ^{13}C NMR chemical shifts (δ_C/ppm)[a]

	C-1	C-2–C-5	C-6	C-7	C-8	C-9	C-10	CMe_2	CMe_2
5	96.1	70.8, 70.6, 70.2 70.1, 67.4	78.0	36.7	158.5	*b*	66.8	110.2, 109.3 108.7	26.1, 25.9, 25.7 25.0, 24.8, 24.1
6	96.3	71.0, 70.7, 70.6 70.5, 67.4	79.6	35.2	158.2	*b*	66.9	110.1, 109.4 108.6	26.1, 26.0, 25.8 25.0, 24.8, 24.2
8[c]	96.0	70.4, 70.3 70.2, 67.5	81.0	36.0	151.9	160.4		109.3 108.6	25.8, 25.6 24.7, 24.0
9[d]	96.2	70.7, 70.4 70.3, 68.1	82.6	35.3	151.8	160.5		109.6 108.7	26.0, 25.7 24.8, 24.2
10	96.2	70.5, 70.4 70.1, 69.0	65.9	42.0	211.2	80.2	66.0	110.9, 109.1 108.6	26.1, 26.0, 25.8 24.9, 24.8, 24.2
11	96.3	72.3, 71.2 70.4, 69.7	*b*	35.6	*b*	78.3	65.1	109.2, 109.0 108.5	26.3, 25.9, 25.8 25.1, 24.8, 24.2
12	96.4	70.6, 70.5, 69.8 69.0, 67.4	*b*	35.6	*b*	78.9	65.9	109.4, 109.1 108.4	26.5, 25.8, 25.3 24.8, 24.3
13	96.1	71.0, 70.5, 70.4 70.3, 69.6, 66.3	77.1	31.6	*b*	78.2	66.9	109.2, 108.7 108.4, 98.6	29.6, 26.6, 26.1, 25.9 25.1, 24.9, 24.3, 19.7
14	96.2	70.8, 70.4, 70.3 70.0, 68.3, 63.9	*e*	31.5	*b*	78.0	65.4	109.7, 108.8 108.4, 100.8	26.6, 26.1, 25.9, 25.3 24.8, 24.4, 24.3, 24.3
15	96.2	72.4, 70.6, 70.4 70.3, 70.0	*b*	35.8	*b*	66.6		109.2, 108.5	25.8, 24.7, 24.2
16	96.3	70.7, 70.5, 70.4 69.4, 67.9	*b*	35.9	*b*	66.7		109.2, 108.5	25.8, 24.7, 24.3
17	96.1	77.5, 70.6 70.3, 67.6	78.1	37.7	158.9	57.8		109.2, 108.6	25.7, 24.7, 24.2
18	96.2	70.5, 70.1, 69.4	66.2	41.7	210.2	68.7		109.2, 108.6	25.7, 24.7, 24.2
19	96.3	72.5, 70.8 70.4, 67.7	125.0	143.1	197.8	79.6	66.4	110.9, 109.6 108.6	25.9, 25.8, 25.7 25.3, 24.7, 24.4

[a] Recorded in $CDCl_3$ at 90 MHz. [b] In the region C-2–C-5. [c] Also 61.8 (OCH_2) and 13.9 (CH_3). [d] Also 61.9 (OCH_2) and 14.0 (CH_3). [e] Not assigned.

yield.[18] In both cases the predominance of *erythro* adducts can be rationalised in terms of the so-called 'inside alkoxy effect' proposed by Houk *et al.*[22]



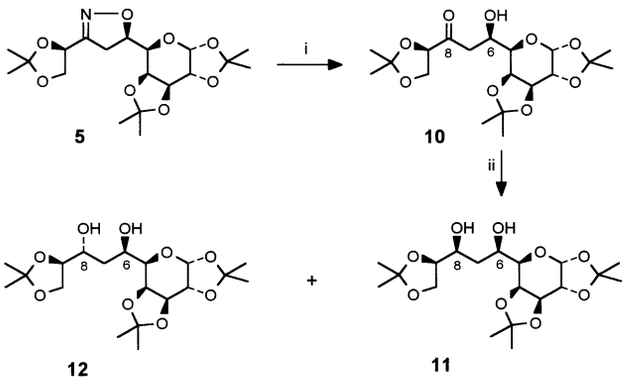
Scheme 3

Isoxazoline ring opening

The next step in the route to higher monosaccharides involves reductive hydrolytic ring opening of the isoxazoline to a β-hydroxy ketone (Scheme 3).

Various techniques have been reported[14] for the cleavage of the N–O bond including hydrogenation with palladium/charcoal or Raney nickel, treatment with molybdenum hexacarbonyl[23] or titanium trichloride,[24] and ozonolysis.[25] For the present work we employed hydrogenation with a palladium/charcoal catalyst in the presence of boric acid, methanol and water. These conditions, which are based on the optimised procedure developed by Curran,[14c] are designed to minimise

epimerisation and competing side-reactions involving over-reduction of the putative β-hydroxy imine intermediate and retro-aldol fragmentation. Using this method the isoxazoline **5** was converted into 7-deoxy-8-osulose derivative **10** in 67% yield (Scheme 4). The product, which was readily detected on TLC



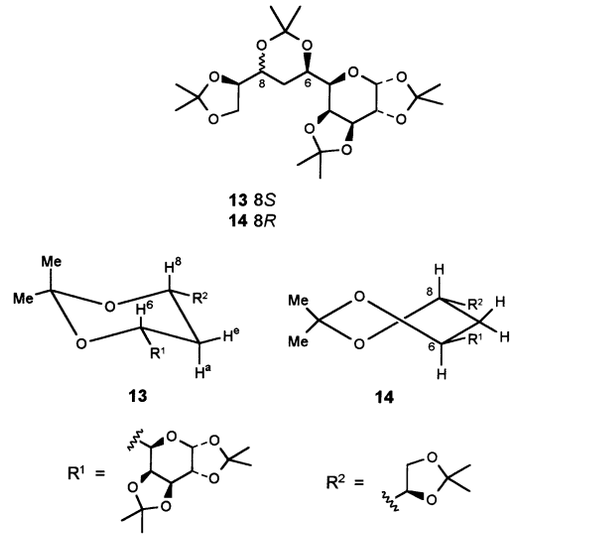
Scheme 4 *Reagents and solvents:* i, H_2, Pd/C, H_3BO_3, aq. MeOH; ii, $NaBH_4$, aq. EtOH

by staining with Brady's reagent, was identified by its spectroscopic properties and its elemental composition (established by high-resolution FAB mass spectroscopy). The presence of the carbonyl group was confirmed by an IR peak at 1722 cm^{-1} and a ^{13}C NMR signal at δ_C 211. In other respects the NMR spectra (Tables 1–3) are broadly similar to those of the isoxazoline starting material, with the only significant deviations being associated with replacement of the isoxazoline unit by a β-hydroxy ketone. The signals for carbons 7 and 9 are displaced to higher chemical shift, and there are corresponding shifts to lower frequency for C-6 and, in the proton spectrum, for the ABX pattern attributable to 6-H and 7ab-H, and for 9-H adjacent to the carbonyl.

Reduction of decos-8-ulose 10

The final step in the sequence involves reduction of the carbonyl group at C-8. This was readily accomplished by treatment with sodium borohydride in ethanol–water to afford a mixture of 7-deoxydecopyranose derivatives **11** and **12** in 60% combined yield. As expected for this reducing agent the degree of selectivity was low (4:5 by HPLC), thus providing access to both diastereomers, which were separated by chromatography. The replacement of the carbonyl group in the starting material by hydroxymethylene results in characteristic changes in the NMR spectra. In the carbon spectrum the carbonyl peak at δ_C 211 is replaced by CHOH signals at δ_C ~70, and there are corresponding shifts for the adjacent C-7 methylene (δ_C 42→36). Similarly the α-proton signals are displaced from δ_H 3.01 and 2.79 for 7-H^{a,b} to δ_H 2.09 and 1.84/1.60 and from δ_H 4.4 to δ_H ~3.7 for 9-H.

In order to determine the configuration of the newly created chiral centre C-8 the 6,8-diols **11** and **12** were converted into the 6,8-*O*-isopropylidene ketals **13** and **14**, by treatment with acetone and 2,2-dimethoxypropane in the presence of a catalytic amount of toluene-*p*-sulfonic acid (PTSA). The diol unit was thus locked in a six-membered 1,3-dioxane ring for which the vicinal coupling constants of the chair conformers are predictable. Examination of the ^1H NMR spectra in the region of the C-7 methylene protons revealed distinctive patterns for two isomers (Fig. 1 and Table 2). One isomer, assigned structure **13**, has typical chair couplings: 7-H^a has identical axial–axial couplings of 11.6 Hz to 6-H and 8-H, whereas 7-H^e shows two small equatorial–axial couplings of 2.5 Hz. Such a chair structure can only be accommodated by the 6*R*,8*S* isomer **13** in which the dioxane substituents at C-6 and C-8 both occupy equatorial positions. The other isomer **14** must necessarily have 6*R*,8*R* stereochemistry for which a chair arrangement would necessitate one of the substituents being in an unfavourable axial position. The ^3J values for compound **14** confirm this prediction, and are best explained in terms of a 2,5-twist boat/skew conformation in which the bulky substituents are pseudo-equatorial (Fig. 1). Nuclear Overhauser enhancement (NOE) measurements provide additional support for the above assignments. Mutual enhancement was observed on irradiation of 1,3-diaxial protons 6-H and 8-H for compound **13**, whereas there was no such interaction for the corresponding protons in compound **14**. Further support for this assignment is provided by their ^{13}C NMR data. The signals for the methyl carbons of the newly formed 6,8-*O*-isopropylidene ketals are distinctive for the two isomers. For compound **13** the axial and equatorial methyl carbon peaks are well separated at δ_C 19.7 and 29.6 respectively ($\Delta\delta_C$ 9.9 ppm), whereas for isomer **14** both fall in the range δ_C 24–27. Previous studies by Buchanan *et al.*[26] have shown that such values are typical of chair and skew arrangements. Furthermore, the signals for the quaternary carbons (*C*Me$_2$) at δ_C 98.5 for compound **13** and δ_C 100.8 for compound **14** are also in accord with the literature values for chair (δ_C 97.1–99.9) and skew (δ_C 100.6–101.1) conformations.[26]

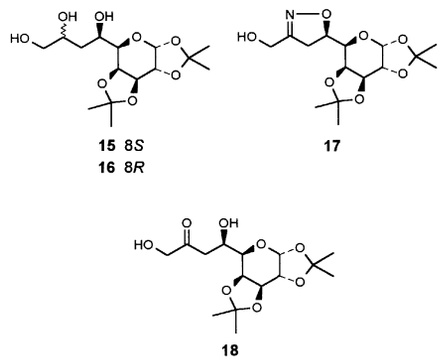


	$J_{6,7a}$	$J_{6,7e}$	$J_{7a,7a}$	$J_{7a,8}$	$J_{7e,8}$
13	11.6	2.5	13.1	2.5	11.6
14	9.2	6.1	13.0	6.3	9.8

Fig. 1 Chair and skew conformations for compounds **13** and **14**

Conversion of the isoxazoline 8 into 7-deoxynonoses 15 and 16

A similar approach was adopted for the preparation of 7-deoxynonopyranose derivatives **15** and **16** from the 3-ethoxycarbonylisoxazoline **8**. In this case, however, no reaction occurred upon subjecting the isoxazoline to the standard hydrogenolysis conditions, the starting material being recovered in quantitative yield. Difficulties in ring opening 3-ethoxycarbonylisoxazolines to γ-amino alcohols have been reported previously,[27] the problem being attributed to conjugation between the substituent and the isoxazoline strengthening the N–O bond. It may therefore be assumed that the same effect prevents the formation of the β-hydroxy ketone in the present case. To overcome this problem the ethoxycarbonylisoxazoline was first converted into the hydroxymethyl derivative **17** by reduction with sodium borohydride in ethanol. The latter isoxazoline was then smoothly converted into the β-hydroxy ketone (7-deoxynonos-8-ulose) **18**, which was readily detectable on TLC by staining with Brady's reagent and identified from its spectroscopic properties [ν_{max}/cm^{-1} 1720; δ_C 210 (C=O)].

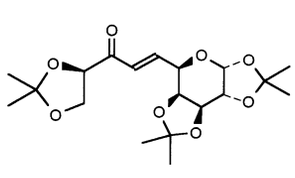


Finally, reduction of the carbonyl group at C-8 with $NaBH_4$/EtOH yielded 7-deoxynonose compounds **15** and **16**. The product ratio (4:5) was determined by HPLC analysis and the individual isomers were separated by chromatography and identified from their NMR spectra (Tables 1–3).

Comparison of the NMR spectra of 1,3-diols **15** and **16** with that of the parent β-hydroxy ketone **18** shows the expected chemical-shift changes associated with the protons attached to C-7 and C-9, *i.e.* those adjacent to the new chiral centre C-8. The signal(s) for 9-H move to lower δ value by 0.6–0.8 ppm, and the corresponding shift for 7-H is even more pronounced ($\Delta\delta_H$ 0.8–1.0 ppm). For the C-7 methylene protons there are also significant differences in the splitting patterns for the two diastereoisomers, and these allow the configuration at the new asymmetric centre (C-8) to be predicted (Fig. 2). In the major isomer (assigned structure **16**) the signals for 7-H^a and 7-H^e each appear as doublets of doublets of doublets ($J_{7a,7e}$ 14.6, $J_{7a,6}$ 3.3, $J_{7a,8}$ 8.9, $J_{7e,6}$ 7.9, $J_{7e,8}$ 3.3 Hz), whereas the minor isomer (assigned structure **15**) exhibits two well defined sets of more widely spaced doublets of triplets ($J_{7a,7e}$ 14.5, $J_{7a,6} = J_{7a,8}$ 10.1, $J_{7e,6} = J_{7e,8}$ 2.3 Hz). The adoption of a hydrogen-bonded chair-type conformation (Fig. 2) for the latter compound in which the hydroxymethylene and pyranose substituents both occupy the sterically less demanding equatorial positions fits the data for structure **15**. Conformer **A** incorporates the hydrogen of the 8-OH group in hydrogen bonding, whereas **B** represents the alternative arrangement involving the hydrogen of the 6-hydroxy group. In both structures 7-H^a would be expected to have two large axial–axial couplings, and 7-H^e two smaller equatorial couplings, as was observed. This isomer is therefore assigned structure **15** with 6*R*,8*S* configuration. In contrast, for the other diastereomer (6*R*,8*R*) the equivalent chair conformations would require one of the bulky substituents to be axial. The observed couplings are consistent with the expected distortion from a chair to a skew-like arrangement.

Dehydration of decos-8-ulose 10 to α-enone 19

In order to increase the range of functionality accessible from the higher sugar isoxazolines a preliminary investigation was carried out of the conversion of decos-8-ulose **10** into the corresponding α,β-unsaturated ketone, *i.e.* dec-6-enosulose **19**. The



dehydration was accomplished by acetylation with acetic anhydride in pyridine which, under the reaction conditions, is followed by spontaneous elimination of acetic acid. The resulting enosulose was identified by its spectroscopic properties and its elemental composition, confirmed by high-resolution mass spectrometry. In the ^{13}C NMR spectrum there are characteristic olefinic peaks at δ_C 125 and 143 for C-6 and C-7 of the α-enone

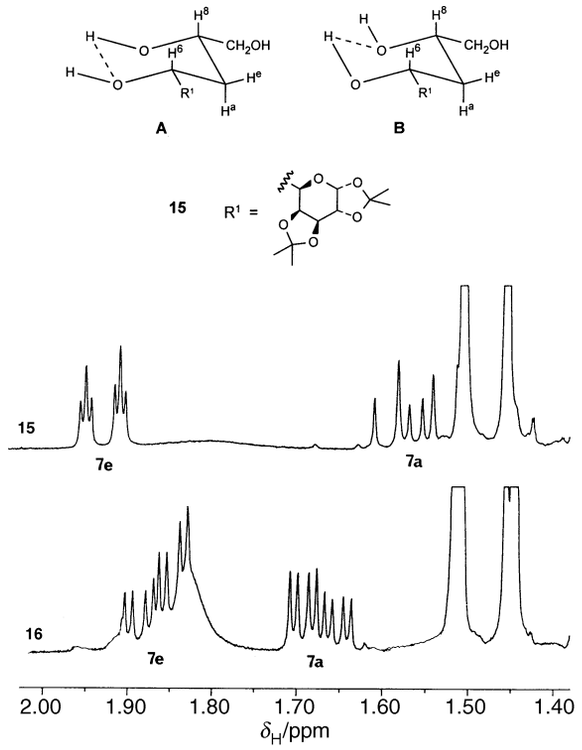


Fig. 2 ^1H NMR signals for 7-H^a/7-H^e for 7- deoxynonose derivatives **15** and **16**

unit; the carbonyl absorption is, as expected, shifted to lower δ value (δ_C 198) compared with the parent osulose (δ_C 211). The ^1H NMR signals for the enone protons appear at δ_H 6.93 and 6.78 with a mutual coupling of 15.8 Hz indicative of *trans*(*E*) geometry. None of the *cis*(*Z*) isomer was detected.

In summary, the present work has demonstrated that nitrile oxide/isoxazoline chemistry can be utilised to provide access to higher-carbon monosaccharides from readily available precursors. The route is flexible; it can accommodate a range of sugar alkenes and nitrile oxides for the cycloaddition step, the substituents on the resulting isoxazoline can be modified leaving the heterocycle intact and its ring-opening reactions have the potential to release various functionality. We therefore consider that this approach should be useful for the synthesis of a variety of higher monosaccharide derivatives. In subsequent papers current investigations into the application of this methodology for the synthesis of octose, nonose and undecose analogues, and also higher-carbon dialdoses, will be reported.

Experimental

The analytical methods and instrumentation were as previously described.[18,20,21] 6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hept-6-enopyranose **3** was prepared according to the literature procedure[18] involving Wittig olefination of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose. The purity of new compounds was established by NMR spectroscopy and by TLC (silica; hexane–Et_2O, 3:1). NMR Data for the products (**5**, **6**, **8**–**18**) are given in Tables 1–3.

2,3-*O*-Isopropylidene-D-glycerohydroximoyl chloride 4[16]

Dry chlorine gas was bubbled slowly through a stirred solution of 2,3-*O*-isopropylidene-D-glyceraldehyde oxime[28] (0.68 g, 4.7 mmol) in dry diethyl ether (100 ml) at −60 °C for *ca.* 5 min (until the solution became an opaque turquoise in colour). After warming to room temperature the mixture was evaporated *in vacuo* without heating. Dry benzene was added and evaporated *in vacuo* several times until the hydroximoyl chloride **4** was obtained as a solid (0.82 g, 98%).

Cycloaddition of 2,3-*O*-isopropylidene-D-glyceronitrile oxide 1 to alkene 3

A solution of 2,3-*O*-isopropylidene-D-glycerohydroximoyl chloride (2.30 g, 12.8 mmol) in dry diethyl ether (40 ml) was added over a period of 12 h using a motorised syringe to an ice-cooled, stirred solution of the alkene (5.00 g, 19.5 mmol) and triethylamine (1.40 g, 13.9 mmol) in diethyl ether (100 ml). After being stirred for a further 4 h the mixture was filtered to separate precipitated triethylamine hydrochloride, and the solvent was removed *in vacuo*. Chromatography of the residue (silica; gradient elution with 9:1→3:2 hexane–diethyl ether) afforded, in order of elution, unchanged alkene (2.40 g, 48% recovery), 3,4-bis[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]furan *N*-oxide **7** (0.13 g, 14%) [Found: *m/z*, 287.124 29 $(M + H)^+$. $C_{12}H_{19}N_2O_6$ requires (*M* + H), 287.124 30]; (5R)-5-(1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*pyranos*-5-*yl*)-3-[(4R)-2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*]-4,5-*dihydroisoxazole* **5** (1.95 g, 38%) as an oil [Found: *m/z*, 400.197 13 $(M + H)^+$. $C_{19}H_{30}NO_8$ requires (*M* + H), 400.197 12]; $[\alpha]_D^{21}$ −62.4 (*c* 0.63, $CHCl_3$); and (5S)-5-(1,2:3,4-*di*-O-*isopropylidene*-α-D-galacto-*pyranos*-5-*yl*)-3-[(4R)-2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*]-4,5-*dihydroisoxazole* **6** (65 mg, 2%) as needles, mp 141–142 °C (from ethanol) [Found: $(M + H)^+$, 400.197 13. $C_{19}H_{30}NO_8$ requires (*M* + H), 400.197 12]; $[\alpha]_D^{21}$ +3.4 (*c* 1.52, $CHCl_3$). The isomer ratio (**5**:**6** = 87:13) was measured from the ^{1}H NMR spectrum of the mixture of adducts by comparison of the anomeric proton signals at δ 5.47 and 5.53.

(5*R*)- and (5*S*)-5-(1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-ethoxycarbonyl-4,5-dihydroisoxazoles 8 and 9

These were prepared (56 and 6%) by cycloaddition of ethoxycarbonylformonitrile oxide, generated by dehydrochlorination of ethyl chloro(hydroxyimino)acetate,[17] to give alkene **3** as previously reported.[18]

(5*R*)-5-(1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-pyranos-5-yl)-3-hydroxymethyl-4,5-dihydroisoxazole 17

A solution of the isoxazoline **8** (500 mg, 1.25 mmol) in ethanol–tetrahydrofuran (THF) was treated with sodium borohydride (6 mol equiv.) and the mixture was stirred at ~20 °C for 16 h. After being poured into water the organic phase was separated, dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford the *title product* as an oil (425 mg, 96%) [Found: $(M + H)^+$, 330.155 25. $C_{15}H_{24}NO_7$ requires (*M* + H), 330.155 26]; $[\alpha]_D^{21}$ −136.3 (*c* 2.03, $CHCl_3$).

Hydrogenolysis of isoxazolines. General procedure

A mixture of the isoxazoline (1 mol equiv.), boric acid (6 mol equiv.) and 10% Pd/C (100 mg per mol equiv. of isoxazoline) in methanol–water (5:1; ~15 ml per 100 mg of isoxazoline) was degassed, flushed several times with hydrogen, and stirred under hydrogen for 18 h. After filtration through a Celite pad the mixture was concentrated *in vacuo* (~20 °C; 1 mmHg). Methanol was added and evaporated off several times (to remove the remaining boric acid as trimethyl borate) to afford the β-hydroxy ketone (8-osulose) as an oil. NMR Spectroscopy indicated that further purification was not necessary.

7-Deoxy-1,2:3,4:9,10-tri-*O*-isopropylidene-D-*erythro*-D-*galacto*-decos-8-ulo-1,5-pyranose 10. *This* was obtained from isoxazoline **5** as an *oil* (67%) using the general procedure [Found: $(M + 2H)^+$, 404.204 64. $C_{19}H_{32}O_9$ requires $(M + 2H)^+$, 404.204 61]; $[\alpha]_D^{21}$ −18.0 (*c* 0.31, $CHCl_3$); ν_{max}(film)/cm^{-1} 3460 (OH) and 1722 (C=O).

7-Deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-nonos-8-ulo-1,5-pyranose 18. *This* was obtained similarly from isoxazoline **8** as an *oil* (86%) [Found: $(M + 2H)^+$, 334.162 75. $C_{15}H_{26}O_8$ requires $(M + 2H)^+$, 334.162 76]; $[\alpha]_D^{21}$ −47.2 (*c* 0.78, $CHCl_3$); ν_{max}(film)/cm^{-1} 3350 (OH) and 1720 (C=O).

Reduction of 8-osuloses 10 and 18 with sodium borohydride. General procedure

A solution of sodium borohydride (0.4 mol equiv.) in water (2 ml) was added to an ice-chilled solution of the β-hydroxy ketone (1.0 mol equiv., ~100 mg) in ethanol–water (3:1; 4 ml). After stirring of the mixture for *ca.* 16 h the ethanol was removed *in vacuo*, a few drops of acetone were added to decompose the excess of reagent, and the mixture was extracted into $CHCl_3$ (5 × 0.5 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford a mixture of alcohols, which were purified by preparative TLC (PLC) (silica; Et_2O–hexane). The product ratios were determined by HPLC (ODS silica; MeOH–H_2O, 55:45).

7-*Deoxy*-1,2:3,4:9,10-*tri*-O-*isopropylidene*-D-ribo-α-D-galacto-*decopyranose* **11** (26%) [Found: $(M + H)^+$, 405.212 43. $C_{19}H_{33}O_9$ requires (M + H), 405.212 44]; $[\alpha]_D^{21}$ −31.1 (*c* 0.82, $CHCl_3$) and 7-*deoxy*-1,2:3,4:9,10-*tri*-O-*isopropylidene*-D-xylo-α-D-galacto-*decopyranose* **12** (34%) [Found: $(M + H)^+$, 405.212 43]; $[\alpha]_D^{21}$ −30.2 (*c* 0.59, $CHCl_3$).

7-*Deoxy*-1,2:3,4-*di*-O-*isopropylidene*-L-threo-α-D-galacto-*nonopyranose* **15** (19%) [Found: $(M + H)^+$, 335.170 60. $C_{15}H_{27}O_8$ requires (*M* + H), 335.170 58]; $[\alpha]_D^{21}$ −50.5 (*c* 0.48, $CHCl_3$) and 7-*deoxy*-1,2:3,4-*di*-O-*isopropylidene*-D-erythro-α-D-galacto-*nonopyranose* **16** (14%) [Found: $(M + H)^+$, 335.170 60]; $[\alpha]_D^{21}$ −45.6 (*c* 0.52, $CHCl_3$).

6,8-Isopropylidene derivatives of 7-deoxydecoses 11 and 12. General procedure

A mixture of the decose (45–60 mg), 2,2-dimethoxypropane (2 ml), dry acetone (2 ml) and a catalytic amount of PTSA was stirred at ~20 °C for 16 h. Saturated aq. $NaHCO_3$ (2–4 drops) was added and the mixture was extracted into dichloromethane. The combined organic layers were dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude ketal, which was purified by PLC (silica; Et_2O–hexane, 1:1).

7-*Deoxy*-1,2:3,4:6,8:9,10-*tetra*-O-*isopropylidene*-D-ribo-α-D-galacto-*decopyranose* **13** (39%) [Found: $(M + H)^+$, 445.243 77. $C_{22}H_{37}O_9$ requires (M + H), 445.243 74]; $[\alpha]_D^{21}$ −47.9 (*c* 0.66, $CHCl_3$).

7-*Deoxy*-1,2:3,4:6,8:9,10-*tetra*-O-*isopropylidene*-D-xylo-α-D-galacto-*decopyranose* **14** (32%) [Found: $(M + H)^+$, 445.243 77]; $[\alpha]_D^{21}$ −28.1 (*c* 0.14, $CHCl_3$).

Dehydration of 7-deoxydecos-8-ulose 10

A solution of decosulose **10** (87 mg, 0.22 mmol) and acetic anhydride (0.1 ml) in pyridine (3 ml) was stirred at ~20 °C for 48 h. The solvent was removed *in vacuo* and the residue was purified by PLC (silica; Et_2O–hexane 1:1) to afford (E)-6,7-*dideoxy*-1,2:3,4:9,10-*tri*-O-*isopropylidene*-D-glycero-α-D-galacto-*dec*-6-*enos*-8-*ulo*-1,5-*pyranose* **19** (38 mg, 46%) as an oil [Found: $(M + H)^+$, 385.186 21. $C_{19}H_{29}O_8$ requires (*M* + H), 385.186 23]; $[\alpha]_D^{21}$ −59.7 (*c* 1.54, $CHCl_3$); ν_{max}(film)/cm^{-1} 1730 (C=O) and 1630 (C=C).

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