Generation and Cycloadditions of 4,5-Dihydrooxazole- and Oxazolidine-4-carbonitrile *N*-Oxides

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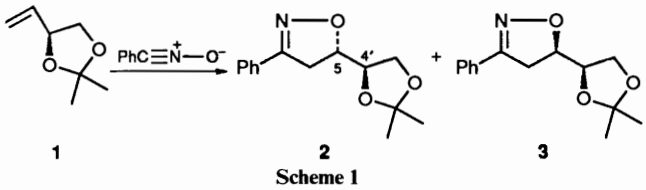
A route to 2-phenyl-4,5-dihydrooxazole-4-carbonitrile *N*-oxide **7** has been developed starting from (*S*)-serine methyl ester and involving dehydration of the 4-nitromethyl derivative **13** using *m*-tolylene diisocyanate and triethylamine. Cycloaddition of the nitrile oxide to styrene afforded a 55:45 mixture of diastereoisomeric dihydroisoxazoles **21** and **22**; furazan *N*-oxides **19** and **20** were also formed in a competing dimerisation. The analogous (*R*)-oxazolidine-4-carbonitrile oxide **8**, also prepared from (*S*)-serine methyl ester, reacted similarly with styrene, oct-1-ene and diethyl fumarate to afford *ca.* 1:1 mixtures of adducts. The structures of the dihydrooxazole–dihydroisoxazole adduct **21** and furazan *N*-oxide **20** were determined by X-ray crystallography.

The formation of 2-isoxazolines (4,5-dihydroisoxazoles) by 1,3-dipolar cycloaddition of nitrile oxides to alkenes has been known for many years,[1] and the scope and mechanism of the reaction have been studied in detail.[2,3] More recently, the topic has received renewed attention in view of the now widespread use of nitrile oxide–isoxazoline chemistry[4] for the synthesis of natural products and analogues. Of particular importance for the successful application of this methodology is an understanding of the factors affecting the stereochemistry of the cycloaddition step. It has been established[5,6] that allylic substituents have a strong influence in determining the π-facial selectivity, and that notably high levels of diastereoselectivity (56–93% d.e.) are observed for cycloaddition to chiral allyl ethers.[5 11] For example, benzonitrile oxide adds to (*S*)-isopropylidenebut-3-ene-1,2-diol **1** to afford an 85:15 mixture of the isoxazolines **2** and **3** (Scheme 1). The preferred formation

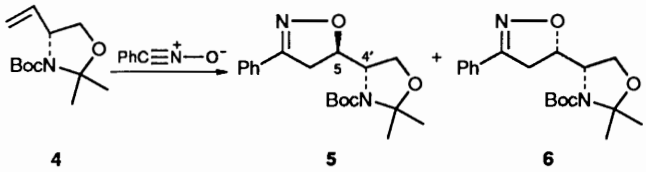


1 2 3

Scheme 1

of the adduct **2**, in which there is an *erythro* relationship between the new asymmetric centre at C-5 of the isoxazoline ring and C-4′ of the dioxolane, has been rationalised by Houk *et al.*[5] in terms of an 'inside alkoxy effect' that involves the allylic oxygen.

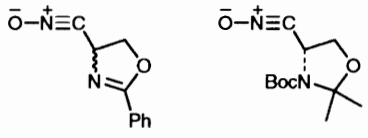
Some examples of the corresponding reactions with chiral allylamine derivatives have also been reported[12,13] but, in general, the degree of selectivity is lower and less predictable. For instance, addition[13] of benzonitrile oxide to chiral vinyloxazolidine **4** gave a 66:34 mixture of the isoxazolines **5** and **6** (Scheme 2). We have examined methods for the



4 5 6

Scheme 2

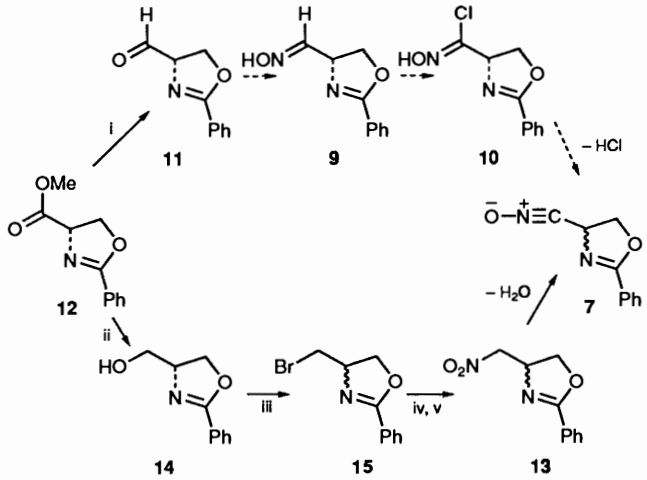
generation of 2-oxazoline- and oxazolidine-4-carbonitrile oxides **7** and **8**, in which the asymmetric centre is in the nitrile oxide component, rather than the dipolarophile, and have investigated their cycloadditions with olefinic dipolarophiles.



7 8

Results and Discussion

Generation of the Nitrile Oxides **7** *and* **8**.—The route to 2-phenyl-2-oxazoline-4-carbonitrile *N*-oxide **7** started from (*S*)-serine methyl ester hydrochloride. The approach initially envisaged (Scheme 3) involved chlorination of the oxime **9**,

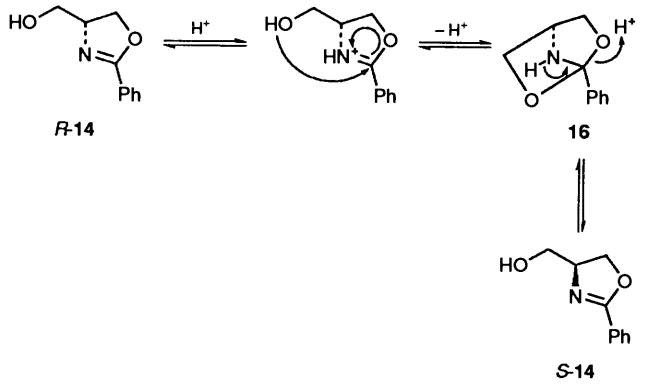


11 9 10 12 7 14 15 13

Scheme 3 *Reagents:* i, DIBAL, PhMe; ii, $LiAlH_4$, Et_2O; iii, $SOBr_2$, PhMe; iv, NaI, Me_2CO; v, $NaNO_2$, Me_2SO

followed by dehydrochlorination of the resulting hydroximoyl chloride **10**. The aldehyde precursor **11**, however, proved difficult to prepare by the literature route.[14] The product is known to be unstable and diisobutylaluminium hydride (DIBAL) reduction of the ester **12**, obtained by treatment of (*S*)-serine methyl ester hydrochloride with ethyl benzimidate, gave only a 20% conversion into the aldehyde. An alternative approach was, therefore, required. Since nitromethyl compounds can be dehydrated to nitrile oxides by the procedure of Mukaiyama,[15] the ester **12** was converted into the nitromethyl compound **13** by reduction to the alcohol **14**, halogenation and reaction with sodium nitrite, as outlined in Scheme 3. The overall yield was 26%. The bromomethyl compound **15** was

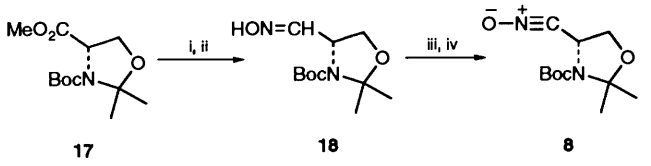
found to have zero optical rotation and its chiral integrity was, therefore, checked by NMR spectroscopy using $Eu(hfc)_3$ as shift reagent. This established that complete racemisation had taken place. It is presumed that this occurred under the acidic conditions of the halogenation step. Protonation of the ring nitrogen, followed by intramolecular attack at C-2 by the hydroxymethyl group, would afford a symmetrical bicyclic intermediate **16** capable of either regenerating (*R*)-**14** or forming its enantiomer (*S*)-**14**, as shown in Scheme 4. The



Scheme 4

procedure used for the generation of the nitrile oxide **7** involved treatment with an isocyanate and catalytic triethylamine in the presence of the dipolarophile. In this way the concentration of the nitrile oxide remains low thus minimising dimerisation to the corresponding furazan *N*-oxide.[16]

(*S*)-Serine methyl ester hydrochloride also provided the source of oxazoline-4-carbonitrile oxide **8** (Scheme 5). The



Scheme 5 *Reagents:* i, DIBAL, PhMe; ii, NH_2OH·HCl, pyridine; iii, NCS, $CHCl_3$; iv, Et_3N

oxazolidine ester derivative **17**[17] was reduced to the corresponding aldehyde which was treated with hydroxylamine to afford the oxime **18** as a 2:3 mixture of *syn* and *anti* isomers. The nitrile oxide was generated without isolation of the intermediate hydroximoyl chloride by chlorination of the oximes *in situ* with *N*-chlorosuccinimide, followed by dehydrochlorination using triethylamine.[18]

Cycloadditions of the Oxazolinecarbonitrile Oxide **7**.—The generation and cycloaddition of nitrile oxide **7** were first examined under typical Mukaiyama conditions with *p*-chlorophenyl isocyanate/triethylamine as dehydrating agent and styrene as the dipolarophile. The only products isolated from this reaction, however, were a diastereoisomeric pair of 3,4-disubstituted furazan *N*-oxides **19** and **20** (52% combined yield) in an isomer ratio of 56:44. These were separated by chromatography and the structure of the minor product was established as the *RR*/*SS* isomer **20** by X-ray crystallography (Fig. 1); the major dimer therefore has the *RS*/*SR* configuration **19**. The structure of compound **20** shows some disorder in the region of the furazan ring, as evidenced by the large elipsoids for the N–O–N unit. This phenomenon is well documented in the literature;[19,20] for example, it is reported that in the crystalline state there are two forms of 3,4-diphenylfurazan *N*-oxide which are distinguished by different torsion angles between the planes

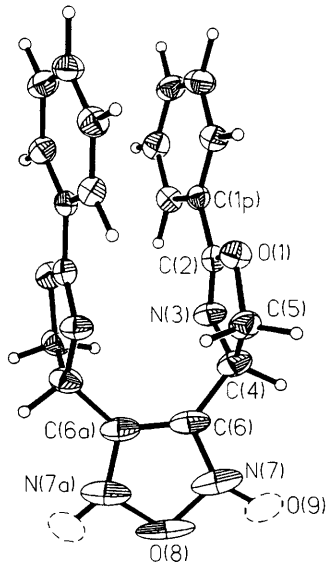
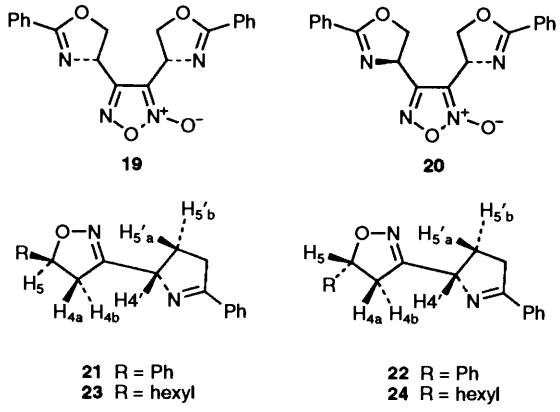


Fig. 1 X-Ray molecular structure of compound **20** showing disorder in the furazan ring; the elipsoids with the dashed boundaries indicate the two alternative positions for O(9)

of the phenyl and heterocyclic rings. In the present case the X-ray structure of **20** is insufficiently well defined to differentiate two forms and, as a result, an exocyclic oxygen atom appears on



[For compounds **19**–**24** only one enantiomer is shown]

both, rather than just one, of the nitrogens of the furazan. As expected, this ring is near planar with no atom displaced by more than 0.004 Å. Another noteworthy feature of the crystal structure is the alignment of the 2-phenyloxazoline substituents, which are twisted (76.8°) with respect to the furazan. Within the crystal the molecule has a two-fold axis of symmetry with the planes of the heterocyclic rings stacked antiparallel; the angle of twist between the pair of oxazolines is 2.0° and the corresponding value of the phenyl rings is 9.7°. The Cremer and Pople puckering parameters[21] (Table 2) for the oxazoline ring show that it is in a near twist conformation (φ = 310.5°). The conjugation between the imine C=N of the oxazoline and the 2-phenyl substituent is reflected in the low torsion angle (11.9°) between them. Although the target isoxazoline cycloadducts were not obtained in this experiment, the formation of the furazan *N*-oxides provided strong evidence that the desired nitrile oxide had been generated under the reaction conditions.

In order to reduce the concentration of the nitrile oxide, and thus minimise the competing dimerisation process, a modified procedure was adopted—tolylene diisocyanate (TDI; 5-methyl-1,3-phenylene diisocyanate) was used in place of the *p*-chlorophenyl isocyanate and, rather than mixing all the

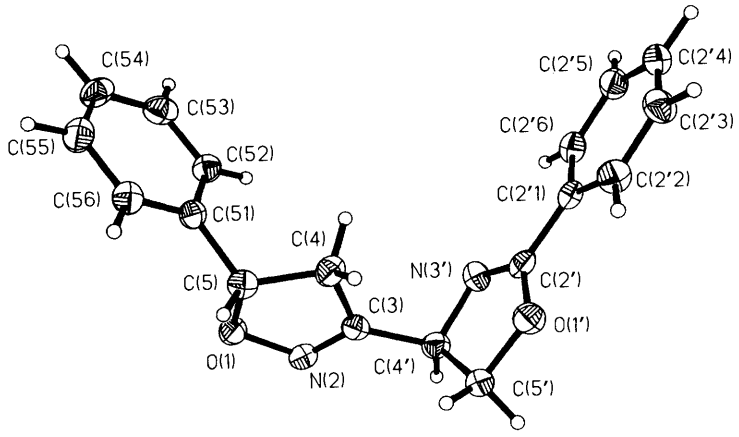


Fig. 2 X-Ray molecular structure of compound **21**

Table 1 Selected ^{1}H NMR data (δ_H/ppm, J_{xy}/Hz) for isoxazoline cycloadducts[a]

	21	**22**	**23**	**24**	**25**[b]	**26**[b]	**27**[b]	**28**[b]	**30**[b]	**31**[b]
4a-H	3.59	3.48	3.17	3.08	3.37	3.39	2.98	2.99	—	—
4b-H	3.05	3.10	2.66	2.73	2.93	2.95	2.58	2.57	4.47	4.30
5-H	5.65	5.64	4.7–4.5	4.6–4.5	5.55	5.54	4.56	4.6–4.5	5.15	5.19
4'-H	5.20	5.25	5.16	5.16	4.78	4.81	4.75	4.76	4.79	4.86
5a'-H	4.73	4.7–4.5	4.7–4.5	4.60	4.10	4.15	4.12	4.13	4.09	4.10
5b'-H	4.63	4.7–4.5	4.7–4.5	4.61	3.95	4.00	4.0–3.8	4.0–3.8	4.09	4.04
J_{4a4b}	17.3	17.3	17.2	17.1	17.0	17.1	16.8	16.9	—	—
J_{4a5}	11.0	11.0	10.5	10.3	10.9	10.9	10.3	10.2	—	—
J_{4b5}	8.8	8.7	8.6	8.5	7.8	8.4	7.9	8.5	5.5	6.3
$J_{4'5a'}$	7.6	8.4	8.0	9.3	6.5	6.5	6.6	6.6	5.0	5.8
$J_{4'5b'}$	10.1	9.4	9.7	8.4	2.6	2.5	2.0	2.0	5.0	2.7
$J_{5a'5b'}$	8.8	—	—	—	9.3	9.3	9.2	9.2	—	9.3
$J_{4a4'}$	0.8	0.8	0.7	—	—	—	—	0.3	—	—
$J_{4b4'}$	0.9	0.8	0.8	—	—	—	—	—	—	—

[a] Recorded at 25 °C in $CDCl_3$ at 360 MHz. [b] Recorded at 60 °C.

Table 2 Cremer and Pople puckering parameters[21] for compounds **20** and **21**

Compd.	Ring	Q/Å	φ/°
20	Oxazoline O(1)–C(2)–N(3)–C(4)–C(5)	0.097	310.5
21	Oxazoline O(1')–C(2')–N(3')–C(4')–C(5')	0.150	129.8
	Isoxazoline O(1)–N(2)–C(3)–C(4)–C(5)	0.131	317.5

reagents at the outset, a solution of the nitromethyloxazoline precursor was added slowly over 4 h by means of motorised syringe pump to a solution of TDI, styrene and triethylamine. On completion, the reaction was quenched by addition of ethylene-1,2-diamine to the mixture and the polymeric urea by-product was filtered off. From the product mixture were isolated, by chromatography, the diastereoisomeric isoxazoline cycloadducts **21** and **22** (59% combined yield) in an isomer ratio of 55:45. The products were identified by their characteristic ^{1}H NMR spectra (Table 1). In addition to the signals for the oxazoline ring protons, each adduct also shows an ABX pattern typical of 2-isoxazolines, with 4a-H and 4b-H resonating at *ca.* 3.5 and 3.0 ppm, respectively, and 5-H at 5.65 ppm. For both compounds there are also long-range couplings of 0.8–0.9 Hz between both 4a-H and 4b-H of the isoxazoline and 4'-H of the oxazoline.

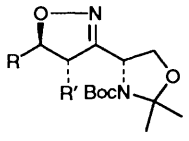
The configurations of the individual isomers were established by obtaining a single-crystal X-ray structure (Fig. 2) of the first-eluted isomer which identified it as (*RS*/*SR*)-5-phenyl-3-(2-phenyl-2-oxazol-4-yl)-2-isoxazoline **21**; thus the slower-eluting adduct has the *RR*/*SS* structure **22**. In the crystal of compound **21** the two heterocyclic rings are near orthogonal with an angle of twist of 88.4° between the best planes involving the five atoms of each ring. The phenyl substituent at the sp^3-hybridised carbon C-5 is also rotated out of the plane of the isoxazoline by 86.6°. In contrast, the conjugation between the phenyl at C-2' and the imine function C(2')=N(3') is reflected in a small angle (13.2°) between the phenyl and oxazoline rings. The puckering parameters (Table 2) for the isoxazoline ring show that its conformation in the crystal is closer to envelope (^4E, φ = 324°) than twist (φ = 306°); C-5 is displaced by 0.21 Å from the best plane through these atoms. The C=N bond length (1.274 Å) and the small torsion angle (1.9°) for O(1)–N(2)=O(3)–C(4) are typical for the localised imine double bond of isoxazolines. The corresponding puckering parameters for the oxazoline (Q = 0.150 Å, φ = 129.8°) indicate that the conformation is largely twist (φ = 126°).

The same procedure applied to the reaction of nitrile oxide **7** with oct-1-ene afforded a 1:1 mixture of the cycloadducts **23** and **24** (77% combined yield). The assignment of structure to the individual isomers in this case was based on comparison with the corresponding styrene adducts **21** and **22**. The first-eluted isomer is assumed to have an *RR*/*SS* configuration * and the other an *RS*/*SR*. Examination of the ^{1}H NMR data for the individual pairs of products supports this conclusion (Table 1). Although most features of the spectra of the two isomers are very similar, the signals for the protons at the 4-position of the

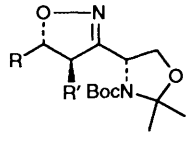
* The priorities of the groups are reversed when phenyl is replaced by hexyl.

isoxazoline ring are distinctive. For the styrene adducts **21** and **22** the δ_H value for 4a-H in the first-eluted isomer **21** is greater than that for **22** ($\Delta\delta$ = 0.11 ppm), whereas the order is reversed for 4b-H ($\Delta\delta$ = −0.05 ppm). The same trend holds for the oct-1-ene adducts **23** and **24** (4a-H, $\Delta\delta$ = 0.09; 4b-H, $\Delta\delta$ = −0.07).

Cycloadditions of the Oxazolidine Nitrile Oxide **8**.—Chlorination of the oxime **18** was accomplished using *N*-chlorosuccinimide (2:1) in the presence of a catalytic amount of pyridine. To the resulting hydroximoyl chloride solution were added an excess of styrene (4:1) followed by, over a period of 6 h, triethylamine (2:1). Work-up of the reaction mixture afforded the 5-phenyl-substituted isoxazolines **25** and **26** (59:41, 65% combined yield) which were separated by chromatography. The adducts showed characteristic ^{1}H NMR ABX patterns for both the oxazoline and isoxazoline fragments (Table 1). At ambient temperature the signals for all the protons of the oxazoline ring and 5-H of the isoxazoline were broad and the vicinal couplings difficult to discern, but at 60 °C the spectra were well resolved.



25 R = Ph, R′ = H
27 R = hexyl, R′ = H
29 R = R′ = CO_2Et



26 R = Ph, R′ = H
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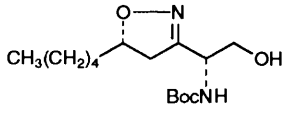

31

This effect has been observed previously for the ester **17**[17] and related systems[22] and has been attributed to a dynamic equilibrium between two conformers of the oxazolidine ring. Oct-1-ene reacted similarly to give the 5-hexylisoxazolines **27** and **28** (70% combined yield) in a ratio of 48:52. The corresponding reaction with diethyl fumarate yielded a mixture of 4,5-diethoxycarbonylisoxazolines **29** and **30** in the ratio 53:47; the individual isomers in the latter reaction were not identified. The structures of the individual adducts for the reactions of the carbonitrile oxide **8** with styrene and oct-1-ene were deduced by correlation with the isoxazolines obtained from the carbonitrile oxide **7**, the configurations of which had been established unambiguously by X-ray crystallography. To this end the slower-eluting cycloadduct from the reaction between the carbonitrile oxide **8** and oct-1-ene was treated with trifluoroacetic acid and water at room temperature, thus completely removing the isopropylidene and *tert*-butoxycarbonyl protecting groups. The resulting amino alcohol **31** was then converted into its 2-oxazoline derivative by treatment with ethyl benzimidate in dichloromethane. Comparison of this compound by TLC and ^{1}H NMR spectroscopy with the adducts **23** and **24**, formed in the reaction of 2-oxazolinecarbonitrile oxide **7** with oct-1-ene, showed that it corresponded to the first-eluted isomer of that reaction. On this basis it was assigned structure **27** with a 5*R*,4′*R* configuration; its isomer is, therefore, 5*S*,4′*R* **28**. By analogy, the diastereoisomer which was eluted first from the reaction with styrene was assigned the 5*S*,4′*R* structure **25** and its isomer 5*R*,4′*S* **26**. A similar correlation was observed in the ^{13}C NMR spectra, which were consistent for both sets of compounds; in each case carbons C-3, C-5 and C-5′ have lower chemical shift ($\Delta\delta$ = 0.1–0.4 ppm) in the slower-eluting adduct.

The minimal π-facial selectivity observed for these cycloadditions in which the asymmetric centre is in the carbonitrile oxide component contrasts with the distinct preference for *erythro* adduct formation for the addition of achiral carbonitrile oxides to some chiral allylamine derivatives.[12,13] Similarly, low selectivities have been reported[23] for the reactions of 1,3-dioxolane-4-carbonitrile oxides. In each case the effect can be attributed to the greater distance between the pre-existing and newly formed stereocentres.

Experimental

Preparative TLC was carried out on Kieselgel GF_{254} silica (0.5 mm layer) containing 13% $CaSO_4$ and a fluorescent indicator. Analytical TLC also used Kieselgel GF_{254} silica (0.2 mm); detection was achieved by UV irradiation or acid-charring (10% H_2SO_4, heat). Kieselgel 60 was used for dry flash column chromatography. Mass spectra were measured on a Kratos MS50TC instrument using the FAB mode. Bruker WP200Y and WH360 spectrometers were used to obtain NMR spectra. Optical rotations $[\alpha]_D$ are expressed in units of 10^{-1} deg cm^2 g^{-1}.

(R)-4-*Hydroxymethyl*-2-*phenyl*-4,5-*dihydrooxazole* **14**.—To a stirred suspension of lithium aluminium hydride (9.86 g, 260 mmol) in dry diethyl ether (500 cm^3) at 0 °C, under an argon atmosphere, was added rapidly a solution of methyl (*S*)-2-phenyl-4,5-dihydrooxazole-4-carboxylate **12**[14] (26.6 g, 130 mmol) in dry diethyl ether (50 cm^3). After the mixture had been stirred for 2 min water (10 cm^3), 20% aqueous NaOH (7.4 cm^3) and water (50 cm^3) were added to it to quench the reaction. The mixture was then stirred for 16 h after which the granular precipitate which had formed was filtered off and washed with diethyl ether. The combined filtrate and washings were concentrated under reduced pressure to *ca.* 50 cm^3, and the precipitated white solid was filtered off, dissolved in dichloromethane and the solution dried ($MgSO_4$). Evaporation of the solution afforded the product as a white solid (15.2 g, 70%), m.p. 92–96 °C (from cyclohexane) (lit.,[24] 99.5 °C); $[\alpha]_D^{20}$ +81 (*c* 1.0 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3350br (OH) and 1640 (C=N); δ_H(200 MHz; $CDCl_3$) 7.78–7.72 (2 H, m, PhH), 7.42–7.22 (3 H, m, PhH) and 4.5–3.5 (6 H, m, 4-H, 5a-H, 5b-H, CH_2OH); δ_C(50 MHz; $CDCl_3$) 165.3 (C-2), 131.2, 128.0 (5PhCH), 126.8 (PhC), 69.0, 67.9 (CH_2OH, C-5) and 63.3 (C-4).

Attempts to prepare (S)-2-*Phenyl*-4,5-*dihydrooxazole*-4-*carbaldehyde* **11**.—Using the procedure of Thornton and Tkaczuk[24] a solution of DIBAL (1 mol dm^{-3} in hexanes; 1.02 cm^3, 1.02 mmol) was added to a cooled (−78 °C) and stirred solution of the ester **12** (0.209 g, 1.02 mmol) in dry dichloromethane (8 cm^3) under nitrogen. After the mixture had been stirred for 3 h methanol (0.4 cm^3) was added to it and stirring continued for 30 min. Chloroform (4 cm^3) and saturated aqueous potassium tartrate (15 cm^3) were then added to the mixture which was then allowed to warm to ambient temperature. The organic layer was separated and the aqueous phase extracted with chloroform (3 × 25 cm^3); the combined organic phase and extracts were then dried and concentrated under reduced pressure. Examination by ^{1}H NMR spectroscopy of the residue showed the presence of traces of the aldehyde **11** (*ca.* 20%). Attempts to oxidise the alcohol **14** with pyridinium chlorochromate[25] and the Swern method[26] also yielded only traces of the aldehyde **11**.

(RS)-4-*Bromomethyl*-2-*phenyl*-4,5-*dihydrooxazole* **15**.—To a stirred solution of thionyl bromide (14.08 g, 67.8 mmol) in dry toluene (40 cm^3) at 0 °C was added a solution of the hydroxymethyl compound **14** (3.0 g, 16.9 mmol) in dry toluene (20 cm^3). The mixture was allowed to warm to room

temperature at which it was stirred for a further 8 h before being made alkaline with saturated aqueous $NaHCO_3$ in order to quench the reaction. The mixture was then poured into water (50 cm^3), the organic layer separated, and the aqueous layer extracted with ethyl acetate (2 × 50 cm^3). The combined organic layers and extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. Kugelrohr distillation (100 °C, 0.007 mmHg) of this afforded the product as a white solid (2.76 g, 68%), m.p. 70–71.5 °C (from di-isopropyl ether) (Found: C, 50.0; H, 4.4; N, 5.8. $C_{10}H_{10}BrNO$ requires C, 50.0; H, 4.2; N, 5.8%); ν_{max}(Nujol)/cm^{-1} 1640 (C=N); δ_H(200 MHz; $CDCl_3$) 7.97–7.91 (2 H, m, PhH), 7.54–7.36 (3 H, m, PhH), 4.60 (1 H, dddd, $J_{4,5b}$ 9.2, $J_{4,5a}$ 6.7, $J_{4,4\alpha}$ 7.5 and $J_{4,4\alpha'}$ 3.6, 4-H), 4.51 (1 H, t, $J_{5b,5a}$ 8.6, 5b-H), 4.34 (1 H, dd, 5a-H), 3.67 (1 H, dd, $J_{4\alpha',4\alpha}$ 10.1, 4α-H) and 3.40 (1 H, dd, 4α'-H); δ_C(50 MHz; $CDCl_3$) 165.5 (C-2), 131.6, 128.3 (5PhCH), 127.1 (PhC), 71.5 (C-5). 67.1 (C-4) and 35.4 (C-4α).

(RS)-4-*Iodomethyl*-2-*phenyl*-4,5-*dihydrooxazole*.—To a solution of sodium iodide (3.12 g, 20.8 mmol) in acetone (20 cm^3) was added a solution of the bromomethyl compound **15** (1.0 g, 4.17 mmol) in acetone (10 cm^3). After the mixture had been heated under reflux for 7 h the solvent was removed under reduced pressure and the residue partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 40 cm^3) and the combined extracts were washed with 10% aqueous sodium metabisulphite (50 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. The residual brown oil was subjected to dry flash chromatography (Et_2O–hexane, 1:1) which yielded the product as a pale yellow solid (0.99 g, 83%); this was purified further by Kugelrohr distillation (150 °C, 0.1 mmHg), m.p. 73.5–74.5 °C [Found: $(M + H)^+$ 287.988 73. $C_{10}H_{11}INO$ requires $(M + H)$ 287.988 72]; ν_{max}(Nujol)/cm^{-1} 1640 (C=N); δ_H(200 MHz; C_6D_6) 8.19–8.10 (2 H, m, PhH), 7.16–7.01 (3 H, m, PhH), 3.97 (1 H, m, 4-H), 3.80 (1 H, dd, $J_{5a,4}$ 9.1 and $J_{5a,5b}$ 8.6, 5a-H), 3.68 (1 H, dd, $J_{5b,4}$ 7.3, 5b-H), 2.91 (1 H, dd, $J_{4\alpha,4\alpha'}$ 10.0 and $J_{4\alpha,4}$ 4.0, 4-αH) and 2.76 (1 H, dd, $J_{4\alpha',4}$ 7,1, 4-α'H); δ_C(50 MHz; $CDCl_3$) 164.8 (C-2), 131.4, 128.1 (5PhCH), 127.0 (PhC), 72.8 (C-5), 66.9 (C-4) and 10.5 (C-4α).

(RS)-4-*Nitromethyl*-2-*phenyl*-4,5-*dihydrooxazole* **13**.—A solution containing (*RS*)-4-iodomethyl-2-phenyl-4,5-dihydrooxazole (0.50 g, 1.74 mmol), phloroglucinol (0.56 g, 3.48 mmol) and sodium nitrite (0.27 g, 4.0 mmol) in dry dimethyl sulphoxide (7 ml) was stirred for 4 days at room temperature. After removal of solvent under reduced pressure from the mixture, the residue was poured into water (10 cm^3) and extracted with ethyl acetate (4 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Dry flash chromatography (EtOAc–light petroleum, 1:1) of the residue furnished a white solid which was recrystallised from hexane to give white needles (0.23 g, 63%), m.p. 82–82.5 °C (Found: C, 57.9; H, 4.8; N, 13.4. $C_{10}H_{10}H_2O_3$ requires C, 58.2; H, 4.9; N, 13.6%); ν_{max}(Nujol)/cm^{-1} 1640 (C=N) and 1545 and 1375 (NO_2); δ_H(200 MHz; $CDCl_3$) 7.94–7.90 (2 H, m, PhH), 7.55–7.36 (3 H, m, PhH), 4.94 (1 H, dddd, $J_{4,5a}$ 9.4, $J_{4,4\alpha}$ 8.6, $J_{4,5b}$ 7.1, $J_{4,4\alpha'}$ 4.7, 4-H), 4.76 (1 H, dd, $J_{4\alpha,4\alpha'}$ 13.5, 4α'-H), 4.64 (1 H, dt, $J_{5a,5b}$ 9.2, 5a-H), 4.42 (1 H, dd, 4α-H) and 4.36 (1 H, dd, 5b-H); δ_C(50 MHz; $CDCl_3$) 166.1 (C-2), 131.9, 128.3 (ArC), 77.5 (C-4α), 70.7 (C-5) and 63.9 (C-4); *m/z* (FAB) 207 $[(M + H)^+]$.

(R)-3-(tert-*Butoxycarbonyl*)-2,2-*dimethyloxazolidine*-4-*carbaldehyde Oxime* **18**.—To a stirred solution of hydroxylamine hydrochloride (0.237 g, 3.92 mmol) in pyridine (10 cm^3) was added a pyridine solution of (*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carbaldehyde (0.5 g, 2.18 mmol), prepared by DIBAL reduction of the oxazolidine ester **17** as described by Garner and Park.[17] After 2 h no aldehyde remained (TLC, EtOAc–hexane, 5% phosphomolybdic acid–EtOH) and the reaction mixture was concentrated under reduced pressure, poured into water and extracted with ethyl acetate (3 × 40 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford a clear viscous oil. Flash chromatography (EtOAc–hexane, 3:17) afforded the aldoxime as a clear oil (0.21 g, 40%) comprising a 2:1 mixture of *anti* and *syn* isomers (Found: C, 54.3; H, 8.4; N, 11.6. $C_{11}H_{20}N_2O_4$ requires C, 54.1; H, 8.2; N, 11.5%); ν_{max}(film)/cm^{-1} 3390 (OH) and 1690 (C=O); δ_H(200 MHz; C_6D_6, 60 °C) 8.1 (1 H, br s, OH), 7.33 (0.6 H, d, $J_{4\alpha,4}$ 6.0, 4α-H), 6.68 (0.4 H, d, $J_{4\alpha,4}$ 5.4, 4α-H), 4.99–4.93 (0.4 H, m, 4-H), 4.36–4.31 (0.6 H, m, 4-H), 3.98 (0.6 H, dd, $J_{5a,5b}$ 9.1, $J_{5a,4}$ 6.9, 5a-H), 3.82–3.74 (1.4 H, m, 5a-, 5b-, 5b-H), 1.53, 1.52, 1.43 (6 H, 3 s, CMe_2) and 1.36 and 1.35 (9 H, 2 s, CMe_3); δ_C(50 MHz; C_6D_6, 60 °C) 153.4, 149.9 (C=O, C=N), 94.5, 94.4 (C-2), 80.5 ($OCMe_3$), 67.0, 66.4 (C-5), 56.6, 53.5 (C-4), 28.5 ($OCMe_3$) and 26.7, 24.5 (CMe_2); *m/z* (FAB) 245 $[(M + H)^+]$.

Cycloadditions of Oxazolinecarbonitrile N-*Oxide* **7**.—(a) *With styrene using* p-*chlorophenyl isocyanate*. A solution of (*RS*)-4-nitromethyl-2-phenyl-4,5-dihydrooxazole **13** (0.15 g, 0.73 mmol), *p*-chlorophenyl isocyanate (0.485 g, 3.16 mmol), styrene (0.152 g, 1.46 mmol) and triethylamine (2 drops) in toluene was stirred at room temperature for 18 h. Diethyl ether (5 cm^3) and ethylene-1,2-diamine (0.15 g, 2.44 mmol) was added to the mixture and stirring was continued for a further 30 min. The precipitate was then filtered off and washed with ethyl acetate and the combined filtrate and washings were concentrated under reduced pressure to give a yellow solid, 66% of which was subjected to preparative TLC (EtOAc–hexane, 1:19, eluted twice) to afford two products: RS/SR-4,5-*bis*(2-*phenyl*-4,5-*dihydrooxazol*-4-*yl*)*furazan* N-*oxide* **19** as a crystalline solid (25 mg, 27%), m.p. 149–150 °C [Found: $(M + H)^+$ 377.124 96. $C_{20}H_{17}N_4O_4$ requires $(M + H)$ 377.124 97]; δ_H(200 MHz; $CDCl_3$) 8.03–7.97 (2 H, m, PhH), 7.92–7.86 (2 H, m, PhH), 7.55–7.33 (6 H, m, PhH), 5.57 (1 H, dd, $J_{4,5b}$ 10.2, $J_{4,5a}$ 7.9, 4-H), 5.48 (1 H, dd, $J_{4',5'a}$ 10.2, $J_{4',5'b}$ 9.0, 4'-H), 5.02 (1 H, dd, $J_{5a,5b}$ 8.9, 5a-H), 4.80 (1 H, dd, $J_{5'a,5'b}$ 8.6, 5'a-H), 4.74 (1 H, dd, 5'b-H) and 4.66 (1 H, dd, 5'b-H). RR/SS-4,5-*bis*(2-*phenyl*-4,5-*dihydrooxazol*-4-*yl*)*furazan* N-*oxide* **20** as a crystalline solid (19 mg, 21%), m.p. 144–145 °C [Found: $(M + H)^+$ 377.124 96. $C_{20}H_{17}N_4O_4$ requires $(M + H)$ 377.124 97]; δ_H(200 MHz; $CDCl_3$) 7.93–7.71 (4 H, m, PhH), 7.52–7.24 (6 H, m, PhH), 5.71 (1 H, dd, *J* 10.5, 9.2, 4-H), 5.65 (1 H, dd, *J* 10.5, 8.9, 4'-H), 4.91 (1 H, t, *J* 8.8, 5a-H) and 4.81–4.62 (3 H, m, 5b-, 5'a-, 5'b-H). The structure of compound **20** was determined by X-ray crystallography—*vide infra*.

(b) *With styrene using* m-*tolylene diisocyanate*. To a solution of TDI (0.174 g, 1.0 mmol), styrene (0.091 g, 0.8 mmol) and triethylamine (0.02 g, 0.2 mmol) in 1,2-dichloroethane (10 cm^3) was added over 4 h a solution of the nitromethyl compound **13** (0.092 g, 0.4 mmol) in 1,2-dichloroethane (6 cm^3). When the addition was complete the reaction mixture was heated under reflux for 1 h, and then cooled to room temperature, treated with ethylene-1,2-diamine (0.072 g, 1.2 mmol) and stirred for a further 30 min. After filtration through Celite, TLC of the crude product (EtOAc–hexane, 3:7) showed incomplete consumption of the starting material. The crude product in 1,2-dichloroethane (5 cm^3) was then added dropwise over 3 h to a solution of styrene (0.092 g, 0.04 mmol), TDI (0.174 g, 1.0 mmol) and triethylamine (0.02 g, 0.2 mmol) in 1,2-dichloroethane (10 cm^3). When the addition was complete the resulting mixture was treated as before. The crude product, after filtration and concentration under reduced pressure was subjected to preparative TLC (EtOAc–hexane 3:7) which furnished two products: RS/SR-5-*phenyl*-3-(2-*phenyl*-4,5-*di*-

hydrooxazol-4-yl)-4,5-*dihydroisoxazole* **21**, a white crystalline solid (42 mg, 32%), m.p. 135–136 °C [Found: $(M + H)^+$ 293.128 98. $C_{18}H_{17}N_2O_2$ requires $(M + H)$ 293.128 99]; and RR/SS-5-*phenyl*-3-(2-*phenyl*-4,5-*dihydrooxazol*-4-*yl*)-4,5-*dihydroisoxazole* **22**, a clear oil (35 mg, 27%) [Found: $(M + H)^+$ 293.128 98. $C_{18}H_{17}N_2O_2$ requires $(M + H)$ 293.128 99]; for ^1H NMR data of compounds **21** and **22**—see Table 1.

(c) *With oct-1-ene.* A solution of the nitromethyloxazoline **13** (0.107 g, 0.52 mmol) in 1,2-dichloroethane was added over 4 h to a refluxing solution of oct-1-ene (0.116 g, 1.04 mmol), triethylamine (0.027 g, 0.26 mmol) and TDI (0.226 g, 1.3 mmol) in 1,2-dichloroethane (7 cm^3), and the mixture heated for a further 2 h. After treatment with ethylene-1,2-diamine and work-up as described above for **21**/**22**, the residue was subjected to dry flash chromatography (hexane, then EtOAc–hexane, 3:17) to afford two products: RR/SS-5-*hexyl*-3-(2-*phenyl*-4,5-*dihydrooxazol*-4-*yl*)-4,5-*dihydroisoxazole* **23**, a clear oil (76 mg, 49%) [Found: $(M + H)^+$ 301.191 60. $C_{18}H_{25}N_2O_2$ requires $(M + H)$ 301.191 59]; and (RS/SR)-5-*hexyl*-2-(2-*phenyl*-4,5-*dihydrooxazol*-4-*yl*)-4,5-*dihydroisoxazole* **24**, a white powder (44 mg, 28%), m.p. 83–84 °C [Found: $(M + H)^+$ 301.191 60. $C_{18}H_{25}N_2O_2$ requires $(M + H)$ 310.191 59]; δ_C(90 MHz; $CDCl_3$) 165.6 (C-2′), 158.2 (C-3), 131.7, 128.3, 128.9 (5PhCH), 127.1 (PhC), 81.1 (C-5), 69.7 (C-5′), 64.0 (C-4′), 39.5 (C-4), 35.0, 31.6, 28.9, 25.3, 22.4 (CH_2) and 13.9 (CH_3); for ^1H NMR data of compounds **23** and **24**—see Table 1.

Cycloadditions of Oxazolidinecarbonitrile N-*Oxide* **8**.—(a) *With styrene.* To a stirred solution of oxazolidine oxime **18** (0.5 g, 2.05 mmol) and pyridine (1 drop) in dry chloroform (10 cm^3) at room temperature was added in one portion *N*-chlorosuccinimide (0.27 g, 2.05 mmol). After 1.5 h, styrene (0.436 g, 4.1 mmol) was added to the mixture followed by a solution of triethylamine (0.21 g, 2.08 mmol) in dry chloroform (10 cm^3) added dropwise over 6 h. After being stirred for a further 1 h the reaction mixture was poured into water (50 cm^3). The organic layer was separated, washed with water (2 × 50 cm^3) and brine (50 cm^3) and dried ($MgSO_4$). Half the crude product was subjected to flash chromatography which afforded two products: (5R,4′R)-5-*phenyl*-3-(3′-tert-*butoxycarbonyl*-2′,2′-*dimethyloxazolidin*-4′-*yl*)-4,5-*dihydroisoxazole* **25** as a clear oil which solidified on storage (0.137 g, 39%), m.p. 71–72 °C (from hexane) [Found: $(M + H)^+$ 347.197 05. $C_{19}H_{27}N_2O_4$ requires $(M + H)$ 347.197 07]; $[\alpha]_D^{20}$ −252.4 (*c* 0.8 in $CHCl_3$); δ_C(50 MHz; $CDCl_3$, 60 °C), 157.8 (C=O), 151.6 (C-3), 140.9 (PhC), 128.4, 127.8, 125.4 (5PhCH), 94.3 (C-2′), 81.8 (C-5), 80.4 ($OCMe_3$), 66.3 (C-5′), 54.6 (C-4′), 42.6 (C-4), 28.2 ($OCMe_3$) and 26.1, 23.7 (CMe_2); and (5S,4R′)-5-*phenyl*-3-(3′-tert-*butoxycarbonyl*-2′,2′-*dimethyloxazolidin*-4′-*yl*)-4,5-*dihydroisoxazole* **26** as a white solid (94 mg, 26%), m.p. 88–89 °C (from hexane) [Found: $(M + H)^+$ 347.197 05. $C_{19}H_{27}N_2O_4$ requires $(M + H)$ 347.197 07]; $[\alpha]_D^{20}$ +69.6 (*c* 1.25 in $CHCl_3$); δ_C(50 MHz; $CDCl_3$, 60 °C) 158.2 (C=O), 151.6 (C-3), 141.0 (PhC), 128.5, 127.9, 125.6 (5PhCH), 84.4 (C-2′), 81.9 (C-5), 80.5 ($OCMe_3$), 66.7 (C-5′), 54.6 (C-4′), 42.7 (C-4), 28.1 ($OCMe_3$), 26.2, 23.6 (CMe_2); for ^1H NMR data of compounds **25** and **26**—see Table 1.

(b) *With oct-1-ene.* To a stirred solution of *N*-chlorosuccinimide (0.167 g, 1.25 mmol) in dry chloroform (6 cm^3) was added the oxime **18** (0.3 g, 1.23 mmol) and pyridine (1 drop). The mixture was heated at 40 °C for 2 h and then cooled to room temperature before oct-1-ene (0.28 g, 2.46 mmol) was added to it. A solution of triethylamine (0.17 g, 1.72 mmol) in dry chloroform (5 cm^3) was then added slowly over 9 h to mixture which, following this, was stirred for a further 1 h. The mixture was then washed with water (3 × 20 cm^3) and brine (20 cm^3) and dried ($MgSO_4$). Flash chromatography of the residue (hexane, then EtOAc–hexane, 12:88) allowed, after rechromatography of overlapping fractions, complete separation of the two diastereoisomers: (5S,4′R)-5-*hexyl*-(3′-tert-*butoxycarbonyl*-2′,2′-*dimethyloxazolidin*-4′-*yl*)-4,5-*dihydroisoxazole* **27** as a clear oil (0.144 g, 33%) [Found: $(M + H)^+$ 355.259 66. $C_{19}H_{35}N_2O_4$ requires $(M + H)^+$ 355.259 68]; $[\alpha]_D^{20}$ −33.5 (*c* 0.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1700; δ_C(90 MHz; $CDCl_3$) 158.3 (C=O), 151.8 (C-3), 94.4 (C-2′), 80.8, 80.5 (C-5, $OCMe_3$), 66.6 (C-5′), 54.8 (C-4′), 39.6 (C-4), 35.1, 31.6, 28.9, 25.2, 22.3 (CH_2), 28.3 ($OCMe_3$), 28.3, 26.2 (CMe_2) and 13.7 (CH_3); and (5R,4′R)-5-*hexyl*-3-(3′-tert-*butoxycarbonyl*-2′,2′-*dimethyloxazolidin*-4-*yl*)-4′,5-*dihydroisoxazoline* **28** as a clear oil (0.159 g, 37%) [Found: $(M + H)^+$ 355.259 68. $C_{19}H_{35}N_2O_4$ requires $(M + H)$ 355.259 66]; $[\alpha]_D^{20}$ −9.54 (*c* 0.65 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1700; δ_C(90 MHz; $CDCl_3$) 158.5 (C=N), 151.8 (C-3), 94.4 (C-2′), 80.9, 80.5 (C-5, $OCMe_3$), 66.7 (C-5′), 54.8 (C-4′), 39.5 (C-4), 35.1, 31.6, 28.9, 25.3, 22.4 (CH_2), 28.3 ($OCMe_3$), 28.2, 26.2 (CMe_2) and 13.7 (CH_3); for ^1H NMR data of compounds **27** and **28**—see Table 1.

(c) *With diethyl fumarate.* *N*-Chlorosuccinimide (0.27 g, 2.05 mmol) was added to a solution of the oxime **18** (0.5 g, 2.05 mmol) and pyridine (1 drop) in dry chloroform (10 cm^3). After 2 h at room temperature diethyl fumarate (0.71 g, 2.08 mmol) was added to the mixture followed by a solution of triethylamine (0.21 g, 2.08 mmol) in chloroform (10 cm^3) added slowly over 16 h. After being stirred for a further 1 h the reaction mixture was washed with water (3 × 30 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on 75% of the residue (EtOAc–hexane, 1:9) afforded two diastereoisomeric adducts 4S,4′R,5S- and 4R,4′R,5R-diethyl 3-(3′-tert-*butoxycarbonyl*-2′,2′-*dimethyloxazolidinyl*)-4,5-*dihydroisoxazole*-4,5-*dicarboxylates* **29** and **30** [combined yield of 0.304 g (36%)]: the first product was eluted as a clear oil [Found: $(M + H)^+$ 415.208 01. $C_{19}H_{31}N_2O_8$ requires $(M + H)$ 415.208 02]; $[\alpha]_D^{20}$ −166.2 (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1740 and 1700 (C=O); δ_C(50 MHz; $CDCl_3$, 60 °C) 168.4, 167.4 (CO_2Et), 155.6 (CO_2Bu^t), 151.6 (C-3), 94.6 (C-2′), 81.3 (C-5), 80.7 ($OCMe_3$), 66.6 (C-5′), 62.1, 61.9 (OCH_2CH_3), 57.9 (C-4), 53.9 (C-4′), 28.1 ($OCMe_3$), 25.6, 24.4 (CMe_2) and 13.8 (OCH_2CH_3); the second product was eluted as a clear oil [Found: $(M + H)^+$ 415.208 01. $C_{19}H_{31}N_2O_8$ requires $(M + H)$ 415.208 02]; $[\alpha]_D^{20}$ +102.1° (*c* 0.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1740 and 1700 (C=O); δ_C(50 MHz; $CDCl_3$, 56 °C) 168.3, 167.4 (CO_2Et), 155.0 (CO_2Bu^t), 151.7 (C-3), 94.7 (C-2′), 82.2 (C-5), 80.7 ($OCMe_3$), 66.0 (C-5′), 62.3, 62.1 (OCH_2CH_3), 56.8 (C-4), 54.5 (C-4′), 29.5, 18.1, 25.8 ($OCMe_3$, CMe_2) and 13.8 (OCH_2CH_3); for ^1H NMR data of compounds **29** and **30**—see Table 1.

Crystal Structure of Furazan N-*Oxide* **20**.—*Crystal data.* $C_{20}H_{16}N_4O_4$, M = 376.4, monoclinic, space group $C2/c$ with a = 13.645(7), b = 12.221(10), c = 11.394(7) Å, β = 115.50(4)°, U = 1715 $Å^3$, D_c = 1.457 g cm^{-3}, Z = 4, μ = 0.098 mm^{-1}.

Data collection and processing. Stoë STADI-4 four-circle diffractometer, graphite-monochromated Mo-Kα *X*-radiation, Oxford Cryosystems low temperature device[27] operating at 150.0(1) K, $\omega/2\theta$ mode using the learnt profile method,[28] 1200 reflections collected on two crystals and merged to give 1014 unique data (R_{int} 0.041), of which 850 with $F \geqslant 4\sigma(F)$ were used in all calculations,

Structure solution and refinement. A previous dataset recorded at 298 K was solved by automatic direct methods[29] but, although the solution appeared to be correct, disorder prevented full refinement. Using this solution with the 150 K data allowed the identification and modelling of disorder in the central 1,2,5-oxadiazole (furazan) ring. With the exception of exocyclic *N*-oxide oxygen the molecule conforms approximately to the crystallographic two-fold symmetry imposed on it; the

exocyclic oxygen was found to be equally disordered over the two positions (see Fig. 1), each of which was therefore included in the refinement model with 50% occupancy. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included in fixed, calculated positions[30] with a common U_{iso} of 0.05 Å^2. The weighting scheme [$w^{-1} = \sigma^2(F) + 0.0002F^2$] led to final convergence with R, R_w = 0.0451 and 0.0540 respectively. S = 1.968 for 133 refined parameters.

Crystal Structure of the Isoxazoline **21**.—*Crystal data.* $C_{18}H_{16}N_2O_2$, M = 292.33, monoclinic, space group $P2_1/n$ with a = 14.624(4), b = 5.492(2), c = 17.709(6) Å, β = 93.31(2)°, U = 1419.9 Å^3, D_c = 1.367 g cm^{-3}, Z = 4, μ = 0.098 mm^{-1}.

Data collection and processing. Stoë STADI-4 four-circle diffractometer, graphite-monochromated Mo-Kα X-radiation, T = 295 K, $\omega/2\theta$-scans by profile-fitting method,[28] 1848 unique reflections ($2\theta_{max}$ 50°, h-15→15, k 0→5, l 0→19) giving 1501 with $F \geq 4\sigma(F)$ for use in all calculations. No significant crystal decay or movement was apparent.

Structure solution and refinement. Automatic direct methods[29] located all non-hydrogen atoms which were then refined anisotropically; hydrogen atoms were located and refined isotropically. At final convergence, R, R_w = 0.039, 0.048 respectively. S = 1.93 for 263 refined parameters. Inlaid atomic scattering factors were used;[30] molecular geometry calculations utilised CALC,[31] and the figures were produced by ORTEP[32] and SHELXTL/PC.[33]

Tables of atomic coordinates, bond lengths and angles, torsion angles, and thermal parameters for compounds **20** and **21** have been deposited at the Cambridge Crystallographic Data Centre.*

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* For details see Instructions for Authors (1994), *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

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