

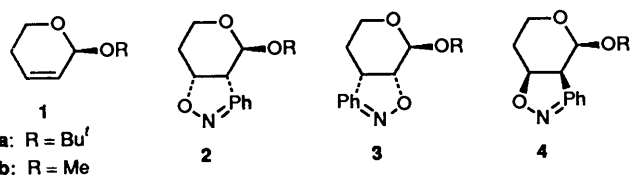
## Regio- and Face-selective Cycloaddition of Benzonitrile Oxide and *C,N*-Diphenylnitrone to 6,8-Dioxabicyclo[3.2.1]oct-3-ene

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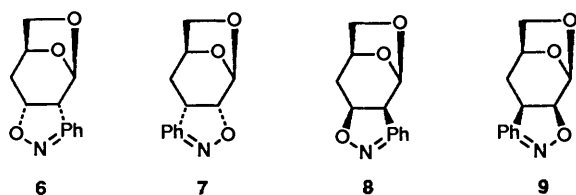
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Benzonitrile oxide, generated by dehydrochlorination of benzohydroximoyl chloride, undergoes regio- and face-selective cycloaddition to 6,8-dioxabicyclo[3.2.1]oct-3-ene **5** yielding a 4:1 mixture of 4,5-dihydroisoxazoles **6** and **7**. Both products have *exo*-stereochemistry resulting from approach of the nitrile oxide from the face opposite the methyleneoxy bridge. The structures of the adducts were determined by <sup>1</sup>H NMR spectroscopy and, in the case of compound **6**, by X-ray crystallography. The corresponding reaction with *C,N*-diphenylnitrone yielded three of the eight possible isoxazolidines, the major isomer being *exo,endo*-adduct **16**.

We have previously described<sup>1</sup> the cycloaddition of benzonitrile oxide to 2-alkoxy-5,6-dihydro-2*H*-pyrans **1** as a model



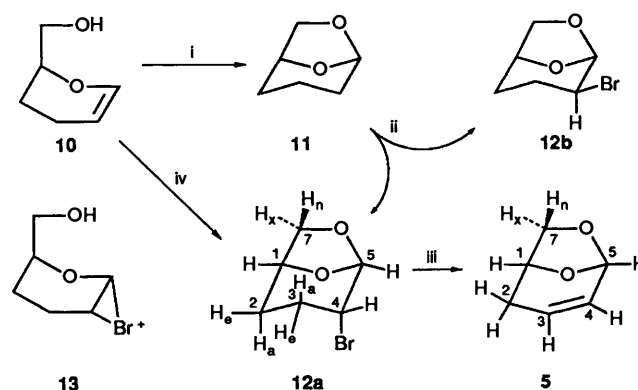
for the corresponding reaction with 2,3-unsaturated pyranosides. Although these alkenes proved to be fairly poor dipolarophiles, giving only *ca.* 40% yields of 2-isoxazoline (4,5-dihydroisoxazoline) cycloadducts, the reactions showed good face- and moderate regio-selectivity. For example, the *tert*-butoxy-substituted alkene **1a** afforded a 3:1 mixture of regioisomers **2a** and **3a**, both of which result from attack of the 1,3-dipole *anti* to the alkoxy substituent. With methoxy analogue **1b** a small amount of the *syn*-adduct **4b** was also isolated in addition to *anti*-adducts **2b** and **3b**. We have now investigated the cycloaddition of benzonitrile oxide to 1*RS*,5*SR*-6,8-dioxabicyclo[3.2.1]oct-3-ene **5**, a racemic analogue of 1,6-anhydropyranoses. This alkene, which is accessible from acrolein dimer,<sup>2,3</sup> has been studied previously as a non-carbohydrate source of carbohydrate derivatives.<sup>2-5</sup> There are four possible isoxazolines **6-9**; reaction can take place



*syn* or *anti* to the methyleneoxy (1,6-anhydro) bridge yielding regioisomeric pairs of *exo*- and *endo*-products.

### Results and Discussion

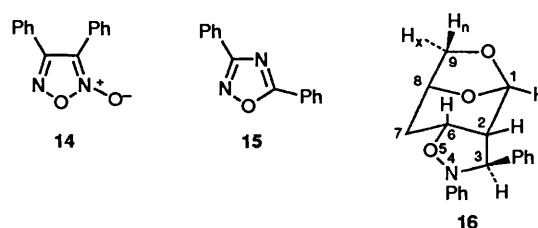
Dioxabicyclooctene **5** was prepared from acrolein-derived alkene **10** by a modification of the route described by Brown *et al.*<sup>3</sup> (Scheme 1). Their original approach involved acid-catalysed ring closure to dioxabicyclooctane **11**, followed by bromination (Br<sub>2</sub>-CCl<sub>4</sub>) to yield a 3:2 mixture of two monobromo derivatives **12a** and **12b**. Only one of these isomers, **12a**, with the bromine axial, is converted into the target alkene **5** on



Scheme 1 Reagents: i, H<sup>+</sup>; ii, Br<sub>2</sub>-CCl<sub>4</sub>; iii, KOH-EtOH; iv, NBS

treatment with base. We have shortened and simplified the process by the use of *N*-bromosuccinimide, which allows alkene **10** to be cyclised and brominated in one operation. Furthermore under these conditions the desired axial bromo isomer **12a** predominates (9:1), presumably due to preferential formation of *anti*-bromonium ion **13**. The reaction is best carried out in dilute solution to avoid polymeric by-products resulting from competing intermolecular ether formation. Bromo compound **12a** was converted into alkene **5** by the established literature procedure.<sup>3</sup>

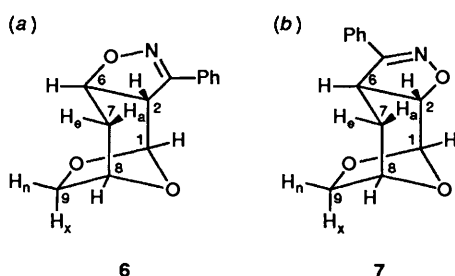
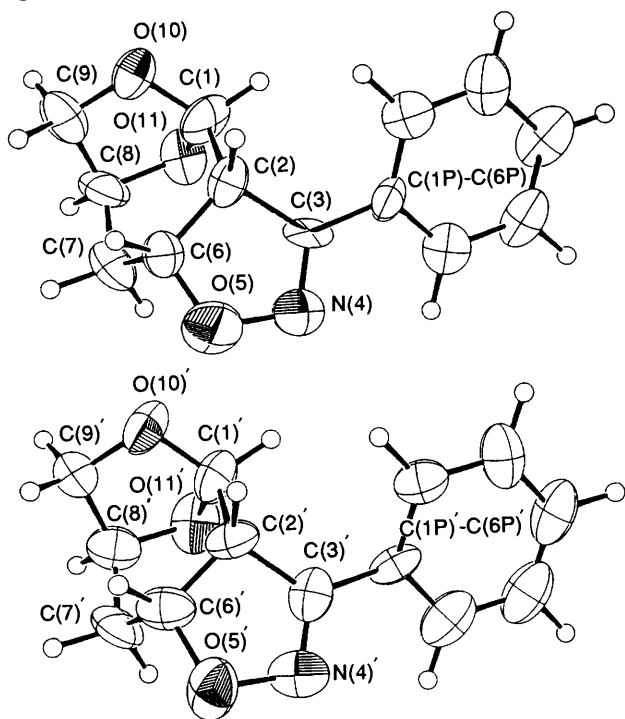
**Cycloaddition of Benzonitrile Oxide.**—In view of the generally low reactivity shown by six-membered cyclic alkenes<sup>1</sup> it was necessary to generate the nitrile oxide in the presence of an excess of the dipolarophile to minimise the competing dimerisation to 3,4-diphenylfuran *N*-oxide **14**. A benzene solution of benzohydroximoyl chloride was added over a period of 24 hours to a refluxing solution of the alkene (1:5) in benzene in the presence of triethylamine. From the reaction mixture were isolated furazan *N*-oxide **14** (5%), oxadiazole **15** (4%) and a fraction comprising a mixture of *exo*-isoxazolines **6** and **7** in a



**Table 1** Selected NMR spectroscopic data<sup>a</sup> for compounds **6**, **7** and **16**

	$\delta_{\text{H}}$			x,y	$J_{x,y}$			$\delta_{\text{C}}$		
	<b>6</b>	<b>7<sup>b</sup></b>	<b>16</b>		<b>6</b>	<b>7</b>	<b>16</b>	<b>6</b>	<b>16</b>	
1-H	5.75	5.74 (5.61)	5.54	1,2	1.1	1.6	1.7	C-1	98.5	99.6
2-H	3.85	4.32 (4.23)	3.00	1,7e	0.9	0.6	—	C-2	53.3	59.2
3-H	—	—	4.72	2,3	—	—	9.4	C-3	156.2	69.7 <sup>c</sup>
6-H	5.12	3.79 (4.06)	4.78	2,6	10.1	9.2	7.5	C-6	74.6	73.2 <sup>c</sup>
7a-H	2.22	1.89 (1.67)	2.0	2,8	—	1.1	0.6	C-7	33.6	32.9
7e-H	2.12	2.01 (2.21)	2.0	6,7a	6.0	9.3	8	C-8	70.8	73.5 <sup>c</sup>
8-H	4.55	4.62 (4.62)	4.56	6,7e	8.2	9.3	8	C-9	68.7	67.4
9n-H	3.83	3.92 (3.82)	3.78	7a,7e	14.6	14.2	—			
9x-H	3.80	3.91 (4.01)	3.84	7a,8	5.6	4.4	—			
				7a,9x	1.4	1.4	0.7			
				7e,8	1.6	1.5	—			
				8,9n	1.4	1.4	1.1			
				8,9x	5.2	5.6	5.2			
				9n,9x	7.3	7.3	7.3			

<sup>a</sup> Recorded in CDCl<sub>3</sub> at 360 MHz (<sup>1</sup>H) and 50 MHz (<sup>13</sup>C). <sup>b</sup> Also recorded in CD<sub>3</sub>COCD<sub>3</sub> ( $\delta_{\text{H}}$ ). <sup>c</sup> Alternative assignments.

**Fig. 1** Conformations of isoxazolines **6** and **7****Fig. 2** Crystal structure of isoxazoline **6** showing the two molecular shapes

combined yield of 71%. The isomer ratio (4:1) was determined by HPLC and <sup>1</sup>H NMR spectroscopy. Examination of the mixture by TLC, HPLC and NMR spectroscopy failed to detect either of the alternative *endo*-isoxazolines **8** and **9**. Oxadiazole **15** has been reported previously<sup>1,6,7</sup> as a by-product of cycloaddition reactions involving benzonitrile oxide. Its formation is attributed variously to parallel triethylamine-

**Table 2** Cremer and Pople puckering parameters<sup>9</sup> for isoxazoline **6** (first row is for unprimed atoms, second for primed)

Ring	$Q(\text{\AA})$	$\theta(^{\circ})$	$\varphi(^{\circ})$
Pyranoid	0.588	144.7	169.0
O-11-C-1-C-2-C-6-C-7-C-8	0.647	145.7	165.4
Dioxolane	0.413		37.6
C-1-O-11-C-8-C-9-O-10	0.410		34.6
Isoxazoline	0.203		145.9
O-5-N-4-C-3-C-2-C-6	0.196		156.2

induced side reactions<sup>6</sup> and fragmentation of unstable 2:1 adducts between benzonitrile oxide and the dipolarophile.<sup>7</sup>

The major product was purified by fractional crystallisation and assigned structure **6** on the basis of its <sup>1</sup>H NMR spectroscopic data (Table 1), the analysis being made using double-irradiation and COSY spectra optimised to show long-range couplings. Proton 2-H appears at lower chemical shift (3.85 ppm) than 6-H (5.12 ppm), thus establishing that the carbon of the nitrile oxide is attached to C-2 adjacent to the anomeric carbon C-1, and the small coupling (1.1 Hz) between 1-H and 2-H indicates that torsion angle 1-H-C-1-C-2-2-H approaches 90° consistent with the adduct having *exo*-stereochemistry. There is also a 1.4 Hz *W*-coupling between 7a-H and 9x-H, and a further long range coupling (0.9 Hz) across the pyran ring between 7e-H and the anomeric proton 1-H. Other noteworthy features of the <sup>1</sup>H NMR spectrum are the large 10 Hz coupling between 2-H and 6-H, *i.e.* involving the protons at the 4- and 5-positions of the 2-isoxazoline moiety, and the splitting pattern for protons 8-, 9x- and 9n-H, which is characteristic of 1,6-anhydropyranose derivatives.<sup>8</sup> This analysis is consistent with the pyran ring adopting a chair conformation (Fig. 1a) with some distortion to accommodate the fused five-membered heterocycles. In the <sup>13</sup>C NMR spectrum there are distinctive signals for the carbons of the isoxazoline ring, with the imine carbon C-3 at 156.2 ppm, and the carbon attached to the oxygen C-6 absorbing at higher frequency (74.6 ppm) than C-2 adjacent to C=N (53.3 ppm).

The regio- and stereo-chemistry of the isoxazoline were confirmed by X-ray crystallography. In the crystal two similar but distinct molecular shapes were discernible (Fig. 2). The Cremer and Pople puckering parameters<sup>9</sup> for the pyran, 1,3-dioxolane and isoxazoline rings (Table 2) show that in both molecules the six-membered ring adopts the distorted chair-like arrangement predicted from the NMR spectroscopic data;

**Table 3** C–O Bond length (pm) for 1,3-dioxolane ring in compound **6** (first row is for unprimed atoms, second for primed)

Difference from mean C–O bond-distance <sup>a</sup>				
C-8	O-11	C-1	O-10	C-9
+1.8	–3.8	+0.6	+2.0	
+1.4	–0.8	–1.6	+0.4	

<sup>a</sup> Mean C–O length is 1.431 pm.**Table 4** Fractional co-ordinates for isoxazoline **6**

	x	y	z
C(1)	0.4712(6)	0.192(3)	0.0627(6)
C(2)	0.5142(6)	0.0510(23)	0.1244(6)
C(3)	0.5620(5)	0.217(3)	0.1790(6)
N(4)	0.5591(6)	0.172(3)	0.2367(6)
O(5)	0.5111(5)	–0.0274(20)	0.2298(5)
C(6)	0.4714(7)	–0.063(3)	0.1622(7)
C(7)	0.4026(7)	0.059(3)	0.1481(7)
C(8)	0.3737(7)	0.180(4)	0.0798(7)
C(9)	0.3682(7)	–0.009(3)	0.0243(7)
O(10)	0.4327(5)	0.0066(16)	0.0156(4)
O(11)	0.4239(5)	0.3550(17)	0.0731(4)
C(1P)	0.6096(5)	0.4047(17)	0.1705(5)
C(2P)	0.6306(5)	0.3831(17)	0.1165(5)
C(3P)	0.6799(5)	0.5471(17)	0.1105(5)
C(4P)	0.7084(5)	0.7328(17)	0.1586(5)
C(5P)	0.6874(5)	0.7545(17)	0.2125(5)
C(6P)	0.6381(5)	0.5905(17)	0.2185(5)
C(1')	0.5583(7)	0.776(3)	0.4746(7)
C(2')	0.6241(6)	0.919(3)	0.5107(7)
C(3')	0.6796(8)	0.776(3)	0.5611(7)
N(4')	0.7370(6)	0.7983(24)	0.5561(7)
O(5')	0.7334(5)	0.9772(20)	0.5063(5)
C(6')	0.6611(6)	1.007(3)	0.4668(7)
C(7')	0.6474(7)	0.857(3)	0.4021(7)
C(8')	0.5764(7)	0.761(3)	0.3813(8)
C(9')	0.5223(7)	0.948(3)	0.3717(7)
O(10')	0.5110(4)	0.9490(18)	0.4332(5)
O(11')	0.5710(5)	0.5916(18)	0.4320(6)
C(1P')	0.6701(4)	0.5914(16)	0.6110(5)
C(2P')	0.6199(4)	0.6427(16)	0.6369(5)
C(3P')	0.6145(4)	0.4922(16)	0.6880(5)
C(4P')	0.6592(4)	0.2905(16)	0.7132(5)
C(5P')	0.7094(4)	0.2392(16)	0.6873(5)
C(6P')	0.7148(4)	0.3896(16)	0.6362(5)

C-6 and O-11 are *ca.* 0.3 and 0.9 Å respectively above and below the plane defined by C-1, C-2, C-7 and C-8. The dioxolane ring incorporating the methylenoxy bridge is mainly in the envelope form  $E_{O(5)}$  with O-11 displaced by *ca.* 0.6 Å from the plane of the other four atoms. The C–O bond lengths in this ring show deviations from the mean value which are generally typical of 1,6-anhydropyranoses. As a consequence of the 'anomeric effect' the two outer bonds in the sequence C-8–O-11–C-1–O-10–C-9 are long and the inner short when compared with the average C–O bond<sup>10</sup> (Table 3). The principal difference in the structures of the two molecules in the asymmetric cell is in their isoxazoline rings. In one it is an envelope ( $\varphi = 145.9^\circ$ ); the torsion angle associated with the imine double bond C-2–C-3=N-4–O-5 is very small ( $0.9^\circ$ ) and C-6 is displaced by 0.32 Å from the plane. In the other there is significant distortion towards the twist conformation ( $\varphi = 156.2^\circ$ ) and the imine torsion angle is  $5.4^\circ$ . In both structures some disruption of the conjugation between the imine and the phenyl ring is evident from the small mean torsion angles ( $21.9^\circ$ ,  $28.5^\circ$ ) between the planes of the phenyl and isoxazoline rings. The atomic co-ordinates are given in Table 4, and bond lengths and angles and torsion angles in Table 5.

The H–C–C–H torsion angles calculated for the crystal structure allow the relative magnitudes of the <sup>1</sup>H NMR couplings to be rationalised. Of particular note are the average of  $30.5^\circ$  for 8-H–C-8–C-9–9x-H and  $91.0^\circ$  for 8-H–C-8–C-9–9n-H which are consistent with the observed couplings of 5.3 and 1.4 Hz and  $20.7^\circ$  corresponding to the 10.1 Hz coupling for 2-H–6-H. Selected torsion angles are compared with observed and calculated<sup>11</sup> coupling constants in Table 6.

A pure sample of the minor cycloadduct was obtained by preparative HPLC, and from its <sup>1</sup>H NMR spectrum it was identified as the *exo*-regioisomer **7**. Full analysis of the spectrum in CDCl<sub>3</sub> was not possible due to overlapping of several signals; however, on changing the solvent to CD<sub>3</sub>-COCD<sub>3</sub> these were resolved and all the spectral parameters could be determined (Table 1). In this case 2-H absorbs at higher frequency than 6-H (4.32 *vs.* 3.79 ppm in CDCl<sub>3</sub>), thus establishing that this isomer has the opposite regiochemistry to that of the major adduct **6**. The small coupling (1.6 Hz) between 1-H and 2-H indicates that the two compounds have the same stereochemistry at C-2, *i.e.* that both result from *exo*-face addition. The other <sup>1</sup>H–<sup>1</sup>H couplings, including long range couplings, closely parallel those of the major isomer, suggesting that both compounds adopt similar conformations (Fig. 1). The preferred formation of regioisomer **6**, with the carbon of the nitrile oxide attached to the carbon adjacent to the anomeric position, is of the same orientation as and somewhat more selective (4:1 *cf.* 3:1) than that previously observed<sup>1</sup> for the corresponding reaction with 2-alkoxy-5,6-dihydropyrans.

Having established that benzonitrile oxide undergoes face-selective cycloaddition, the corresponding reaction with *C,N*-diphenylnitrone (PhCH=N<sup>+</sup>Ph–O<sup>–</sup>) was investigated. In this case the 1,3-dipole has a prochiral centre and there are eight possible adducts: *exo*- and *endo*-isoxazolidines for each pair of regioisomers resulting from attack at the *exo*- and *endo*-faces of the dipolarophile. Treatment of alkene **5** with a slight excess (1:1.02) of the nitron in toluene under reflux for 24 hours afforded, in addition to unchanged nitron (54% recovered), three isoxazolidine cycloadducts in the ratio 68:18:14 (by HPLC) and with a combined yield of 47%, *i.e.* a near quantitative conversion based on consumed nitron. Although the adducts were not readily separable by preparative chromatography the major isomer was purified by crystallisation. It was identified from its <sup>1</sup>H NMR spectrum as the *exo,endo*-adduct **16** in which the carbon of the nitron is attached to C-2 adjacent to the anomeric centre. As for the isoxazoline derived from benzonitrile oxide the regiochemistry was established from the relative positions of the signals due to 2-H and 6-H; 6-H resonates at higher frequency, 4.78 *cf.* 3.0 ppm. The small coupling (1.7 Hz) between 1-H and 2-H, similar to that observed for isoxazoline **6**, also suggests that they have the same stereochemistry at the ring junctions and thus that reaction has taken place at the *exo*-face of the dipolarophile. The 9.4 Hz coupling between 2-H and 3-H at the new asymmetric centre C-3 is consistent with both *syn* and *anti* arrangements for the H–C–C–H unit. The stereochemistry at C-3 was therefore determined by NOE measurements (Table 7). The diagnostic observations are: (i) irradiation of the anomeric proton 1-H causes enhancement of 3-H but not C-Ph, (ii) irradiation of 6-H affects 9-H, and (iii) the signal for 3-H is not enhanced by irradiation of 2-H and *vice versa*. By showing the proximity of 6-H to methylenoxy bridge proton 9-H observation (ii) also confirms the *exo*-face selectivity proposed above. Observations (i) and (iii) establish that 2-H and 3-H have an *anti* relationship, with the 2-H–C-2–C-3–H torsion angle approaching  $180^\circ$ .

Although neither of the other two isoxazolidines could be isolated in pure form and their structures remain uncertain it is

**Table 5** Bond lengths (Å), angles and torsion angles (°) for isoxazoline **6** (first column for unprimed atoms, second for primed)

C(1)–C(2)	1.520(20)	1.539(21)
C(1)–O(10)	1.437(18)	1.415(18)
C(1)–O(11)	1.393(18)	1.423(19)
C(2)–C(3)	1.531(19)	1.498(21)
C(2)–C(6)	1.543(19)	1.501(20)
C(3)–N(4)	1.297(19)	1.270(20)
C(3)–C(1P)	1.464(17)	1.512(18)
N(4)–O(5)	1.428(17)	1.408(17)
O(5)–C(6)	1.426(18)	1.486(18)
C(6)–C(7)	1.526(21)	1.543(21)
C(7)–C(8)	1.525(23)	1.504(22)
C(8)–C(9)	1.526(23)	1.465(22)
C(8)–O(11)	1.449(20)	1.445(20)
C(9)–O(10)	1.451(18)	1.435(18)
C(2)–C(1)–O(10)	108.6(11)	109.5(12)
C(2)–C(1)–O(11)	113.6(12)	108.1(12)
O(10)–C(1)–O(11)	105.0(11)	105.8(12)
C(1)–C(2)–C(3)	116.1(11)	118.3(12)
C(1)–C(2)–C(6)	111.5(11)	114.3(12)
C(3)–C(2)–C(6)	99.4(10)	99.3(12)
C(2)–C(3)–N(4)	113.7(12)	115.3(13)
C(2)–C(3)–C(1P)	125.6(11)	124.8(12)
N(4)–C(3)–C(1P)	120.7(12)	119.5(13)
C(3)–N(4)–O(5)	107.7(11)	109.3(12)
N(4)–O(5)–C(6)	110.4(10)	106.2(10)
C(2)–C(6)–O(5)	104.4(11)	105.6(11)
C(2)–C(6)–C(7)	115.9(12)	116.6(12)
O(5)–C(6)–C(7)	109.6(12)	107.4(11)
C(6)–C(7)–C(8)	113.6(13)	106.9(12)
C(7)–C(8)–C(9)	113.2(13)	118.7(14)
C(7)–C(8)–O(11)	107.2(13)	108.2(13)
C(9)–C(8)–O(11)	100.5(12)	104.4(13)
C(8)–C(9)–O(10)	104.5(12)	104.3(12)
C(1)–O(10)–C(9)	106.0(10)	105.9(11)
C(1)–O(11)–C(8)	103.4(11)	99.5(11)
C(3)–C(1P)–C(2P)	119.3(10)	118.6(10)
C(3)–C(1P)–C(6P)	120.5(10)	121.0(10)
O(10)–C(1)–C(2)–C(3)	–176.7(11)	–175.5(12)
O(10)–C(1)–C(2)–C(6)	70.5(14)	68.1(15)
O(11)–C(1)–C(2)–C(3)	66.9(15)	69.7(16)
O(11)–C(1)–C(2)–C(6)	–45.9(16)	–46.7(16)
C(2)–C(1)–O(10)–C(9)	–95.0(12)	–87.7(13)
O(11)–C(1)–O(10)–C(9)	26.8(13)	28.6(14)
C(2)–C(1)–O(11)–C(8)	74.0(14)	73.8(13)
O(10)–C(1)–O(11)–C(8)	–44.5(13)	–43.4(13)
C(1)–C(2)–C(3)–N(4)	–131.2(13)	–132.0(15)
C(1)–C(2)–C(3)–C(1P)	51.2(18)	41.6(20)
C(6)–C(2)–C(3)–N(4)	–11.5(15)	–7.8(17)
C(6)–C(2)–C(3)–C(1P)	170.9(12)	165.8(13)
C(1)–C(2)–C(6)–O(5)	141.9(11)	143.7(12)
C(1)–C(2)–C(6)–C(7)	21.2(16)	24.6(18)
C(3)–C(2)–C(6)–O(5)	18.9(13)	16.8(14)
C(3)–C(2)–C(6)–C(7)	–101.7(13)	–102.3(14)
C(2)–C(3)–N(4)–O(5)	–0.9(16)	–5.4(18)
C(1P)–C(3)–N(4)–O(5)	176.8(11)	–179.3(11)
C(2)–C(3)–C(1P)–C(2P)	21.8(18)	34.5(18)
C(2)–C(3)–C(1P)–C(6P)	–163.5(11)	–152.4(12)
N(4)–C(3)–C(1P)–C(2P)	–155.7(12)	–152.2(13)
N(4)–C(3)–C(1P)–C(6P)	19.1(18)	20.9(19)
C(3)–N(4)–O(5)–C(6)	14.7(15)	16.6(15)
N(4)–O(5)–C(6)–C(2)	–21.6(14)	–21.1(14)
N(4)–O(5)–C(6)–C(7)	103.1(13)	104.0(12)
C(2)–C(6)–C(7)–C(8)	–26.7(18)	–30.8(17)
O(5)–C(6)–C(7)–C(8)	–144.5(13)	–148.9(12)
C(6)–C(7)–C(8)–C(9)	–56.7(18)	–57.0(18)
C(6)–C(7)–C(8)–O(11)	53.3(16)	61.6(15)
C(7)–C(8)–C(9)–O(10)	88.1(15)	95.3(15)
O(11)–C(8)–C(9)–O(10)	–25.9(14)	–25.2(15)
C(7)–C(8)–O(11)–C(1)	–75.6(14)	–85.7(14)
C(9)–C(8)–O(11)–C(1)	42.9(14)	41.6(14)
C(8)–C(9)–O(10)–C(1)	0.4(14)	–1.6(14)
C(3)–C(1P)–C(2P)–C(3P)	174.8(10)	173.2(10)
C(3)–C(1P)–C(6P)–C(5P)	–174.7(10)	–173.0(10)

assumed, in view of the established preference for *exo*-face attack, that one is the regioisomer of **16** and the other an *exo*-isoxazolidine, *i.e.* epimeric at C-3. In any case, the predominant formation of isomer **16** established that the preferred reaction pathway for *C,N*-diphenylnitrone, like that for benzonitrile oxide, is at the face opposite the methylenoxy bridge.

### Experimental

Preparative TLC was performed on Kieselgel GF<sub>254</sub> silica (0.5 mm layer) containing 13% CaSO<sub>4</sub> and a fluorescent indicator. Analytical TLC also used Kieselgel GF<sub>254</sub> silica (0.2 mm); detection was achieved by UV irradiation or acid-charring (10% H<sub>2</sub>SO<sub>4</sub>, heat). Kieselgel 60 silica was used for column chromatography. Analytical and preparative HPLC were performed as previously described.<sup>1</sup> Mass spectra were recorded on Kratos MS902 and MS50TC instruments. Bruker WP200Y and WH360 spectrometers were used to obtain NMR spectra.

**1SR,5SR-6,8-Dioxabicyclo[3.2.1]oct-3-ene 5.**—To a stirred solution of 2-hydroxymethyl-3,4-dihydro-2*H*-pyran (9.98 g, 87.5 mmol) in dry tetrachloromethane (500 cm<sup>3</sup>) was added *N*-bromosuccinimide (15.6 g, 87.5 mmol) in one portion and the mixture stirred for 18 h. Most of the solvent was removed under reduced pressure and the residue partitioned between dichloromethane (150 cm<sup>3</sup>) and water (150 cm<sup>3</sup>). The organic layer was dried (MgSO<sub>4</sub>), the solvent removed and the residue distilled to afford 4-bromo-6,8-dioxabicyclo[3.2.1]octane **12a** as a pale yellow oil (8.46 g, 50%), b.p. 70 °C at 1.3 mmHg;  $\delta_{\text{H}}$  (360 MHz; CDCl<sub>3</sub>) 5.40 (5-H), 4.51 (1-H), 3.93 (4-H), 3.90 (7n-H), 3.81 (7x-H), 2.40 (3a-H), 2.23 (2a-H), 1.90 (3e-H) and 1.38 (2e-H);  $J_{\text{x-y}}$  (Hz) 1–2a 3.0, 1–2e 1, 1–3e 1, 1–4 < 1, 1–7n 0.8, 1–7x 5.0, 2a–2e 14.3, 2a–3a 12.9, 2a–3e 5.1, 2a–7x 1.5, 2e–3a 5.4, 2e–3e 1.2, 2e–4 1.1, 2e–5 1, 3a–3e 15.3, 3a–4 5.2, 3e–4 1, 3e–5 1, 4–5 < 1 and 7n–7x 7.2;  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 101.4 (C-5), 73.0 (C-1), 67.6 (C-7), 46.9 (C-4), 24.6 and 24.1 (C-2,3).

A solution of KOH (2.22 g, 36 mmol) and bromo derivative **12a** from the previous stage (4.70 g, 24.4 mmol) in ethanol (50 cm<sup>3</sup>) was heated under reflux for 24 h. After filtration and removal of the solvent by distillation at atmospheric pressure, water (50 cm<sup>3</sup>) was added and the mixture extracted continuously with diethyl ether for 10 h. The ether extract was dried, concentrated and the residue distilled under vacuum to afford 6,8-dioxabicyclo[3.2.1]oct-3-ene **5** as a colourless liquid (1.55 g, 56%), b.p. 80 °C at 16 mmHg (lit.,<sup>4</sup> 58 °C at 1 mmHg);  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 5.69 (3-H), 5.52 (4-H), 5.24 (5-H), 4.43 (1-H), 3.72 (7x-H), 3.48 (7n-H), 2.55 (2a-H) and 1.69 (2b-H);  $J_{\text{x-y}}$  (Hz) 1–2a 6, 1–2b 1, 1–3 1.5, 1–7x 6, 2a–2b 18, 2a–3 4, 2a–7n 2, 2b–3 2, 2b–7x 1.5, 3–4 10, 4–5 3 and 7n–7x 7;  $\delta_{\text{C}}$  (50 MHz) 128 (C-3), 125 (C-4), 95 (C-5), 71 (C-1), 68 (C-7) and 33 (C-2).

**Cycloaddition of Benzonitrile Oxide.**—To a solution of alkene **5** (1.52 g, 13.6 mmol) and triethylamine (0.41 g, 4.1 mmol) in dry benzene (25 cm<sup>3</sup>) under reflux was added a solution of benzohydroximoyl chloride<sup>12</sup> (0.43 g, 2.7 mmol) in benzene (10 cm<sup>3</sup>) over 24 h using a motorised syringe. The mixture was heated for a further 16 h and filtered through Celite; the resulting solution was concentrated and the residual dipolarophile removed by evaporation under vacuum (< 1 mmHg). Flash chromatography (silica, 5 → 25% EtOAc in hexane) of the residue afforded in order of elution: 3,5-diphenyl-1,2,4-oxadiazole<sup>1</sup> (11 mg, 4%), 3,4-diphenylfurazan *N*-oxide<sup>1</sup> (15 mg, 5%) and a mixture of isoxazolines **6** and **7** (401 mg, 71%). From the mixture was isolated by crystallisation from diethyl ether 1RS,2RS,6RS,8SR-3-phenyl-5,10,11-trioxo-4-azatricyclo-[6.2.1.0<sup>2,6</sup>]undec-3-ene **6**, m.p. 124 °C (Found: C, 67.6; H, 5.7; N, 6.1. C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub> requires C, 67.5; H, 5.6; N,

**Table 6** Selected H-C-C-H torsion angles (°) for isoxazoline **6** with observed and calculated<sup>a</sup> coupling constants (Hz) (first row is for unprimed atoms, second for primed)

	$H_{x,y}$							
	1,2	2,6	6,7a	6,7e	7a,8	7e,8	8,9x	8,9n
Angle/θ	67.3	21.6	29.7	148.6	57.9	60.7	32.2	89.2
	66.3	19.9	32.2	152.8	57.3	63.7	28.8	93.0
$J_{\text{calc}}$	2.1	7.1	6.3	8.0	3.0	2.7	6.0	1.4
	2.2	7.3	6.0	8.5	3.1	2.4	6.4	1.5
$J_{\text{obs}}$	1.1	10.1	6.0	8.2	5.6	1.6	5.3	1.4

$${}^a {}^3J = 7.76 \cos^2\theta - 1.1 \cos\theta + 1.4 \text{ (ref. 11)}$$

**Table 7** NOE data for isoxazolidine **16**

Protons	1,2	1,3	1,NPh <sub>o</sub>	2,6	2,NPh <sub>o</sub>	3,NPh <sub>o</sub>	3,CPh <sub>m,p</sub>	6,9n
Enhancement (%)	6	3	3	8	3	5	10	2

6.1%);  $m/z$  231 ( $M^+$ ); for NMR data see Table 1. The minor isomer was separated by preparative HPLC (silica, hexane-EtOAc, 9:1) and identified as 1RS,2RS,6SR,8SR-5-phenyl-3,10,11-trioxa-4-azatricyclo[6.2.1.0<sup>2,6</sup>]undec-4-ene **7**; for NMR data see Table 1. The isomer ratio **6**:**7** was determined as 4:1 from the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the crude product mixture.

**Cycloaddition of C,N-Diphenylnitron (N-Phenylbenzylideneamine N-Oxide).**—A solution of alkene **5** (514 mg, 4.6 mmol) and *N*-phenylbenzylideneamine-*N*-oxide (925 mg, 4.7 mmol) in dry toluene (15 cm<sup>3</sup>) was heated under reflux for 14 h. Concentration and chromatography of the residue afforded unchanged nitron (500 mg) and a fraction comprising a mixture of isoxazolidines (663 mg, 47%). HPLC analysis (reverse phase ODS-TMS, H<sub>2</sub>O-MeOH, 40:60) showed the presence of three isomers in the ratio 68:18:14. The major isomer was isolated as white needles by fractional crystallisation from diethyl ether and identified as 1RS,2RS,3RS,6RS,8SR-3,4-diphenyl-5,10,11-trioxa-4-azatricyclo[6.2.1.0<sup>2,6</sup>]undecane **16**, m.p. 158 °C (Found: C, 73.9; H, 6.5; N, 4.5. C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub> requires C, 73.8; H, 6.2; N, 4.5%);  $m/z$  309.1365 ( $M^+$ , C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub> requires 309.1365); for NMR data – see Table 1.

**Crystal Data.**—C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>,  $M = 231.25$ . Monoclinic,  $a = 21.284(5)$ ,  $b = 5.2090(9)$ ,  $c = 21.684(5)$  Å.  $\beta = 110.433(17)^\circ$ ,  $V = 2252.8$  Å<sup>3</sup> (by least-squares refinement on diffractometer angles for 13 reflections with  $2\theta = 35\text{--}39^\circ$ ,  $\lambda = 1.54184$  Å), space group  $P2_1/n$ ,  $Z = 8$ ,  $D_{\text{calc}} = 1.364$  g cm<sup>-3</sup>. Colourless plates,  $0.46 \times 0.25 \times 0.14$  mm;  $\mu(\text{Cu } K\alpha) = 7.60$  cm<sup>-1</sup>,  $F(000) = 976$ .

**Data collection and processing.** STADI-4 four circle diffractometer, graphite-monochromated Cu  $K\alpha$  X-radiation,  $T = 298$  K,  $\omega/2\theta$  scans, 3579 reflections measured ( $2\theta_{\text{max}} = 120^\circ$ ,  $h = 23 \rightarrow 22$ ,  $k = 0 \rightarrow 5$ ,  $l = 0 \rightarrow 24$ ), 2405 unique ( $R_{\text{int}} = 0.017$ ), giving 879 with  $F > 6\sigma(F)$ . An empirical absorption correction was made using  $\Psi$ -scans and a correction for linear isotropic decay ( $\sim 8\%$ ) was incorporated in the data reduction.

**Structure solution and refinement.** Automatic direct methods<sup>13</sup> located all non-hydrogen atoms which were then refined anisotropically; iterative cycles of least-squares refinement and difference Fourier synthesis<sup>14</sup> indicated hydrogen atoms which were thereafter refined in fixed, calculated positions with a fixed isotropic parameter ( $U = 0.08$  Å<sup>2</sup>). The phenyl ring was constrained to be an ideal, rigid hexagon. The weighting scheme  $w^{-1} = \sigma^2(F) + 0.0008F^2$  gave satisfactory agreement analyses, and in the final cycle  $(\Delta/\sigma)_{\text{max}}$  was 0.05. At final convergence  $R$  and  $R_w$  were 0.0757 and 0.0893, respectively,  $S = 1.185$  for 142 refined parameters. A difference Fourier synthesis using all unique data revealed no feature above  $0.79 e \text{ \AA}^{-3}$ . Inlaid atomic scattering factors were used<sup>14</sup>; molecular geometry calculations utilised CALC,<sup>15</sup> and the figures were produced by ORTEP.<sup>16</sup> Tables of thermal parameters and hydrogen atom co-ordinates have been deposited with the CCDC.\*

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