Stereoselective Addition of Benzonitrile Oxide and *N*-Benzyl-*C*-phenylnitrone to (5*RS*,6*SR*)-5,6-Dihydro-6-ethyl-5-methylpyran-2(2*H*)-one. Crystal Structure of (1*RS*,4*RS*,5*RS*,6*RS*,9*SR*)-8-Benzyl-1,5-dimethyl-4-ethyl-9-phenyl-3,7-dioxa-8-azabicyclo [4.3.0]nonan-2-one.

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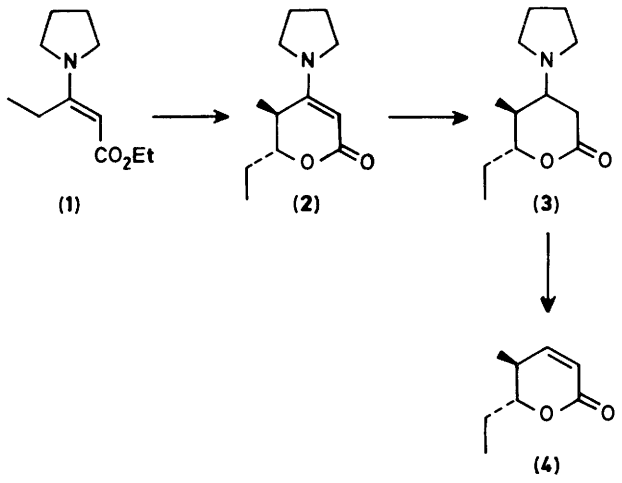
Addition of benzonitrile oxide and *N*-benzyl-*C*-phenylnitrone to (5*RS*,6*SR*)-6-ethyl-5,6-dihydro-5-methyl-2*H*-pyran-2-one (**4**) took place stereoselectively *syn* to the allylic methyl substituent. Methylation of the nitrone adducts (**7**) and (**8**) using lithium di-isopropylamide and methyl iodide involved retention of configuration at C-1 although a small amount of ring-opening and closing occurred in the latter case to give the methylated isoxazolidine (**11**) as a minor product. The structure of (1*RS*,4*RS*,5*RS*,6*RS*,9*SR*)-8-benzyl-4-ethyl-1,5-dimethyl-9-phenyl-3,7-dioxa-8-azabicyclo[4.3.0]nonan-2-one (**10**) was confirmed by an *X*-ray structure determination.

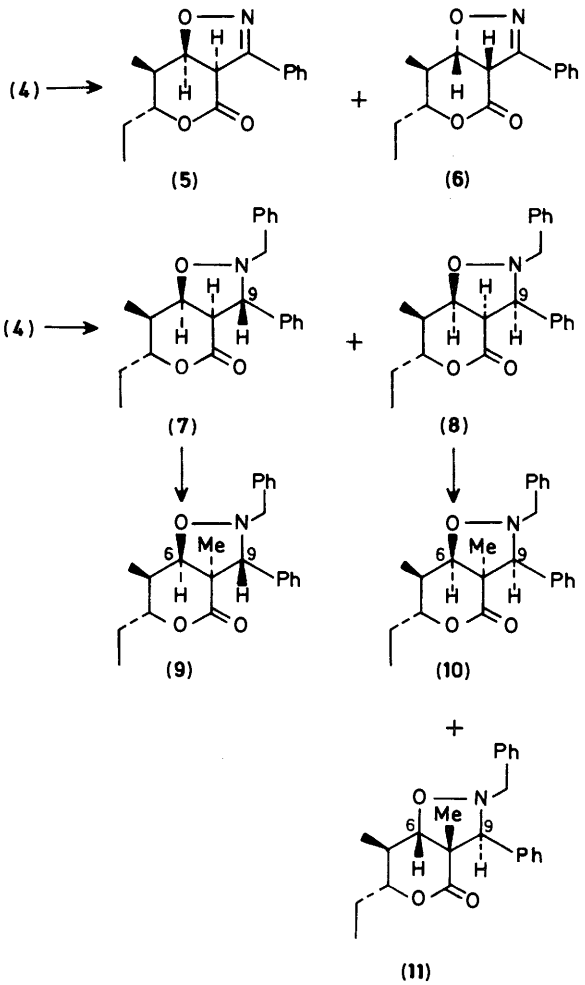
Nitrile oxides[1] and nitrones[2] are now widely used in organic synthesis. The stereoselectivity of addition of these 1,3-dipoles to alkenes is an important consideration when their use in a particular synthesis is being planned. We here report on the stereoselectivity of addition of benzonitrile oxide and *N*-benzyl-*C*-phenylnitrone to (5*RS*,6*SR*)-6-ethyl-5,6-dihydro-5-methyl-2*H*-pyran-2-one (**4**), a study which was carried out in advance of a proposed natural product synthesis.

Results and Discussion

trans-6-Ethyl-5,6-dihydro-5-methyl-2*H*-pyran-2-one (**4**) was prepared using the procedures described by Schlessinger.[3] Thus the enamino ester (**1**)[4] was condensed with propanal to give the enaminodihydro-2*H*-pyran-2-one (**2**) (83%) which was reduced using lithium in liquid ammonia to provide the tetrahydropyranone (**3**) (83%). A Cope elimination then gave the desired 5,6-dihydro-2*H*-pyran-2-one (**4**) (62%).



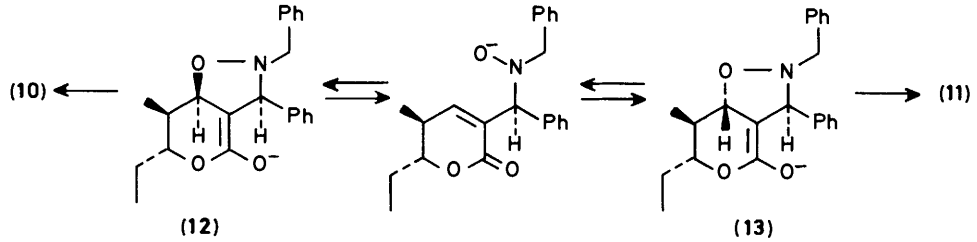
Cycloaddition of benzonitrile oxide[5] and *N*-benzyl-*C*-phenylnitrone[6] to the dihydropyranone (**4**) was found to be highly regio- and stereo-selective occurring preferentially *syn* to the allylic 5-methyl substituent. Benzonitrile oxide, generated *in situ* from α-chlorobenzaldoxime and triethylamine gave the adducts (**5**) and (**6**) in 73 and 1% isolated yields, and *N*-benzyl-*C*-phenylnitrone gave the adducts (**7**) and (**8**) in isolated yields of 37 and 44%. In the latter case, no products were isolated which had been formed by addition *anti* to the allylic 5-methyl substituent.

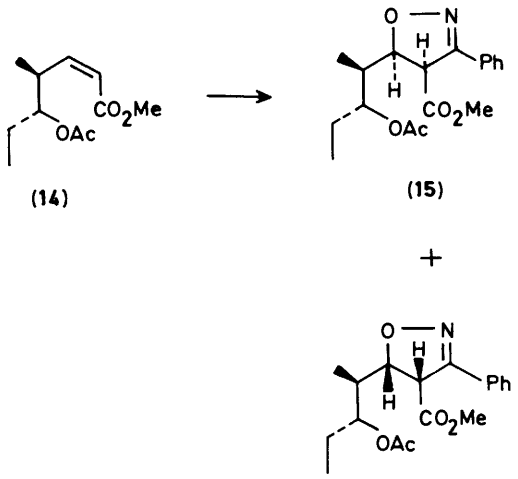


Methylation of the nitrone adducts at C-1 using lithium di-isopropylamide and methyl iodide helped to establish their stereochemistry at C-9. It was found that methylation of adduct (**7**) gave compound (**9**) with retention of configuration, and that methylation of adduct (**8**) gave mainly (**10**), together with a small amount of isomer (**11**), formed presumably by ring-opening of the intermediate isoxazolidine enolate (**12**), followed by ring-closing to give enolate (**13**). This would then be methylated to give the *cis*-fused product. The *endo*-5-*trig* processes involved in this ring-opening and closing are usually unfavourable. The adduct (**8**) is somewhat strained with the 9-phenyl substituent lying under the lactone ring. Despite this strain only a small amount of ring-opening is observed due to the stereoelectronic barrier.[7]

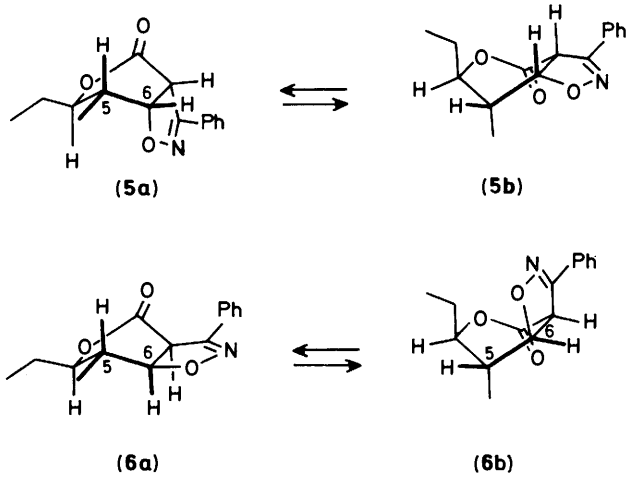
Thus, benzonitrile oxide and *N*-benzyl-*C*-phenylnitrone add to dihydropyran-2(2*H*)-one (**4**) stereoselectively, *syn* to the allylic 5-methyl substituent. The high stereoselectivity observed is of some interest, and may be due to a preference for pseudoaxial approach of the dipolar reagents to the conjugate C-4.[8] In contrast, the addition of benzonitrile oxide to the open-chain acetoxy ester (**14**), prepared from dihydro-2*H*-pyran-2-one (**4**) by hydrolysis, esterification with diazomethane, and acetylation, was not stereoselective, and gave rather a low yield, due to competing nitrile oxide dimerization, of two adducts provisionally identified as (**15**) and (**16**), ratio *ca.* 1:1.

The formation of both C-9 epimers (**7**) and (**8**) in the nitrone addition to the dihydropyran-2-one (**4**) has precedent in the formation of an analogous mixture from the addition of *C*,*N*-diphenylnitrone to cyclohexenes, and may be due to (*Z*)–(*E*)-nitrone equilibration prior to cycloaddition.[2,9]





Initially, structures were assigned to products (**5**)—(**11**) on the basis of ^{1}H n.m.r. data (see Table 1); the Scheme shows possible conformations of the dihydroisoxazoles (**5**) and (**6**). For isomer (**5**), in both likely conformations (**5a**) and (**5b**), the torsional angle between 5-H and 6-H is of the order of 60°, whereas for isomer (**6**), it is more like 180° in the preferred conformation (**6a**). Therefore the major dihydroisoxazole adduct was assigned structure (**5**), $J_{5,6}$ = 3 Hz, the minor adduct being (**6**), $J_{5,6}$ = 7.5 Hz. The C(5)–C(6) stereochemistry of isoxazolidines (**7**)—(**11**) was similarly assigned. The configuration at C-9 for the methylated isoxazolidines (**9**)—(**11**) was established using n.O.e. data since, as shown in Table 1, irradiation of the 1-methyl group caused significant enhancements for *syn* vicinal protons. The structures of the nitrone adducts (**7**) and (**8**) followed from those assigned to the methylated adducts (**9**)—(**11**).



Scheme

These assignments were confirmed by an *X*-ray crystal structure determination for the methylated isoxazolidine (**10**). The Figure shows a representation of the molecule in which the stereochemistry is as depicted in formula (**10**).

Of interest from the crystal structure determination is the deviation of the isoxazolidine nitrogen from planarity; N(8) lies 0.54 Å out of the plane defined by C(9), O(7), and C(14). The tetrahedral nature of this nitrogen is also shown by its bond angles; these are listed in Table 3. A measure of the geometry of the nitrogen is given by the sum of its bond angles which is O(7)N(8)C(14) + O(7)N(8)C(9) + C(9)N(8)C(14) = 105.0 + 102.0 + 113.7 = 320.7°, some 40° less than the 360° required of a planar nitrogen. The lactone ring in (**10**) is boat-like, with the carbonyl oxygen, O(2), some 3.13 Å from the closest point, C(21), on the C(9) phenyl substituent. The H(5)–H(6) torsional angle is 52°, consistent with the ^{1}H n.m.r. coupling constant, $J_{5,6}$ = 2.7 Hz, as discussed above. The bond length and bond angle data determined for isoxazolidine (**10**) are given in Tables 2 and 3.

Experimental

I.r. spectra were measured on Perkin-Elmer 257 and 297 spectrophotometers, and ^{1}H n.m.r. spectra on a Bruker WH-

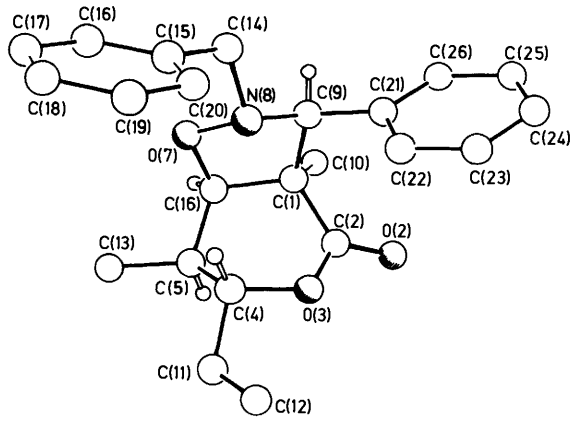


Figure. Ball and stick picture of the isoxazolidine (**10**) showing the crystallographic numbering scheme used

Table 1. Selected ^{1}H n.m.r. data for dihydroisoxazoles and isoxazolidines.

		% n.O.e. on irradiation of 1-Me	
Compd	$J_{5,6}$(Hz)	6-H	9-H
(**5**)	3		
(**6**)	7.5		
(**7**)	3.5		
(**8**)	3.5		
(**9**)	3.1	12	0
(**10**)	3.0	15.4	13
(**11**)	8.5	14	0

Table 2. Bond lengths (Å)

C(1)–C(2)	1.514(3)	C(1)–C(6)	1.548(3)
C(1)–C(9)	1.560(3)	C(1)–C(10)	1.516(4)
C(2)–O(2)	1.208(2)	C(2)–O(3)	1.337(3)
O(3)–C(4)	1.460(3)	C(4)–C(5)	1.513(3)
C(4)–C(11)	1.508(3)	C(5)–C(6)	1.506(3)
C(5)–C(13)	1.522(3)	C(6)–O(7)	1.438(2)
O(7)–N(8)	1.457(2)	N(8)–C(9)	1.458(3)
N(8)–C(14)	1.460(3)	C(9)–C(21)	1.511(3)
C(11)–C(12)	1.503(4)	C(14)–C(15)	1.498(4)
C(15)–C(16)	1.369(3)	C(15)–C(20)	1.370(4)
C(16)–C(17)	1.359(4)	C(17)–C(18)	1.343(5)
C(18)–C(19)	1.368(5)	C(19)–C(20)	1.416(6)
C(21)–C(22)	1.380(3)	C(21)–C(26)	1.380(3)
C(22)–C(23)	1.375(3)	C(23)–C(24)	1.377(4)
C(24)–C(25)	1.362(4)	C(25)–C(26)	1.386(3)

Table 3. Bond angles (°)

C(2)–C(1)–C(6)	112.6(2)	C(2)–C(1)–C(9)	109.4(2)
C(6)–C(1)–C(9)	101.3(2)	C(2)–C(1)–C(10)	109.0(2)
C(6)–C(1)–C(10)	112.5(2)	C(9)–C(1)–C(10)	111.9(2)
C(1)–C(2)–O(2)	122.1(2)	C(1)–C(2)–O(3)	120.1(2)
O(2)–C(2)–O(3)	117.7(2)	C(2)–O(3)–C(4)	121.8(1)
O(3)–C(4)–C(5)	108.9(2)	O(3)–C(4)–C(11)	104.7(2)
C(5)–C(4)–C(11)	115.5(2)	C(4)–C(5)–C(6)	108.9(2)
C(4)–C(5)–C(13)	113.4(2)	C(6)–C(5)–C(13)	110.7(2)
C(1)–C(6)–C(5)	114.0(2)	C(1)–C(6)–O(7)	106.4(2)
C(5)–C(6)–O(7)	112.4(2)	C(6)–O(7)–N(8)	104.8(1)
O(7)–N(8)–C(9)	102.0(1)	O(7)–N(8)–C(14)	105.0(1)
C(9)–N(8)–C(14)	113.7(2)	C(1)–C(9)–N(8)	102.7(2)
C(1)–C(9)–C(21)	116.0(1)	N(8)–C(9)–C(21)	111.8(2)
C(4)–C(11)–C(12)	113.8(2)	N(8)–C(14)–C(15)	111.2(2)
C(14)–C(15)–C(16)	121.8(2)	C(14)–C(15)–C(20)	119.9(2)
C(16)–C(15)–C(20)	118.3(3)	C(15)–C(16)–C(17)	122.1(3)
C(16)–C(17)–C(18)	120.2(3)	C(17)–C(18)–C(19)	120.6(3)
C(18)–C(19)–C(20)	119.0(3)	C(15)–C(20)–C(19)	119.8(3)
C(9)–C(21)–C(22)	121.3(2)	C(9)–C(21)–C(26)	120.3(2)
C(22)–C(21)–C(26)	118.4(2)	C(21)–C(22)–C(23)	121.2(2)
C(22)–C(23)–C(24)	120.0(2)	C(23)–C(24)–C(25)	119.3(2)
C(24)–C(25)–C(26)	121.0(2)	C(21)–C(26)–C(25)	120.0(2)

Table 4. Atom co-ordinates ($\times 10^4$)

Atom	*x*	*y*	*z*
C(1)	1 764(2)	6 019(2)	1 371(1)
C(2)	1 020(2)	6 376(2)	618(1)
O(2)	−36(1)	6 715(2)	478(1)
O(3)	1 539(1)	6 387(1)	89(1)
C(4)	2 708(2)	5 707(2)	160(1)
C(5)	2 850(2)	4 472(2)	670(1)
C(6)	2 844(2)	5 024(2)	1 390(1)
O(7)	3 927(1)	5 803(2)	1 736(1)
N(8)	3 601(1)	7 284(2)	1 579(1)
C(9)	2 439(2)	7 375(2)	1 736(1)
C(10)	932(2)	5 418(3)	1 774(1)
C(11)	2 685(2)	5 328(3)	−592(1)
C(12)	2 570(3)	6 586(3)	−1 077(1)
C(13)	3 984(2)	3 593(3)	727(2)
C(14)	4 569(2)	8 089(3)	2 072(1)
C(15)	5 662(2)	8 199(3)	1 804(1)
C(16)	6 668(2)	7 374(3)	2 074(1)
C(17)	7 655(3)	7 453(3)	1 826(2)
C(18)	7 666(3)	8 358(3)	1 299(2)
C(19)	6 689(3)	9 211(4)	1 005(2)
C(20)	5 666(3)	9 136(4)	1 270(2)
C(21)	1 806(2)	8 767(2)	1 493(1)
C(22)	1 951(2)	9 469(2)	905(1)
C(23)	1 335(2)	10 705(3)	666(1)
C(24)	553(2)	11 259(3)	1 013(1)
C(25)	409(2)	10 580(3)	1 597(1)
C(26)	1 031(2)	9 338(3)	1 843(1)

300 spectrometer (300 MHz). M.p.s were determined on a Buchi 510 apparatus, and are uncorrected. Mass spectra were measured on V. G. Micromass 16F and ZAB-IF spectrometers. T.l.c. was carried out using aluminium foil backed pre-coated plates (Merck Kieselgel 60), flash chromatography using Merck Silica 60, and short column chromatography using Merck Kieselgel 60 H.

All solvents were dried and distilled before use. Ether refers to diethyl ether throughout; light petroleum refers to the fraction b.p. 40—60 °C.

(5*RS*,6*SR*)-6-*Ethyl*-5,6-*dihydro*-5-*methyl*-4-*pyrrolidin*-1-*yl*-2H-*pyran*-2-*one* (**2**).—A solution of ethyl 3-pyrrolidin-1-ylpent-2-enoate (**1**) (9.85 g, 50 mmol)[4] in THF (15 ml) was added dropwise to lithium di-isopropylamide from n-butyl-lithium in hexane (1.7M; 30.9 ml, 52.5 mmol) and di-isopropylamine (55 mmol) at −78 °C. After 30 min, freshly distilled propanal (4.0 ml, 55 mmol) was added, and the mixture stirred at −78 °C for 5 min, allowed to warm to 20 °C over *ca.* 30 min, and then stirred for an additional 30 min. Aqueous NH_4Cl (100 ml) was added, and the product extracted into CH_2Cl_2. The organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed on basic alumina using ether–methanol as the eluant, to give the *title pyranone* (**2**) (8.66 g, 83%), m.p. 81—83 °C (from ether) (Found: C, 68.8; H, 9.15; N, 6.8%. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.1; N, 6.7%); $\nu_{max.}$ 1 672 and 1 578 cm^{-1}; $\delta_H(CDCl_3)$ 0.96 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.31 (3 H, d, *J* 7 Hz, 5-Me), 1.51 and 1.92 (each 1 H, m, *Me*CH_2), 1.97 (4 H, m, 2 × CH_2), 2.42 (1 H, q, *J* 7 Hz, 5-H), 3.19 and 3.41 (each 2 H,

m, 2 × *H*CHN), 4.05 (1 H, dd, *J* 6, 7.5 Hz, 6-H), and 4.45 (1 H, s, 3-H); *m/z* (e.i.) 209 (M^+).

(5RS,6SR)-6-*Ethyl*-5,6-*dihydro*-5-*methyl*-2H-*pyran*-2-*one* (**4**).—Freshly cut lithium pieces (0.31 g, 45 mmol) were added to a vigorously stirred solution of the enamino lactone (**2**) (3.13 g, 15 mmol) and t-butyl alcohol (1.13 ml, 12 mmol) in THF (50 ml) and liquid NH_3 (*ca.* 120 ml) at −70 °C. The blue colour was allowed to develop, the mixture stirred for an additional 5 min, and solid NH_4Cl added. The NH_3 was allowed to evaporate, water (30 ml) was added, and the product was extracted into CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated under reduced pressure, and the residue purified by flash chromatography, using $CHCl_3$–methanol as the eluant, to provide the reduced enamino lactone (**3**) (2.63 g, 83%), as an oil; $\nu_{max.}$(film) 1 725 cm^{-1}; *m/z* (e.i.) 211 (M^+).

The lactone (**3**) was dissolved in toluene (40 ml), and *meta*-chloroperbenzoic acid (80%; 3.63 g, 16.8 mmol) added with ice cooling. After stirring for 24 h at 20 °C, triethylamine (8.7 ml, 62.5 mmol) was added, and the mixture heated at 100 °C for 30 min. The reaction mixture was then cooled, diluted with ether, washed with aqueous sodium bisulphite, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then filtered through silica using light petroleum–ether (3:1) as the eluant, to give the *title pyranone* (**4**) (1.08 g, 62%), as an oil; $\nu_{max.}$(film) 1 720, 1 458, 1 385, 1 237, 1 083, 1 002, and 817 cm^{-1}; $\delta_H(CDCl_3)$ 1.05 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.13 (3 H, d, *J* 7.5 Hz, 5-Me), 1.77 (2 H, m, CH_2), 2.50 (1 H, m, 5-H), 4.03 (1 H, ddd, *J* 4, 7.5, 10 Hz, 6-H), 5.96 (1 H, dd, *J* 2.5, 9.5 Hz, 3-H), and 6.65 (1 H, dd, *J* 2, 9.5 Hz, 4-H); *m/z* (c.i.) 141 (M^+ + H).

4-*Ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*non*-8-*en*-2-*ones* (**5**) *and* (**6**).—Triethylamine (0.56 ml, 4 mmol) was slowly added to a solution of the 2*H*-pyran-2-one (**4**) (280 mg, 2 mmol) and α-chlorobenzaldoxime (0.62 g, 4 mmol) [5] in ether (20 ml) at 0 °C, and the mixture was stirred at 20 ° C for 12 h. After the addition of water, the product was extracted into ether, and the combined extracts dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel, using benzene–ethyl acetate (10:1) as the eluant, gave two products. The first eluted product was (1RS,4RS,5RS,6RS)-4-*ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*non*-8-*en*-2-*one* (**5**) (378 mg, 73%), m.p. 102—103 °C (from ethyl acetate–light petroleum) (Found: C, 69.4; H, 6.75; N, 5.6. $C_{15}H_{17}NO_3$ requires C, 69.45; H, 6.6; N, 5.4%); $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.09 (3 H, d, *J* 7 Hz, 5-Me), 1.46 and 1.72 (each 1 H, m, HC*H*), 1.94 (1 H, m, 5-H), 4.22 (1 H, ddd, *J* 3.5, 7.5, 10.5 Hz, 4-H), 4.68 (1 H, d, *J* 11 Hz, 1-H), 4.93 (1 H, dd, *J* 3, 11 Hz, 6-H), 7.3 (3 H, m, ArH), and 7.81 (2 H, m, ArH); *m/z* (e.i.) 259 (M^+). The second eluted product was identified as (1RS,4SR,5SR,6RS)-4-*ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]-*non*-8-*en*-2-*one* (**6**) (5 mg, 1%) (Found: M^+, 259.1208. $C_{15}H_{17}NO_3$ requires *M*, 259.1208); $\nu_{max.}$($CHCl_3$) 1 750 cm^{-1}; $\delta_H(CDCl_3)$ 1.05 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.24 (3 H, d, *J* 7 Hz, 5-Me), 1.64 and 1.86 (each 1 H, m, *H*CH), 2.10 (1 H, m, 5-H), 4.08 (1 H, ddd, *J* 3.5, 7.5, and 9.5 Hz, 4-H), 4.46 (1 H, d, *J* 11.5 Hz, 1-H), 4.70 (1 H, dd, *J* 7.5, 11.5 Hz, 6-H), 7.40 (3 H, m, ArH), and 7.79 (2 H, m, ArH); *m/z* (e.i.) 259 (M^+).

8-*Benzyl*-4-*ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*-[4.3.0]*nonan*-2-*ones* (**7**) and (**8**).—A solution of the dihydro-2*H*-pyran-2-one (**4**) (1.08 g, 7.73 mmol) and *N*-benzyl-*C*-phenylnitrone (3.26 g, 18.0 mmol) [6] in toluene (8 ml) was heated under reflux for 33 h. Concentration under reduced pressure gave a residue which was chromatographed on silica, using ether–light petroleum (1:1) as the eluant. The first eluted product was (1RS,4RS,5RS,6RS,9SR)-8-*benzyl*-4-*ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*nonan*-2-*one* (**7**) (1.015 g, 37%), m.p. 104.5—105.5 °C (from ether–light petroleum) (Found: C, 75.1; H, 7.2; N, 3.95. $C_{22}H_{25}NO_3$ requires C, 75.2; H, 7.1; N, 4.0%); $\nu_{max.}$($CHCl_3$) 1 727 cm^{-1}; $\delta_H(CDCl_3)$ 1.03 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.07 (3 H, d, *J* 7 Hz, 5-Me), 1.58 and 1.81 (each 1 H, m, HC*H*Me), 1.90 (1 H, m, 5-H), 3.47 (1 H, t, *J* 8.5 Hz, 1-H), 3.71 (1 H, d, *J* 14.5 Hz, *H*CHPh), 3.73 (1 H, d, *J* 8.5 Hz, 9-H), 4.03 (1 H, d, *J* 14.5 Hz, HC*H*Ph), 4.41 (1 H, ddd, *J* 3, 7.5, and 10.5 Hz, 4-H), 4.46 (1 H, dd, *J* 3, 8.5 Hz, 6-H), and 7.4 (10 H, m, aromatic H); *m/z* (c.i.) 352 (M^+ + H). The second eluted product was (1RS,4RS,5RS,6RS,9RS)-8-*benzyl*-4-*ethyl*-5-*methyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*nonan*-2-*one* (**8**) (1.205 g, 44%), m.p. 87—88 °C (from ether–light petroleum) (Found: C, 74.95; H, 7.2; N, 4.0. $C_{22}H_{25}NO_3$ requires C, 75.2; H, 7.1; N, 4.0%); $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1}; $\delta_H(CDCl_3)$ 0.94 (3 H, t, *J* 7 Hz, MeCH_2), 0.98 (3 H, d, *J* 7 Hz, 5-Me), 1.50 and 1.75 (each 1 H, m, *H*CHMe), 1.82 (1 H, m, 5-H), 3.76 (1 H, d, *J* 14 Hz, *H*CHPh), 3.95 (1 H, t, *J* 8.5 Hz, 1-H), 4.06 (1 H, d, *J* 14 Hz, HC*H*Ph), 4.34 (1 H, d, *J* 8.5 Hz, 9-H), 4.51 (1 H, dd, *J* 3.5, 8.5 Hz, 6-H), 4.72 (1 H, ddd, *J* 4, 7, 10 Hz, 4-H), and 7.37 (10 H, m, ArH); *m/z* (c.i.) 352 (M^+ + H).

(1RS,4RS,5RS,6RS,9RS)-8-*Benzyl*-4-*ethyl*-1,5-*dimethyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*nonan*-2-*one* (**9**).—A solution of the isoxazolidine (**7**) (150 mg, 0.43 mmol) in THF (0.5 ml) was added to a solution of lithium di-isopropylamide in THF (1.3 ml; 0.5M) under argon at −78 °C. After 15 min, a solution of methyl iodide and hexamethylphosphoric triamide in THF (0.62 ml; 1M in each) was added, and the mixture was stirred at −78 °C for 8 h. The mixture was allowed to warm to 20 °C slowly, aqueous NH_4Cl was added, and the product was extracted into CH_2Cl_2. The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give an oil. This was purified by flash chromatography using light petroleum–ether as the eluant, to give (1RS,4RS,5RS,6RS,9RS)-8-*benzyl*-4-*ethyl*-1,5-*dimethyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*-[4.3.0]*nonan*-2-*one* (**9**) (96 mg, 62%), m.p. 97 °C (from light petroleum–ether) (Found: C, 75.75; H, 7.5; N, 3.95. $C_{23}H_{27}NO_3$ requires C, 75.6; H, 7.4; N, 3.85%); $\nu_{max.}$($CHCl_3$) 3 015 and 1 723 cm^{-1}; $\delta_H(CDCl_3)$ 1.00 (3 H, s, 1-Me), 1.04 (3 H, t, *J* 7.5 Hz, *Me*CH_2), 1.07 (3 H, d, *J* 7 Hz, 5-Me), 1.55 and 1.80 (each 1 H, m, Me*H*CH), 1.90 (1 H, m, 5-H), 3.73 (1 H, d, *J* 14.5 Hz, *H*CHPh), 3.84 (1 H, s, 9-H), 3.96 (1 H, d, *J* 3 Hz, 6-H), 4.12 (1 H, d, *J* 14.5 Hz, HC*H*Ph), 4.48 (1 H, ddd, *J* 3, 7.5, 10.5 Hz, 4-H), and 7.74 (10 H, m, ArH); *m/z* (c.i.) 366 (M^+ + H).

8-*Benzyl*-4-*ethyl*-1,5-*dimethyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*nonan*-2-*ones* (**10**) and (**11**).—The isoxazolidine (**8**) (351 mg, 1.0 mmol) was methylated using lithium di-isopropylamide, methyl iodide, and hexamethylphosphoric triamide, in THF as described above. Column chromatography of the crude product using light petroleum–ether (2:1) gave two fractions. The first eluted material was identified as (1RS,4SR,5SR,6RS,9RS)-8-*benzyl*-4-*ethyl*-1,5-*dimethyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.3.0]*nonan*-2-*one* (**11**) (36 mg, 10%), m.p. 141—143 °C (from light petroleum–ether) (Found: C, 75.5; H, 7.3; N, 3.9. $C_{23}H_{27}NO_3$ requires C, 75.6; H, 7.4; N, 3.85%); $\nu_{max.}$($CHCl_3$) 3 020 and 1 733 cm^{-1}; $\delta_H(CDCl_3)$ 1.04 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.05 (3 H, s, 1-Me), 1.09 (3 H, d, *J* 7 Hz, 5-Me), 1.58 (1 H, m, *H*CHMe), 1.81 (2 H, m, HC*H*Me + 5-H), 3.63 (1 H, d, *J* 15 Hz, *H*CHPh), 3.67 (1 H, d, *J* 8.5 Hz, 6-H), 4.02 (1 H, d, *J* 15 Hz, HC*H*Ph), 4.05 (1 H, m, 4-H), 4.23 (1 H, s, 9-H), 7.33 (8 H, m, ArH), and 7.63 (2 H, m, ArH); *m/z* (e.i.) 365 (M^+). The second eluted material was identified as (1RS,4RS,5RS,6RS,9SR)-8-*benzyl*-4-*ethyl*-1,5-*dimethyl*-9-*phenyl*-3,7-*dioxa*-8-*azabicyclo*-[4.3.0]*nonan*-2-*one* (**10**) (297 mg, 82%), m.p. 124—125 °C (from light petroleum–ether) (Found: C, 75.8; H, 7.55; N, 3.95. $C_{23}H_{27}NO_3$ requires C, 75.6; H, 7.4; N, 3.85%); $\nu_{max.}$($CHCl_3$) 3 020 and 1 723 cm^{-1}; $\delta_H(CDCl_3)$ 0.93 (3 H, d, *J* 7 Hz, 5-Me),

1.02 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.53 (3 H, s, 1-Me), 1.54 (1 H, m, *H*CHMe), 1.82 (2 H, m, HC*H*Me + 5-H), 3.57 (1 H, d, *J* 14.5 Hz, *H*CHPh), 3.75 (1 H, s, 9-H), 4.04 (1 H, d, *J* 3 Hz, 6-H), 4.05 (1 H, d, *J* 14.5 Hz, HC*H*Ph), 5.05 (1 H, ddd, *J* 3,7,10 Hz, 4-H), and 7.36 (10 H, m, ArH); *m/z* (c.i.) 366 (M^+ + H).

Methyl (4RS,5SR)-5-*Acetoxy*-4-*methylhept*-2-*enoate* (**14**).—A mixture of the 2*H*-pyran-2-one (**4**) (280 mg, 2 mmol) and aqueous lithium hydroxide (60 ml; 0.1M) was stirred for 3 h at 20 °C. The resulting homogeneous solution was washed with CH_2Cl_2, acidified with dilute aqueous HCl, and extracted into CH_2Cl_2. The combined extracts were cooled in ice, and treated with an excess of diazomethane. Acetic acid was added to destroy the excess diazomethane, and the solution was washed consecutively with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, using light petroleum–ether, (2:1) as the eluant, to give *methyl* (4RS,5SR)-5-*hydroxy*-4-*methyl*-cis-*hept*-2-*enoate* (215 mg, 63%) as an oil; $\nu_{max.}$(film) 3 430, 1 720, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 0.97 (3 H, t, *J* 7.5 Hz, $MeCH_2$), 1.05 (3 H, d, *J* 6.5 Hz, 4-Me), 1.39 and 1.55 (each 1 H, m, *H*CHMe), 2.00 (1 H, br s, OH), 3.40 (1 H, m, 5-H), 3.54 (1 H, m, 4-H), 3.72 (3 H, s, CO_2Me), 5.87 (1 H, d, *J* 11.5 Hz, 2-H), and 6.21 (1 H, dd, *J* 10, 11.5 Hz, 3-H); *m/z* (c.i.) 173 (M^+ + H).

Acetyl chloride (0.38 ml, 5.45 mmol) was added to a solution of this hydroxy ester (0.52 g, 3.03 mmol) and pyridine (0.49 ml, 6.06 mmol) in ether (37 ml). After 14.5 h at 20 °C, the solution was washed with hydrochloric acid (3M; 20 ml) and water, dried ($MgSO_4$), and concentrated under reduced pressure. Filtration through silica, using light petroleum–ether (10:1) as the solvent gave *methyl* (4RS,5SR)-5-*acetoxy*-4-*methyl*-cis-*hept*-2-*enoate* (**14**) (0.46 g, 71%) as an oil; $\nu_{max.}$(film) 1 720 and 1 642 cm^{-1}; $\delta_H(CDCl_3)$ 0.87 (3 H, t, *J* 7.5 Hz, $MeCH_2$), 1.02 (3 H, d, *J* 7 Hz, 4-Me), 1.54 (2 H, m, $MeCH_2$), 2.06 (3 H, s, MeCO), 3.72 (3 H, s, CO_2Me), 3.83 (1 H, m, 4-H), 4.85 (1 H, dt, *J* 5.5, 7.5 Hz, 5-H), 5.82 (1 H, dd, *J* 1, 11.5 Hz, 2-H), 6.17 (1 H, dd, *J* 10, 11.5 Hz, 3-H); *m/z* (c.i.) 215 (M^+ + H).

Addition of Benzonitrile Oxide to the Heptenoate (**14**).—A solution of the ester (**14**) (214 mg, 1 mmol) and α-chlorobenzaldoxime (187 mg, 1.2 mmol) in toluene (5 ml) was heated under reflux under a dry nitrogen atmosphere for 22 h.[10] Concentration under reduced pressure, and flash chromatography using light petroleum–ether, gradient elution, gave three fractions. The first fraction was the unchanged ester (**14**) (148 mg). The second fraction was predominantly an adduct, provisionally identified as either (**15**) or (**16**) (20 mg, 6%); $\nu_{max.}(CHCl_3)$ 1 738 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t, *J* 7 Hz, $MeCH_2$), 1.14 (3 H, d, *J* 6.5 Hz, *Me*CH), 1.64 (2 H, m, $MeCH_2$), 2.12 (3 H, s, MeCO), 2.50 (1 H, m, MeC*H*), 3.74 (3 H, s, CO_2Me), 4.24 (1 H, d, *J* 9.5 Hz, 4-H), 4.51 (1 H, dd, *J* 8.5, 9.5 Hz, 5-H), 4.82 (1 H, dt, *J* 5, 6.5 Hz, C*H*OAc), 7.40 (3 H, m, ArH), and 7.69 (2 H, m, ArH); *m/z* (c.i.) 334 (M^+ + H). The third fraction was also an adduct, provisionally identified as either (**15**) or (**16**) (14 mg, 4%); $\nu_{max.}(CHCl_3)$ 1 735, 1 605, and 1 558 cm^{-1}; $\delta_H(CDCl_3)$ 0.96 (3 H, t, *J* 7.5 Hz, $MeCH_2$), 1.05 (3 H, d, *J* 7 Hz, *Me*CH), 1.70 (2 H, m, $MeCH_2$), 2.12 (3 H, s, MeCO), 2.38 (1 H, m, MeC*H*), 3.72 (3 H, s, CO_2Me), 4.28 (1 H, d, *J* 8.5 Hz, 4-H), 4.58 (1 H, dd, *J* 8.5, 10 Hz, 5-H), 5.13 (1 H, dt, *J* 4, 8 Hz, C*H*OAc), 7.43 (3 H, m, ArH), and 7.69 (2 H, m, ArH); *m/z* (c.i.) 334 (M^+ + H).

Crystal Data for the Isoxazolidine (**10**).—$C_{23}H_{27}NO_3$, M_r = 365.4, monoclinic, a = 11.501(2), b = 9.439(1), c = 19.587(3) Å, β = 106.67(1)°, U = 2037 Å^3, space-group $P2_1/c$, Z = 4, D_c = 1.20 g cm^{-3}, μ(Cu-K_α) = 6 cm^{-1}. Refined unit cell parameters were obtained by centering 18 reflections on a Nicolet R3m diffractometer. 2 091 Independent reflections ($\theta \leqslant 50°$) were measured with Cu-K_α radiation (graphite monochromator) using the omega-scan measuring routine. Of these, 1922 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The crystals are stable both in air and under *X*-ray irradiation, there being no significant change in the counts from two check reflections measured every 50 reflections during the data collection. The data were corrected for Lorentz and polarisation factors. No absorption corrections were applied.

The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The hydrogen positions were idealised (C–H = 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2U_{eq.}(C)$, and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares to R = 0.041, R_w = 0.050, $[w^{-1} = \sigma^2(F) + 0.000\,76F^2]$. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

Table 4 lists the fractional atomic co-ordinates of the non-hydrogen atoms. Tables 2 and 3 give the bond lengths and valence angles respectively. The anisotropic thermal parameters, the hydrogen co-ordinates and temperature factors are available as a supplementary publication [SUP No. 56354 (4 pp)].* The calculated and observed structure factors are available on request from the Editorial Office.

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* For details of the supplementary publications scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

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