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The nitrile oxide/isoxazoline approach to eleven-carbon monosaccharides: cycloaddition of D- and L-arabinonitrile oxides to 5,6-dideoxyhex-5-enofuranoses and characterisation of the resulting 2-isoxazolines☆

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Abstract

Cycloaddition of 2,3:4,5-di-*O*-isopropylidene-D-arabinonitrile oxide **5**, generated by base-induced dehydrochlorination of hydroximoyl chloride **10**, to D-Glc-derived alkene **7** afforded an 89:11 diastereomeric mixture of (5*R*)- and (5*S*)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-4,5-dihydroisoxazoles **11** and **12**. The corresponding reaction of nitrile oxide **5** with D-Man-derived alkene **8** proceeded similarly yielding 4,5-dihydroisoxazoles **17** and **18** (82:18). Comparable levels of π-facial selectivity (66–76% d.e.) in favour of 5R-adducts were observed for the reactions of L-Ara-derived nitrile oxide **6** with alkenes **7** and **8** to form dihydroisoxazoles **23**/**24** and **25**/**26**, thus demonstrating that the configuration of the nitrile oxide component in the cycloaddition has little effect on the stereochemical outcome of the reaction. The structure of dihydroisoxazoline **23** was determined by X-ray crystallography, and cycloadducts **11**, **12**, **17**, **18**, **23**–**26** were identified from their physical and spectroscopic properties by comparison with those of known analogues prepared from the same alkenes.

Keywords: Nitrile oxide cycloadditions; 2-Isoxazolines (4,5-dihydroisoxazoles); Undecose derivatives; X-ray crystallography

1. Introduction

Monosaccharides having a backbone of seven or more carbon atoms, i.e., heptoses, octoses, nonoses, etc., are collectively referred to as higher-carbon sugars [2]. Compared with the pentoses and hexoses which occur both in the free form and as components of numerous biopolymers, these chain-extended monosaccharides are less abundant and are usually found as subunits of natural products of varied biological function.

Eleven-carbon monosaccharides are of particular interest as they have been identified in several nucleoside antibiotics. For instance, the anthelmintic agent hikizimycin (also named anthelmycin) incorporates the aminoundecose hikosamine **1** [3,4]. Other examples include the tunicamycins [5], which exhibit antimicrobial, antifungal and antiviral activ-

☆ For a preliminary description of part of this work, see Ref [1].

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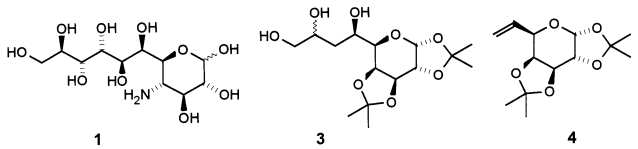
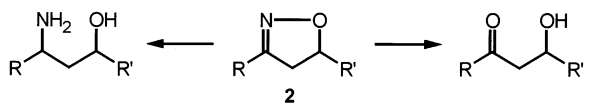
ity, and the herbicidins [6] which possess both antibiotic and herbicidal properties. The identification of such long-chain monosaccharides and recognition of the key roles they play when incorporated into larger structures has stimulated interest in developing effective methods for their synthesis. The structural complexity of these polyhydroxylated compounds presents a synthetic challenge, particularly in terms of the stereochemical control of the required carbon–carbon bond forming reactions. Several approaches have been adopted including iterative one, two, three and four carbon extensions of aldoses, convergent carbohydrate couplings and stereoselective syntheses from non-carbohydrate precursors. Techniques employed for the assembly of undecose carbon skeletons include Wittig-olefination/osmylation [4,7,8], radical coupling reactions [9], aldol [10,11] and nitroaldol additions [12], four-carbon extensions via butenolides [13,14], diene–aldehyde cyclocondensations [15], and addition reactions of carbohydrate-based enolates [10,16]. Methods based on 2-(trimethylsilyl)thiazole chemistry [17] and the so-called 'naked-sugar approach' involving modification of 7-oxanorbornenyl derivatives [11] have also been reported. In this and the following paper we describe a new route, based on nitrile oxide/isoxazoline chemistry [18], which provides access to 11-carbon sugars from readily available starting materials.



1 3 4

1,3-Dipolar cycloaddition of nitrile oxides ($RC{\equiv}N^{+}-O^{-}$) to alkenes affords 2-isoxazolines (4,5-dihydroisoxazoles, **2**) from which various functionality including β-hydroxyketones and γ-aminoalcohols can be released by cleavage of the N–O bond (Scheme 1). In recent years, this methodology has been widely used



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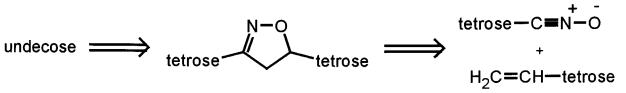
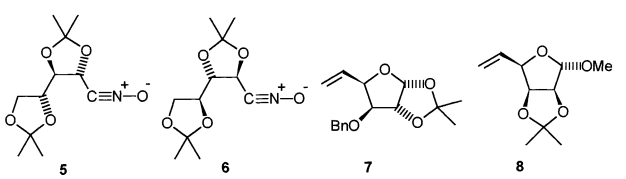
Scheme 1.



Scheme 2.

for the synthesis of natural products and analogues [18]. We have recently reported [19] its application for the preparation of nonose and decose derivatives; for example, the key carbon–carbon bond forming step in the synthesis of nonose derivative **3** involves 1,3-dipolar cycloaddition of a two-carbon nitrile oxide ($EtO_2CC{\equiv}N^{+}-O^{-}$) to the 6,7-dideoxyhept-6-enopyranoside **4** derived from D-Gal. We considered that this methodology would also be well suited for the construction of 11-carbon monosaccharides. Several possible combinations of 1,3-dipole (nitrile oxide) and olefinic dipolarophile components are conceivable, e.g., 4-carbon nitrile oxide plus 7-carbon alkene, 5-carbon nitrile oxide plus 6-carbon alkene, etc. For the present investigation we chose to use five-carbon nitrile oxides with six-carbon dipolarophiles as much of the desired stereochemical features of the target undecoses is already present in the starting materials, which are themselves readily accessible by established literature procedures. The approach, which is illustrated in Scheme 2, involves chain-elongation at the non-reducing terminus of ω-unsaturated hexoses by cycloaddition with pentose-derived nitrile oxides, followed by hydrogenolysis of the resulting isoxazolines. To demonstrate the feasibility of the route we selected D- and L-arabinonitrile oxides **5** and **6** as the 1,3-dipole components and D-Glc- and D-Man-derived 5,6-dideoxy-hex-5-enofuranosides **7** and **8** as the dipolarophiles.



5 6 7 8

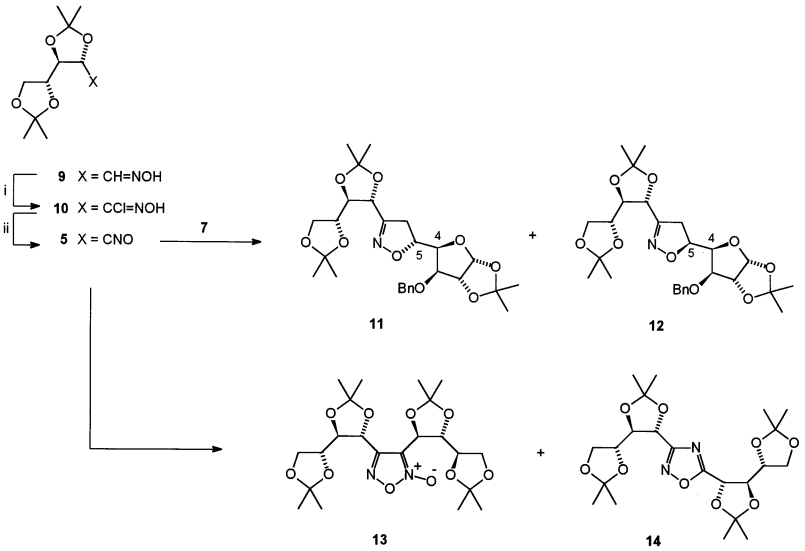
2. Results and discussion

The dipolarophile components 5,6-dideoxy-α-D-*xylo*- and α-D-*lyxo*-hex-5-enofuranosides

7 [20] and **8** [21] were synthesised by reduction of the corresponding 5,6-dimesylates using a zinc–copper couple and sodium iodide as previously reported [22]. As both alkenes decomposed slowly on prolonged storage, they were prepared immediately prior to use. The nitrile oxides **5** and **6** were generated from the corresponding oximes via the hydroximoyl chlorides using a procedure based on that developed by Torssell et al. [23], which involves in situ chlorination with *N*-chlorosuccinimide followed by base-induced dehydrochlorination. The D-Ara oxime precursor was prepared in four steps and 30% overall yield from the parent D-Ara using the approach described by Tronchet et al. [24] involving conversion to the 2,3:4,5-diisopropylidene derivative via the diethyl dithioacetal, with subsequent oximation using hydroxylamine hydrochloride/pyridine. The L-Ara oxime was obtained similarly in 28% overall yield. Both oximes were formed as approx. 5:1 mixtures of *E* and *Z* isomers as judged by ^{1}H NMR spectroscopy, and were used as such for the conversion to the nitrile oxides.

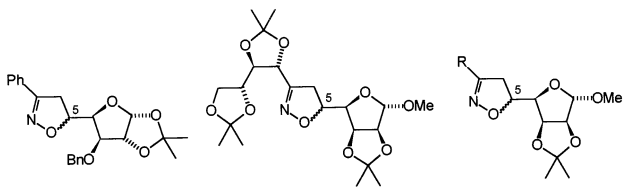
Cycloaddition reactions.—In order to minimise the formation of unwanted dimeric by-products, which are a common feature of nitrile oxide cycloaddition reactions [25], the nitrile oxides were generated in situ in the presence of an excess of the dipolarophile. In a typical experiment, *N*-chlorosuccinimide and a catalytic amount of pyridine were added to a chloroform solution of the oxime (1 equiv) to generate the hydroximoyl chloride, which was not isolated. The alkene (1.5 equiv) was added, the mixture cooled to 0 °C, and a chloroform solution of triethylamine (1.1 equiv) delivered over 10–12 h by means of a motorised syringe. After removal of the triethylamine hydrochloride by washing with water, the diastereomeric isoxazoline cycloadducts were separated from the excess alkene and dimeric by-products by chromatography. A small quantity of the adduct mixture was used for isomer ratio measurement by ^{1}H NMR spectroscopy, and the remainder subjected to further chromatography to afford the individual isoxazolines. The products were characterised by ^{1}H and ^{13}C NMR spectroscopy, optical rotation measurements and FAB mass spectrometry. Chemical formulae were verified by elemental analysis and/or high resolution mass spectrometry. The D-Ara-derived hydroximoyl chloride **10** has been prepared and isolated previously by Tronchet et al. [26] via direct chlorination of the oxime, and its conversion to nitrile oxide **5** and trapping as its isoxazole cycloadduct by reaction with phenylacetylene has also been described [27]. The corresponding L-arabinonitrile oxide **6**, however, has not been reported.

Cycloaddition of D-arabinonitrile oxide **5** to D-*xylo*-hex-5-enofuranoside **7** afforded after chromatography unreacted alkene (35% recovered), an inseparable mixture of two oxadiazoles both incorporating two nitrile oxide fragments, followed by a fraction containing 5*R*- and 5*S*-3-tetritolyl-5-tetrofuranosyl-isoxazolines **11** and **12** in 71% combined yield (Scheme 3). The main nitrile oxide dimer was identified as the 1,2,5-oxadiazole *N*-oxide **13** [27] by mass spectrometry and from the characteristic ^{13}C NMR signals for the heterocyclic ring carbons at 110 (C-3) and 156 ppm (C-4), together with peaks for the carbons of the two distinct tetritolyl moieties. It is well established [25] that 1,2,5-oxadiazole *N*-oxides—commonly called furoxans or furazan *N*-oxides—are the principal products formed from nitrile oxides in the absence of a dipolarophile. Evidence for a second dimeric compound was provided by mass spectrometry and by the presence in the ^{13}C NMR spectrum of satellite peaks for the oxadiazole ring carbons and for the carbons of the tetritolyl substituents, and it was thus tentatively assigned 1,2,4-oxadiazole structure **14**. Formation of such 1,2,4-oxadiazoles accompanying cycloadducts of nitrile oxides generated by triethylamine-mediated dehydrochlorination of hydroximoyl halides has been reported previously [28] and has been attributed [29] to alternative base-induced dimerisation pathways. The individual isoxazolines **11** and **12** were separated by further chromatography and the major product purified by crystallisation. The two adducts are readily identified as isoxazolines from their NMR spectra (Tables 1–3). In each case, the heterocyclic ring protons give rise to a characteristic ABX system with 5-H, which is adjacent to the ring oxy-



Scheme 3. Reagents: (i) NCS, pyridine; (ii) Et_3N.

gen, at highest chemical shift; the ^3J values of 8–11 Hz for 5-H/6-Ha,b and the geminal coupling of ~17 Hz for 6-Ha/6-Hb are also typical of 3,5-disubstituted isoxazolines [18d,19]. The ^1H NMR spectra, which for both isomers show considerable overlap for the protons at the 4-, 9-, 10- and 11-positions, were interpreted using COSY spectra and selective decoupling experiments; full analysis of the ^{13}C NMR data was accomplished with the aid of $^1H-^{13}C$ correlation spectra. The isomer ratio (89:11) was measured from the ^1H NMR spectrum of the product mixture by comparison of the anomeric proton signals which are well separated ($\Delta\delta$ 0.09 ppm) despite the remoteness of this nucleus from the centre of asymmetry. The individual diastereomers were identified by comparison of their physical and spectroscopic properties with those of isoxazolines **15** and **16**, obtained from the corresponding reaction of benzonitrile oxide with the same alkene, the structures of which had previously been established unambiguously by X-ray crystallography [31]. The NMR data are distinctive for each pair of adducts (see Tables 1–3). In particular, the signals for the anomeric proton are at lower chemical shift for the major isomers ($\Delta\delta = -0.09$ for **11**/**12**, -0.11 for **15**/**16**), whereas 5-H and 6a,b-H are all at higher frequency ($\Delta\delta$ 5-H = 0.14 for **11**/**12**, 0.11 for **15**/**16**; $\Delta\delta$ 6a-H = 0.34 for **11**/**12**, 0.35 for **15**/**16**; $\Delta\delta$ 6b-H = 0.62 for **11**/**12**, 0.58 for **15**/**16**). In the ^{13}C NMR spectrum C-6



15 5*R*
16 5*S*

17 5*R*
18 5*S*

19 R = Ph, 5*R*
20 R = Ph, 5*S*
21 R = CO_2Et, 5*R*
22 R = CO_2Et, 5*S*

resonates at higher chemical shift for the major isomer ($\Delta\delta = +1.2$ for both **11**/**12** and **15**/**16**), whereas the order is reversed for C-5 ($\Delta\delta = -2.5$ for both **11**/**12** and **15**/**16**). Smaller but consistent shifts are observed for 2-H, 3-H, 4-H, C-1, C-7, and Ph*C*H_2. Differences in the physical properties of the individual diastereomers are also useful in assigning structure; the major adducts have the more negative optical rotations (**11** $-69.5°$, **12** $+20.4°$; **15** $-99.9°$, **16** $-20.3°$), and have a greater R_f value for TLC on silica. Similar spectroscopic and physical property correlations have been used to identify diastereomeric pairs of isoxazolines resulting form nitrile oxide cycloadditions to various carbohydrate alkenes [18e,19,30,31]. The major isomer was therefore assigned structure **11**, which like **15**, has R configuration at the newly created asymmetric centre C-5 and an erythro relationship between this carbon and the adjacent carbon (C-4). It follows that the minor isomer must have structure **12**. Neither of the other two possible cycloadducts in which

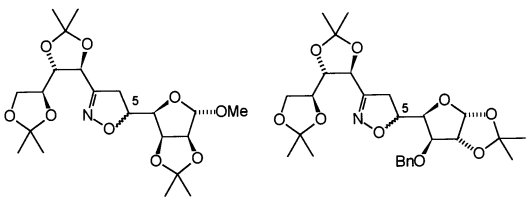
Table 1
^{1}H NMR chemical shifts (δ_H/ppm)[a]

	1-H	2-H	3-H	4-H	5-H	6-H	8-H	9-H	10-H	11-H	$PhCH_2$[b]	OMe	Me
11	5.88	4.59	4.05	4.15	4.94	3.20	4.73	4.21	4.16	3.94	4.61		1.29, 1.32, 1.38
						3.20				4.10	4.67		1.42, 1.43, 1.46
12	5.97	4.64	3.94	4.23	4.80	2.86	4.61	4.05	4.10	3.93	4.39		1.29. 1.30, 1.32
							2.58			4.06	4.68		1.35, 1.37, 1.45
15[c]	5.94	4.64	4.14	4.23	5.10	3.55					4.71		1.25, 1.31
						3.45					4.71		
16[c]	6.05	4.70	4.05	4.34	4.99	3.20					4.44		1.27, 1.35
							2.87					4.73	
17	4.84	4.52	4.72	3.96	4.91	3.14	4.70	4.16	4.13	3.94		3.25	1.27, 1.29, 1.37
						3.14				4.07			1.40, 1.41, 1.42
18	4.95	4.55	4.68	4.00	4.79	3.22	4.70	4.15	4.15	3.96		3.33	1.27, 1.31, 1.38
						2.86				4.09			1.40, 1.41, 1.42
23	4.86	4.52	4.72	4.00	4.87	3.17	4.69	4.19	4.13	3.93		3.27	1.26, 1.29, 1.36
						3.08				4.06			1.39, 1.41, 1.41
24	4.93	4.52	4.65	3.93	4.80	3.27	4.68	[d]	[d]	[d]		3.30	1.25, 1.30, 1.36
						2.79							1.37, 1.39, 1.41
25	5.89	4.58	4.06	4.18	4.91	3.23	4.70	4.19	4.15	4.09	4.63		1.29, 1.32, 1.38
						3.14				3.95	4.66		1.40, 1.42, 1.46
26	5.97	4.66	3.95	4.19	4.85	3.02	4.65	[e]	[e]	4.07	4.42		1.30, 1.31, 1.35
						2.56				3.91	3.91		1.36, 1.40, 1.44

[a] Recorded in $CDCl_3$ at 360 MHz.
[b] Also δ 7.2–7.7 (Ph).
[c] See Ref [31].
[d] 4.06–4.16 (3 × H, 2nd order multiplet).
[e] 4.05–4.13.

the oxygen of the nitrile oxide is attached to C-6 rather than C-5 of the dipolarophile were detected; the reaction is therefore regiospecific and diastereoselective (78% d.e.) in favour of the product with D-*arabino*-D-*gluco* configuration, i.e., with *erythro* stereochemistry for C-4–C-5.

The corresponding reaction of D-arabinonitrile oxide **5** with D-Man-derived hex-5-enofuranoside **8** under similar conditions afforded an 41:9 mixture of isoxazolines **17** and **18** in 57% combined yield. The individual isomers were identified by comparison of their spectroscopic data and physical properties with those reported [31] for the pairs of diastereomeric 3-phenyl- and 3-ethoxycarbonyl-isoxazolines **19**/**20** and **21**/**22**, formed by cycloaddition of benzonitrile oxide and ethoxycarbonylformonitrile oxide, respectively, to the same alkene. For example, the major adduct again has the less positive optical rotation (**17** + 15.1°, **18** + 64.4°), compared with literature [33] values for **19**/**20** (−35.2°/+24.8°) and **21**/**22** (−43.8°/+90.0°). The major adduct was thus assigned D-*arabino*-D-*manno* structure **17** and the minor isomer D-*arabino*-L-*gulo* structure **18**.



23 5*R*
24 5*S*

25 5*R*
26 5*S*

Having established effective procedures for the generation of the D-arabinonitrile oxide and characterised its isoxazoline cycloadducts with typical hex-5-enofuranosides, the corresponding reactions of the L-antipode **6** with the same alkenes were examined. Of particular interest is the effect of inverting the configuration of the 1,3-dipole component on the stereochemical outcome of the cycloaddition process. L-Arabinonitrile oxide **6** was generated from 2,3:4,5-di-*O*-isopropylidene-L-arabinose oxime using the same chlorination–dehydrochlorination protocol. Reaction with D-*lyxo*-hex-5-enofuranoside **8** afforded a pair of diastereomeric isoxazolines in the ratio 83:17 and 61% combined yield. X-ray crystal structure analysis of the major isomer, vide infra, showed that the adduct has L-*arabino*-D-*manno*-structure **23**, and that the newly-created asymmetric centre C-5 again has R

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

	1–2	2–3	3–4	4–5	5–6	6a–6b	8–9	9–10	10–11	11a–11b	PhCH_2
11	3.7	<1	3.2	7.8	8.8 8.8	[b]	6.5	6.7	4.6 6.1	8.3	11.8
12	3.9	<1	3.8	7.8	10.9 8.9	17.4	6.9	7.0	4.7 6.1	8.9	12.0
15[c]	3.7	<1	3.7	8.2	9.8 7.5	17.2					[b]
16[c]	3.9	<1	3.9	7.6	10.9 9.8	16.8					11.8
17	<1	5.9	3.7	5.9	9.1 9.1	[b]	6.4	6.8	4.4 6.0	8.5	
18	<1	5.9	3.7	8.6	10.5 9.0	17.3	6.9	[b]	4.5 6.1	8.5	
23	<1	5.9	3.7	6.2	10.7 8.1	17.5	6.6	6.8	4.8 6.1	8.5	
24	<1	5.9	3.8	8.6	10.5 8.7	17.4	6.7	[b]	[b] [b]	8.3	
25	3.7	<1	3.2	8.0	10.5 7.5	17.8	6.6	6.6	4.7 6.1	8.4	11.6
26	3.9	<1	4.2	7.3	11.0 8.4	17.1	6.7	[b]	4.5 [b]	8.0	12.0

[a] Recorded in $CDCl_3$ at 360 MHz.
[b] Not determined.
[c] See Ref [31].

configuration. The minor isomer therefore has L-*arabino*-L-*gulo* structure **24**. L-Arabinonitrile oxide **6** reacted similarly with D-Glc-derived alkene **7** to give a 22:3 mixture of L-*arabino*-D-*gluco* isoxazoline **25** (59%) and L-*arabino*-L-*ido* isomer **25** (8%).

π-Facial selectivity.—The ratios of diastereomeric isoxazolines resulting from cycloaddition of the D- and L-arabinonitrile oxides **5** and **6** to hex-5-enofuranosides **7** and **8** are compared in Table 4 with those reported [31–33] for the corresponding reactions of benzonitrile oxide and ethoxycarbonylformonitrile oxide with the same dipolarophiles. The isomer ratios for the series of nitrile oxides are broadly similar, with typical d.e. values of 70–88% for reactions with alkene **7**, and 64–66% d.e. with alkene **8**. In all cases the major adduct has R configuration at the newly created asymmetric centre C-5 and an erythro relationship for C-4 – C-5. The preponderance of erythro adducts is typical of nitrile oxide cycloadditions to chiral allyl ethers [31–35], and can be rationalised in terms of the 'inside alkoxy effect' proposed by Houk et al. [35]; the preferred transition state is considered to have the largest substituent anti, the smallest (H) 'outside', and the alkoxy group in the 'inside' position. For 5,6-dideoxy-5-enofuranosides the anti substituent is linked via the five-membered sugar ring to the alkoxy in the 'inside' position as illustrated in Fig. 1. There may also be a contribution to the observed erythro-selectivity attributable to the homoallylic alkoxy group at C-3, which in such cyclic systems is known to reinforce the effect of the allylic group when there is a threo relationship between these two substituents [31–33]. Of particular note are the near identical isomer ratios found for cycloadditions involving the D- and L-arabinonitrile oxides: 78 cf 76% d.e. for addition to alkene **5**, and 64 cf 66% for addition to alkene **6**. It is thus concluded that inversion of configuration at the asymmetric centre adjacent to the carbon of the nitrile oxide moiety has negligible effect. In contrast, for the addition of nitrile oxides to chiral allyl ethers where the centre of asymmetry is adjacent to the alkene there is a distinct preference for erythro-adduct formation. Low diastereoselectivities have also been observed for cycloadditions involving other chiral nitrile oxides, e.g., in the reactions of 1,3-dioxolane-4-carbonitrile oxide [18e,36] and

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

	C-1	C-2–C-4	C-5	C-6	C-7	C-8–C-10	C-11	CMe_2	CMe_2	CH_2Ph	PhC	PhCH	OMe
11	104.9	80.2, 81.2 82.4	76.9	37.2	156.7	74.3, 75.9 78.6	66.5	109.5, 110.4 111.6	24.8, 25.9, 26.2 26.4, 26.5, 26.7	72.2	137.1	127.4, 127.7 128.2	
12	105.5	81.6, 81.6 81.6	79.4	36.0	156.4	72.4, 74.2 78.4	66.4	109.5, 110.4 111.9	24.8, 26.2, 26.4 26.4, 26.7, 26.7	71.4	136.7	127.9, 128.0 128.4	
15[c]	105.1	80.5, 81.4 82.8	77.1	38.2	156.8			111.8	26.1, 26.7	72.6	137.3 129.3	126.7, 127.8, 127.9 128.4, 128.6, 130.0	
16[c]	105.6	81.6, 81.8 81.9	79.6	37.0	156.1			112.0	26.3, 26.8	71.6	136.7 129.2	126.5, 127.9, 128.1 128.5, 129.9, 130.1	
17	107.1	79.1, 79.5 84.7	77.9	36.5	157.5	74.5, 76.0 78.6	66.6	109.7, 110.6 112.5	24.2, 25.0, 25.6 26.4, 26.5, 26.9				54.6
18	107.4	80.0, 81.1 84.7	79.6[b]	36.6	156.7	74.4, 74.6 78.7[b]	66.6	109.7, 110.6 112.8	24.6, 24.9, 25.8 26.4, 26.5, 26.8				54.7
23	107.0	79.0, 79.1 84.7	78.0	36.7	157.5	74.3, 75.9 78.6	66.5	109.6, 110.5 112.4	24.2, 24.9, 25.6 26.4, 26.4, 26.8				54.5
24	107.3	80.0, 81.2 84.6	74.5	36.8	156.6	74.5, 75.9 78.6	66.7	109.6, 110.4 112.8	24.6, 24.8, 25.8 26.4. 26.4, 26.7				54.6
25	105.0	80.4, 81.3 82.6	77.0	37.6	157.5	74.4, 75.9 78.7	66.6	109.7, 110.6 111.8	25.0, 26.0, 26.4 26.4, 16.6, 26.8	72.4	137.3	127.5, 127.8 128.3	
26	105.6	81.7, 81.9 82.0	79.4	36.3	156.3	74.4, 75.9 78.6	66.7	109.7, 110.4 112.0	24.9, 26.4, 26.4 26.4, 26.8, 12.8	71.5	136.7	127.9, 128.1 128.4	

[a] Recorded in $CDCl_3$ at 90 MHz.
[b] Alternative assignments.
[c] See Ref [31].

Table 4
Selectivity of nitrile oxide cycloadditions to alkenes **7** and **8**

Nitrile oxide	Erythro:threo ratio	
	D-*xylo*-alkene **7**	D-*lyxo*-alkene **8**
PhCNO	90:10[a] 94:6[b]	82:18[a]
EtO_2CCNO	86:14[a] 85:15[b]	82:18[a]
D-Ara-CNO **5**	89:11	82:18
L-Ara-CNO **6**	88:12	83:17

[a] Ref [31].
[b] Ref [32].

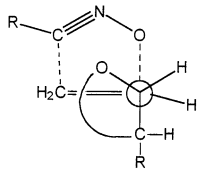


Fig. 1. Preferred transition state for cycloaddition of nitrile oxides to alkenes **7** and **8**.

oxazoline-4-carbonitrile oxides [37] with achiral alkenes. In each case, the minimal influence of adjacent asymmetric centres in the nitrile oxide component can be attributed to the greater distance between the pre-existing and newly formed stereocentres (Fig. 2).

Structure of isoxazoline **23**.—For the reaction of L-Ara-derived nitrile oxide **6** with D-*lyxo*-hex-5-enofuranoside **8** the configurations of the individual diastereomeric cycloadducts were confirmed by obtaining a single-crystal structure of the first-eluted isomer, which was identified as (5*R*)-5-(2,3-*O*-isopropylidene-1-*O*-methyl-α-D-*lyxo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-L-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**23**); the slower-eluting adduct therefore has 5S structure **24**. Unambiguous identification of the adducts **23** and **24** allows the structures of the other isomeric pairs of isoxazolines to be assigned with confidence on the basis of TLC R_f values, and NMR and optical rotation data [19e].

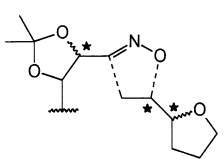


Fig. 2. Proximity of asymmetric centres in the nitrile oxide and dipolarphile components.

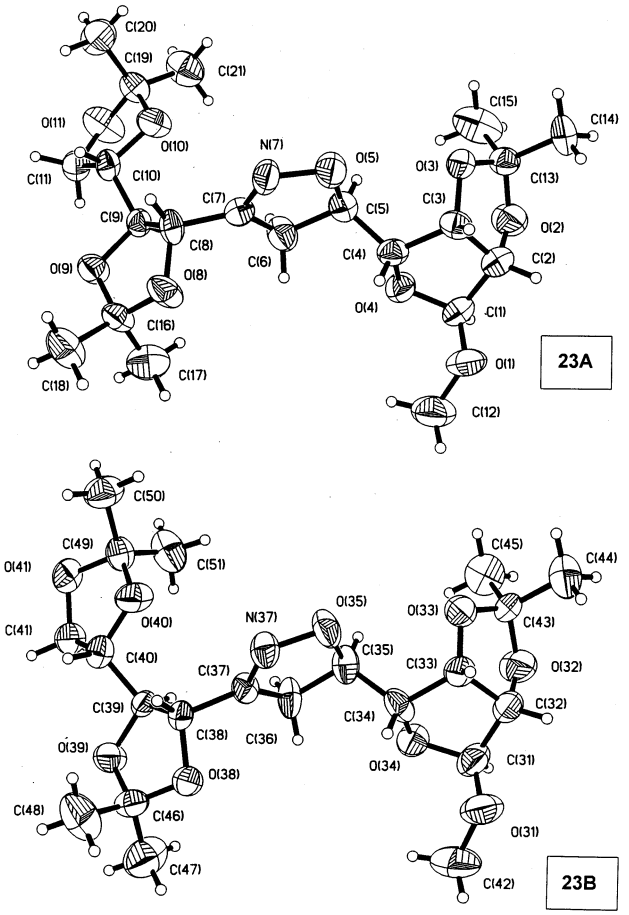


Fig. 3. Crystal structure of isoxazoline **23** showing the two molecular shapes **23A** and **23B**.

In the crystal two similar but distinct molecular shapes **23A** and **23B** were discernible (Fig. 3). The Cremer and Pople puckering parameters [38,39] for the isoxazoline, furanoside, and three 1,3-dioxolane rings are given in Table 5. There are significant differences in the shapes of the two molecules in both the furanoside and isoxazoline regions. In **23A** the furanoside ring adopts the twist conformation $^{O\text{-}4}T_{C\text{-}1}$ with $\phi = 18°$, whereas for **23B** $\phi = 12°$, indicating that its conformation is intermediate between twist ($\phi = 18°$) and envelope ($^{O\text{-}4}E$, $\phi = 0°$). The ϕ value of 351° for the isoxazoline in **23A** shows that in this molecule the ring adopts a conformation midway between twist ($^{O\text{-}5}T_{C\text{-}5}$, $\phi = 345°$) and envelope ($^{O\text{-}5}E$, $\phi = 360°$). In contrast, for molecule **23B** the isoxazoline with $\phi = 325°$ is almost completely in the envelope form $E_{C\text{-}5}$ ($\phi = 324°$); the torsion angle associated with the imine

double bond O-5–N-7 = C-7–C-6 is 0.26° and C-5 lies 0.164 Å out of the best plane through these four atoms. The C=N bond lengths (1.282 Å for **23A**, 1.269 Å for **23B**) are typical for the localised imino portion of 2-isoxazolines. In both **23A** and **23B** the three 1,3-dioxolane rings have conformations intermediate between twist and envelope. Selected H–C–C–H torsion angles from the X-ray data are compared with the observed and calculated [40] ^3J values in Table 6. Although satisfactory correlation is found for some of the data, e.g., $J_{1,2}$, $J_{2,3}$, $J_{8,9}$, and $J_{10,11a}$, there are significant deviations elsewhere. As previously noted [33,41] the relationship between the observed and calculated J values for the isoxazoline ring protons can be inconsistent. Another noteworthy feature of the crystal structure is the antiperiplanar relationship between 4-H and 5-H at the junction of the furanoside and isoxazoline, for which the observed torsion angle H-4–C-4–C-5–H-5 is 178.1 and 176.9° in the two crystalline forms. In solution the corresponding ^{1}H–^{1}H coupling is 6.2 Hz, which is significantly smaller than the calculated value (10.3 Hz). There is a similar inconsistency for H-9–C-9–C-10–H-10, for which the observed and calculated ^3J values are 6.8 and 10.2 Hz, respectively. These deviations suggest that where there is the possibility of free rotation, i.e., at C-4–C-5 and C-9–C-10, the preferred conformation in solution differs markedly from that in the crystal.

In conclusion, the 1,3-dipolar cycloaddition of arabinose-derived nitrile oxides to 5,6-dideoxyhex-5-enofuranosides provides a mild method for the regiospecific and diastereoselective construction of the 11-carbon framework of undecoses. The isoxazoline cycloadducts are now available for conversion to undecose derivatives by reductive hydrolytic ring opening.

3. Experimental

General methods and materials.—Melting points were measured on a Gallenkamp capillary apparatus and are uncorrected. Microanalyses were obtained using a Perkin–Elmer 2400 instrument. Optical rotations were measured at 21 °C on a Perkin–Elmer 141 polarimeter using 1.8 mL of filtered solution. The ^{1}H and ^{13}C NMR spectra were recorded with Brucker WP200SY, AX250 and WH360 or Varian VXR600 spectrometers on solutions in $CDCl_3$ with Me_4Si as internal standard. FAB^+ and high-resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Infrared spectra were recorded as films or Nujol mulls using a Perkin–Elmer 781 spectrometer. Preparative TLC was carried out on glass plates coated with a layer of Kieselgel GF_{254} (0.5 mm) which contained 13% $CaSO_4$ and a fluorescent indicator. E. Merck aluminium-backed plates coated with Kieselgel GF_{254} (0.2 mm) were used for analytical TLC; detection was by UV or sulfuric acid charring. Dry flash chromatography was carried out using Kieselgel GF_{254} and eluted under water pump vacuum. 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**7**) [20] (89%) and methyl 5,6-dideoxy-2,3-di-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranoside (**8**) [21] (96%) were prepared by reduction (Zn–Cu, NaI) of the corresponding 5,6-dimesylates as previously reported [22,33]. The isomer ratios of the isoxazoline cyclo-

Table 5
Cremer and Pople puckering parameters[a] for the two crystalline forms of isoxazoline **23**

Ring	Atoms	Q (Å)		ϕ (°)	
		23A	**23B**	**23A**	**23B**
Isoxazoline	O-5–N-7–C-7–C-6–C-5	0.026	0.101	351	325
Furanoside	O-4–C-1–C-2–C-3–C-4	0.349	0.342	18	12
Dioxolane	O-2–C-13–O-3–C-3–C-2	0.248	0.274	11	10
Dioxolane	O-8–C-16–O-9–C-9–C-8	0.319	0.304	99	160
Dioxolane	O-10–C-19–O-11–C-11–C-10	0.305	0.313	31	263

[a] Ref [31].

Table 6
Selected torsion angles involving hydrogen [H(X)–C(X)–C(Y)–H(Y)] for the two crystalline forms of isoxazoline **23** with observed and calculated[a] coupling constants

		H_X, H_Y									
		1,2	2,3	3,4	4,5	5,6a	5,6b	8,9	9,10	10,11a	10,11b
Angle (°)	**23A**	−89.4	−12.0	−15.7	178.1	121.4	−1.0	155.1	−177.0	−3.4	−124.3
	23B	−89.6	−11.4	−18.3	176.9	113.7	−8.6	151.1	175.7	−26.2	−147.8
J_{calc} (Hz)	**23A**	1.4	7.7	7.5	10.3	4.1	8.1	8.8	10.2	8.0	4.5
	23B	1.4	7.8	7.4	10.2	3.1	7.9	8.3	10.2	6.7	7.9
J_{obs} (Hz)	**23**	<1	5.9	3.7	6.2	8.1	10.7	6.6	6.8	6.1	4.8

[a] $7.76\cos^2\theta - 1.1\cos\theta + 1.4$ (see Ref [40]).

adducts were measured from the ^{1}H NMR spectra of the crude reaction products.

2,3:4,5-Di-O-isopropylidene-D-arabinose oxime **9** *[24].*—This was prepared in 95% yield from 2,3:4,5-di-*O*-isopropylidene-D-arabinose [42] by standard literature procedures [43] using $NH_2OH{\cdot}HCl/Na_2CO_3$ in MeOH–water. NMR spectroscopy indicated that the product was a ca. 5:1 mixture of E and Z isomers.

2,3:4,5-Di-O-isopropylidene-L-arabinose oxime.—This was prepared (93%) similarly to a ca. 5:1 mixture of E and Z isomers from 2,3:4,5-di-*O*-isopropylidene-L-arabinose [42].

Cycloaddition of D-*arabinonitrile oxide* **5** *to* D-xylo-*hex-5-enofuranoside* **7**.—A solution of 2,3:4,5-di-*O*-isopropylidene-D-arabinose oxime **9** (1.20 g, 4.9 mmol) in dry $CHCl_3$ (5 mL) was added to a suspension of *N*-chlorosuccinimide (0.65 g, 4.9 mmol) in dry $CHCl_3$ (5 mL) and dry pyridine (0.05 mL) and the mixture stirred at room temperature for 30 min. The alkene **7** (2.03 g, 7.3 mmol) in dry $CHCl_3$ (5 mL) was added and the solution cooled in an ice–salt bath. Triethylamine (0.54 g, 5.4 mmol) in $CHCl_3$ (35 mL) was added over 11 h by means of a motorised syringe pump and the mixture stirred for a further 10 h. The solution was washed with water (2 × 20 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo to afford a syrup. Dry flash chromatography on silica (15–30% Et_2O in hexane, gradient elution) afforded the following compounds in order of elution: unreacted **7** (0.71 g, 35%); an inseparable mixture (0.20 g) of 3,4-di-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)furazan-*N*-oxide (**13**) [27] [δ_C (50 MHz, $CDCl_3$) 24.9, 26.1, 26.2, 26.8 (8 CH_3), 67.1, 67.2 (CH_2), 71.3, 73.0 75.7, 76.5, 76.6, 79.9 (CH), 109.7, 109.9, 111.4, 111.7, 112.2 (CMe_2, C-3), 156.0 (C-4); (FAB) HRMS: Calcd for $C_{22}H_{35}N_2O_{10}$ $[M+H]^+$: *m/z* 487.22915. Found: *m/z* 487.22918] together with traces of 3,5-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-1,2,4-oxadiazole (**14**) [δ_C (50 MHz, $CDCl_3$) 156.1 (C-3), 161.7 (C-5); (FAB) HRMS: Calcd for $C_{22}H_{35}N_2O_9$ $[M+H]^+$ 471.23424. Found: *m/z* 471.23428]; and a pair of diastereomeric isoxazolines **11** and **12** in the ratio of 89:11. The major isomer, which eluted first, was obtained as a white solid and was identified as (5*R*)-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**11**) (1.60 g, 63%) [mp 74–75 °C (from EtOH); $[\alpha]_D^{21}$ −60.5° (*c* 0.44 in $CHCl_3$); Anal. Calcd for $C_{27}H_{37}NO_9$: C, 62.4; H, 7.2; N, 2.7. Found: C, 62.4; H, 7.3; N, 2.7]. The minor isomer, which was isolated as an oil, was identified as (5*S*)-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**12**) (0.20 g, 8%) ($[\alpha]_D^{21}$ +20.4° (*c* 1.22 in $CHCl_3$); (FAB) HRMS: Calcd for $C_{27}H_{38}NO_9$ $[M+H]^+$: *m/z* 520.25464. Found: *m/z* 520.25463). For NMR data of isoxazolines **11** and **12**, see Tables 1–3.

Cycloaddition of D-*arabinonitrile oxide* **5** *to* D-lyxo-*hex-5-enofuranoside* **8**.—Using the procedure described above, oxime **9** (0.90 g, 3.7 mmol) with alkene **8** (1.10 g, 5.5 mmol) yielded in order of elution unreacted **8** (0.52 g,

47%); an inseparable mixture (0.09 g) of furazan-*N*-oxide **13** and 1,2,4-oxadiazole **14**; (5*R*)-5-(2,3-*O*-isopropylidene-1-*O*-methyl-α-D-*lyxo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**17**) (0.75 g, 46%) [mp 86–87 °C (from EtOH); $[\alpha]_D^{21}$ +15.1° (*c* 1.45 in $CHCl_3$); Anal. Calcd for $C_{21}H_{33}NO_9$: C, 56.9; H, 7.5; N, 3.2. Found: C, 56.4; H, 7.7; N, 3.2; (FAB) HRMS: Calcd for $C_{21}H_{34}NO_9$ $[M+H]^+$: *m*/*z* 444.22334. Found: *m*/*z* 444.22334]; and (5*S*)-5-(2,3-*O*-isopropylidene-1-*O*-methyl-α-D-*lyxo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**18**) (0.18 g, 11%) [mp 77–79 °C (from 1:1 Me_2CHOH–hexane); $[\alpha]_D^{20}$ +68.0° (*c* 0.93 in $CHCl_3$); (FAB) HRMS: Calcd for $C_{21}H_{34}NO_9$ $[M+H]^+$: *m*/*z* 444.22334. Found: *m*/*z* 444.22333]; isomer ratio **17**:**18** = 82:18. For NMR data of isoxazolines **17** and **18**, see Tables 1–3.

Cycloaddition of L-*arabinonitrile oxide* **6** *to* D-xylo-*hex-5-enofuranoside* **7**.—Using the procedure described above 2,3:4,5-di-*O*-isopropylidene-L-arabinose oxime (1.00 g, 4.1 mmol) with alkene **7** (1.69 g, 6.1 mmol) yielded in order of elution unreacted **7** (0.92 g, 54%); an inseparable mixture (0.11 g) of nitrile oxide dimers; (5*R*)-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-L-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**25**) (1.26 g, 59%) [mp 99–100 °C (from EtOH); $[\alpha]_D^{19}$ −99.9° (*c* 0.93 in $CHCl_3$); Anal. Calcd for $C_{27}H_{37}NO_9$: C, 62.4; H, 7.2; N, 2.7. Found: C, 62.2; H, 7.3; N, 2.75]; and (5*S*)-5-(3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-L-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**26**) (0.17 g, 8%) [mp 121–122 °C (from EtOH); $[\alpha]_D^{20}$ −20.3° (*c* 0.29 in $CHCl_3$); (FAB) HRMS: Calcd for $C_{27}H_{38}NO_9$ $[M+H]^+$: *m*/*z* 520.25464. Found: *m*/*z* 520.25463]; isomer ratio **25**:**26** = 88:12. For NMR data of isoxazolines **25** and **26**, see Tables 1–3.

Cycloaddition of L-*arabinonitrile oxide* **6** *to* D-lyxo-*hex-5-enofuranoside* **8**.—Using the procedure described above 2,3:4,5-di-*O*-isopropylidene-L-arabinose oxime (0.96 g, 3.9 mmol) with alkene **8** (1.18 g, 5.9 mmol) yielded in order of elution unreacted **8** (0.69 g, 58%); an inseparable mixture (0.11 g) of nitrile oxide dimers; (5*R*)-5-(2,3-*O*-isopropylidene-1-*O*-methyl-α-D-*lyxo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-L-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**23**) (0.78 g, 45%) [mp 88–89 °C (from hexane); $[\alpha]_D^{19}$ −45.8° (*c* 0.53 in $CHCl_3$); Anal. Calcd for $C_{21}H_{33}NO_9$: C, 56.9; H, 7.5; N, 3.2. Found: C, 56.8; H, 7.7; N, 3.5]; and (5*S*)-5-(2,3-*O*-isopropylidene-1-*O*-methyl-α-D-*lyxo*-tetrofuranos-4-yl)-3-(1,2:3,4-di-*O*-isopropylidene-L-*arabino*-tetritol-1-yl)-4,5-dihydroisoxazole (**24**) (0.27 g, 16%) ($[\alpha]_D^{19}$ +11.1° (*c* 0.61 in $CHCl_3$); (FAB) HRMS: Calcd for $C_{21}H_{34}NO_9$ $[M+H]^+$: *m*/*z* 444.22334. Found: *m*/*z* 444.22333); isomer ratio **23**:**24** = 83:17. For NMR data of isoxazolines **23** and **24**, see Tables 1–3.

Crystal structure determination of isoxazoline **23**.—$C_{21}H_{33}NO_9$, $M = 443.5$, monoclinic, space group $P2_1$, $a = 17.281(10)$, $b = 5.409(4)$, $c = 26.437(13)$ Å, $\beta = 107.06(4)°$, $V = 2362.4$ Å^3, refined using 32 2θ values, with $25 < 2\theta < 27°$, Mo K_α radiation, $\lambda = 0.71073$ Å, $Z = 4$, $d_x = 1.25$ g cm^{-3}, $\mu = 0.097$ mm^{-1}, $T = 293$ K, $F(000) = 952$. Colourless plates, $0.80 \times 0.56 \times 0.12$ mm. 2499 Data collected, Stoë Stadi-4 diffractometer, $\omega/2\theta$ mode with on-line profile fitting, $5.0 < 2\theta < 40.0°$, $-16 < h < 15$, $0 < k < 5$, $0 < l < 25$. Three standard reflections collected every 2 h, maximum drift correction 2%. No absorption correction. Structure solved by direct methods using SHELXS [44] and refined using SHELXL [44], using scattering factors therein. All non-hydrogen atoms refined anisotropically, with loose restraints to equivalence the two independent molecules; hydrogen atoms inserted in calculated positions with fixed U = 0.10 Å^2. Weighting scheme $w^{-1} = \sigma^2(F^2) + 0.08P^2$, $P = (\max(F_o^2, 0) + 2F_c^2)$. At convergence (max $\Delta/\sigma = 0.010$) $R_1 = 0.053$ (for 1587 data with $I > 2\sigma(I)$. $wR_2 = 0.120$, $S = 1.07$ for 559 parameters and 93 restraints. Final difference synthesis gave no feature outside the range −0.18 to +0.18 e Å^{-3}. Atomic coordinates and equivalent isotropic displacement parameters are listed in Table 7. Tables of bond lengths and angles, torsion angles, atomic co-

Table 7
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for isoxazoline **23**

	x	y	z	U_{eq} [a]
C-1	6080(5)	3860(20)	6012(3)	71(3)
O-1	5421(4)	5383(16)	5914(3)	98(2)
C-2	6732(5)	4920(20)	6467(4)	81(3)
O-2	7292(4)	3078(15)	6727(2)	89(2)
C-3	7238(5)	6594(16)	6209(3)	55(3)
O-3	8039(3)	5796(12)	6434(2)	62(2)
C-4	6916(5)	5909(18)	5624(3)	56(3)
O-4	6435(3)	3700(12)	5596(2)	67(2)
C-5	7548(5)	5366(19)	5351(3)	65(3)
O-5	8002(3)	7625(15)	5355(2)	84(2)
C-6	7223(5)	4672(19)	4768(3)	73(3)
C-7	7525(5)	6756(18)	4508(3)	48(2)
N-7	7939(4)	8359(17)	4834(3)	68(2)
C-8	7360(5)	7192(17)	3931(3)	53(2)
O-8	6540(3)	7892(12)	3718(2)	72(2)
C-9	7449(4)	4895(16)	3613(3)	48(2)
O-9	6854(3)	5389(12)	3117(2)	65(2)
C-10	8251(5)	4587(17)	3513(3)	49(2)
O-10	8819(3)	4018(13)	4013(2)	71(2)
C-11	8303(5)	2398(18)	3168(3)	62(3)
O-11	8909(4)	879(13)	3490(3)	95(2)
C-12	4758(5)	4540(30)	5504(4)	120(5)
C-13	8082(5)	4010(20)	6838(3)	61(3)
C-14	8377(5)	5220(20)	7368(3)	94(4)
C-15	8640(6)	1990(20)	6767(4)	117(4)
C-16	6216(5)	6641(18)	3227(3)	59(3)
C-17	5573(5)	4940(20)	3288(4)	104(4)
C-18	5879(5)	8550(20)	2800(3)	95(4)
C-19	9383(5)	2278(18)	3917(3)	58(3)
C-20	10054(5)	3620(20)	3791(3)	100(4)
C-21	9679(5)	688(19)	4390(3)	93(3)
C-31	8763(6)	7380(20)	−1045(4)	80(3)
O-31	9498(4)	8528(16)	−841(3)	105(3)
C-32	8187(5)	9230(20)	−1396(4)	70(3)
O-32	7545(4)	7896(15)	−1758(2)	94(2)
C-33	7750(5)	10464(17)	−1034(3)	58(2)
O-33	6922(3)	10159(12)	−1293(2)	68(2)
C-34	8037(5)	8971(19)	−522(3)	66(3)
O-34	8388(4)	6765(13)	−653(2)	70(2)
C-35	7378(5)	8257(18)	−278(3)	63(3)
O-35	7070(3)	10552(13)	−107(2)	74(2)
C-36	7663(6)	6712(18)	223(3)	73(3)
C-37	7612(5)	8523(18)	635(3)	50(3)
N-37	7295(4)	10574(16)	452(3)	60(2)
C-38	7886(4)	8129(17)	1220(3)	51(3)
O-38	8735(3)	7625(12)	1369(2)	61(2)
C-39	7527(4)	5846(16)	1400(3)	47(2)
O-39	8175(4)	4932(12)	1828(2)	72(2)
C-40	6810(5)	6357(17)	1591(3)	56(3)
O-40	6202(4)	7473(12)	1171(2)	72(2)
C-41	6398(5)	4091(19)	1730(3)	69(3)
O-41	5562(3)	4720(12)	1555(2)	68(2)
C-42	10106(6)	6950(30)	−535(4)	155(6)
C-43	6822(5)	9090(20)	−1798(3)	61(3)
C-44	6635(6)	11050(20)	−2218(4)	97(4)
C-45	6163(6)	7200(20)	−1898(4)	103(4)
C-46	8888(5)	6200(20)	1839(4)	68(3)
C-47	9547(6)	4470(20)	1868(4)	120(5)
C-48	9089(6)	7960(20)	2309(4)	121(4)
C-49	5456(5)	6223(17)	1088(3)	60(3)
C-50	4789(5)	8020(20)	1074(4)	88(3)
C-51	5288(6)	4630(20)	606(3)	102(4)

[a] U_{eq} is defined as one-third of the trace of the orthogonalised U_{ij} tensor.

ordinates involving hydrogen, and thermal parameters are given as supplementary tables, which have been deposited with the Cambridge Crystallographic Data Centre.

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