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X=Y-ZH Systems as Potential 1,3-Dipoles. Part 47.[1] Tandem Nucleophilic Substitution-1,3 Dipolar Cycloaddition Reactions of Oximes With Epoxides and Dipolarophiles

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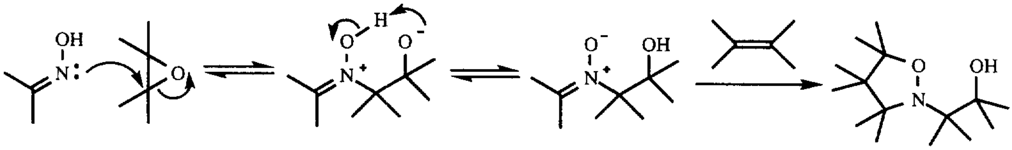
Abstract: Regiospecific nucleophilic substitution reactions involving attack of the nitrogen atom of oximes on epoxides are used to generate nitrones which are then trapped in 1,3-dipolar cycloaddition reactions. These tandem processes are shown to be flexible and to have wide synthetic scope for the construction of complex molecular frameworks. © 1997 Elsevier Science Ltd.

Our continuing interest in the use of oximes in organic synthesis has led us to develop a wide range of cascade routes to isoxazolidine based cycloadducts *via* nitrone intermediates. A particularly versatile strategy involves the reaction between an oxime and an electrophilic reagent to effect *N*-substitution with concomitant loss of the labile oxime hydroxyl proton followed by 1,3-dipolar cycloaddition between the resulting nitrone and a suitable dipolarophile. Initial studies concerned with the reaction between oximes and epoxides have shown the latter to be suitable as electrophilic reagents in these cascades allowing rapid access to a wide range of heterocyclic frameworks. In this paper we report more fully on our preliminary studies[2] of such cascade reactions.

Ring opening of epoxides by various nucleophiles (*e.g.*, alkoxides, amines, halogens etc.) has been extensively studied[3-5] and various catalysts have been reported both to promote epoxide opening and to improve regioselectivity in these processes.[6-8] Our studies have shown that regiospecific nucleophilic ring opening reactions of epoxides by oximes generates nitrones in good yield. The nitrones can then be trapped by dipolarophiles to give isoxazolidines also in good yield (*Scheme 1*).



Scheme 1

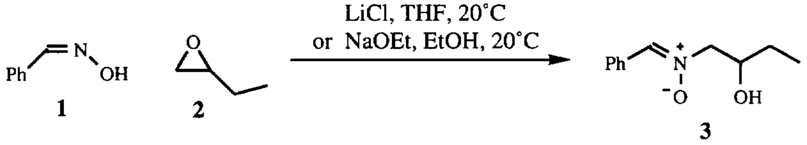
Class	Epoxide opening	Cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular

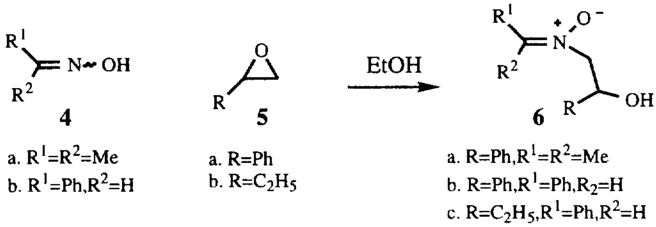
Table 1

Cascade reactions involving nitrone formation coupled with a subsequent cycloaddition reaction have four broad synthetic variants depending on the intermolecular or intramolecular nature of each of the two distinct steps (*Table 1*). We report herein on the development of such cascade reactions and highlight examples of each of the four Classes.

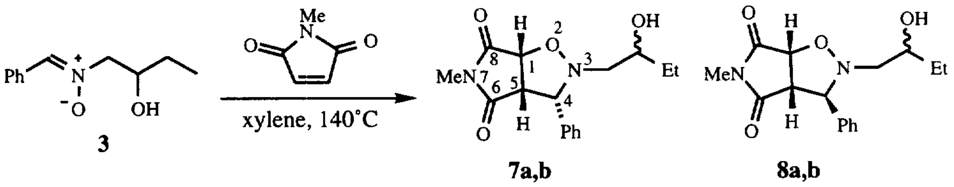
Class 1 Processes:

Class 1 processes involve intermolecular epoxide opening followed by an intermolecular cycloaddition. An example of this class is provided by the reaction of Z-benzaldoxime **1** with 1,2-epoxybutane **2** (THF, LiCl, 20°C, 18h) which affords nitrone **3** regiospecifically in 70% yield. The addition of LiCl promotes ring opening of the epoxide by coordinating with the oxygen atom. In the absence of LiCl the reaction does not take place at room temperature. Nitrone formation also occurred when the sodium salt of Z-benzaldoxime **1** was treated with an excess (10 mol equiv) of **2** at room temperature for 6h (60%). Kliegel has previously reported[9,10] similar ring opening reactions with oximes and has demonstrated the generation of nitrones **6a-c** from oximes **4 a,b** and epoxides **5a,b** albeit in very low yield (3-6%).



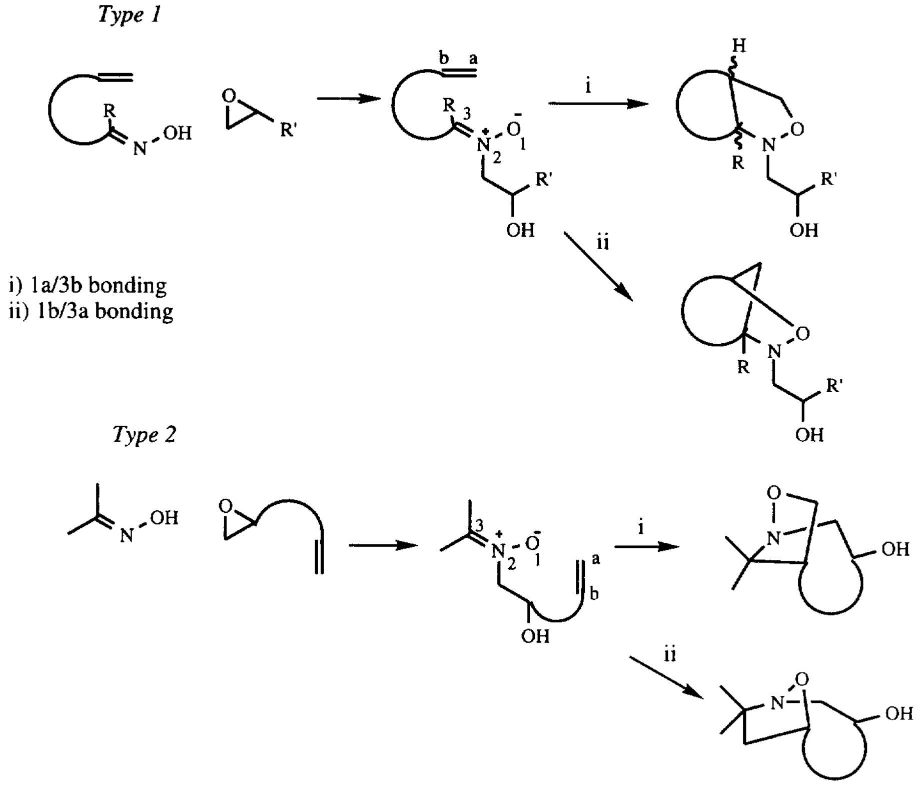


Nitrone **3** when heated in xylene with *N*-methylmaleimide (NMM) at 140°C for 45 min afforded a 1:1·8 mixture of *exo*- and *endo*-cycloadducts **7a,b** and **8a,b** respectively (90% combined yield) each of which comprised a 1:1 mixture of diastereoisomers. The stereochemistry of the cycloadducts was assigned on the basis of data obtained from n.O.e difference spectra (see Experimental section).



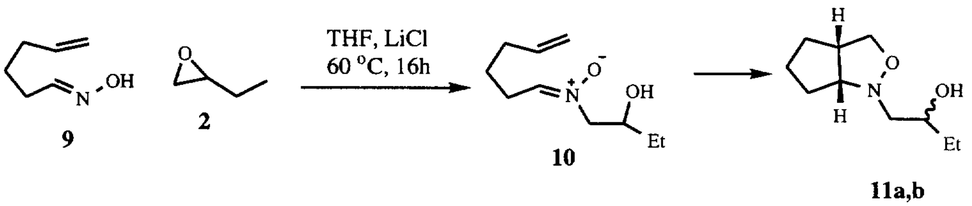
Class 2 Processes:

Class 2 processes involve intermolecular epoxide opening followed by an intramolecular cycloaddition. This class provides potentially attractive and flexible synthetic methodology because the dipolarophile can be located within the oxime (*Scheme 2, Type 1*), such that when the oxime reacts with the epoxide a *C*-alkenyl nitrone is generated. Alternatively both the dipolarophile and epoxide can be located within the same molecule in which case an *N*-alkenyl nitrone is generated upon reaction with the epoxide (*Scheme 2, Type 2*).

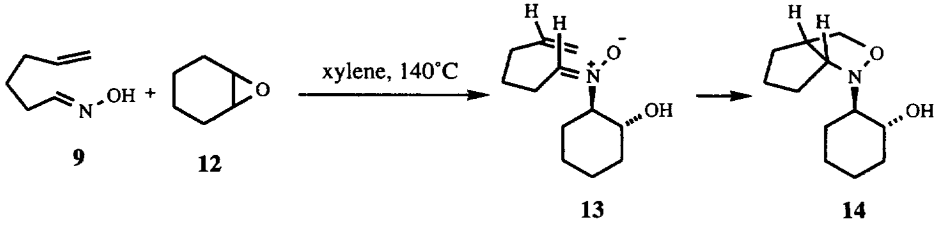


Scheme 2

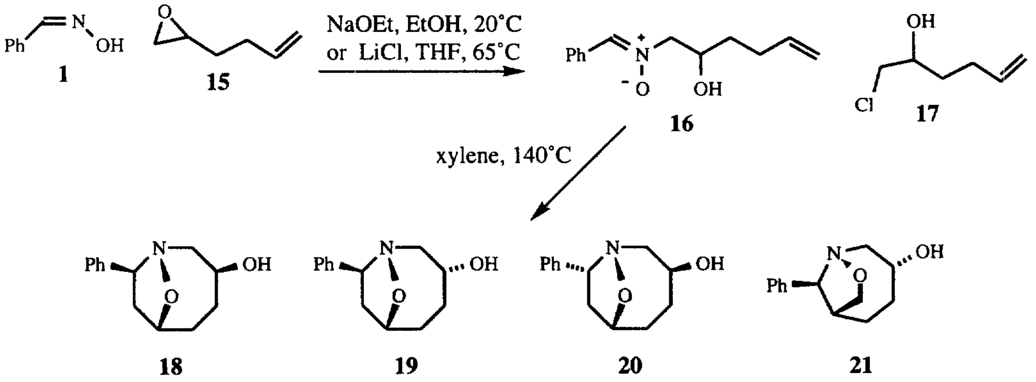
An example of a *Type 1* system is provided by the reaction of 5-hexenaldoxime **9** with an excess of 1,2-epoxybutane **2** in the presence of LiCl (THF, 60°C, 16h) to afford a 1:1 mixture of diastereoisomers **11a,b** (60% combined yield) *via* nitrone **10**.



Intermolecular ring opening of epoxides occurs in the absence of a catalyst but requires high temperature. Thus 5-hexenaldoxime **9** on heating in boiling xylene (140°C, 2½ days) with a ten fold excess of cyclohexane oxide **12** undergoes 50% conversion (of oxime) into a single cycloadduct **14** in 30% yield. The S_N^2 ring opening of the epoxide **12** leads to nitrone **13** which then undergoes cycloaddition to afford **14** as a single isomer. Stereochemical assignments in **14** were made on the basis of data from n.O.e experiments.



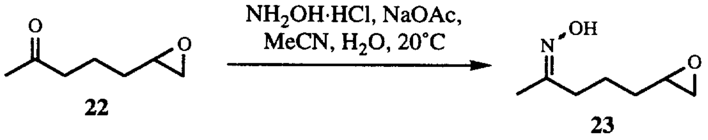
An example of the *Type 2* system is shown below. In this case the dipolarophile is incorporated into epoxide component **15**. Reaction of *Z*-benzaldoxime **1** with an excess of 1,2-epoxy-5-hexene **15** (LiCl, THF, 60°C, 16h) afforded **16** albeit in low yield (28%). Examination of the ^{1}H nmr spectrum of the crude product suggested possible competitive formation of the chlorohydrin **17**. Notably the sodium salt of **1** reacted with **15** (EtOH, 20°C, 6h) to produce **16** in 55% yield. Heating nitrone **16** in xylene at 140°C (24 h) afforded a 12:8:2:1 mixture of cycloadducts **18-21** in 79% yield. All assignments are supported by 2D-COSY and n.O.e. data. The isomeric ratio of **18**:**19**:**20** reflects steric interactions in their respective transition states which arise from destabilizing interactions between the OH and CH(Ph)CH_2 bridge in **19** and the Ph and the four carbon bridge in **20**. Isomer **21** is the least sterically hindered of the stereoisomers that could arise from the alternative cycloaddition regiochemistry.



Class 3 Processes:

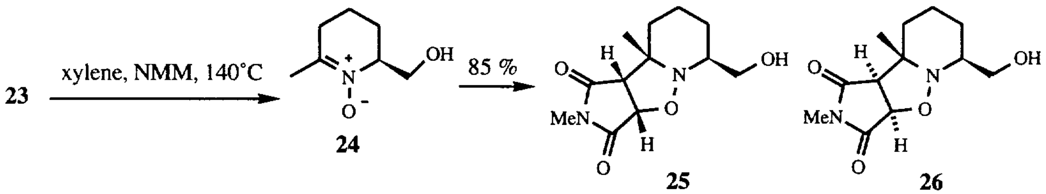
Class 3 processes involve intramolecular epoxide opening generating a cyclic nitrone followed by an intermolecular cycloaddition. As such, this class requires the incorporation of epoxide functionality into the same component as the oxime. Oxime **23** was prepared by oximation of the known[11] epoxyketone **22** (*Scheme 3*). Upon treatment with NMM in boiling xylene the oxime **23** afforded a 1:6 mixture of **25** and **26** together with a third minor isomer (combined yield, 85%). The intermediate nitrone **24** is formed *via* a 6-*exo*-tet cyclisation. Stereochemistries of **25** and **26** were assigned on the basis of n.O.e difference spectra (see

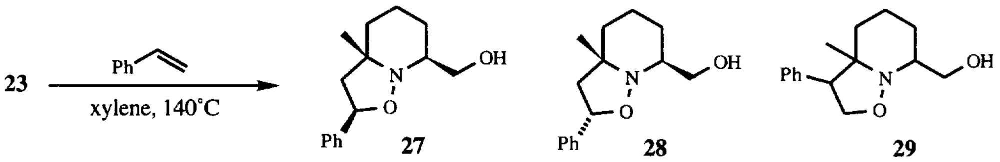
Experimental section). The stereochemistry of the products indicates that addition of NMM to the nitrone occurs from the face opposite to the bulky hydroxymethyl group.



Scheme 3

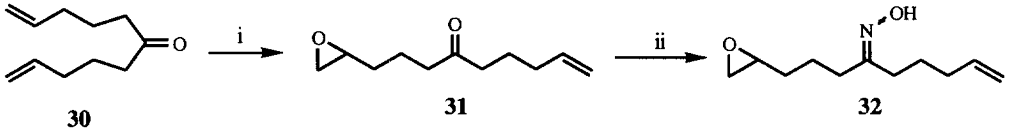
Nitrone **24** also underwent cycloaddition with unactivated dipolarophiles such as styrene. Thus treatment of oxime **23** with styrene in xylene (140°C, 8h) afforded a 3:2 mixture of *exo*- and *endo*-isomers **27** and **28** (50% yield). Assignment of stereochemistry is again based on n.O.e data. The alternative 4-substituted isoxazolidines **29** were not observed.





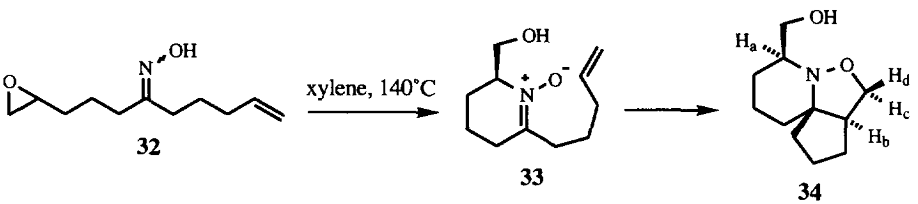
Class 4 Processes:

Oxime **32** was designed for this study and prepared as outlined (*Scheme 4*). Mono-epoxidation (40%) of symmetrical ketone **30**[12] was realized with MCPBA at high dilution. The oximation of **31** was achieved under standard conditions. Class 4 reactions are illustrated by heating **32** (xylene, 140°C, 6h). The nitrone **33** was trapped in an intramolecular cycloaddition without isolation to give cycloadduct **34** in 90% yield. Stereochemistry of **34** was assigned using n.O.e difference spectra recorded in d_{10}-xylene. Irradiation of the signal attributed to H_c (δ 2·84) effected enhancements in the signals for H_a (δ 1·80, 5·8%), H_b (δ 3·65, 5%) and H_d (δ 1·90, 16%) so showing the *cis*-relationship between H_a and H_b.



i, MCPBA, CH$_2$Cl$_2$, 20°C; ii, NH$_2$OH·HCl, NaOAc, MeCN, H$_2$O, 20°C

Scheme 4



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba MOD 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. ^1H Nuclear magnetic resonance spectra were recorded using either a General Electrics QE300 spectrometer (300 MHz) or using a Bruker AM-400 spectrometer (400 MHz)in the solvents specified. Flash column chromatography was performed using silica gel 60 (Merck 9385). Petroleum ether (b.p. 40-60°C), ethyl acetate and methanol were distilled prior to use. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl prior to use.

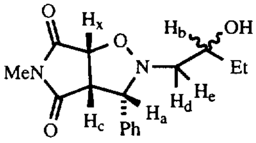
***C*-Phenyl-*N*-(2-hydroxybutyl)nitrone 3**. (*Z*)-Benzaldoxime **1** (1·00 g, 8·26 mmol) and 1,2-epoxybutane **2** (6·00 g, 82·6 mmol) were stirred in a saturated solution of LiCl in tetrahydrofuran (30ml) at room temperature for 18 h. After addition of water (20 ml) the mixture was extracted with chloroform (2 x 30ml), the combined organic layers dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residual solid crystallised from petroleum ether (b.p. 40-60°C)-diethyl ether to afford the *product* **3** as colourless plates (1·05 g, 70%). m.p. 103-104°C; (Found: C, 68·6; H, 8·0; N, 7·2. $C_{11}H_{15}NO_2$ requires C, 68·4; H, 7·8; N, 7·2%); *m/z* (%) 193 (M^+, 44), 164 (17), 135 (8), 91 (72), 118 (100); δ_H ($CDCl_3$) 8·20 (2H, m, ArH), 7·45 (3H, m, ArH), 7·37 (1H, s, PhC*H*=N), 4·57 (1H, d, *J* 3·5 Hz, OH), 4·13 (1H, m, C*H*OH), 4·02 (1H, dd, *J* 12·5 and 2 Hz, NCH_aH_b), 3·87 (1H, dd, *J* 12·5 and 8·5 Hz, NCH_aH_b), 1·54 (2H, m, CH_2CH_3), 1·02 (3H, t, *J* 7·5 Hz, CH_2CH_3); δ_C ($CDCl_3$) 142, 137, 134·5, 134, 76·5, 76, 32, 10.

3-(2'-Hydroxybutyl)-7-methyl-4-phenyl-3,7-diaza-2-oxabicyclo[3.3.0]octane-6,8-dione 7a,b and **8a,b**. A solution of nitrone **3** (0·50 g, 2·50 mmol) and *N*-methylmaleimide (0·29 g, 2·50 mmol) in xylene (15ml) was stirred and heated at 140°C for 45 min. The xylene was removed *in vacuo* and the crude product purified by preparative t.l.c eluting with 9:1 v/v ether-ethyl acetate to afford a 1·8:1·8:1:1 mixture of products **7a**, **7b**, **8a** and **8b** (0·68 g, 90%). *m/z* (%) (mixed isomers) 304 (M^+, 3), 245 (14), 91 (100);
7a: Colourless rods from diethyl ether-ethyl acetate. m.p. 135-137°C; (Found: C, 63·25; H, 6·75; N, 9·5. $C_{16}H_{20}N_2O_4$ requires C, 63·15; H, 6·6; N, 9·2%); δ_H ($CDCl_3$) 7·30 (3H, m, ArH), 7·14 (2H, m, ArH), 4·90 (1H, d, *J* 7·5 Hz, H_x), 4·00 (1H, d, *J* 8·5 Hz, H_a), 3·78 (1H, m, H_b), 3·67 (1H, dd, *J* 8·5 and 7·5 Hz, H_c), 2·97 (3H, s, NMe), 2·78 (1H, dd, *J* 14, 3·5 Hz, H_d), 2·60 (1H, dd, *J* 14, 7 Hz, H_c), 2·39 (1H, broad s, OH), 1·43 (2H, m, CH_2CH_3), 0·88 (3H, t, *J* 7·5 Hz, CH_2CH_3).

7b: Colourless needles from diethyl ether. m.p. 133-134°C; (Found: C, 62·95; H, 6·65; N, 8·8. $C_{16}H_{20}N_2O_4$ requires C, 63·15; H, 6·6; N, 9·2%); δ_H ($CDCl_3$) 7·30 (3H, m, ArH), 7·10 (2H, m, ArH), 4·90 (1H, d, *J* 7·5 Hz, H_x), 4·00 (1H, d, *J* 8·5 Hz, H_a), 3·85 (1H, m, H_b), 3·71 (1H, dd, *J* 8·5 and 7 5 Hz,

H_c), 2·97 (3H, s, NMe), 2·66 (2H, m, H_d and H_e), 2·49 (1H, broad s, OH), 1·40 (2H, m, $C\mathit{H}_2CH_3$), 0·89 (3H, t, J 7·5 Hz, $CH_2C\mathit{H}_3$).

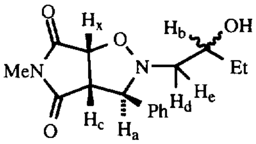
8a and **8b** (mixture): (Found: C, 63·05; H, 6·7; N, 9·05. $C_{16}H_{20}N_2O_4$ requires C, 63·15; H, 6·6; N, 9·2%); δ_H ($CDCl_3$) 7·30 (5H, m, ArH), 4·99 (2H, d, J 7·5 Hz, H_x), 4·30 and 4·10 (1H, 2 x broad s, H_c), 3·73 (2H, m, H_a and H_b), 3·08 and 3·07 (3H, 2 x s, NMe), 2·80-2·40 (3H, m, H_d, H_e and OH), 1·35 (2H, m, $C\mathit{H}_2CH_3$), 0·88 (3H, m, $CH_2C\mathit{H}_3$).



7a,b

Enhancement (%)

Irradiated hydrogen	H_a	H_b	H_c	H_d	H_e	H_x
H_a			8·1			
H_c	6·9				4·5	6·2
H_d	1·1	3·3			10·9	
H_e	6·1	2·4		9·8		
H_x			5·1			



8a,b

Enhancement (%)

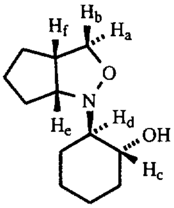
Irradiated hydrogen	H_a	H_b	H_c	H_d,H_e	H_x	OH
H_a			7·7	5·6		
H_c	6·9				6·3	
H_x			5·0			0·5
Ph	2·8					

2-(2'-Hydroxybutyl)-2-aza-3-oxabicyclo[3.3.0]octane 11a and 11b. A solution of 5-hexenaldoxime **9** (0·50 g, 4·40 mmol) and epoxybutane **2** (3·20 g, 44·00 mmol) in a saturated solution of LiCl in tetrahydrofuran (15 ml) was held at reflux for 16 h. The reaction mixture was cooled, water (20 ml) added, the mixture extracted with chloroform (2 x 25ml), the combined organic layers dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residual oil was purified by preparative t.l.c. eluting with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether to afford a 1:1 mixture of *products* **11a** and **11b** (0·39 g, 60%) as a colourless oil. (Found: C, 64·85; H, 10·1. $C_{10}H_{19}NO_2$ requires: C, 64·85; H, 10·35%); *m/z* (%) (mixed isomers) 185 (M^+, 33), 142 (100).

11a: δ_H ($CDCl_3$) 4·08 (1H, t, J 8·5 Hz, $OC\mathit{H}_aH_b$), 3·70 (1H, m, $NC\mathit{H}CC$), 3·36 (1H, dd, J 8·5 and 6·5 Hz, $OCH_a\mathit{H}_b$), 3·25 (1H, m, $NC\mathit{H}_aH_b$), 3·17 (1H, s, OH), 2·97 (1H, m, $C\mathit{H}OHEt$), 2·81 (1H, dd, J 13 and 2·5 Hz, $NCH_a\mathit{H}_b$), 2·55 (1H, dd, J 13 and 9·5 Hz, CH), 1·54 (8H, m, 8H, 4 x CH_2), 0·97 (3H, t, J 7·5 Hz, $CH_2C\mathit{H}_3$).

11b: δ_H ($CDCl_3$) 4·08 (1H, t, J 8·5 Hz, $OC\mathit{H}_aH_b$), 3·76 (1H, m, $NC\mathit{H}CC$), 3·40 (1H, dd, J 8·5 and 5·5 Hz, $OCH_a\mathit{H}_b$), 2·80 (1H, dd, J 13 and 3 Hz, $NC\mathit{H}_aH_b$), 2·70 (1H, dd, J 13 and 8·5 Hz, $NCH_a\mathit{H}_b$), 1·57 (8H, m, 4 x CH_2), 0·95 (3H, t, J 7·5 Hz, $CH_2C\mathit{H}_3$).

2-(2'-Hydroxycyclohexyl)-2-aza-3-oxabicyclo[3.3.0]octane 14. A solution of 5-hexenaldoxime **9** (0·50 g, 4·40 mmol) and cyclohexene epoxide (4·30 g, 44·00 mmol) in xylene (10 ml) was held at reflux for 60 h. Removal of the xylene and excess cyclohexene epoxide *in vacuo* gave a dark brown oil that was subjected to column chromatography eluting with 2:3 v/v petroleum ether (b.p. 40-60°C)-diethyl ether to afford the *product* **14** (0·14 g, 30%) as a colourless oil. (Found: C, 68·6; H, 9·65. $C_{12}H_{21}NO_2$ requires C, 68·2, H, 10·0%); *m/z* (%) 211 (M^+, 4), 98 (100); δ_H ($CDCl_3$) 4·57 (1H, broad s, 1H, OH), 4·10 (1H, t, *J* 8 Hz, H_b), 3·63 (1H, m, H_c), 3·52 (1H, m, H_d), 3·45 (1H, dd, *J* 8 and 6·5 Hz, H_a), 2·94 (1H, m, H_e), 2·50 (1H, m, H_f), 1·66 (10H, m, 5 x CH_2), 1·22 (4H, m, 2 x CH_2).



14

Enhancement (%)

		OH	H_a	H_b	H_c	H_d	H_e	H_f
Irradiated hydrogen	OH				5·1			
	H_b		20·0			5·5		
	H_c	5·1						
	H_d	4·6						
	H_e					3·3		3·5
	H_f			2·1			6·1	

***C*-Phenyl-*N*-(2-hydroxy-5-hexenyl)nitrone 16**. A solution of (*Z*)-benzaldoxime **1** (1·00 g, 8·20 mmol) and 1,2-epoxy-5-hexene **15** (8·10 g, 82·00 mmol) in tetrahydrofuran (30 ml) saturated with LiCl was stirred and held at 60°C for 16 h. Upon removal of the solvent *in vacuo* the residue was partitioned between chloroform (50 ml) and water (30 ml), the organic layer separated and the aqueous layer extracted with a further portion of chloroform (50 ml). The combined organic layers were dried over anhydrous magnesium sulphate, the solvent removed *in vacuo*, the residual yellow oil triturated with petroleum ether (b.p. 40-60°C) and the resulting solid crystallized from petroleum ether (b.p. 40-60°C)-diethyl ether to afford the *product* **16** (0·54 g, 30%) as colourless plates. m.p. 132-134°C; (Found: C, 71·2; H, 7·7; N, 6·5. $C_{13}H_{17}NO_2$ requires C, 71·25; H, 7·8; N, 6·4%); *m/z* (%) 219 (M^+, 21), 203 (29), 202 (100), 164 (25), 112 (87) and 91 (95); δ_H ($CDCl_3$) 8·20 (2H, m, ArH), 7·80 (3H, m, ArH), 7·35 (1H, s, PhC*H*=N), 5·81 (1H, m, C*H*=CH_2), 5·02 (2H, m, CH=CH_2), 4·60 (1H, d, *J* 3·5 Hz, OH), 4·20 (1H, m, C*H*OH), 4·00 (1H, dd, *J* 12·5 and 2 Hz, NC$H_a$$H_b$), 3·80 (1H, dd, *J* 12·5 and 8·5 Hz, NC$H_a$$H_b$), 2·20 (2H, m, C$H_2$CH=$CH_2$),1.60 (2H, m, CH_2).

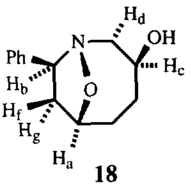
Cycloadducts 18, 19, 20 and **21**. A solution of *C*-phenyl-*N*-(2-hydroxy-5-hexenyl)nitrone **16** (0·50 g, 2·20 mmol) in xylene (10 ml) was held at reflux for 24 h. After removal of the solvent *in vacuo* the residue was purified by preparative t.l.c eluting with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether to afford a 12:8:2:1 mixture of the *products* **18, 19, 20** and **21** (0·38 g, 79%). (Found: C, 71·0; H, 7·85; N, 6·3. $C_{13}H_{17}NO_2$ requires C, 71·2; H, 7·8; N, 6·4%); *m/z* (%) 219 (M^+, 63), 202 (23), 91 (100).

18: Colourless needles from diethyl ether. m.p. 78-80°C; δ_H ($CDCl_3$) 7·30 (4H, m, ArH), 7·20 (1H, m, ArH), 4·70 (1H, q, *J* 6·5 Hz, H_a), 4·27 (1H, dd, *J* 7·5 and 5 Hz, H_b), 4·10 (1H, broad s, H_c), 3·60 (1H, dd, *J* 14 and 6 Hz, H$_d$), 3·10 (1H, dd, *J* 14 and 3·5 Hz, H$_e$), 2·54 (2H, m, H$_f$ and H$_g$), 2·37 (1H, d, *J* 8·5 Hz, OH), 2·20 (1H, m, H$_h$), 2·10 (1H, m, H$_j$), 1·90 (1H, m, H$_k$), 1·60 (1H, m, H$_j$).

19: Colourless rods from diethyl ether-ethyl acetate. m.p. 106-108°C; δ_H (CDCl$_3$) 7·30 (4H, m, ArH), 7·20 (1H, m, ArH), 4·60 (1H, m, H$_a$), 4·50 (1H, dd, *J* 8·5 and 5 Hz, H$_b$), 4·27 (1H, m, H$_c$), 3·88 (1H, dd, *J* 13·5 and 5 Hz, H$_e$), 2·80 (1H, dd, *J* 13·5 and 7·5 Hz, H$_d$), 2·66 (1H, m, H$_g$), 2·40 (1H, m, H$_f$), 2·07-1·87 (3H, m, H$_i$, H$_j$ and H$_k$), 1·66 (1H, m, H$_h$).

20: Colourless rods from diethyl ether-ethyl acetate. m.p. 92-93°C; δ_H (CDCl$_3$) 7·36-7·27 (5H, m, ArH), 4·80 (1H, m, H$_a$), 4·70 (1H, dd, *J* 11·5 and 7 Hz, H$_b$), 3·94 (1H, m, H$_c$), 3·29 (1H, dd, *J* 13·5 and 5·5 Hz, H$_e$), 2·97 (1H, d, *J* 10 Hz, OH), 2·64 (1H, m, H$_f$), 2·49 (1H, dd, *J* 13·5 and 2·5 Hz, H$_d$), 2·30-2·00 (3H, m, H$_g$, H$_h$ and H$_j$), 1·70 (2H, m, H$_i$ and H$_k$).

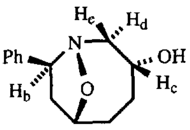
21: Colourless oil. 7·44-7·25 (5H, m, ArH), 4·70 (1H, m, H$_a$), 4·16 (1H, m, H$_b$), 3·89 (1H, m, H$_c$), 3·78 (1H, dd, *J* 7·5 and 1·5 Hz, H$_d$), 3·60 (1H, dd, *J* 15·5 and 4·5 Hz, H$_e$), 3·09 (1H, dd, *J* 15·5 and 5 Hz, H$_f$), 2·88 (1H, m, H$_g$), 2·24 (1H, m, H$_h$), 2·05 (1H, m, H$_i$), 1·93 (1H, m, H$_j$), 1·69 (1H, m, H$_k$).



18

Enhancement (%)

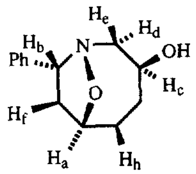
Irradiated hydrogen	H$_a$	H$_b$	H$_c$	H$_d$	H$_f$	H$_g$
H$_a$		2·2	1·8	1·8	4·0	
H$_b$	1·7		2·6			6·9
H$_c$		2·0		1·5		
H$_d$	3·1	3·1	4·9			



19

Enhancement (%)

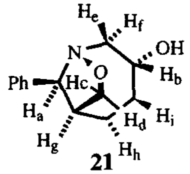
Irradiated hydrogen	H$_b$	H$_c$	H$_d$	H$_e$
H$_b$			4·0	
H$_c$			0·9	2·3
H$_d$	4·8			12·1
H$_e$		2·5		11·9



20

Enhancement (%)

Irradiated hydrogen	H$_a$	H$_c$	H$_d$	H$_e$	H$_f$	Ph
H$_b$					2·8	1·7
H$_c$			3·1			
H$_d$	1·1	5·1		16·9		4·5
H$_h$		1·3				



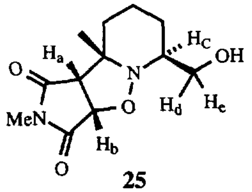
21

Enhancement (%)

Irradiated hydrogen	H_a	H_b	H_c	H_d	H_e	H_f	H_g
H_b				1·6	2·2	1·1	
H_d		1·5	12·1				
H_e		2·1				8·6	
H_f	3·1						3·1
H_h	1·4						1·4
H_i		0·7		1·4			

6,7-Epoxyheptan-2-one oxime 23. A solution of 6,7-epoxyheptan-2-one **22** (1·28 g, 10·00 mmol) in acetonitrile (30 ml) was treated with hydroxylamine hydrochloride (1·04 g, 15·00 mmol) and sodium acetate (1·23 g, 15·00 mmol) in water (10 ml) at room temperature for 3 h. The solvent was removed *in vacuo*, and the residue partitioned between chloroform (50 ml) and water (30 ml). The organic layer was dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to afford the product **23** (1·14 g, 80%), as a colourless oil. (Found: C, 55·35; H, 8·5. $C_7H_{13}NO_2$ requires C, 55·6; H, 8·65%); *m/z* (%) 143 (M^+, 46), 126 (43), 112 (31), 73 (100). δ_H ($CDCl_3$) 8·50 (1H, broad s, OH), 2·90, 2·76 and 2·60 (3H, 3 x m, CH_2OCH), 2·26 (2H, t, *J* 7·5 Hz, $CH_2C{=}N$), 1·90 (3H, s, Me), 1·75-1.50 (4H, m, 2 x CH_2).

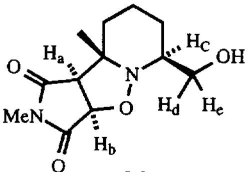
Cycloadducts 25 and **26**. A stirred solution of 6,7-epoxyheptan-2-one oxime **23** (0·50 g, 3·40 mmol) and *N*-methylmaleimide (0·39 g, 3·40 mmol) in xylene (15 ml) was held at reflux with stirring for 45 min. Removal of xylene *in vacuo* gave a pale brown gum which consisted of a 1:6 mixture of **25** and **26**. Filtration of a solution of the crude material through a short column of silica eluting with 1:1 v/v methanol-diethyl ether followed by trituration with diethyl ether afforded the *products* **25** and **26** (0·73 g, 85%), as a 1:6 isomeric mixture. *m/z* (%) (mixed isomers) 254 (M^+, 1), 233 (100), 41 (16). **25**: δ_H ($CDCl_3$) 4·88 (1H, d, *J* 8 Hz, H_b), 3·70 (1H, m, H_d), 3·55 (1H, m, H_e), 3·25 (1H, d, *J* 8 Hz, H_a), 3·00 (3H, s, NMe), 2·63 (1H, m, H_c), 2·40 (1H, broad s, OH), 2·38 (1H, m, CH_aH_b), 1·80-1·60 (5H, m, CH_aH_b and 2 x CH_2), 1.36 (3H, s, Me). **26**: Colourless rods from diethyl ether-ethyl acetate. m.p. 160-162°C; (Found: C, 56·45; H, 7·2; N, 10·85. $C_{12}H_{18}N_2O_4$ requires C, 56·7; H, 7·15; N, 11·0%); δ_H ($CDCl_3$) 5·16 (1H, 1H, *J* 8·5 Hz, H_b), 3·78 (1H, dd, *J* 11, 3·5 Hz, H_d), 3·70 (1H, d, *J* 8·5 Hz, H_a), 3·63 (1H, dd, *J* 11 and 4 Hz, H_e), 3·00 (3H, s, 3H, NMe), 2·70 (1H, m, H_c), 2·60-2·40 (1H, broad s, OH), 2·25 (1H, m, CH_aH_b), 1·73 (3H, m, CH_aH_b and CH_2), 1·50 (2H, m, CH_2), 1·20 (3H, s, Me).



25

Enhancement (%)

Irradiated hydrogen	H_a	H_b	H_c	Me
H_a		8·6		2·1
H_b	6·2			
H_c	10·3	1·8		



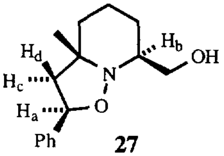
26

	Enhancement (%)		
Irradiated hydrogen	H_a	H_b	H_c
H_a		4·2	4·2
H_b	4·2		4·2
H_c	4·8	6·0	

2-Hydroxymethyl-6-methyl-8-phenyl-1-aza-9-oxabicyclo[4.3.0]nonane 27 and **28**. A solution of 6,7-epoxyheptan-2-one oxime **23** (0·30 g, 2·09 mmol) and *N*-methylmaleimide (0·23 g, 2·09 mmol) in xylene (10ml) was held at reflux for 8 hours. After removal of the xylene *in vacuo* the crude product was purified by preparative t.l.c eluting with 9:1 v/v diethyl ether-ethyl acetate to afford the separated *products* **27** and **28** in the ratio of 3:2.

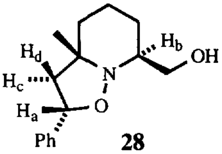
27: (0·15 g, 30%); Colourless rods from ether-petroleum ether. m.p. 67-68°C; (Found: C, 73·0; H, 8·7; N, 5·6. $C_{15}H_{21}NO_2$ requires C, 72·9; H, 8·55; N, 5·65%); δ_H ($CDCl_3$) 7·80 (5H, m, ArH), 5·49 (1H, dd, *J* 11 and 5 Hz, H_a), 3·72 (2H, m, CH_2OH), 2·95 (1H, m, H_b), 2·80 (1H, t, *J* 11 Hz, H_c), 1·96 (1H, dd, *J* 11 and 5 Hz, H_d), 1·93 (1H, m, $\mathrm{C}H_a\mathrm{H_b}$), 1.70-1.35 (5H, m, $\mathrm{CH_a}H_b$ and 2 x CH_2), 1.30 (3H, s, Me).

28: (0·10 g, 20%); Colourless oil. δ_H ($CDCl_3$) 7·32 (5H, m, ArH), 5·30 (1H, dd, *J* 12 and 8 Hz, H_a), 3·90 (1H, m, $\mathrm{OC}H_a\mathrm{H_b}$), 3·50 (1H, m, $\mathrm{OCH_a}H_b$), 2·60 (1H, m, H_b), 2·50 (1H, t, *J* 12 Hz, H_c), 2·30 (1H, dd, *J* 12 and 8 Hz, H_d), 1·98 (1H, m, $\mathrm{C}H_a\mathrm{H_b}$), 1·70-1·40 (5H, m, $\mathrm{CH_a}H_b$ and 2 x CH_2), 1·40 (3H, s, Me).



27

	Enhancement (%)				
Irradiated hydrogen	H_a	H_b	H_c	H_d	Me
H_a		10·2	3·2		
H_b	15·1				
H_c	7·7			18·0	
H_d	1·3		9·8		
Me				2·9	



28

	Enhancement (%)				
Irradiated hydrogen	H_a	H_b	H_c	H_d	Me
H_a		0·9	1·9	5·2	5·2
H_c				8·0	
H_d		10·4			
Me	2·5			1·2	

1,2-Epoxy-10-undecen-6-one 32. *m*-Chloroperbenzoic acid (50%, 3·16 g, 9·20 mmol) in dichloromethane (50 ml) was added dropwise to a solution of 1,10-undecadien-6-one **31** (1·60 g, 9·60 mmol) in dichloromethane (150 ml) at 0°C over 2 h and the reaction mixture was stirred at room temperature for a further 16 h. After washing with saturated sodium bicarbonate (100 ml) the organic layer was dried over anhydrous magnesium sulphate, the solvent removed *in vacuo* and the residue subjected to column chromatography. Elution with 1:1 v/v petroleum ether (b.p. 40-60°C)-diethyl ether afforded the *product* **32** (0·70 g, 40%), as a colourless oil. (Found: C, 72·5; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%); *m/z* (%) 182 (M^+, 3), 128 (71), 97 (90), 69 (76); δ_H ($CDCl_3$) 5·70 (1H, m, CH=CH2), 5·00 (2H, m, CH=CH_2), 2·90 (1H, m, H_a), 2·74 (1H, t, *J* 4 Hz, H_c), 2·45 (5H, m, H_b and 2 x CH_2CO), 2·05 (2H, q, *J* 7 Hz, $CH_2CH=CH_2$), 1·80-1·40 (6H, m, 3 x CH_2).

1,2-Epoxy-10-undecen-6-one oxime 33. A solution of 1,2-epoxy-10-undecen-6-one **32** (0·55 g, 3·00 mmol) in acetonitrile (10 ml) was treated with hydroxylamine hydrochloride (0·32 g, 4·50 mmol) and sodium acetate (0·37 g, 4·50 mmol) in water (5 ml) at room temperature for 3 h. The solvent was removed *in vacuo*, and the residue partitioned between chloroform (30 ml) and water (10 ml). The organic layer was dried over anhydrous magnesium sulphate and the solvent *in vacuo* to afford the *product* **33** (0·53 g, 90%), as a colourless oil. (Found: C, 66·75; H, 9·75; N, 7·1. $C_{11}H_{19}NO_2$ requires C, 66·95; H, 9·7; N, 7·1%); *m/z* (%) 197 (M^+, 4), 182 (4), 166 (58), 143 (55), 112 (100); δ_H ($CDCl_3$) 8·50 (1H, broad s, OH), 5·80 (1H, m, $CH=CH_2$), 5·01 (2H, m, CH=CH_2), 2·94, (1H, m, H_c), 2·76 (1H, m, H_b), 2·53 (1H, m, H_a), 2·37 (2H, m, CH_2), 2·22 (2H, m, CH_2), 2·09 (2H, m, CH_2), 1·60 (6H, m, 3 x CH_2).

Cycloadduct 34. A solution of 1,2-epoxy-10-undecen-6-one oxime **32** (0·50 g, 3·18 mmol) in xylene (5 ml) was held at reflux for 6 h. The xylene was removed *in vacuo* and the residue subjected to column chromatography. Elution with diethyl ether afforded the *product* **34** (0·45 g, 90%), as a colourless oil. (Found: C, 66·9; H, 9·9; N, 7·25. $C_{11}H_{19}NO_2$ requires C, 66·95; H, 9·7; N, 7·1 %); *m/z* (%) 197 (M^-, 3), 166 (100); δ_H (d_{10}-xylene) 3·65 (1H, t, *J* 8·5 Hz, H_b), 3·40 (1H, dd, *J* 10·5 and 3 Hz, CH_aH_bOH), 3·20 (1H, dd, 1H, *J* 10·5 and 4·5 Hz, CH_aH_bOH), 2·84 (1H, dd, *J* 8·5 and 4 Hz, H_c), 2·70 (1H, broad s, OH), 1·90 (1H, m, H_d), 1·80 (1H, m, H_a), 1·74 (2H, m, CH_2), 1·20-0·80 (10H, m, 5 x CH_2).

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REFERENCES

1. Part 46. Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron*, **1995**, *51*, 13347-13356.
2. Grigg, R.; Markandu, J. *Tetrahedron Lett.*, **1989**, *30*, 5489-5492.
3. Choudory, B.M., Rani, S.S.; Kantam, M.L. *Synth. Comm.*, **1990**, *20*, 2313-2317.
4. Wang, C.-L.J.; Gregory, W.A.; Wuonola, M.A. *Tetrahedron*, **1989**, *45*, 1323-1326.
5. Alvares, E.; Nuñez, M.T.; Martín, V.S. *J. Org. Chem.*, **1990**, *55*, 3429-3431.
6. Chong, J.M.; Sharpless, K.B. *J. Org. Chem.*, **1985**, *50*, 1560-1563.
7. Iranpoor, N.; Baltork, I.M. *Tetrahedron Lett.*, **1990**, *31*, 735-738.
8. Sassaman, M.B.; Prakash, G.K.S.; Olah, G.A. *J. Org. Chem.*, **1990**, *55*, 2016-2018.
9. Kliegel, W. *Liebigs Ann. Chem.*, **1970**, *733*, 192-194.
10. Kliegel, W.; Enders, B.; Becker, H. *Liebigs Ann. Chem.*, **1982**, *733*, 1712-1721.
11. Wasserman, H.H.; Rusiecki, V. *Tetrahedron Lett.*, **1988**, *29*, 4977-4980.
12. Cresp, T.M.; Probert, C.L.; Sondheimer, F. *Tetrahedron Lett.*, **1978**, 3955-3958.

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