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

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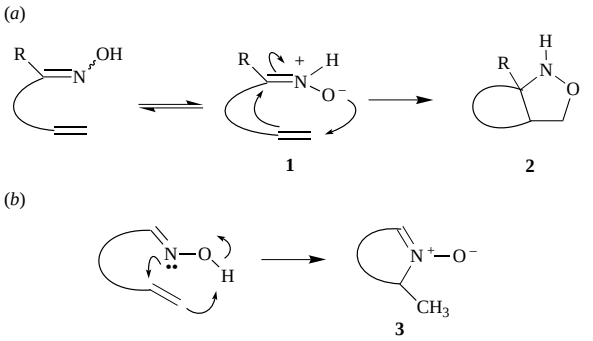
Thermally induced cyclization of the *anti*-alkenyl oximes *E*-7a,b and *E*-17a,b affords cyclic α-alkoxycarbonylnitrones 8 and the 6,7-bicyclic nitrones 18, respectively. The *syn*-oximes *Z*-7b and *Z*-17b react *via* an alternate pathway to give exclusively the fused isoxazolidine derivatives 10b 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

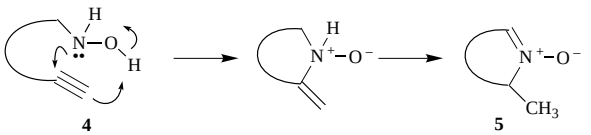
The 1,3-dipolar cycloaddition can accomplish the synthesis of a range of highly functionalised stereochemically complex five-membered rings. The isoxazolidines/isoxazolines which are the primary adducts from reaction between nitrones and alkenes/alkynes have a labile N–O bond easily cleaved under reductive or oxidative conditions, consequently this reaction is often used as a key step in targeted syntheses.[1] The most general methods for nitrone 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 nitrone 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-nitrone **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



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 nitrone **3**. Numerous examples exist where the olefinic moiety is activated (electron 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

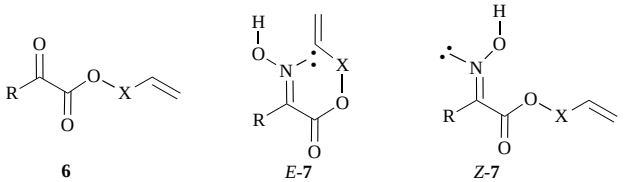


Scheme 2 Dipole formation from alkynylhydroxylamines

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



a R = Me, X = CH_2
b R = Ph, X = CH_2
c R = Ph, X = $CHBu^t$
d R = Ph, X = CH_2CH_2

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 ^{1}H NMR

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

Compound	λ_{max}/nm MeOH	λ_{max}/nm 0.03% Methanolic NaOH	^{13}C NMR resonance of imino carbon atom (δ/ppm)[a]
E-**7a**	221.77	260.11	149.2
E-**7b**	243.44, 233.44, 218.43	273.44, 243.44, 225.11	151.6
Z-**7b**	209.45	210.11	149.6
E-**7c**	—	—	151.4
Z-**7c**	—	—	148.7
E-**7d**	243.44, 208.44	273.44, 225.11, 206.78	151.8
Z-**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**

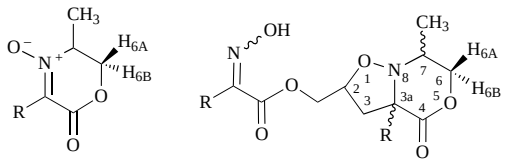
Compound	Molecular formula	Yield (%)	Physical properties	C Found (%) (Requires)	H	N
6b	$C_{11}H_{10}O_3$	81	bp: 126–128 °C, 0.1 mmHg	69.19 (69.47)	5.40 (5.26)	0 (0)
6d	$C_{12}H_{12}O_3$	90	bp: 90–94 °C, 0.3 mmHg	70.37 (70.59)	5.94 (5.88)	0 (0)
16a	$C_{11}H_{12}O_2$	85	bp: 93–95 °C, 2.0 mmHg mp: 29–30 °C	75.21 (75.00)	6.84 (6.82)	0 (0)
16b	$C_{16}H_{14}O_2$	90	bp: 110–112 °C, 0.03 mmHg	80.54 (80.67)	5.72 (5.88)	0 (0)
Z-**7b**	$C_{11}H_{11}NO_3$	38	bp: 110–112 °C, 0.5 mmHg	64.17	5.07	6.84
E-**7b**		55	mp: 90–94 °C (benzene–pet. spirit)	(64.39)	(5.37)	(6.87)
Z-**7c**	$C_{15}H_{19}NO_3$	45	R_f 0.48 (Et_2O–pet. spirit, 1:4)	69.08	7.32	5.33[a]
E-**7c**		20	mp: 110–111 °C (benzene–pet. spirit)	(68.97)	(7.28)	(5.36)
Z-**7d**	$C_{12}H_{13}NO_3$	49	bp: 138 °C, 0.025 mmHg	65.48	5.67	6.21[a]
E-**7d**		47	mp: 46–48 °C (benzene–pet. spirit)	(65.75)	(5.94)	(6.39)
E-**17a**	$C_{11}H_{13}NO_2$	94	mp: 69–71 °C (benzene–pet. spirit)	69.33 (69.11)	7.08 (6.81)	7.59 (7.33)
Z-**17b**	$C_{16}H_{15}NO_2$	70	mp: 100–101 °C (benzene–hexane)	75.77	6.04	5.81[a]
E-**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 $J_{^{13}C,^{1}H}$ coupling constants for aldoximes.[10] In this case assignment was based largely on UV π→π* 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 Cα-substituent in the *E*-oxime series whilst no effect was observed with the *Z*-isomers (Table 1).

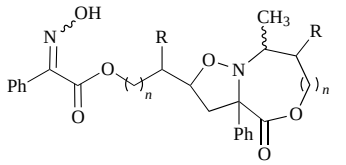
The propensity for (*E*)-prop-2-enyl 2-(hydroxyimino)propanoate to behave as a dipole precursor was investigated: heating a solution of *E*-**7a** in each of MeOH, DMF or C_6H_6 at reflux temperature resulted only in returned starting material. In boiling xylene reaction was slow, however heating in 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

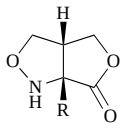


8a R = Me
b R = Ph

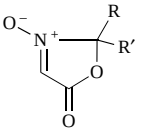
9a R = Me
b R = Ph



9c R = Bu^t, *n* = 0
9d R = H, *n* = 1



10a R = Me
b R = Ph



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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**

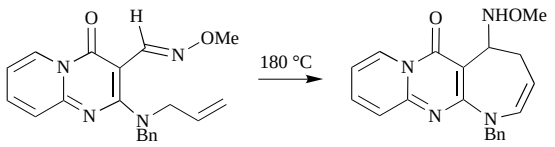
Compound	Molecular formula	Yield (%)	Physical properties	C Found (%) (Requires)	H	N
8a	$C_6H_9NO_3$	85	bp: 115–120 °C, 0.5 mmHg	50.20 (50.35)	6.44 (6.34)	9.67 (9.79)
8b	$C_{11}H_{11}NO_3$	85	mp: 94–95 °C (benzene–pet. spirit)	64.56 (64.68)	5.37 (5.35)	6.83 (6.78)
8c	$C_{15}H_{19}NO_3$	33	mp: 93–95 °C (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 Found (%) (Requires)	H	N
10a	$C_6H_9NO_3$	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.

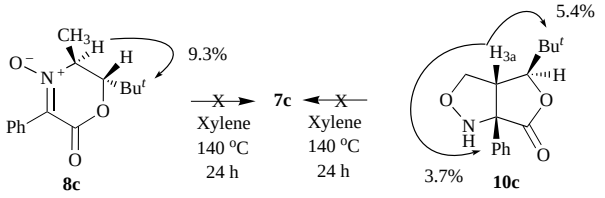
molecular selenium-induced cyclizations of α-alkenyloximes generating 1,2-oxazines or cyclic nitrones respectively,[13a] and Noguchi's group have demonstrated that only the *E*-oxime ethers **12** participate in an intramolecular azepine-forming



E-**12** **13**

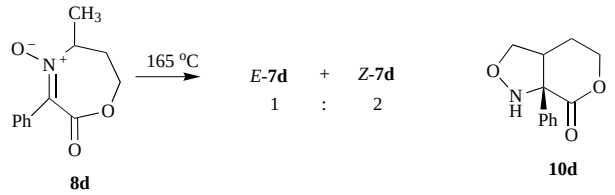
reaction whilst *Z*-isomers remain unchanged under the same experimental conditions.[13b]

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**

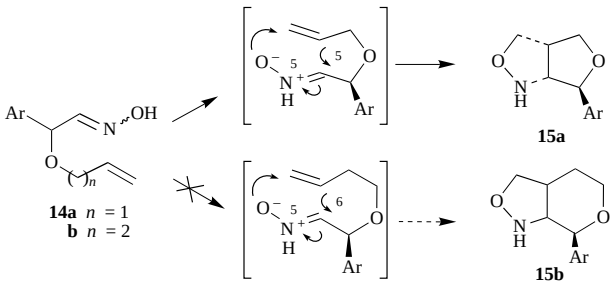


were heated in boiling xylene and the following points noted (i) the isomers were shown to be devoid of thermal stability and (ii) in each case reaction was slower than that observed for the unsubstituted analogue **7b**. Following the heating of *E*-**7c** the reaction products comprised a 5:3:1:5 mixture 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 process[14] 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 coworkers 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 antici-

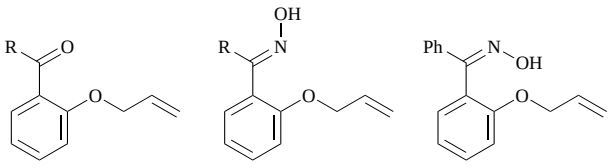


pated pyranoisoxazolone **10d** resulted. Clearly both oximes *E*- and *Z*-**7d** suffer partial isomerization under the reaction conditions studied. The failure of *Z*-**7d** to partake in the IOOC reaction sequence is consistent with Hassner's observations that whilst the unsaturated aldoximes **14a**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



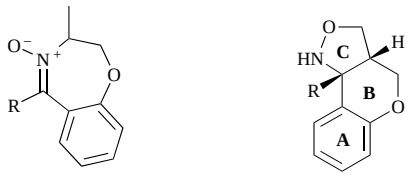
formation to the furoisoxazoles **15a** the homologous **14b** failed to form the corresponding pyranoisoxazoles **15b** under the same experimental conditions.[5d] These results suggest that the transition state required for the formation of the 6,5-bicyclic skeleton is more difficult to attain than 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 ^{13}C NMR data with the *E*-isomer having the more downfield imino carbon signal ($CDCl_3$, 155.7 *vs*. 158.6 ppm).

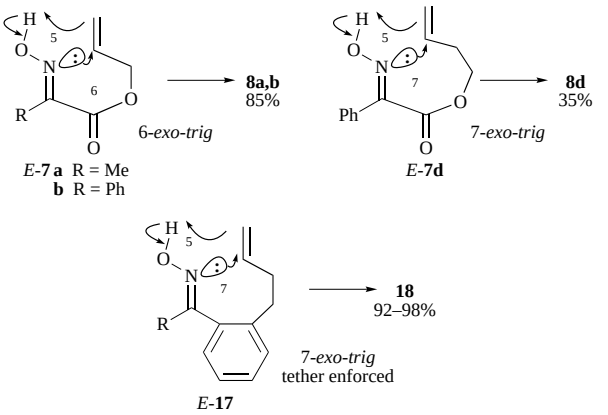
The oxime *E*-**17a** underwent quantitative conversion to the 6,7-bicyclic dipole **18a** following heating (14 h) in boiling xylene, *E*-**17b** reacted similarly giving **18b** after just 5 h heating. Clearly the incorporation of the aryl ring in the chain linking the oxime to the alkene significantly 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.

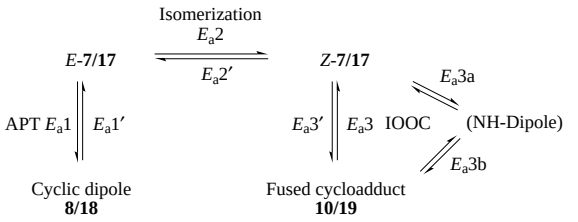
Conclusions

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 aldoximes 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. ^{1}H 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 cm^3) 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. $NaHCO_3$ (2 × 150 cm^3) and then H_2O (150 cm^3). The organic layer was collected, dried (Na_2SO_4) 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, OCH_2), 5.40 (m, 2H, CH=CH_2), 6.02 (m, 1H, C*H*=CH_2), 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 (OCH_2), 119.5 (CH=*C*H_2), 128.7 (2 × *m*-Ar-C), 129.7 (2 × *o*-Ar-C), 130.6 (*p*-Ar-C), 133.1 (Ar-C), 134.7 (*C*H=CH_2), 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-ol[17] (1.48 g, 13 mmol) and a catalytic amount of toluene-*p*-sulfonic acid were stirred in benzene (60 cm^3) 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. $NaHCO_3$ solution (2 × 100 cm^3) and then H_2O (100 cm^3). After drying (Na_2SO_4) 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=CH_2), 5.90 (m, 1H, C*H*=CH_2), 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 (*C*Me_3), 66.2 (OCH), 119.5 (CH=*C*H_2), 130.0–128.8 (4 × Ar-C), 134.8 (*C*H=CH_2), 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 cm^3) 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. $NaHCO_3$ (2 × 100 cm^3) and then H_2O (2 × 100 cm^3). The organic layer was collected, dried (Na_2SO_4) 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, OCH_2CH_2), 4.38 (t, 2H, OCH_2), 5.08 (m, 2H, CH=CH_2), 5.77 (m, 1H, C*H*=CH_2), 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 (OCH_2CH_2), 64.7 (OCH_2), 117.5 (CH=*C*H_2), 128.5 (2 × *m*-Ar-C), 129.6 (2 × *o*-Ar-C), 132.9 (*p*-Ar-C), 134.5 (Ar-C), 134.6 (*C*H=CH_2), 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 procedure[18] 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 H_2O (50 cm^3) at 70 °C for 14 h. The reaction mixture was allowed to cool to room temp., and extracted with CH_2Cl_2 (2 × 50 cm^3). The organic layers were combined, washed with H_2O (2 × 50 cm^3), dried (Na_2SO_4) and concentrated to yield the crude products as a yellow gum. Separation by flash chromatography (Et_2O : 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, OCH_2), 5.35 (m, 2H, CH=CH_2), 6.00 (m, 1H, C*H*=CH_2), 7.39 (m, 3H, Ar-H), 7.57 (m, 2H, 2 × *o*-Ar-H), 8.64 (br s, 1H, OH); δ_C 66.4 (OCH_2) 119.6 (CH=*C*H_2), 126.4 (*m*-Ar-C), 128.8 (*o*-Ar-C), 130.5 (*p*-Ar-C), 130.9 (Ar-C), 131.0 (*C*H=CH_2), 149.6 (C=N), 163.4 (C=O). *E*-**7b**: δ_H 4.77 (d, 2H, OCH_2), 5.29 (m, 2H, CH=CH_2), 5.93 (m, 1H, C*H*=CH_2), 7.44 (m, 3H, Ar-H), 7.52 (m, 2H, 2 × *o*-Ar-H), 10.22 (br s, 1H, OH); δ_C 66.6 (OCH_2), 119.4 (CH=*C*H_2), 127.8 (*m*-Ar-C), 128.1 (*o*-Ar-C), 128.6 (*p*-Ar-C), 129.9 (Ar-C), 131.4 (*C*H=CH_2), 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 H_2O (60 cm^3) at 65 °C for 25 h. The reaction mixture was allowed to cool to room temp., before extracting with CH_2Cl_2 (4 × 80 cm^3). The organic layers were combined, washed with water (50 cm^3), dried (Na_2SO_4) and concentrated to yield the crude products as a colourless gum. Purification by flash chromatography (Et_2O : 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, OC*H*, *J* 6.59), 5.59 (m, 1H, C*H*=CH_2), 5.89 (d, 2H, CH=CH_2, *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 (*C*Me_3), 67.0 (OCH), 118.0 (CH=*C*H_2), 130.2–126.6 (4 × Ar-C), 130.5 (*C*H=CH_2), 148.7 (C=N), 163.5 (C=O). *E*-**7c**: δ_H 0.97 (s, 9H, 3 × Me), 4.70 (d, 1H, OC*H*, *J* 6.59), 5.52 (m, 1H, C*H*=CH_2), 5.81 (d, 2H, CH=CH_2, *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 (*C*Me_3), 67.3 (OCH), 118.0 (CH=*C*H_2), 129.9–128.1 (4 × Ar-C), 130.1 (*C*H=CH_2), 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 H_2O (250 cm^3) at 90 °C for 13 h. The reaction mixture was allowed to cool to room temp., and was then extracted with CH_2Cl_2 (3 × 200 cm^3). The organic layers were combined, washed with H_2O (2 × 150 cm^3), dried (Na_2SO_4) and concentrated to yield the crude products as a yellow gum, separation by flash chromatography (Et_2O : 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, OCH_2CH_2), 4.45 (t, 2H, OCH_2), 5.12 (m, 2H, CH=CH_2), 5.82 (m, 1H, C*H*=CH_2), 7.40 (m, 3H, Ar-H), 7.57 (m, 2H, 2 × *o*-Ar-H), 9.30 (br s, 1H, OH); δ_C 32.9 (OCH_2CH_2), 65.1 (OCH_2), 117.8 (CH=*C*H_2), 126.5 (*m*-Ar-C), 128.8 (*o*-Ar-C), 129.3 (*p*-Ar-C), 130.5 (Ar-C), 133.4 (*C*H=CH_2), 151.7 (C=N), 163.7 (C=O). *E*-**7d**: δ_H 2.41 (m, 2H, OCH_2CH_2), 4.30 (t, 2H, OCH_2), 5.05 (m, 2H, CH=CH_2), 5.75 (m, 1H, C*H*=CH_2), 7.42 (m, 3H, Ar-H), 7.5 (m, 2H, 2 × *o*-Ar-H), 10.1 (br s, 1H, OH); δ_C 32.8 (OCH_2CH_2), 65.1 (OCH_2), 117.7 (CH=*C*H_2), 128.0 (*m*-Ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 129.8 (Ar-C), 133.5 (*C*H=CH_2), 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 cm^3) 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 $CHCl_3$ (3 cm^3) and allowed to stand at room temp. (0.5 h), the precipitated hydroquinone was removed *in vacuo*, and the filtrate was concentrated under reduced pressure. Purification of the crude products by flash chromatography (Et_2O : 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, Et_2O–hexane, mp 128–130 °C) and **9a(ii)** (0.10 g, 4%, colourless cubic crystals, Et_2O–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, Me^7, *J* 6.60), 1.61 (s, 3H, Me^{3a}), 2.12 (s, 3H, Me′), 2.52 (m, 2H, H^{3A} and H^{3B}), 3.21 (m, 1H, H^7), 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, H^2 and $OCH^{2'}$), 9.70 (br s, 1H, OH); δ_C 10.6 (Me^7), 14.4 (Me^{3a}), 25.5 (Me′), 41.4 (C^3), 55.6 (C^7), 65.0 ($OCH^{2'}$), 69.1 (C^6), 70.1 (C^{3a}), 76.5 (C^2), 149.6 (C=N), 163.5 (C=O, ester), 171.6 (C_4, C=O) (Found: C, 50.64; H, 5.99; N, 9.61. $C_{12}H_{18}N_2O_6$ requires C, 50.35; H, 6.29; N, 9.79%). **9a(ii)**: δ_H 1.23 (d, 3H, Me^7, *J* 6.59), 1.64 (s, 3H, Me^{3a}), 2.12 (s, 3H, Me′), 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, H^7), 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, H^2 and $OCH^{2'}$), 9.98 (br s, 1H, OH); δ_C 10.70 (Me^7), 14.5 (Me^{3a}), 29.8 (Me′), 43.3 (C^3), 52.6 (C^7), 65.3 ($OCH^{2'}$), 69.6 (C^6), 69.7 (C^{3a}), 73.8 (C^2), 149.1 (C=N), 163.5 (C=O), 172.4 (C^4, C=O) (Found: C, 50.40; H, 6.40; N, 9.52. $C_{12}H_{18}N_2O_6$ requires C, 50.35; H, 6.29; N, 9.79%). **8a**: δ_H 1.58 (d, 3H, Me^5, *J* 6.78), 2.23 (s, 3H, Me^3), 4.19 (m, 1H, H^5), 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 (Me^5), 14.4 (Me^3), 62.9 (C^5), 67.1 (C^6), 135.1 (C^3, C=N), 159.2 (C^2, 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 H_2O (90 cm^3) at 100 °C was stirred for 48 h. The reaction mixture was cooled to room temp., and was extracted with CH_2Cl_2 (4 × 100 cm^3). The organic layers were combined, dried (Na_2SO_4) and concentrated to give a yellow solid (0.65 g, 20%), which was purified by flash chromatography (Et_2O) 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 (C^4), 69.4 (C^3), 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 cm^3) 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 $CHCl_3$ (3 cm^3) 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 (Et_2O : 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, H^7), 4.35 (m, 2H, $H^{1'A}$ and $H^{1'B}$), 4.80 and 4.73 (2 × dd, 2 × 1H, H^{6A} and H^{6B}), 4.95 (m, 1H, H^2), 8.73–7.19 (2 × m, 10H, Ar-H),

10.15 (br s, 1H, OH); δ_C 15.9 (Me), 45.8 (C^3), 56.6 (C^7), 65.5 ($OCH^{2'}$), 68.6 (C^6), 74.3 (C^{3a}), 74.6 (C^2), 140.0–126.2 (8 × Ar-C), 149.5 (C=N), 162.9 (C_4, C=O), 171.1 (C=O, ester) (Found: C, 64.56; H, 5.39; N, 6.49. $C_{22}H_{22}N_2O_6$ requires C, 64.39; H, 5.35; N, 6.78%). **8b**: δ_H 1.66 (d, 3H, Me^5), 4.33 (m, 2H, H^{6B} and H^5), 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 (C^5), 66.9 (C^6), 134.5–127.5 (4 × Ar-C), 136.2 (C^3, C=N), 158.9 (C^2, C=O).

(3a*S,6a*S**)-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 cm^3) 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 $CHCl_3$ (2.5 cm^3) 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 (Et_2O : 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 H, $J_{3B,3a}$ 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 (C^4), 75.2 (C^3), 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 H_2O (120 cm^3) at 100 °C for 18 h. The reaction mixture was allowed to cool to room temp. and the aqueous solution was extracted with CH_2Cl_2 (4 × 100 cm^3). The organic layers were combined, dried (Na_2SO_4) 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 (Et_2O : 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 (Et_2O–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 cm^3) 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 $CHCl_3$ (2 cm^3) 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 (Et_2O : 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, H^4, $J_{4,3a}$ 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 (CMe_3), 34.7 (CMe_3), 53.6 (C^{6a}), 69.4 (C^3), 96.6 (C^4), 134.7–126.4 (4 × Ar-C), 160.4 (C_6, C=O). NOEDS experimental results indicate *cis* stereochemistry at the ring junction, irradiation of H^{3a} caused a 3.7% enhancement on the *o*-ArH; H^{3a} and H^4 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, Me^5, *J* 7.33), 3.99 (s, 1H, H^6), 4.28 (q, 1H, H^5, *J* 7.33), 7.34 (m, 3H, *m*- and *p*-Ar-H), 7.59 (m, 2H, *o*-Ar-H); δ_C 20.5 (Me^5), 25.8 (CMe_3), 35.9 (CMe_3), 64.9 (C^5), 85.0 (C^6), 130.1–128.0 (4 × Ar-C), 158.1 (C=N), 162.4 (C^2, C=O). NOEDS experimental results indicate a *trans* relationship between the methyl group on C^5 and the Bu^t group on C^6; irradiation of H^5 causes a 9.3% enhancement on the Bu^t group and a 3.8% enhancement on Me^5; irradiation of H^6 causes a 3.3% enhancement on H^5, a 3.5% enhancement on Me^5 and a 5.4% enhancement on the Bu^t group.

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

A solution of the oxime *E*-**7d** (3.00 g, 13.70 mmol) in xylene (900 cm^3) 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 $CHCl_3$ (5 cm^3) 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 (Et_2O : 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 nitrone **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 $OCH_2CH^{2'}$), 2.20 (dd, 1H, H^{3B}, $J_{3B,3A}$ 12.82, $J_{3B,2}$ 8.80), 3.27 (m, 1H, H^8), 3.72 (dd, 1H, H^{3A}, $J_{3A,3B}$ 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, H^2, H^{6A} and $OCH_2CH^{2'}$), 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 (C^7 and $OCH_2CH^{2'}$), 50.4 (C^3), 53.6 (C^8), 62.5 ($OCH_2CH^{2'}$), 64.0 (C^6), 73.7 (C^{3a}), 82.8 (C^2), 140.9–125.2 (10 × Ar-C), 149.4 (C=N), 163.6 (C_4, C=O), 171.7 (C=O, ester) (Found: C, 65.99; H, 5.99; N, 6.21. $C_{24}H_{26}N_2O_6$ 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 $OCH_2CH^{2'}$), 2.16 (dd, 1H, H^{3B}, $J_{3B,3A}$ 13.19, $J_{3B,2}$ 8.06), 3.20 (m, 1H, H^8), 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, H^2), 4.28 (m, 3H, H^{6A}, $OCH_2CH^{2'}$, $J_{6A,6B}$ 12.46, $J_{6A,7A/7B}$ 8.80), 7.61–7.25 (3 × m, 10 × Ar-H and Ar′-H), 9.62 (br s, 1H, OH); δ_C 19.0 (Me), 36.9 and 32.5 (C^7 and $OCH_2CH^{2'}$), 53.8 (C^8), 50.4 (C^3), 63.1 ($OCH_2CH^{2'}$), 64.2 (C^6), 74.1 (C^{3a}), 83.1 (C^2), 141.2–125.6 (8 × Ar-C), 149.7 (C=N), 163.2 (C^4, C=O), 171.6 (C=O, ester) (Found: C, 65.76; H, 5.96; N, 6.10. $C_{24}H_{26}N_2O_6$ 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, H^5, 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 (C^7), 64.6 (C^8), 66.1 (C^6), 136.2–128.4 (4 × Ar-C, C^3 and C=N), 165.8 (C^2 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 cm^3) 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 H_2O (200 cm^3) and this aqueous solution was extracted with Et_2O (4 × 100 cm^3). The combined organic layers were

collected, dried ($MgSO_4$) 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, OCH_2), 5.35 (m, 2H, CH=CH_2), 6.06 (m, 1H, CH=CH_2), 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 (OCH_2), 112.9 (Ar-C), 118.2 (CH=CH_2), 120.8 (Ar-C), 128.8 (Ar-C), 130.4 (Ar-C), 132.7 (Ar-C), 133.5 (CH=CH_2), 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 cm^3) 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 H_2O (100 cm^3) and the resulting aqueous solution was extracted with Et_2O (4 × 75 cm^3). The organic layers were combined, dried ($MgSO_4$) 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, OCH_2), 5.05 (m, 2H, CH=CH_2), 5.72 (m, 1H, CH=CH_2), 7.0 (m, 2H, Ar-H), 7.49 (m, 5H, Ar-H), 7.84 (m, 2H, Ar-H); δ_C 68.9 (OCH_2), 112.7 (Ar-C), 116.9 (CH=CH_2), 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=CH_2), 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 cm^3) 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 CH_2Cl_2 (250 cm^3), washed with H_2O (5 × 200 cm^3) and dried (Na_2SO_4). 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, OCH_2), 5.25 (m, 2H, CH=CH_2), 5.95 (m, 1H, CH=CH_2), 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 (OCH_2), 117.3 (CH=CH_2), 133.5 (CH=CH_2), 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 cm^3) 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 CH_2Cl_2 (150 cm^3) and transferred to a separating funnel. The organic layer was washed with H_2O (5 × 100 cm^3), dried (Na_2SO_4) and concentrated to yield the isomeric oximes which were purified by flash chromatography (Et_2O : 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, OCH_2), 5.12 (m, 2H, CH=CH_2), 5.77 (m, 1H, CH=CH_2), 7.47–6.97 (5 × m, 9 × Ar-H), 9.54 (br s, 1H, OH); δ_C 69.1 (OCH_2), 112.9 (CH=CH_2), 135.8 (CH=CH_2), 156.0–116.7 (9 × Ar-C), 155.7 (C=N). *E*-**17b**: δ_H 4.29 (d, 2H, OCH_2), 5.05 (m, 2H, CH=CH_2), 5.60 (m, 1H, CH=CH_2), 7.53–6.83 (5 × m, 9 × Ar-H), 10.10 (br s, 1H, OH); δ_C 70.3 (OCH_2), 112.1 (CH=CH_2), 135.6 (CH=CH_2), 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 cm^3) 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, Me^3, J 5.86), 2.43 (s, 3H, Me^5), 4.56–4.40 (m, 3H, H^{2A}, H^{2B} and H^3), 7.32–7.02 (3 × m, 4H, Ar-H); δ_C 10.9 (Me^3), 17.4 (Me^5), 62.8 (C^2), 79.1 (C^3), 141.3–120.8 (6 × Ar-C), 154.0 (C^5, 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 cm^3) 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 (Et_2O : 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, H^3), 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 (C^2), 81.1 (C^3), 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 cm^3) 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 (Et_2O : 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 (C^3 and C^4), 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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