

The influence of oxime stereochemistry in the generation of nitrones from ω -alkenyloximes by cyclization or 1,2-prototropy

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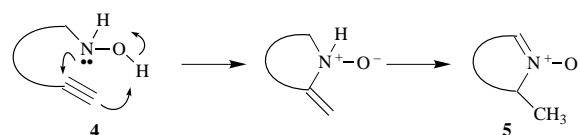
Thermally induced cyclization of the *anti*-alkenyl oximes *E*-7a,b and *E*-17a,b affords cyclic α -alkoxycarbonylnitrones **8** and the 6,7-bicyclic nitrones **18**, respectively. The *syn*-oximes *Z*-7b and *Z*-17b react via an alternate pathway to give exclusively the fused isoxazolidine derivatives **10b** and **19b**, respectively. These oximes are configurationally stable at high temperatures with the energy barrier to isomerization being significantly greater than that to cyclization/cycloaddition. Neither the *tert*-butyl derivative **7c** nor the ε -alkenyl oxime **7d** share this characteristic and in these cases the products of thermal activation are independent of the geometry of the starting oxime. For **7c** the energy barriers to oxime rotation and cyclization or cycloaddition are sufficiently close to allow all three reactions to proceed. With **7d**, *cis*-*trans* isomerization and cyclization are the only observed reactions.

Introduction

The 1,3-dipolar cycloaddition can accomplish the synthesis of a range of highly functionalised stereochemically complex five-membered rings. The isoxazolidines/isoxazolines which are the primary adducts from reaction between nitrones and alkenes/alkynes have a labile N–O bond easily cleaved under reductive or oxidative conditions, consequently this reaction is often used as a key step in targeted syntheses.¹ The most general methods for nitron preparation include oxidation of secondary amines (useful for the preparation of both cyclic and acyclic nitrones)² and condensation between an *N*-substituted hydroxylamine and a carbonyl compound.³ Many nitrones are isolable, stable compounds especially those with a *C*-aryl substituent and in the absence of any stabilizing substituent the nitron may dimerize or trimerize and so may be best generated *in situ*. In a recent communication we have described the preparation of highly functionalized cyclic nitrones from alkenyl oximes.⁴

ω -Alkenyloximes may form nitrones by one of two routes; they may tautomerize to form an acyclic NH-nitron **1**, the dipolar structure represents the less stable tautomer and to date no examples of the unsubstituted dipole have been isolated, their existence being substantiated through the formation of an intramolecular cycloaddition product **2**.⁵ This tandem process has been named the intramolecular oxime olefin cycloaddition reaction (IOOC) [Scheme 1(a)].^{5c} Secondly alkenyloximes may

deficient),^{5b,6a} unassisted cyclization is much less common^{5b,6b,6c} and to date has generally involved only aldoximes [Scheme 1(b)].^{5b,6c} Alkynylhydroxylamines **4** undergo a related pericyclic reaction effective for the formation of 5-, 6- and 7-membered cyclic nitrones **5**. An initial ene-like cyclization (reverse Cope elimination)⁷ is followed by proton transfer and tautomerism (Scheme 2).^{7a} In the current example the N–O–H unit of the

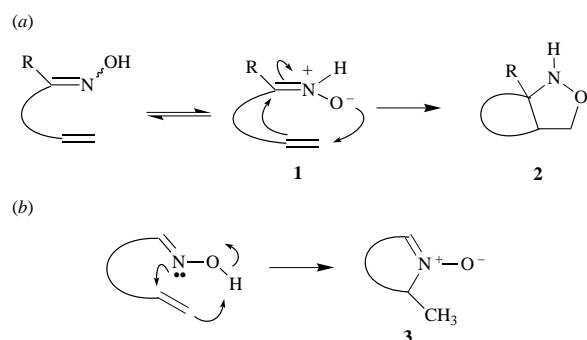


Scheme 2 Dipole formation from alkynylhydroxylamines

oxime adds across the internal C=C double bond in a concerted fashion giving the cyclic dipole. For certain oximes the two modes of reactivity illustrated in Scheme 1 are in competition and the preferred reaction path in any given case will be that of lowest energy.

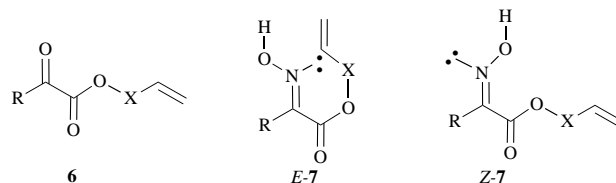
Results and discussion

The oximes **7** were prepared in two steps from their parent α -keto acids; esterification with the corresponding alcohol proceeded in high yield to give the α -oxo esters **6** which were converted to the oximes **7** following reaction with hydroxylamine (Tables 1 and 2). Transformation of **6a** gave a single diastereoisomer *E*-7a (65%) whilst **6b,c,d** each gave both



Scheme 1 Dipole formation from oximes; (a) intramolecular oxime-olefin cycloaddition (IOOC) and (b) intramolecular 1,3-azaprotio cyclotransfer reaction (APT)

undergo an intramolecular cyclization reaction [1,3-azaprotio cyclotransfer (APT)]^{5b} forming the cyclic nitron **3**. Numerous examples exist where the olefinic moiety is activated (electron



- a R = Me, X = CH₂
- b R = Ph, X = CH₂
- c R = Ph, X = CHBu^t
- d R = Ph, X = CH₂CH₂

anti and *syn* isomers, with the *E*- and *Z*-isomers being easily separated by flash chromatography. Oxime stereochemical assignment can be made in a number of ways; by ¹H NMR

Table 1 Selected UV–Visible and ^{13}C NMR data for the oximes **7**

Compound	$\lambda_{\text{max}}/\text{nm}$		^{13}C NMR resonance of imino carbon atom (δ/ppm) ^a
	MeOH	0.03% Methanolic NaOH	
<i>E</i> - 7a	221.77	260.11	149.2
<i>E</i> - 7b	243.44, 233.44, 218.43	273.44, 243.44, 225.11	151.6
<i>Z</i> - 7b	209.45	210.11	149.6
<i>E</i> - 7c	—	—	151.4
<i>Z</i> - 7c	—	—	148.7
<i>E</i> - 7d	243.44, 208.44	273.44, 225.11, 206.78	151.8
<i>Z</i> - 7d	250.10, 213.44	256.78, 208.44	149.8

^a ^{13}C NMR spectra were taken in CDCl_3 .

Table 2 Analytical data for the α -oxo esters **6** and **16** and the corresponding oximes **7** and **17**

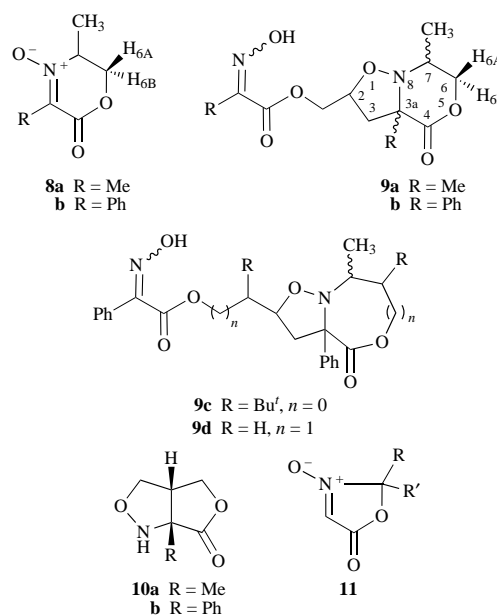
Compound	Molecular formula	Yield (%)	Physical properties	C H N		
				Found (%) (Requires)		
6b	$\text{C}_{11}\text{H}_{10}\text{O}_3$	81	bp: 126–128 °C, 0.1 mmHg	69.19 (69.47)	5.40 (5.26)	0 (0)
6d	$\text{C}_{12}\text{H}_{12}\text{O}_3$	90	bp: 90–94 °C, 0.3 mmHg	70.37 (70.59)	5.94 (5.88)	0 (0)
16a	$\text{C}_{11}\text{H}_{12}\text{O}_2$	85	bp: 93–95 °C, 2.0 mmHg mp: 29–30 °C	75.21 (75.00)	6.84 (6.82)	0 (0)
16b	$\text{C}_{16}\text{H}_{14}\text{O}_2$	90	bp: 110–112 °C, 0.03 mmHg	80.54 (80.67)	5.72 (5.88)	0 (0)
<i>Z</i> - 7b	$\text{C}_{11}\text{H}_{11}\text{NO}_3$	38	bp: 110–112 °C, 0.5 mmHg	64.17	5.07	6.84
<i>E</i> - 7b		55	mp: 90–94 °C (benzene–pet. spirit)	(64.39)	(5.37)	(6.87)
<i>Z</i> - 7c	$\text{C}_{15}\text{H}_{19}\text{NO}_3$	45	R_f 0.48 (Et ₂ O–pet. spirit, 1:4)	69.08	7.32	5.33 ^a
<i>E</i> - 7c		20	mp: 110–111 °C (benzene–pet. spirit)	(68.97)	(7.28)	(5.36)
<i>Z</i> - 7d	$\text{C}_{12}\text{H}_{13}\text{NO}_3$	49	bp: 138 °C, 0.025 mmHg	65.48	5.67	6.21 ^a
<i>E</i> - 7d		47	mp: 46–48 °C (benzene–pet. spirit)	(65.75)	(5.94)	(6.39)
<i>E</i> - 17a	$\text{C}_{11}\text{H}_{13}\text{NO}_2$	94	mp: 69–71 °C (benzene–pet. spirit)	69.33 (69.11)	7.08 (6.81)	7.59 (7.33)
<i>Z</i> - 17b	$\text{C}_{16}\text{H}_{15}\text{NO}_2$	70	mp: 100–101 °C (benzene–hexane)	75.77	6.04	5.81 ^a
<i>E</i> - 17b		23	mp: 123–124 °C (benzene–hexane)	(75.89)	(5.93)	(5.53)

^a Microanalytical data reported for the major oxime isomer only; satisfactory data have also been obtained for the minor isomer.

utilization of through-space effects,⁸ by ^{13}C or ^{15}N NMR spectra studies,⁹ and by examination of $J_{\text{C,H}}$ coupling constants for aldoximes.¹⁰ In this case assignment was based largely on UV $\pi \rightarrow \pi^*$ absorption; (*E*)-1,2-hydroxyiminoketones are known to exhibit a bathochromic shift when their spectra, recorded in basic solution (MeOH–NaOH), are compared with those measured in neutral solution (MeOH), whereas *Z*-isomers show no such effect.¹¹ The *anti* oximes *E*-**7a,b,c**, showed a shift of *ca.* 30 nm under these conditions whilst the *syn*-isomers *Z*-**7b,c** showed very little change. Additionally in each case the ^{13}C -resonance signal for the hydroxyimino carbon atom for the *E*-isomers appeared downfield of the corresponding signal for the *Z*-isomers. Finally irradiation of the hydroxyimino proton gave a positive enhancement on to the C α -substituent in the *E*-oxime series whilst no effect was observed with the *Z*-isomers (Table 1).

The propensity for (*E*)-prop-2-enyl 2-(hydroxyimino)propanoate to behave as a dipole precursor was investigated: heating a solution of *E*-**7a** in each of MeOH, DMF or C_6H_6 at reflux temperature resulted only in returned starting material. In boiling xylene reaction was slow, however heating in boiling mesitylene effected complete conversion of the substrate to products. The dipole **8a** was isolated in 85% yield and mixed isomers of the dimeric compounds **9a** in 5% yield. None of the alternative bicyclic furoisoxazolone **10a** was detected. 1,3-Oxazolin-5-one 3-oxides **11**, the 5-ring analogues of **8**, have been generated from reaction of isonitroso Meldrum's acid with various ketones.¹²

The separated oxime isomers *E*- and *Z*-**7b** were independently heated in boiling xylene. After 30 h the *anti*-oxime *E*-**7b** had reacted exclusively in a 6-*exo-trig* cyclization affording **8b** in 85% yield whilst the *syn*-oxime *Z*-**7b** reacted more slowly



yielding the furoisoxazolone **10b** (70% conversion of starting material after 36 h) (Tables 3 and 4). Evidently each oxime is geometrically stable under the reaction conditions and the *Z*-isomer reacts only by path (a), whilst the *E*-oxime reacts specifically *via* path (b), Scheme 1. That oxime geometry may have a defining influence on reactivity has been observed in many cases,¹³ for example in a recent report Tiecco *et al.* have shown that, depending on its geometry, the oxime group can act as either an oxygen or a nitrogen nucleophile in the intra-

Table 3 Analytical data for the cyclic nitrones **8** and **18**

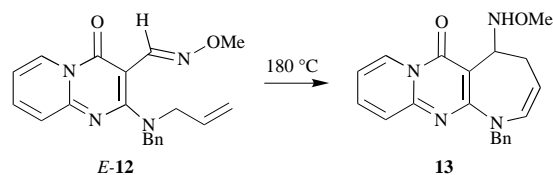
Compound	Molecular formula	Yield (%)	Physical properties	C H N		
				Found (%) (Requires)		
8a	C ₆ H ₉ NO ₃	85	bp: 115–120 °C, 0.5 mmHg	50.20 (50.35)	6.44 (6.34)	9.67 (9.79)
8b	C ₁₁ H ₁₁ NO ₃	85	mp: 94–95 °C (benzene–pet. spirit)	64.56 (64.68)	5.37 (5.35)	6.83 (6.78)
8c	C ₁₅ H ₁₉ NO ₃	33	mp: 93–95 °C (benzene–pet. spirit)	69.07 (68.97)	7.34 (7.28)	5.49 (5.36)
8d	C ₁₂ H ₁₃ NO ₃	32	mp: 105–107 °C (benzene–pet. spirit)	65.56 (65.75)	6.04 (5.94)	6.21 (6.39)
18a	C ₁₁ H ₁₃ NO ₂	98	bp: 119–123 °C, 0.6 mmHg	68.91 (69.11)	6.74 (6.81)	7.54 (7.33)
18b	C ₁₆ H ₁₅ NO ₂	92	mp: 119–120 °C (benzene–pet. spirit)	75.79 (54.77)	5.77 (6.22)	5.63 (5.53)

Table 4 Analytical data for the isoxazolo-fused adducts **10** and **19**

Compound	Molecular formula	Yield (%)	mp/°C ^a	C H N		
				Found (%) (Requires)		
10a	C ₆ H ₉ NO ₃	4	80–81	50.43 (50.35)	6.44 (6.34)	10.02 (9.79)
10b	C ₁₁ H ₁₁ NO ₃	66	133–136	64.66 (64.39)	5.15 (5.37)	6.68 (6.83)
10c	C ₁₅ H ₁₉ NO ₃	7	136–137	68.99 (68.97)	7.44 (7.28)	5.29 (5.36)
19b	C ₁₆ H ₁₅ NO ₂	58	110–112	75.69 (75.89)	5.66 (5.93)	5.34 (5.53)

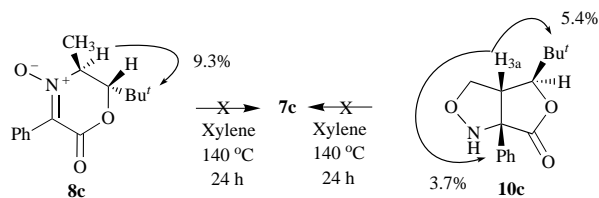
^a From benzene–pet. spirit.

molecular selenium-induced cyclizations of α -alkenyloximes generating 1,2-oxazines or cyclic nitrones respectively,^{13a} and Noguchi's group have demonstrated that only the *E*-oxime ethers **12** participate in an intramolecular azepine-forming



reaction whilst *Z*-isomers remain unchanged under the same experimental conditions.^{13b}

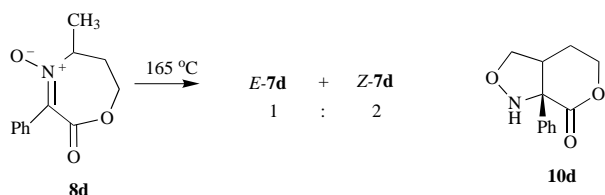
In an effort to probe the generality of the reaction (*E*-**7**→**8** and *Z*-**7**→**10**) and in particular its tolerance to substitution and ring size the oximes **7c,d** were prepared. It was anticipated that the introduction of a *tert*-butyl substituent on the alkenyl chain in the oximes **7c** may invoke diastereoselectivity in both the APT reaction (leading to **8c**) and in the IOOC reaction (leading to **10c**). The separated oxime isomers *E*-**7c** and *Z*-**7c**



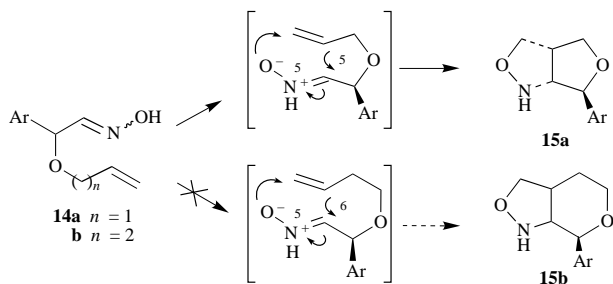
were heated in boiling xylene and the following points noted (i) the isomers were shown to be devoid of thermal stability and (ii) in each case reaction was slower than that observed for the unsubstituted analogue **7b**. Following the heating of *E*-**7c** the reaction products comprised a 5:3:1:5 mixture of

the *syn*-oxime *Z*-**7c**, returned *anti*-oxime *E*-**7c**, furoisoxazolone **10c** and the cyclic dipole **8c**. The same products were obtained in a 4:1:1:2 ratio following reaction with the *Z*-oxime *Z*-**7c**. That oxime interconversion occurs directly rather than by retrocyclization of the dipole **8c** is evident from the thermal stability of the latter which remains unchanged after heating in boiling xylene for 24 h. The cycloadduct **10c** is also stable under these reaction conditions. Significantly the cyclization and cycloaddition products are formed diastereospecifically; for the dipole **8c** NOEDS studies indicate the methyl and *tert*-butyl substituents are *trans* orientated while for the cycloadduct **10c** irradiation of the H^{3a} proton causes an enhancement on the cross-ring *o*-Ar protons (3.7%) and on the *tert*-butyl group (5.4%) indicating it has a *cis* relationship to both substituents.

The 7-*exo-trig* cyclization is also an allowed process¹⁴ and we envisaged that the *E*-isomer of the ϵ -alkenyl oxime **7d** may cyclize to the 7-membered oxazepinone *N*-oxide **8d**. Indeed 7-membered nitrones have been prepared by Holmes and co-workers by cyclization of alk-6-ynylhydroxylamines by the general mechanism outlined in Scheme 2.^{7a} Following heating of *E*-**7d** in refluxing xylene, **8d** was formed in 32% yield with unreacted oxime present as a 1:1.1 mixture of *E*- and *Z*-isomers, and a trace amount of the dimeric adducts **9d** accounting for the rest of the reaction material. The low yield of dipole may be attributed to a combination of the following; the increased entropy of activation required for the formation of a 7-membered ring, the reversible nature of dipole formation and/or the influence of the allyl- and butenyl-oxycarbonyl group on the relative reactivity of the olefinic centres in **7b** and **7d**. In contrast to the stability of the 6-membered dipole **8c**, simply heating a solution of **8d** in boiling mesitylene generated a 1:2 ratio of the isomeric oximes *E*- and *Z*-**7d**. When the *syn*-oxime *Z*-**7d** was heated in boiling xylene the reaction products comprised unreacted oxime (75%), as a 2:5 mixture of *E*- and *Z*-isomers, and the cyclic dipole **8d** (15%); none of the anti-

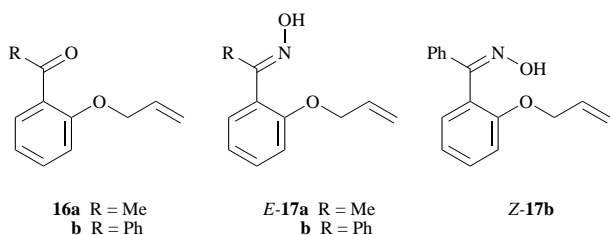


pated pyranoisoxazolone **10d** resulted. Clearly both oximes *E*- and *Z*-**7d** suffer partial isomerization under the reaction conditions studied. The failure of *Z*-**7d** to partake in the IOOC reaction sequence is consistent with Hassner's observations that whilst the unsaturated aldoximes **14a** underwent smooth trans-



formation to the furoisoxazoles **15a** the homologous **14b** failed to form the corresponding pyranoisoxazoles **15b** under the same experimental conditions.^{5d} These results suggest that the transition state required for the formation of the 6,5-bicyclic skeleton is more difficult to attain than the corresponding 5,5-skeleton. That this difficulty can be overcome by judicious positioning of the aldoxime and alkene functions is suggested from Oppolzer's observation that 2-allyloxybenzaldehyde oxime participates in an IOOC reaction giving the 6,6,5-tricycle **19c**.^{5g}

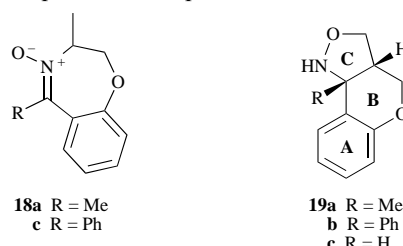
In an effort to facilitate the 7-*exo-trig* cyclization the ϵ -alkenyl oximes **17** were prepared. By reducing the flexibility of the tether uniting the oxime with the olefinic moiety these reacting centres should more easily adopt the transition state required for intramolecular cyclization—the aryl ring in **17** may therefore be described as a steric buttress.¹⁵ Allyl bromide condenses with *o*-hydroxyacetophenone and *o*-hydroxybenzophenone to give the alkenyl ethers **16**; oximation of **16a** yielded *E*-**17a** as a single stereoisomer whilst **16b** reacted to give a 1:3 mixture of the *E*- and *Z*-isomers of **17b**. Configurational assignment of *E*-**17a** is based on a 9.8% enhancement on the *o*-Ar-H signal upon irradiation of the hydroxy proton, the



geometrical isomers *E*-**17b** and *Z*-**17b** are distinguished on the basis of their ¹³C NMR data with the *E*-isomer having the more downfield imino carbon signal (CDCl₃, 155.7 vs. 158.6 ppm).

The oxime *E*-**17a** underwent quantitative conversion to the 6,7-bicyclic dipole **18a** following heating (14 h) in boiling xylene, *E*-**17b** reacted similarly giving **18b** after just 5 h heating. Clearly the incorporation of the aryl ring in the chain linking the oxime to the alkene significantly reduces the conformational mobility of the reacting centres in *E*-**17** making dipole formation facile compared to that previously observed with the open

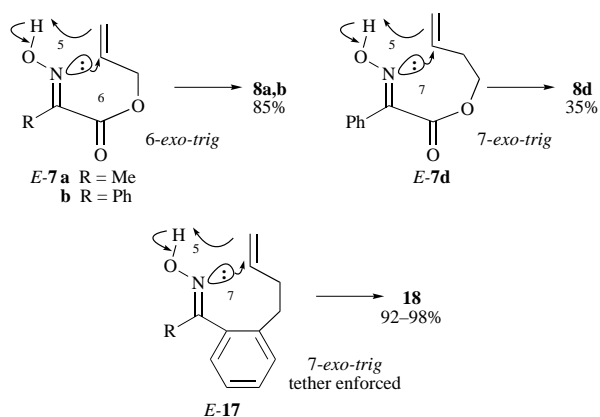
chain substrate *E*-**7d**. The *syn*-oxime *Z*-**17b** also reacted in a chemospecific manner and after 50 h heating in refluxing xylene the reaction products comprised the benzofuroisoxazole **19b**



(58%) and unchanged oxime (25%). The cycloadduct was obtained as a single diastereoisomer with *cis* stereochemistry at the BC ring junction assigned on the basis of NOEDS results.

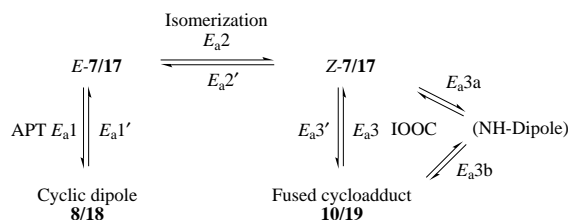
Conclusions

In all the cyclization reactions hydroquinone (1% w/v) was added to the reaction solvent to prevent its decomposition on prolonged heating and since both the dipoles (**8** and **18**) and the cycloadducts (**10** and **19**) form in such high yields under these conditions a radical based reaction mechanism is not favoured in either reaction path (Scheme 1). Formation of the cyclic nitrones is *via* a concerted pericyclic mechanism and the *anti*-oxime isomers *E*-**7a,b** readily attain the necessary geometry for the 6,5-bicyclic transition state (Scheme 3), therefore the APT



Scheme 3

reaction does not suffer competition from oxime isomerization or tautomerism to the corresponding NH-dipole under the reaction conditions ($E_a1 < E_a2$, Scheme 4). The oxime *E*-**7c** on



Scheme 4

the other hand with its bulky *tert*-butyl substituent displays remarkable sensitivity to substitution and oxime isomerization and cycloaddition (IOOC) compete effectively with the proposed APT reaction ($E_{a1} \sim E_{a2} \sim E_{a3}$). In the case of the ϵ -alkenyl oxime *E*-**7d** a 7,5-bicyclic transition state must be reached to allow formation of the oxazepinone *N*-oxide **8d** (Scheme 3), this requirement places significant demands on the open chain structure and consequently dipole generation is accompanied by *E*/*Z* oxime isomerization, however the *Z*-**7d** so

formed is unable to undergo the IOOC reaction as the energy barrier to the formation of the 6,5-bicyclic adduct **10d** is too great ($E_{a1} \sim E_{a2} < E_{a3}$). The conformationally constrained analogues *E*-**17** more easily attain the necessary approach of reacting centres for the 7-*exo-trig* cyclization (Scheme 3) and they thermally cyclize to the corresponding benzoxazepine *N*-oxides **18** in excellent yield.

With the *syn*-oxime isomers *Z*-**7b** and *Z*-**17b** attainment of the transition state for direct formation of cyclic dipoles is impossible to achieve. Therefore there are only two reaction paths available to these substrates *viz.* isomerization to the *E*-oxime (and then possible cyclization) or a tautomerism to the corresponding NH-dipole and intramolecular cycloaddition (IOOC). The open chain δ -alkenyl oxime *Z*-**7b** and the conformationally restricted ϵ -alkenyl oxime *Z*-**17b** reacted chemospecifically *via* the IOOC route giving single stereoisomeric isoxazolo fused adducts in each case, no oxime isomerization occurred ($E_{a3} < E_{a2}'$). On the contrary, the *tert*-butyl substituted δ -alkenyl oxime *Z*-**7c** and the open chain ϵ -alkenyl oxime *Z*-**7d** suffered from facile oxime interconversion and when equilibrium had been reached the products from thermal activation of these *syn*-oximes were identical to those obtained from the corresponding *anti*-isomers under the same experimental conditions.

Interestingly, whilst an attempt to isomerize *E*-**7a** to the *Z*-isomer by heating in boiling water resulted in the loss of much of the reaction material, the furoisoxazolone **10a** was isolated in small yield (4%) together with unchanged starting oxime (16%). Similar treatment of *E*-**7b** gave the adduct **10b** in 67% yield together with both *E*- and *Z*-oxime isomers (10 and 15%, respectively). These observations suggest that oxime isomerization is more facile in water and indeed it has earlier been noted that the relative stability of iminoxyl radicals from benzaldehyde oxime shows a remarkable solvent dependency.¹⁶

The relatively slow rate of oxime isomerization compared with simple imines has recently been exploited in a study of the effect of *E/Z* isomerization on the asymmetric hydrogenation of prochiral C=N bonds.^{13c} The enantioselectivity of the reaction was shown to reflect the *E/Z* ratio of 1-acetonaphthone oxime. The oximes **7** and **17** chosen in this study, like 1-acetonaphthone oxime, are conjugated ketoximes and therefore the barrier to rotation is expected to be high and the products of reaction likely to reflect the geometry of the starting oxime. In contrast the oximes **14** employed in Hassner's thermal IOOC study are all unconjugated aldioximes carrying a single substituent on the α -carbon atom, the barrier to geometrical inversion would therefore be expected to be much lower thus explaining why in this case the products of reaction are independent of the stereochemistry of the starting oximes.^{5c,d}

Thermal cyclization of the conjugated *E*-alkenyl oximes *E*-**7a,b** and *E*-**17** provides easy access to geometry fixed α -alkoxycarbonylnitrones **8** and benzoxazepine *N*-oxides **18**, respectively. These interesting nitrones are reactive 1,3-dipoles and their cycloadditive behaviour will be discussed in a forthcoming paper.

Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. ¹H NMR spectra were recorded using a JEOL EX90 FT NMR and a JEOL EX270 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference and deuteriochloroform as solvent. *J* Values are given in Hz. Flash column chromatography was carried out on silica gel 60 (Merck 9385, 70–230 mesh, 40–60 mesh), analytical TLC plates were purchased from Merck. Samples were located by UV illumination using a portable Spectroline Hanovia lamp (λ 254 nm) or by the use of iodine staining. All solvents used were purified by standard

procedures and *pet. spirit* refers to that fraction of petroleum spirits boiling between 40–60 °C.

Prop-2-enyl benzoylformate **6b**

A solution of benzoylformic acid (4.0 g, 27 mmol), prop-2-en-1-ol (2.35 g, 40 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in benzene (100 cm³) was boiled in reflux (16 h) using a Dean–Stark apparatus. The reaction mixture was allowed to cool to room temp., washed firstly with sat. aq. NaHCO₃ (2 × 150 cm³) and then H₂O (150 cm³). The organic layer was collected, dried (Na₂SO₄) and concentrated to furnish the crude product as a yellow oil. Following fractional distillation the title compound was obtained as a colourless oil (4.1 g, 81%). δ_{H} 4.87 (d, 2H, OCH₂), 5.40 (m, 2H, CH=CH₂), 6.02 (m, 1H, CH=CH₂), 7.50 (t, 2H, *m*-Ar-H), 7.65 (t, 1H, *p*-Ar-H), 8.01 (d, 2H, *o*-Ar-H); δ_{C} 66.2 (OCH₂), 119.5 (CH=CH₂), 128.7 (2 × *m*-Ar-C), 129.7 (2 × *o*-Ar-C), 130.6 (*p*-Ar-C), 133.1 (Ar-C), 134.7 (CH=CH₂), 163.2 (C=O, ester), 185.9 (C=O, ketone).

4,4-Dimethylpent-1-en-3-yl benzoylformate **6c**

Benzoylformic acid (1.60 g, 11 mmol), 4,4-dimethylpent-1-en-3-ol¹⁷ (1.48 g, 13 mmol) and a catalytic amount of toluene-*p*-sulfonic acid were stirred in benzene (60 cm³) at reflux using a Dean–Stark apparatus for 13 h (care was taken to ensure that the temperature of the oil bath did not rise above 100 °C). The reaction mixture was allowed to cool to room temp. before washing firstly with sat. aq. NaHCO₃ solution (2 × 100 cm³) and then H₂O (100 cm³). After drying (Na₂SO₄) the organic layer was concentrated to yield the crude product, a yellow oil (2.04 g, 75%), which was used without further purification. (During the concentration step, the temperature of the water bath was not allowed to rise above 65 °C.) δ_{H} 1.04 (s, 9H, 3 × Me), 4.83 (d, 1H, OCH, *J* 6.60), 5.50 (m, 2H, CH=CH₂), 5.90 (m, 1H, CH=CH₂), 7.65–7.47 (2 × m, 3H, 2 × *m* and *p*-Ar-H), 7.99 (m, 2H, *o*-Ar-H); δ_{C} 25.6 (3 × Me), 34.4 (CMe₃), 66.2 (OCH), 119.5 (CH=CH₂), 130.0–128.8 (4 × Ar-C), 134.8 (CH=CH₂), 163.6 (C=O, ester), 186.6 (C=O, ketone).

But-3-enyl benzoylformate **6d**

A solution of benzoylformic acid (11.80 g, 79 mmol), but-3-en-1-ol (8.64 g, 120 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in benzene (325 cm³) was boiled under reflux (9 h) using a Dean–Stark apparatus. The reaction mixture was allowed to cool to room temp., washed firstly with sat. aq. NaHCO₃ (2 × 100 cm³) and then H₂O (2 × 100 cm³). The organic layer was collected, dried (Na₂SO₄) and concentrated to furnish the crude product as a yellow oil. Following fractional distillation, **6d** was obtained as a colourless oil (14.4 g, 90%). δ_{H} 2.40 (m, 2H, OCH₂CH₂), 4.38 (t, 2H, OCH₂), 5.08 (m, 2H, CH=CH₂), 5.77 (m, 1H, CH=CH₂), 7.39 (t, 2H, *m*-Ar-H), 7.59 (t, 1H, *p*-Ar-H), 7.98 (d, 2H, *o*-Ar-H); δ_{C} 32.5 (OCH₂CH₂), 64.7 (OCH₂), 117.5 (CH=CH₂), 128.5 (2 × *m*-Ar-C), 129.6 (2 × *o*-Ar-C), 132.9 (*p*-Ar-C), 134.5 (Ar-C), 134.6 (CH=CH₂), 163.2 (C=O, ester), 186.0 (C=O, ketone).

(*E*)-Prop-2-enyl 2-(hydroxyimino)propanoate *E*-**7a**

The title compound was prepared according to literature procedure¹⁸ and was obtained as colourless plates (5.11 g, 65%), mp 86 °C (lit.,¹⁸ 84–86 °C).

Prop-2-enyl 2-(hydroxyimino)-2-phenylacetate *Z*-**7b** and *E*-**7b**

The α -keto ester **6b** (1.20 g, 6.3 mmol), hydroxylamine hydrochloride (0.66 g, 9.5 mmol) and sodium acetate (0.78 g, 9.5 mmol) were stirred in H₂O (50 cm³) at 70 °C for 14 h. The reaction mixture was allowed to cool to room temp., and extracted with CH₂Cl₂ (2 × 50 cm³). The organic layers were combined, washed with H₂O (2 × 50 cm³), dried (Na₂SO₄) and concentrated to yield the crude products as a yellow gum. Separation by flash chromatography (Et₂O:*pet. spirit*, 1:2.2)

gave the *syn*-isomer **Z-7b** a colourless oil (0.49 g, 38%) and the *anti*-isomer **E-7b** a white solid which crystallized to colourless needles (0.71 g, 55%). **Z-7b**: δ_{H} 4.89 (d, 2H, OCH₂), 5.35 (m, 2H, CH=CH₂), 6.00 (m, 1H, CH=CH₂), 7.39 (m, 3H, Ar-H), 7.57 (m, 2H, 2 × *o*-Ar-H), 8.64 (br s, 1H, OH); δ_{C} 66.4 (OCH₂) 119.6 (CH=CH₂), 126.4 (*m*-Ar-C), 128.8 (*o*-Ar-C), 130.5 (*p*-Ar-C), 130.9 (Ar-C), 131.0 (CH=CH₂), 149.6 (C=N), 163.4 (C=O). **E-7b**: δ_{H} 4.77 (d, 2H, OCH₂), 5.29 (m, 2H, CH=CH₂), 5.93 (m, 1H, CH=CH₂), 7.44 (m, 3H, Ar-H), 7.52 (m, 2H, 2 × *o*-Ar-H), 10.22 (br s, 1H, OH); δ_{C} 66.6 (OCH₂), 119.4 (CH=CH₂), 127.8 (*m*-Ar-C), 128.1 (*o*-Ar-C), 128.6 (*p*-Ar-C), 129.9 (Ar-C), 131.4 (CH=CH₂), 151.6 (C=N), 163.2 (C=O).

4,4-Dimethylpent-1-en-3-yl 2-(hydroxyimino)-2-phenylacetate **Z-7c** and **E-7c**

The α -keto ester **6c** (1.97 g, 8.0 mmol), hydroxylamine hydrochloride (0.83 g, 12.0 mmol) and sodium acetate (1.11 g, 13.50 mmol) were stirred in H₂O (60 cm³) at 65 °C for 25 h. The reaction mixture was allowed to cool to room temp., before extracting with CH₂Cl₂ (4 × 80 cm³). The organic layers were combined, washed with water (50 cm³), dried (Na₂SO₄) and concentrated to yield the crude products as a colourless gum. Purification by flash chromatography (Et₂O:pet. spirit, 1:6) gave recovered starting material (0.59 g, 30%), *syn*-isomer **Z-7c** a colourless oil (0.93 g, 49%) and *anti*-isomer **E-7c** a white solid which crystallized to colourless needles (0.43 g, 20%). **Z-7c**: δ_{H} 1.02 (s, 9H, 3 × Me), 4.86 (d, 1H, OCH, *J* 6.59), 5.59 (m, 1H, CH=CH₂), 5.89 (d, 2H, CH=CH₂, *J* 15.38), 7.39 (m, 3H, *m*- and *p*-Ar-H), 7.55 (m, 2H, *o*-Ar-H), 9.02 (br s, 1H, OH); δ_{C} 29.1 (3 × Me), 33.3 (CMe₃), 67.0 (OCH), 118.0 (CH=CH₂), 130.2–126.6 (4 × Ar-C), 130.5 (CH=CH₂), 148.7 (C=N), 163.5 (C=O). **E-7c**: δ_{H} 0.97 (s, 9H, 3 × Me), 4.70 (d, 1H, OCH, *J* 6.59), 5.52 (m, 1H, CH=CH₂), 5.81 (d, 2H, CH=CH₂, *J* 15.39), 7.42 (m, 3H, *m*- and *p*-Ar-H), 7.52 (m, 2H, *o*-Ar-H), 10.18 (br s, 1H, OH); δ_{C} 29.3 (3 × Me), 34.0 (CMe₃), 67.3 (OCH), 118.0 (CH=CH₂), 129.9–128.1 (4 × Ar-C), 130.1 (CH=CH₂), 151.4 (C=N), 163.6 (C=O).

But-3-enyl 2-(hydroxyimino)-2-phenylacetate **Z-7d** and **E-7d**

The α -keto ester **6d** (11.12 g, 55 mmol), hydroxylamine hydrochloride (5.70 g, 82 mmol) and sodium acetate (6.7 g, 82 mmol) were stirred in H₂O (250 cm³) at 90 °C for 13 h. The reaction mixture was allowed to cool to room temp., and was then extracted with CH₂Cl₂ (3 × 200 cm³). The organic layers were combined, washed with H₂O (2 × 150 cm³), dried (Na₂SO₄) and concentrated to yield the crude products as a yellow gum, separation by flash chromatography (Et₂O:pet. spirit, 1:12), gave **Z-7d** a yellow oil which was further purified by fractional distillation (5.9 g, 49%) and **E-7d** as a white solid which was further purified by crystallization (5.6 g, 47%). **Z-7d**: δ_{H} 2.52 (m, 2H, OCH₂CH₂), 4.45 (t, 2H, OCH₂), 5.12 (m, 2H, CH=CH₂), 5.82 (m, 1H, CH=CH₂), 7.40 (m, 3H, Ar-H), 7.57 (m, 2H, 2 × *o*-Ar-H), 9.30 (br s, 1H, OH); δ_{C} 32.9 (OCH₂CH₂), 65.1 (OCH₂), 117.8 (CH=CH₂), 126.5 (*m*-Ar-C), 128.8 (*o*-Ar-C), 129.3 (*p*-Ar-C), 130.5 (Ar-C), 133.4 (CH=CH₂), 151.7 (C=N), 163.7 (C=O). **E-7d**: δ_{H} 2.41 (m, 2H, OCH₂CH₂), 4.30 (t, 2H, OCH₂), 5.05 (m, 2H, CH=CH₂), 5.75 (m, 1H, CH=CH₂), 7.42 (m, 3H, Ar-H), 7.5 (m, 2H, 2 × *o*-Ar-H), 10.1 (br s, 1H, OH); δ_{C} 32.8 (OCH₂CH₂), 65.1 (OCH₂), 117.7 (CH=CH₂), 128.0 (*m*-Ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 129.8 (Ar-C), 133.5 (CH=CH₂), 149.8 (C=N), 163.3 (C=O).

5,6-Dihydro-3,5-dimethyl-1,4-oxazin-2-one *N*-oxide **8a**

A solution of the oxime **E-7a** (2.75 g, 19 mmol) in mesitylene (500 cm³) at 165 °C was stirred under a nitrogen atmosphere for 28 h in the presence of hydroquinone (1% w/v). The reaction mixture was cooled to room temp., and the solvent removed under reduced pressure (100 °C, 0.50 mmHg) to give a brown gummy residue which was taken up in CHCl₃ (3 cm³) and allowed to stand at room temp. (0.5 h), the precipitated hydro-

quinone was removed *in vacuo*, and the filtrate was concentrated under reduced pressure. Purification of the crude products by flash chromatography (Et₂O:pet. spirit, 2:1) gave unchanged oxime (0.14 g, 5%), small amounts of two indistinguishable diastereomeric dimeric adducts **9a(i)** (0.06 g, 2%, colourless cubic crystals, Et₂O–hexane, mp 128–130 °C) and **9a(ii)** (0.10 g, 4%, colourless cubic crystals, Et₂O–hexane, mp 170–172 °C) and the dipole **8a**, a highly viscous orange oil which was further purified to a pale yellow oil by fractional distillation (2.34 g, 85%). **9a(i)**: δ_{H} 1.18 (d, 3H, Me⁷, *J* 6.60), 1.61 (s, 3H, Me^{3a}), 2.12 (s, 3H, Me¹), 2.52 (m, 2H, H^{3A} and H^{3B}), 3.21 (m, 1H, H⁷), 4.03 (dd, 1H, H^{6B}, *J*_{6B,7} 10.26, *J*_{6B,6A} 10.99), 4.24 (dd, 1H, H^{6A}, *J*_{6A,7} 8.06, *J*_{6A,6B} 10.99), 4.51 and 4.34 (2 × m, 1 × 2H, 1 × 1H, H² and OCH²), 9.70 (br s, 1H, OH); δ_{C} 10.6 (Me⁷), 14.4 (Me^{3a}), 25.5 (Me¹), 41.4 (C³), 55.6 (C⁷), 65.0 (OCH²), 69.1 (C⁶), 70.1 (C^{3a}), 76.5 (C²), 149.6 (C=N), 163.5 (C=O, ester), 171.6 (C₄, C=O) (Found: C, 50.64; H, 5.99; N, 9.61. C₁₂H₁₈N₂O₆ requires C, 50.35; H, 6.29; N, 9.79%). **9a(ii)**: δ_{H} 1.23 (d, 3H, Me⁷, *J* 6.59), 1.64 (s, 3H, Me^{3a}), 2.12 (s, 3H, Me¹), 2.26 (dd, 1H, H^{3A}, *J*_{3A,2} 6.60, *J*_{3A,3B} 13.19), 2.88 (dd, 1H, H^{3B}, *J*_{3B,2} 8.79, *J*_{3B,3A} 13.19), 3.13 (m, 1H, H⁷), 4.03 (t, 1H, H^{6B}, *J*_{6B,7B}, *J*_{6B,6A} 10.99), 4.24 (dd, 1H, H^{6A}, *J*_{6A,7} 8.80, *J*_{6A,6B} 10.99), 4.40 (m, 3H, H² and OCH²), 9.98 (br s, 1H, OH); δ_{C} 10.70 (Me⁷), 14.5 (Me^{3a}), 29.8 (Me¹), 43.3 (C³), 52.6 (C⁷), 65.3 (OCH²), 69.6 (C⁶), 69.7 (C^{3a}), 73.8 (C²), 149.1 (C=N), 163.5 (C=O), 172.4 (C⁴, C=O) (Found: C, 50.40; H, 6.40; N, 9.52. C₁₂H₁₈N₂O₆ requires C, 50.35; H, 6.29; N, 9.79%). **8a**: δ_{H} 1.58 (d, 3H, Me⁵, *J* 6.78), 2.23 (s, 3H, Me³), 4.19 (m, 1H, H⁵), 4.30 (dd, 1H, H^{6B}, *J*_{6B,5} 5.68, *J*_{6B,6A} 12.10), 4.62 (dd, 1H, H^{6A}, *J*_{6A,5} 3.66, *J*_{6A,6B} 12.27); δ_{C} 11.8 (Me⁵), 14.4 (Me³), 62.9 (C⁵), 67.1 (C⁶), 135.1 (C³, C=N), 159.2 (C², C=O).

(3a*S**,6a*R**)-Tetrahydro-6a-methylfuro[3,4-*c*]isoxazol-6-one **10a**

A solution of the oxime **E-7a** (3.21 g, 22.50 mmol) in H₂O (90 cm³) at 100 °C was stirred for 48 h. The reaction mixture was cooled to room temp., and was extracted with CH₂Cl₂ (4 × 100 cm³). The organic layers were combined, dried (Na₂SO₄) and concentrated to give a yellow solid (0.65 g, 20%), which was purified by flash chromatography (Et₂O) to give unchanged oxime **E-7a** (0.50 g, 16%) and the adduct **10a** (0.13 g, 4%), which crystallized to colourless cubic crystals. Careful evaporation (70 °C, 15 mmHg) of the aqueous layer gave a brown gummy residue (0.19 g, 6%) which was decomposed organic material. δ_{H} 1.58 (s, 3H, Me), 3.08 (m, 1H, H^{3a}), 3.99 (dd, 1H, H^{4B}, *J*_{4B,4A} 6.59, *J*_{4B,3a} 8.80), 4.15 (dd, 1H, H^{4A}, *J*_{4A,4B} 6.60, *J*_{4A,3a} 2.94), 4.22 (dd, 1H, H^{3B}, *J*_{3B,3A} 9.53, *J*_{3B,3a} 2.93), 4.54 (dd, 1H, H^{3A}, *J*_{3A,3B} 9.53, *J*_{3A,3a} 8.06), 5.45 (br s, 1H, NH); δ_{C} 17.0 (Me), 47.8 (C^{3a}), 67.6 (C⁴), 69.4 (C³), 77.6 (C^{6a}), 176.1 (C=O). NOEDS experimental results indicate *cis* stereochemistry at the ring junction, irradiation of H^{3a} caused a 2.9% enhancement on the methyl group.

5,6-Dihydro-5-methyl-3-phenyl-1,4-oxazin-2-one *N*-oxide **8b**

A solution of the oxime **E-7b** (0.90 g, 4.39 mmol) in xylene (250 cm³) was stirred at 138 °C under a nitrogen atmosphere for 30 h in the presence of hydroquinone (1.0% w/v). The reaction mixture was cooled to room temp., and the solvent was removed under reduced pressure (100 °C, 0.25 mmHg). The solid residue was taken up in CHCl₃ (3 cm³) and allowed to stand at room temp. (0.5 h), the precipitated hydroquinone was removed by filtration *in vacuo* and the filtrate was concentrated under reduced pressure. Purification of the crude mixture by flash chromatography (Et₂O:pet. spirit, 2:1) gave unchanged starting oxime **E-7b** (0.020 g, 2%), a dimeric adduct **9b** (0.06 g, 7%, colourless cubic crystals, mp 155–158 °C, benzene–pet. spirit) and the dipole **8b** (0.77 g, 85%). **9b**: δ_{H} 1.19 (d, 3H, Me, *J* 6.59), 2.52 and 2.48 (2 × dd, 2 × 1H, H^{3A} and H^{3B}), 3.25 (m, 1H, H⁷), 4.35 (m, 2H, H^{1A} and H^{1B}), 4.80 and 4.73 (2 × dd, 2 × 1H, H^{6A} and H^{6B}), 4.95 (m, 1H, H²), 8.73–7.19 (2 × m, 10H, Ar-H),

10.15 (br s, 1H, OH); δ_C 15.9 (Me), 45.8 (C³), 56.6 (C⁷), 65.5 (OCH²), 68.6 (C⁶), 74.3 (C^{3a}), 74.6 (C²), 140.0–126.2 (8 × Ar-C), 149.5 (C=N), 162.9 (C₄, C=O), 171.1 (C=O, ester) (Found: C, 64.56; H, 5.39; N, 6.49. C₂₂H₂₂N₂O₆ requires C, 64.39; H, 5.35; N, 6.78%). **8b**: δ_H 1.66 (d, 3H, Me⁵), 4.33 (m, 2H, H^{6B} and H⁵), 4.70 (dd, 1H, H^{6A}, $J_{6A,5}$ 3.30, $J_{6A,6B}$ 11.72), 7.44 (m, 3H, *m*- and *p*-Ar-H), 7.70 (m, 2H, 2 × *o*-Ar-H); δ_C 14.7 (Me), 64.8 (C⁵), 66.9 (C⁶), 134.5–127.5 (4 × Ar-C), 136.2 (C³, C=N), 158.9 (C², C=O).

(3aS*,6aS*)-Tetrahydro-6a-phenylfuro[3,4-c]isoxazol-6-one 10b

Method A. A solution of the oxime **Z-7b** (0.76 g, 3.7 mmol) in xylene (225 cm³) was stirred at 138 °C under a nitrogen atmosphere for 36 h in the presence of hydroquinone (1.0% w/v). The reaction mixture was cooled to room temp. and the solvent removed under reduced pressure (100 °C, 0.5 mmHg). The gummy residue was taken up in CHCl₃ (2.5 cm³) and allowed to stand at room temp. (0.5 h), the precipitated hydroquinone removed by filtration *in vacuo*, and the filtrate was concentrated. Purification of the crude products by flash chromatography (Et₂O:pet. spirit, 1.0:2.5) gave unchanged starting oxime **Z-7b** (0.22 g, 29%), and the adduct **10b**, a viscous yellow oil which solidified upon trituration (pet. spirit) (0.5 g, 66%). **10b**: δ_H 3.57 (m, 1H, H^{3a}), 4.21 (m, 2H, H^{4A} and H^{4B}), 4.40 (dd, 1H, H^{3A}, $J_{3A,3B}$ 9.89, $J_{3A,3a}$ 2.02), 4.63 (dd, 1H, H^{3B}, $J_{3B,3A}$ 9.89, $J_{3B,3a}$ 7.14), 5.92 (br s, 1H, NH), 7.55–7.29 (2 × m, 5H, Ar-H); δ_C 49.4 (C^{3a}), 70.8 (C⁴), 75.2 (C³), 78.6 (C^{6a}), 133.5–126.5 (4 × Ar-C), 176.6 (C=O); NOEDS indicated *cis* fusion at the ring junction, irradiation of H^{3a} caused a 4.3% enhancement on the *o*-ArH.

Method B. Aqueous preparation of 10b. The oxime **E-7b** (1.50 g, 7.3 mmol) was stirred in H₂O (120 cm³) at 100 °C for 18 h. The reaction mixture was allowed to cool to room temp. and the aqueous solution was extracted with CH₂Cl₂ (4 × 100 cm³). The organic layers were combined, dried (Na₂SO₄) and concentrated to yield the crude products as a yellow gum (1.46 g, 97%). This residue was taken up in benzene–pet. spirit and allowed to stand at 0 °C overnight, adduct **10b** crystallized as colourless rods which were collected by filtration (0.85 g, 57%). The filtrate was concentrated and further purified by flash chromatography (Et₂O:pet. spirit, 1.0:1.5) giving three fractions. Fraction one, a viscous yellow oil, contained unchanged starting oxime **E-7b** (0.15 g, 10%). Fraction two gave oxime **Z-7b** (0.22 g, 15%) as a yellow gum. Fraction three (a diethyl ether strip) gave adduct **10b**, which upon crystallization (Et₂O–pet. spirit) gave colourless rods (0.16 g, 11%, 67% total).

Thermal reaction of oxime E-7c. Preparation of 8c and 10c

A solution of the *anti*-oxime **E-7c** (0.91 g, 3.50 mmol) in xylene (250 cm³) was heated at 140 °C under a nitrogen atmosphere for 35 h in the presence of hydroquinone (1.0% w/v). The reaction mixture was cooled to room temp., and the solvent removed under reduced pressure (100 °C, 0.5 mmHg). The yellow gummy residue was taken up in CHCl₃ (2 cm³) and allowed to stand at room temp. for 0.5 h, the precipitated hydroquinone was filtered off *in vacuo* and the filtrate was concentrated. The crude products were isolated by flash chromatography (Et₂O:pet. spirit, 1:4) to give the *syn*-oxime (**Z-7c**, 0.30 g, 33%), the unchanged *E*-oxime (**E-7c**, 0.20 g, 22%), the cycloadduct **10c** (0.064 g, 7%), a yellow gum which solidified upon standing to give colourless needles, mp 136–137 °C (benzene–pet. spirit) and the dipole **8c** a yellow gum which was crystallized from benzene–pet. spirit to give colourless cubic crystals (0.30 g, 33%), mp 93–95 °C. (3aR*,4S*,6aS*)-Tetrahydro-4-tert-butyl-6a-phenylfuro[3,4-c]isoxazol-6-one **10c**: δ_H 0.97 (s, 9H, 3 × Me), 3.25 (m, 1H, H^{3a}), 3.82 (d, 1H, H⁴, $J_{4,3a}$ 6.59), 4.32 (dd, 1H, H^{3A}, $J_{3A,3a}$ 9.52, $J_{3A,3B}$ 3.86), 4.50 (dd, 1H, H^{3B}, $J_{3B,3A}$ 9.52, $J_{3B,3a}$ 5.86), 6.11 (br s, 1H, NH), 7.47–7.23 (2 × m, 5H, Ar-H); δ_C 26.0 (CMe₃), 34.7 (CMe₃), 53.6 (C^{6a}), 69.4 (C³), 96.6 (C⁴), 134.7–126.4 (4 × Ar-C), 160.4 (C₆, C=O). NOEDS experi-

mental results indicate *cis* stereochemistry at the ring junction, irradiation of H^{3a} caused a 3.7% enhancement on the *o*-ArH; H^{3a} and H⁴ are deduced to have a *trans* relationship as they show no mutual enhancement on irradiation. (5R*,6S*)-6-tert-butyl-5,6-dihydro-5-methyl-3-phenyl-1,4-oxazin-2-one **N-oxide 8c**: δ_H 1.00 (s, 9H, 3 × Me), 1.70 (d, 3H, Me⁵, J 7.33), 3.99 (s, 1H, H⁶), 4.28 (q, 1H, H⁵, J 7.33), 7.34 (m, 3H, *m*- and *p*-Ar-H), 7.59 (m, 2H, *o*-Ar-H); δ_C 20.5 (Me⁵), 25.8 (CMe₃), 35.9 (CMe₃), 64.9 (C⁵), 85.0 (C⁶), 130.1–128.0 (4 × Ar-C), 158.1 (C=N), 162.4 (C², C=O). NOEDS experimental results indicate a *trans* relationship between the methyl group on C⁵ and the Bu^t group on C⁶; irradiation of H⁵ causes a 9.3% enhancement on the Bu^t group and a 3.8% enhancement on Me⁵; irradiation of H⁶ causes a 3.3% enhancement on H⁵, a 3.5% enhancement on Me⁵ and a 5.4% enhancement on the Bu^t group.

6,7-Dihydro-5-methyl-3-phenyl-5H-1,4-oxazepin-2-one N-oxide 8d

A solution of the oxime **E-7d** (3.00 g, 13.70 mmol) in xylene (900 cm³) was stirred at 140 °C under a nitrogen atmosphere for 24 h in the presence of hydroquinone (1.0% w/v). The reaction mixture was cooled to room temp., and the solvent removed under reduced pressure (100 °C, 0.2 mmHg). The yellow gummy residue was taken up in CHCl₃ (5 cm³) and allowed to stand at room temp. for 0.5 h, the precipitated hydroquinone was filtered off *in vacuo* and the filtrate concentrated. Purification of the crude products by flash chromatography (Et₂O:pet. spirit, 1:4) gave oxime **Z-7d** as a colourless oil (0.90 g, 30%), unchanged starting oxime **E-7d** (0.85 g, 28%), two indistinguishable stereoisomeric dimeric adducts **9d(i)** (0.06 g, 2.0%, pale yellow crystals, mp 130–131 °C from benzene–pet. spirit) and **9d(ii)** (0.035 g, 1.2%, pale yellow crystals, mp 114–116 °C from benzene–pet. spirit) and the nitron **8d** as a yellow gum which was triturated and crystallized from benzene–pet. spirit to give pale yellow cubic crystals (0.95 g, 32%). **9d(i)**: δ_H 1.25 (d, 3H, Me, J 5.87), 2.16–1.61 (m, 4H, H^{7A}, H^{7B} and OCH₂CH²), 2.20 (dd, 1H, H^{3B}, $J_{3B,3A}$ 12.82, $J_{3B,2}$ 8.80), 3.27 (m, 1H, H⁸), 3.72 (dd, 1H, H^{3A}, $J_{3A,2}$ 12.82, $J_{3A,2}$ 6.96), 3.86 (dd, 1H, H^{6B}, $J_{6B,6A}$ 2.09, $J_{6B,7A/7B}$ 3.23), 4.43–4.24 (3 × m, 4H, H², H^{6A} and OCH₂CH²), 7.63–7.25 (3 × m, 10 × Ar-H), 9.63 (br s, 1H, OH); δ_C 18.6 (Me), 36.5 and 32.1 (C⁷ and OCH₂CH²), 50.4 (C³), 53.6 (C⁸), 62.5 (OCH₂CH²), 64.0 (C⁶), 73.7 (C^{3a}), 82.8 (C²), 140.9–125.2 (10 × Ar-C), 149.4 (C=N), 163.6 (C₄, C=O), 171.7 (C=O, ester) (Found: C, 65.99; H, 5.99; N, 6.21. C₂₄H₂₆N₂O₆ requires C, 65.75; H, 5.94; N, 6.39%). **9d(ii)**: δ_H 1.20 (d, 3H, Me, J 6.59), 2.14–1.67 (3 × m, 4H, H^{7A}, H^{7B} and OCH₂CH²), 2.16 (dd, 1H, H^{3B}, $J_{3B,3A}$ 13.19, $J_{3B,2}$ 8.06), 3.20 (m, 1H, H⁸), 3.64 (dd, 1H, H^{3A}, $J_{3A,2}$ 7.33, $J_{3A,3B}$ 13.19), 3.86 (dd, 1H, H^{6B}, $J_{6B,6A}$ 12.46, $J_{6B,7A/7B}$ 6.60), 4.14 (m, 1H, H²), 4.28 (m, 3H, H^{6A}, OCH₂CH², $J_{6A,6B}$ 12.46, $J_{6A,7A/7B}$ 8.80), 7.61–7.25 (3 × m, 10 × Ar-H and Ar^r-H), 9.62 (br s, 1H, OH); δ_C 19.0 (Me), 36.9 and 32.5 (C⁷ and OCH₂CH²), 53.8 (C⁸), 50.4 (C³), 63.1 (OCH₂CH²), 64.2 (C⁶), 74.1 (C^{3a}), 83.1 (C²), 141.2–125.6 (8 × Ar-C), 149.7 (C=N), 163.2 (C₄, C=O), 171.6 (C=O, ester) (Found: C, 65.76; H, 5.96; N, 6.10. C₂₄H₂₆N₂O₆ requires C, 65.75; H, 5.94; N, 6.39%). **8d**: δ_H 1.57 (d, 3H, Me, J 6.45), 2.11 (m, 1H, H^{6A}), 2.42 (m, 1H, H^{6B}), 4.57–4.30 (2 × m, 3H, H⁵, H^{7A} and H^{7B}), 7.42 (m, 2H, *m*- and *p*-Ar-H), 8.07 (m, 2H, *o*-Ar-H); δ_C 15.6 (Me), 34.6 (C⁷), 64.6 (C⁸), 66.1 (C⁶), 136.2–128.4 (4 × Ar-C, C³ and C=N), 165.8 (C² and C=O).

2-(Prop-2-enyloxy)acetophenone 16a

2-Hydroxyacetophenone (14.96 g, 0.11 mol), allyl bromide (19.96 g, 0.165 mol) and potassium carbonate (22.8 g, 0.165 mol) were stirred using mechanical agitation in dry acetone (250 cm³) under reflux for 85 h. The reaction mixture was allowed to cool to room temp., and the solvent was removed under reduced pressure. To the viscous yellow residue was added H₂O (200 cm³) and this aqueous solution was extracted with Et₂O (4 × 100 cm³). The combined organic layers were

collected, dried (MgSO₄) and concentrated to yield the crude product as a yellow oil. Following fractional distillation **16a** (15.1 g, 78%) was obtained as a colourless oil which solidified upon standing giving colourless plates. δ_{H} 2.62 (s, 3H, Me), 4.62 (d, 2H, OCH₂), 5.35 (m, 2H, CH=CH₂), 6.06 (m, 1H, CH=CH₂), 6.95 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 7.75 (m, 1H, Ar-H); δ_{C} 31.9 (Me), 69.4 (OCH₂), 112.9 (Ar-C), 118.2 (CH=CH₂), 120.8 (Ar-C), 128.8 (Ar-C), 130.4 (Ar-C), 132.7 (Ar-C), 133.5 (CH=CH₂), 158.0 (Ar-C), 199.9 (C=O).

2-(Prop-2-enyloxy)benzophenone **16b**

2-Hydroxybenzophenone (3.96 g, 20 mmol), allyl bromide (3.6 g, 30 mmol) and potassium carbonate (4.15 g, 0.3 mmol) were stirred using mechanical agitation in acetone (150 cm³) under reflux for 40 h. The reaction mixture was allowed to cool to room temp., and the reaction solvent was evaporated under reduced pressure. To the yellow oily residue was added H₂O (100 cm³) and the resulting aqueous solution was extracted with Et₂O (4 × 75 cm³). The organic layers were combined, dried (MgSO₄) and concentrated to furnish the crude product. Following fractional distillation **16b** (4.0 g, 90%) was obtained as a colourless oil. δ_{H} 4.46 (m, 2H, OCH₂), 5.05 (m, 2H, CH=CH₂), 5.72 (m, 1H, CH=CH₂), 7.0 (m, 2H, Ar-H), 7.49 (m, 5H, Ar-H), 7.84 (m, 2H, Ar-H); δ_{C} 68.9 (OCH₂), 112.7 (Ar-C), 116.9 (CH=CH₂), 120.8 (Ar-C), 128.1 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 129.9 (Ar-C), 132.3 (Ar-C), 132.8 (CH=CH₂), 138.1 (Ar-C), 156.3 (Ar-C), 196.6 (C=O).

(E)-2'-(Prop-2-enyloxy)acetophenone oxime **E-17a**

The ketone **16a** (6.00 g, 34.0 mmol), hydroxylamine hydrochloride (2.84 g, 40.0 mmol) and pyridine (3.16 g, 40.0 mol) were stirred in EtOH (150 cm³) at 78 °C for 13 h. The reaction mixture was allowed to cool to room temp., and after standing overnight, the reaction solvent was removed under reduced pressure, leaving a yellow gummy residue which was taken up in CH₂Cl₂ (250 cm³), washed with H₂O (5 × 200 cm³) and dried (Na₂SO₄). The organic layer was concentrated to furnish the crude product which solidified upon trituration with pet. spirit (6.1 g, 94%). δ_{H} 2.17 (s, 3H, Me), 4.48 (d, 2H, OCH₂), 5.25 (m, 2H, CH=CH₂), 5.95 (m, 1H, CH=CH₂), 6.85 (m, 2H, Ar-H), 7.23 (m, 2H, Ar-H), 9.35 (br s, 1H, OH); δ_{C} 15.5 (Me), 69.2 (OCH₂), 117.3 (CH=CH₂), 133.5 (CH=CH₂), 154.6–112.8 (6 × Ar-C), 155.0 (C=N).

2'-(Prop-2-enyloxy)benzophenone oxime **Z-17b** and **E-17b**

The ketone **16b** (4.45 g, 20 mmol), hydroxylamine hydrochloride (1.67 g, 24 mmol) and pyridine (5.56 g, 70 mmol) were stirred in EtOH (150 cm³) at reflux for 16 h. The reaction mixture was cooled to room temp., and left to stand overnight. The solvent was removed under reduced pressure leaving a yellow viscous oil which was taken up in CH₂Cl₂ (150 cm³) and transferred to a separating funnel. The organic layer was washed with H₂O (5 × 100 cm³), dried (Na₂SO₄) and concentrated to yield the isomeric oximes which were purified by flash chromatography (Et₂O:pet. spirit, 1:6) and recrystallized to give the *syn*-isomer **Z-17b** as colourless rods (3.55 g, 70%) and the *anti*-isomer **E-17b** as colourless cubic crystals (1.05 g, 21%). **Z-17b**: δ_{H} 4.47 (d, 2H, OCH₂), 5.12 (m, 2H, CH=CH₂), 5.77 (m, 1H, CH=CH₂), 7.47–6.97 (5 × m, 9 × Ar-H), 9.54 (br s, 1H, OH); δ_{C} 69.1 (OCH₂), 112.9 (CH=CH₂), 135.8 (CH=CH₂), 156.0–116.7 (9 × Ar-C), 155.7 (C=N). **E-17b**: δ_{H} 4.29 (d, 2H, OCH₂), 5.05 (m, 2H, CH=CH₂), 5.60 (m, 1H, CH=CH₂), 7.53–6.83 (5 × m, 9 × Ar-H), 10.10 (br s, 1H, OH); δ_{C} 70.3 (OCH₂), 112.1 (CH=CH₂), 135.6 (CH=CH₂), 158.2–116.4 (9 × Ar-C), 158.6 (C=N).

2,3-Dihydro-3,5-dimethyl-1,4-benzoxazepine *N*-oxide **18a**

A solution of the oxime **E-17a** (1.43 g, 7.50 mmol) in xylene (225 cm³) was heated at 140 °C under an atmosphere of nitrogen for 14 h. The reaction mixture was cooled to room temp.,

and the solvent was removed under reduced pressure (100 °C, 0.6 mmHg) to give the crude product **18a** as a highly viscous orange oil. The pure product was obtained as a yellow oil following fractional distillation (1.4 g, 98%). δ_{H} 1.33 (d, 3H, Me³, *J* 5.86), 2.43 (s, 3H, Me⁵), 4.56–4.40 (m, 3H, H^{2A}, H^{2B} and H³), 7.32–7.02 (3 × m, 4H, Ar-H); δ_{C} 10.9 (Me³), 17.4 (Me⁵), 62.8 (C²), 79.1 (C³), 141.3–120.8 (6 × Ar-C), 154.0 (C⁵, C=N).

2,3-Dihydro-3-methyl-5-phenyl-1,4-benzoxazepine *N*-oxide **18b**

A solution of freshly recrystallized oxime **E-17b** (0.90 g, 3.6 mmol) was stirred in xylene (300 cm³) at reflux under an atmosphere of nitrogen for 5 h in the presence of hydroquinone (1% w/v). The reaction mixture was cooled to room temp., and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (Et₂O:pet. spirit, 1:9) to give the unchanged oxime (**17b**, 0.02 g, 2%) and the dipole **18b**, a yellow gum which was triturated from pet. spirit and crystallized to give colourless needles of the title compound (0.83 g, 92%). δ_{H} 1.43 (d, 3H, Me, *J* 6.60), 4.43 (dd, 1H, H^{2B}, *J*_{2B,2A} 10.26, *J*_{2B,3} 2.93), 4.47 (m, 1H, H³), 4.72 (dd, 1H, H^{2A}, *J*_{2A,3} 10.99, *J*_{2A,2B} 10.26), 7.37–6.98 (2 × m, 7H, Ar-H), 7.60–7.81 (m, 2H, ArH); δ_{C} 11.8 (Me), 64.3 (C²), 81.1 (C³), 142.9–121.8 (10 × Ar-C), 155.6 (C=N).

(3a*S**,9b*S**)-9b-Phenyl-1,3a,4,9b-tetrahydro-3*H*-benzofuro[4,3-*c*]isoxazole **19b**

A solution of the oxime **Z-17b** (1.04 g, 4.11 mmol) in refluxing xylene (350 cm³) was stirred under an atmosphere of nitrogen for 50 h in the presence of hydroquinone (1% w/v). The reaction mixture was cooled to room temp., and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (Et₂O:pet. spirit, 1:1) to give the ketone **16b** (0.12 g, 12%) as a viscous pale yellow oil, unchanged oxime **Z-17b** (0.26 g, 25%), and the cycloadduct **19** as a yellow gum which solidified upon trituration and gave colourless cubic crystals from benzene–pet. spirit (0.6 g, 58%). δ_{H} 3.14 (m, 1H, H^{3a}), 3.78 (dd, 1H, H^{4A}, *J*_{4A,4B} 8.06, *J*_{4A,3a} 5.13), 3.95 (dd, 1H, H^{3A}, *J*_{3A,3B} 11.73, *J*_{3A,3a} 9.52), 4.17 (dd, 1H, H^{4B}, *J*_{4B,4A} 8.06, *J*_{4B,3a} 7.33), 4.32 (dd, 1H, H^{3B}, *J*_{3B,3A} 11.72, *J*_{3B,3a} 4.40), 5.61 (br s, 1H, NH), 7.00–6.82 (2 × m, 3H, Ar-H), 7.35–6.82 (3 × m, 4H, Ar-H), 7.49 (m, 2H, *o*-Ar^{9b}-H); δ_{C} 50.1 (C^{3a}), 67.3 and 66.0 (C³ and C⁴), 72.4 (C^{9b}), 145.1–117.3 (10 × Ar-C). NOEDS experimental results indicate *cis* stereochemistry at the ring junction; irradiation of H^{3a} caused a 4.2% enhancement on the cross ring ArH.

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