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# α-Oximono-esters as precursors to heterocycles – generation of oxazinone *N*-oxides and cycloaddition to alkene dipolarophiles

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Preparation of a series of terminally and internally substituted δ-alkenyl and δ-alkynyl esters **6**,**7** and **9**, potential precursors to oxazin-2-one nitrones, has been attempted. Condensation between pyruvic or benzoylformic acid and the appropriate alcohol proceeded smoothly in some cases whilst allylic transposition was a major feature in other cases – most especially during reactions with α-vinylbenzyl alcohol. Oximation of pyruvic acid derivatives furnished *E*-oxime isomers whilst benzoylformic acid derivatives afforded mixed geometrical isomers. The *E*-oxime of **4a**[1] carrying an internal Me group undergoes facile thermal cyclisation affording nitrones **1c** and **1d** in good yield. Oximes *E*-**5a**,**b** with a terminal methyl substituent on the alkene moiety furnish nitrone only under the influence of an external electrophile [PhSeBr/$AgBF_4$]. A terminal Ph substituent on **5c**,**d** prohibits formation of the cyclic dipole irrespective of reaction conditions, and whilst **5d** reacts to afford a bicyclic isoxazolofuranone **13** by an IOOC reaction (intramolecular oxime olefin cyclisation) **5c** remains thermally inert. Finally δ-alkynyl oximes **9c**,**d** also failed to cyclise. The regio- and stereochemical characteristics of the cycloadditions between the new dipoles and electron poor olefinic dipolarophiles have been investigated. The conditions needed for reaction were rather forcing since the dipoles are somewhat stabilised by the adjacent alkoxycarbonyl group. All reactions proceeded regiospecifically to give adducts with 5-substituted isoxazolidine rings whilst diastereoselectivity varied with the choice of dipolarophile and the steric demands of the nitrone substituents. The phenylselenyl dipole **10a** could not be trapped by any dipolarophiles bar dimethyl acetylenedicarboxylate.

## Introduction

Intermolecular cycloaddition to nitrones is attractive for the construction of *N*-containing compounds and indeed nitrones have played an important role in the synthesis of various classes of drugs. Both the primary adducts – isoxazolidines/$\Delta^4$-isoxazolines and their derivatives have potential for biological interest. We have recently reported the preparation of α-alkoxycarbonyl nitrones **1a**,**b** from cyclisation of *E*-oximino esters **2a**,**b**, the propensity with which the new dipoles cycloadd to acetylenic dipolarophiles and the tendency of the primary cycloadducts to rearrange to pyrrolo-fused bicycles.[1,2] In order to test the tolerance of the oxime substrate to structural diversity we have since prepared analogous oximino-amides **2c**–**e** and found them to cyclise to the piperazinone nitrones **3**.[3] To further explore the generality of the reaction we aimed to prepare nitrones substituted at C-2 and bearing a group, other than methyl, at the C-3 position. We now report our findings on the preparation the targeted oximes **4** and **5**, and on novel cycloaddition reactions of the dipoles **1** and **10** with monosubstituted alkenes.

## Results and discussion

### Substrate preparation

Nitrones **1a** and **1b**, without a substituent at the C-2 position were prepared following thermal activation of the *E*-isomer of the parent oximes, **2a**,**b** as reported earlier.[2] To introduce a group at the C-2 position of the nitrone it is necessary to prepare oximes of general structure **4** bearing a substituent at the allylic position. If the group at the nitrone C-3 position is to be other than methyl, then oximes of general structure **5**, terminally substituted on the alkene moiety are required. Accordingly pyruvic acid and benzoylformic acid were reacted in turn with 3-buten-2-ol, α-vinylbenzyl alcohol, 2-buten-1-ol (crotyl alcohol) and cinnamyl alcohol.

We have already reported that pyruvic acid and 3-buten-2-ol condense upon heating in boiling benzene in the presence of a catalytic amount of *p*-TsOH (Dean–Stark trap) to provide **6a** in 80% yield.[1] In contrast, under the same experimental conditions benzoylformic acid reacted with this branched alcohol to furnish, as an inseparable mixture, the terminally substituted product **7b** (23%) together with the expected ester **6b** (59%). Thermal, Lewis acid or transition metal catalysed [3,3]-sigmatropic rearrangement of allylic esters is well known. For example, treatment of either 1-but-2-enyl acetate or 2-but-3-enyl acetate with 5 mol% $Pd(PPh_3)_4$ in $CDCl_3$ lead, after just 1 h, to a 58 : 42 equilibrium mixture in favour of the linear isomer.[4] Allylic esters have also been shown to isomerise upon standing in $CHCl_3$ in the presence of an acid catalyst, rearrangement is slow at rt but fast at elevated temperatures, it can also be effected by exposure to $SiO_2$ or alumina.[5,6] Thus, it is likely that **7b** arises from **6b** by way of an allylic transposition. Indeed we observe a significant change in the ratio of **6b** : **7b**, from ~2.5 : 1 to ~1 : 1, when a neat sample was re-examined following standing for 5 months at rt. Heating this equimolar solution of **6b** and **7b** in refluxing benzene (6 h) caused a further drift towards the terminally substituted isomer [**6b** : **7b** 1 : 1.1]. However, in the presence of a catalytic amount of *p*-TsOH the degree of isomerisation is more significant and after 6 h the isomeric ratio has changed to 1 : 1.3 in favour of **7b**.

Reaction between α-vinylbenzyl alcohol and either of pyruvic acid or benzoylformic acid failed to furnish the targeted ester **6c/6d** with an allylic phenyl substituent, instead the products were the terminally substituted α-keto esters **7c** (31%) and **7d** (37%). A second product accompaning the ester in the case of **7c** was shown by independent experimentation to be dicinnamyl ether **8**. Dicinnamyl ether is known in the literature having been characterised by Frimer[7] following reaction of cinnamyl bromide with superoxide. We have demonstrated that α-vinylbenzyl alcohol is stable upon heating alone in boiling

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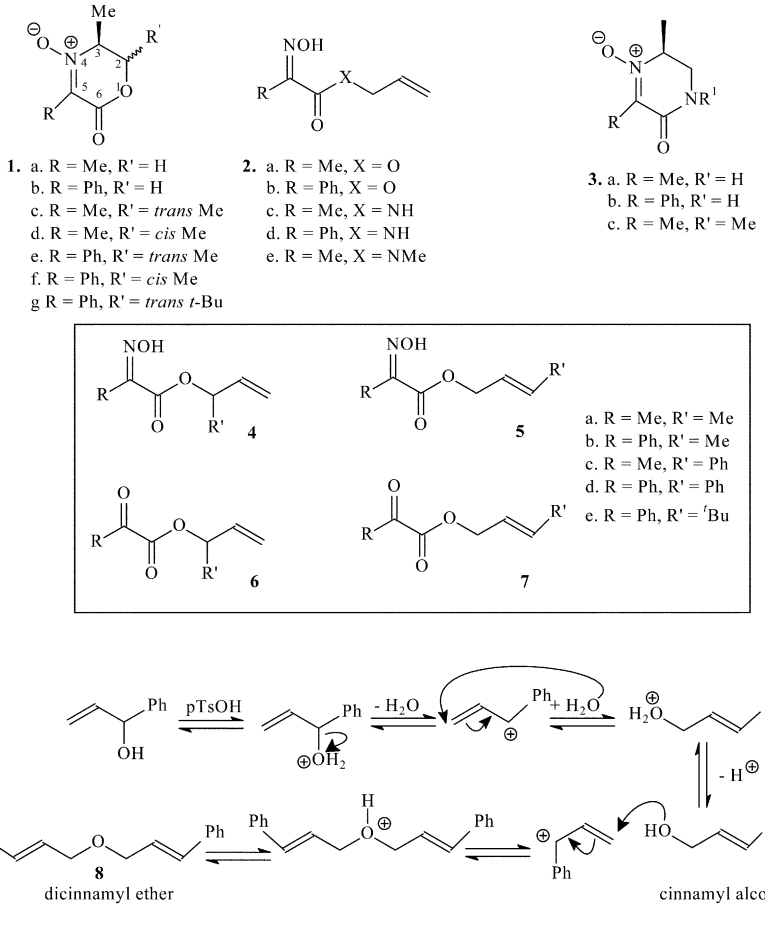



**Scheme 1**

benzene (75 min), however, in the presence of *p*-TsOH, (cat.) dicinnamyl ether is isolated as the only identifiable product (26%). We propose the ether arises by way of an acid catalysed rearrangement of α-vinylbenzyl alcohol leading to cinnamyl alcohol, attack of this alcohol on the resonance stabilised cation and deprotonation affords dicinnamyl ether as summarised in Scheme 1. If this mechanism is indeed operating then reaction of the α-keto acids with "α-vinylbenzyl alcohol" may afford the terminally substituted allylic esters **7c/7d** by either or both of the following mechanisms: (i) a condensation between the reactants followed by an allylic rearrangement of the primary ester **6c/6d** or (ii) an initial rearrangement of α-vinylbenzyl alcohol to cinnamyl alcohol followed by condensation to give **7c/7d** directly. The latter proposition is disfavoured on two grounds. Firstly, a search of the chemical literature indicates that there are no reports of simple thermal isomerisation of cinnamyl alcohols to vinylbenzyl alcohols or *vice versa*, however, Crilly and co-workers do report an indirect isomerisation of the *m*-chloro derivative of vinylbenzyl alcohol to *m*-chlorocinnamyl alcohol by way of a Pd(II) catalysed isomerisation of the corresponding acetate.[8] Secondly when pyruvic acid and cinnamyl alcohol were combined directly (*p*-TsOH, $C_6H_6$, Dean–Stark) a mixture resulted from which the ester **7c** could be isolated in only 3% yield.

Reaction between pyruvic acid and 2-buten-1-ol furnished the desired ester **7a** in 93% yield. The same alcohol reacted with benzylformic acid to yield inseparable isomeric esters with the methyl substituent at the terminal **7b** (72%) and the internal position **6b** (9%). Condensation between propargyl alcohol and the α-ketoacids provided the alkynic esters **9a**,**b** in moderate yield with no side products.

It is apparent that esters **6a** and **7a**, derived from pyruvic acid in reaction with either of the butenols, are thermally stable whilst the corresponding esters, **6b** and **7b**, derived from benzoylformic acid, are both subject to skeletal rearrangement. In attaining the transition state [Fig. 1] for sigmatropic rearrangement the esters **6** and **7** lose their O=C–C=O conjugative stabilisation. This loss is more significant for the methyl derivatives than for the phenyl derivatives where Ph–C=O conjugation is possible. Hence the activation energy for rearrangement of the phenyl substituted substrates **6b/7b** is expected to be lower than that for their methyl analogues **6a/7a**.

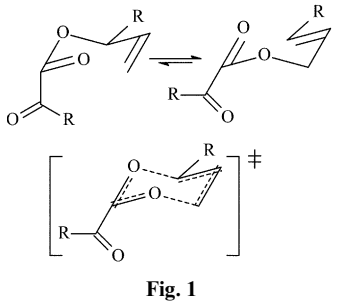
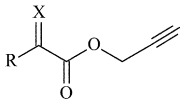


**Fig. 1**

The α-keto esters **6a** and **7a**, bearing an allylic or terminal methyl substitutent respectively, reacted smoothly with $NH_2OH$ furnishing the corresponding oximes *E*-**4a**[1] (90%) and *E*-**5a** (80%) in each case as a single geometrical isomer. The esters **6b** and **7b** were available as impure samples (each carrying the other as a contaminant), in each case following oximation, [$NH_2OH{\cdot}HCl$, pyridine, EtOH, rt] purification of the product mixture was successful only in that it delivered separate samples of *E*-**4b**/*E*-**5b** as well as *Z*-**4b**/*Z*-**5b**. For each reaction the ratio of the oximes **4b**:**5b** reflected that of the starting esters **6b**:**7b**, thus no skeletal rearrangement occurred during oxime formation. The esters **7c** and **7d**, with a terminal phenyl substituent, oximated smoothly and *E*-**5c** was isolated in 44% yield as a single isomer whilst **5d** formed as a mixture of geometrical isomers, *E*-**5d** (29%) and *Z*-**5d** (41%). The terminal alkyne

functionality on **9a**,**b** did not interfere with oxime formation and *E*-**9c** (68%), was formed from **9a** whilst *E*-**9d** (86%) and *Z*-**9d** (13%) resulted from reaction of **9b**.



**9.** a. R = Me, X = O
b. R = Ph, X = O
c. R = Me, X = NOH
d. R = Ph, X = NOH

It is reported in the literature that α-oxo-oximes should have s-*trans*-conformation about both the O=C–C=N moiety and the oximino functionality,[9,10] thus, the observation that the pyruvic acid derivatives **4a**, **5a** and **5c** are stereochemically pure oximes with *E*-configuration is as expected. That both *E*- and *Z*-oximes arise from benzoylformic acid suggests the steric and electronic factors promoting the *E*- over the *Z*-isomer are more finely balanced in the case of **4b**,**5b** and **5d**. Cerfontain[9] has found that *E*-α-oxo-oxime derivatives having a phenyl group on the iminyl carbon experience a steric clash between the aryl ring and the oxime oxygen atom which forces the phenyl ring to be out of conjugation with the C=N whilst the C=N–C=O groups are fully conjugated. In contrast no steric clash operates to prevent a co-planar arrangement of the phenyl and the imine groups of the *Z*-isomers of the same oxime (prepared from the *E*-isomer by photoisomerisation), however, there is reduced conjugation between C=O and C=N. The oximes **4** and **5** are α-ester-oximes accordingly the stabilisation derived from C=N–C(O)=O conjugation is less significant than that afforded to Cerfontain's α-oxo analogues and evidently it is the case that planarity of the phenyl and C=N groups (available to the *Z*-isomer only) is a good compromise for the full conjugation of the C=N–C(O)=O moieties (available to the *E*-isomer only) thus both *E*- and *Z*-isomers of the C-phenyl α-ester-oximes **4b**,**5b** and **5d** result.

### Oxime reactivity

We have already reported that *E*-**4a** cyclises by an APT[11] (azaprotio cyclotransfer) reaction to a mixture of diastereomeric nitrones **1c** (50%) and **1d** (10%) upon heating in boiling xylene,[1] the major isomer has the C-2 and C-3 methyl groups *trans* orientated. *E*-**5a** with a terminal methyl group is isomeric with *E*-**4a** yet it failed to cyclise upon heating in boiling xylene. This lack of reactivity can be attributed to a more crowded transition state for the APT reaction. The effect of increasing pressure on the reactivity of organic substrates is well recognised[12] and to this end *E*-**5a** was heated in toluene in a sealed tube. As a control experiment **2a**, which cyclises to **1a** upon heating in boiling xylene (30 h) at atmospheric pressure, was heated in toluene at 210 °C. After 16 h the reaction mixture comprised a 2 : 1 mixture of nitrone and unreacted oxime. However, the terminally substituted oxime *E*-**5a** failed to react under these conditions. In a further effort to facilitate cyclisation the electrophile induced approach pioneered by Grigg[13] and others[14–17] was exploited. $I_2$, NBS, $AgBF_4$, PhSeCl, PhSeBr and $Ph_2Se_2$ have all been reported in the literature as activators of electron rich double bonds/allenes towards intramolecular attack by oximes. Of this selection only PhSeBr afforded any promise of reactivity with the substrate, *E*-**5a** however, the complexity of the reaction mixture precluded isolation of any pure products. When PhSeBr was paired with $AgBF_4$ reaction was more selective and the nitrone **10a** was isolated in 67% yield.

The *C*-phenyl oximes *E*-**4b** and *Z*-**4b** responded quite differently to thermal activation. Thus, *Z*-**4b**, taken together with *Z*-**5b** as a 25% contaminant, yielded a complex mixture of products following heating in boiling xylene. Independent experimentation showed *Z*-**5b** to be stable to thermal activation, thus, all new products are attributed to reactivity of *Z*-**4b**. Separation of the crude mixture after heating for 30 h (140 °C) returned unreacted *Z*-**5b** and provided evidence for formation of two diastereomeric nitrones **1e** (19%) and **1f** (3%) and three diastereomeric bicyclic isoxazolofuranones of general structure **11a** (11%, 20% and 17%). Whilst it was not possible to obtain analytically pure samples of any of these new products $^1$H NMR spectral data clearly supports their existence. Further, based on a comparison of the $^1$H NMR resonance positions of the 2-H and C-2 & C-3 methyl protons for the diastereomers of **1e** with **1c** [2-H, 4.45 ppm] and **1d** [2-H, 4.82 ppm][1] it can be concluded that the major nitrone **1e** has, as expected, the C-2 and C-3 methyl groups *trans*-disposed, this arrangement results in the 2-H proton resonating ~0.4 ppm upfield of the corresponding proton in its diastereomeric nitrone. The C-2 and C-3 methyl protons in the *trans*-isomers, **1c** and **1e**, have a more downfield shift than the analogous protons on the *cis*-isomers **1d** and **1f**. It is somewhat surprising that *Z*-**4b** reacts without selectivity since, under the same reaction conditions, its unsubstituted partner *Z*-**2b** furnishes the isoxazolofuranone **12** exclusively. It is apparent that the allylic methyl group on **4b** influences the relative activation energies for the steps involved in oxime isomerisation, the IOOC reaction and the APT reaction such that all paths of reactivity become possible [Fig. 2].

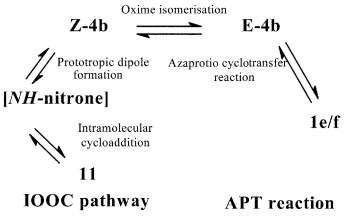
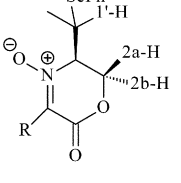



**Fig. 2**

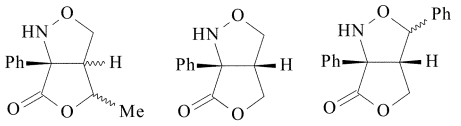
The oxime *E*-**5b** has a terminal methyl susbtituent and as observed with *E*-**5a** this substituent effectively blocks a thermally induced APT reaction. However, the phenylselenyl substituted nitrone **10b** was obtained in 57% yield under the combined influence of PhSeBr and $AgBF_4$. The solution conformation adopted by the oxazinone ring in nitrones **10** is such that in the $^1$H NMR spectrum of **10a** and **10b** ($CDCl_3$) both the methylenic protons couple weakly to the 3-H proton, with 2a-H appearing as a slightly broad doublet whilst 2b-H is observed as a doublet of doublets [$J$ ~ 12 & 3 Hz].




**10.** a. R = Me
b. R = Ph

The oximes **5c** and **5d** both have a terminal Ph substituent, **5c** was obtained solely as the *E*-isomer and it failed to react following heating or activation with PhSeBr/$AgBF_4$. Oxime **5d** is the only oxime bearing a terminally substituted alkene moiety which showed reactivity under simple thermal conditions. Following heating a solution of either *E*-**5d** or *Z*-**5d** in boiling xylene the isoxazolofuranone **13** was the only isolable product, yields varied with *E*-**5d** furnishing **13** in 36% yield and *Z*-**5d** yielding **13** in 74% yield. Oxime **2b**, the terminally unsubstituted analogue of **5d** shows configurational stability with its *E*-isomer cyclising to nitrone **1b** and, as reported above, its *Z*-isomer participating in the IOOC reaction leading to the bicycle **12**. The $^1$H NMR spectral data of **13** showed broad

resonance signals for the protons attached to the bicyclic ring. Spectra recorded over the range −60 °C to +50 °C indicate a persistence in conformational mobility at the lower temperatures and a failure to reach coalescence at +50 °C.



**11** **12** **13**

We offer a three-pronged explanation for the observed difference in reactivity of **5d** with that of **5b** and **5c**. The arguments centre around the enhanced dipolarophilic power of an alkene bearing a terminal phenyl [as in **5c** and **5d**] over a terminal methyl substituent [as in **5a** and **5b**] – indeed styrene is recognised as a superior dipolarophile to propene.[18] The second consideration is the ease with which geometrical oxime isomers may interconvert. Isomerisation may occur by one of two modes (i) in-plane inversion or (ii) out-of-plane rotation.[19] Delocalisation of electron density from the aryl ring to the oxime C=N bond may decrease the double bond character of the later so facilitating the isomerisation of the *C*-phenyl oximes **5b** and **5d** by out-of-plane rotation. The final considerations takes cognizance of the energetics of the steps involved in the IOOC reaction which has two distinct steps, prototropic dipole formation and intramolecular dipolar cycloaddition. Given that oximes exist with a small equilibrium concentration of the corresponding *NH* nitrone[20,21] the rate determining step in the formation of isoxazolofuranones should be the cycloaddition step.

Thus, *E*-**5b** fails to undergo a thermally induced APT reaction since the terminal alkene substituent raises the activation energy for cyclisation to nitrone and yet whilst *E*-/*Z*-oxime isomerisation is likely a viable option for the *C*-phenyl substrate no products result from the IOOC reaction as the RCH=CHMe is not a sufficiently reactive dipolarophilic moiety, indeed *Z*-**5b** is independently shown to be unreactive.

That *E*-**5c** is immune to thermal treatment is in keeping with the failure of terminally substituted derivatives to undergo APT reaction. That no IOOC products result – even though this substrate carries a "good" dipolarophilic unit (RCH=CHPh) suggests a prohibitively higher barrier to *E*-/*Z*-oxime isomerisation for the pyruvic acid derivative.

The apparent ease with which *E*-/*Z*-**5d** participate in a thermal IOOC reaction is explained on the basis that (i) the APT reaction is unfavourable due to the presence of the terminal alkene substituent (ii) *E*-/*Z*-oxime isomerisation is facile for benzoylformic acid derivatives and (iii) this substrate has a good internal dipole trap (*viz*. RCH=CHPh).

The oxime **9c** with a terminal alkyne functionality failed to cyclise under simple thermal conditions or upon heating in a sealed tube (toluene, 210 °C, 9.5 h). Nitrone formation by intramolecular attack of oximes[11] or hydroxylamines[22] onto triple bonds is known, however **9c** was returned unchanged following treatment with $AgBF_4$ ($CH_2Cl_2$, rt or reflux).

### Cycloaddition reactions

The electron withdrawing effect of the α-alkoxycarbonyl group suggested that the dipoles **1** may participate in inverse electron demand cycloaddition reactions and indeed Katagiri has successfully trapped related 5-membered dipoles with electron rich dipolarophiles albeit under the influence of high reaction pressure or Lewis acid catalysis, Fig. 3(a).[23] It has also been reported recently[24,25] that analogous six-membered nitrones, with a C-3 phenyl group and C-5 unsubstituted, can be trapped under mild reaction conditions by dipolarophiles, *e.g.* ethyl vinyl ether, Fig. 3(b). In all cases the selectivity of the cycloaddition is attributed to a transition state involving the least sterically

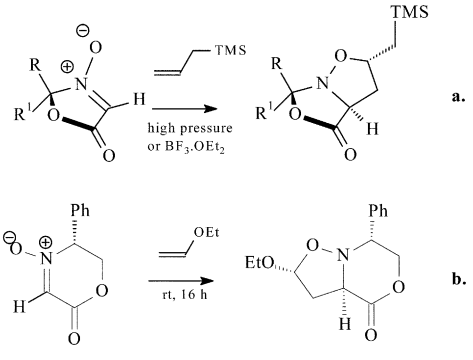



**Fig. 3**

demanding *exo*-approach. The same dipoles failed to react with *N*-methyl maleimide suggesting the cycloadditions to be LUMO nitrone controlled.[24]

Under thermal activation, both **1a** and **1b** failed to react with any of ethyl vinyl ether, methoxypropene, cyclohexene or norbornylene. Thus, the electronic and steric factors permitting cycloaddition to the electron rich dipolarophiles must be so finely balanced that the steric bulk of C-5 methyl/phenyl substituent on nitrones **1a/b** is sufficient to prevent reaction taking place. Cycloaddition also failed with either *N*-methyl or *N*-phenyl maleimide, in contrast styrene and acyclic monosubstituited electron poor alkenes made good traps for these dipoles.

The nitrones **1a** and **1b** cycloadded to styrene following heating with a large excess of the dipolarophile. For each dipole, regiospecific formation of a 5-substituted isoxazolidine unit resulted and the 2-H proton in each adduct resonated as a doublet of doublets close to 5 ppm. Reaction with the methyl substituted dipole was complete after 5.5 h and **14a** was furnished as a single diastereomer, analysis of NOEDS data indicates **14a** results from a transition state involving an *exo*-addition of the dipolarophile to the face of the dipole opposite the C-3 methyl group – designated the α-face, Fig. 4. The phenyl substituted dipole **1b** reacted selectively to afford, after 8 h heating, the *exo*-adduct **14b** (86%); the minor adduct **15** (8%) was obtained as an enriched mixture, its relative stereochemistry could not be assigned using the NOEDS approach as the protons of the C-2 and the C-3a phenyl groups are coincident. The strong preference for an *exo*-addition of styrene to cyclic nitrones is expected.[26,27]

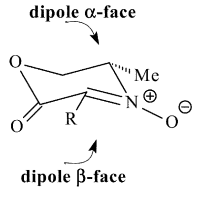
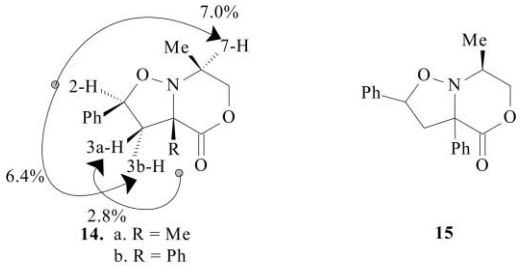



**Fig. 4**




**14.** a. R = Me
b. R = Ph

NOEDS results shown for **14a**

**15**

Reaction between phenyl vinyl sulfone and the dipoles **1a**–**d** proceeded with high regio- and stereoselectivity, in each case only a single diastereomeric cycloadduct, **16a**–**d**, was isolated. The product yield varied with the substitution pattern on the

**Table 1** Reaction between nitrones **1** and phenyl vinyl sulfone

| | Nitrone | Solvent | Temperature | Time/h | Product (%) | Returned nitrone (%) |
|---|---|---|---|---|---|---|
| | **1a** | Xylene | 140 °C | 36 | **16a** (85) | 8 |
| | **1b** | Xylene | 140 °C | 42 | **16b** (44) | 48 |
| | **1c** | Toluene | 110 °C | 72 | **16c** (30) | 60 |
| | **1d** | Toluene | 110 °C | 192 | **16d** (29) | 56 |

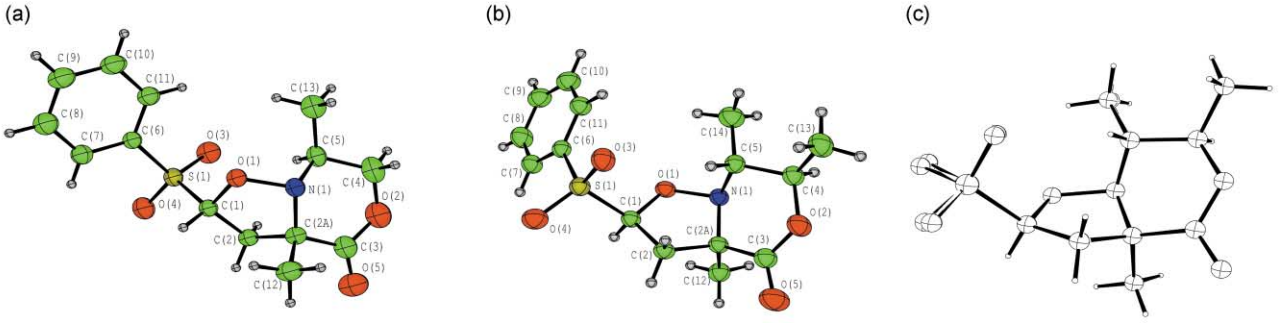



**Fig. 5**

dipole (Table 1). The enhanced conjugation of the aryl substituted dipole **1b** with respect to its methyl analogue **1a** accounts for its reduced reactivity[28] and the sluggish reactivity of **1c** and **1d**, with their additional site of substitution is likely due to the increased steric demands of these dipoles.

Characterisation of the cycloadducts **16** as having 5-substituted isoxazolidine rings rests with the appearance in the $^1$H NMR spectrum of the 2-H proton as doublets of doublets, $\delta$ 4.71 to 5.05.[29] That all four adducts share the same relative stereochemistry is known from analysis of NOEDS data as well as X-ray crystallographic analysis.[30–33] The OSCAIL representation of **16a** and **16c**, crystallised from benzene and $Et_2O$–petroleum ether respectively, are shown in Figs 5a and 5b. The crystallographic data for **16a** reveals that five of the atoms in the oxazinone ring (*N*-1, *C*-1, *C*-2, *O*-2 *C*-3) approximate a plane, *C*-1 has the greatest deviation from this plane (0.055 Å) and *C*-4 lies out of the plane by 0.692 Å. The dihedral angle for *H*-4a *C*-4 *C*-5 *H*-5 is 177.8° and for *H*-4b *C*-4 *C*-5 *H*-5 (crystal numbering) is 60.5°, inspection the $^1$H NMR spectrum of the same adduct shows the magnitude of $J_{6b,7}$ (11 Hz) and $J_{6a,7}$ (3.3 Hz) (structure numbering) to be in good agreement with that predicted by the Karplus curve[34]. That the bicyclic framework of **16c** has the same solid state conformational preference can be clearly seen from Fig. 5c which shows a fit of the two structures based on the atoms of the isoxazolidine ring and the peripheral sulfur atom; the mean error on fitting the six pairs of atoms pairs is 0.0199 Å. The data for **16a** reveals that there are two molecules in each asymmetric unit and these are held together by two weak C-H···O(4) H-bonds to a molecule of benzene of crystallization [Fig. 6]; the interatomic H···O(4) distance is 2.648 Å and the C–H···O(4) angle is 98.02° (crystal numbering) (Tables 2 and 3). The relative stereochemistry of **16b** could not be assigned from NOEDS studies as unambiguous discrimination between the $SO_2Ph$ and the 3a aryl protons was not possible. On the other hand, the structure of **16d** was readily available from NOEDS studies, pertinent results are summarised in the drawing. The relative configuration of **16a–d** indicates cycloaddition occurred by way of an *endo*-addition of phenyl vinyl sulfone to the α-face of the nitrone. The *endo*-preference is as may be expected on the basis of secondary orbital considerations.

The *C*-methyl nitrone **1a** reacts with methyl vinyl ketone in boiling xylene (140 °C) to furnish four diastereomers **17a–d** in 38, 12, 10 and 5% yield respectively. Repeating the reaction in toluene (110 °C) saw an improvement in selectivity and **17a** (68%) and **17b** (10%) were the only isolable adducts. An examination of the $^1$H NMR spectral data of **17** indicates that for

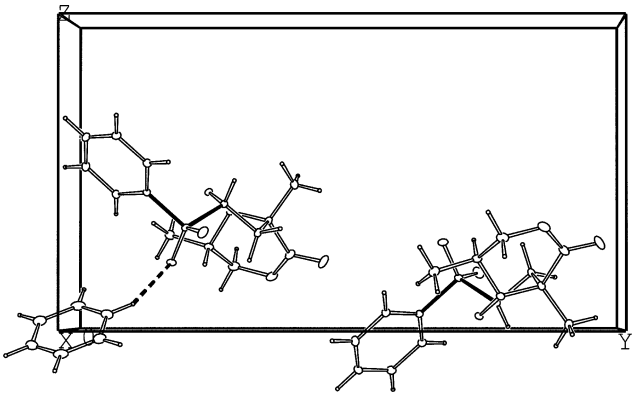
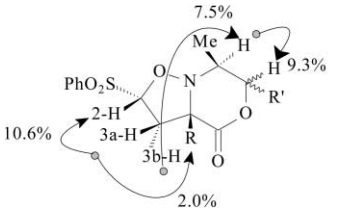


**Fig. 6**




**16.** a. R = Me, R' = H
b. R = Ph, R' = H
c. R = Me, R' = *trans* Me
d. R = Me, R' = *cis* Me

NOEDS results shown for **16d**

**17c** and **17d** the 6b-H is significantly deshielded, appearing ~0.8 ppm downfield of the corresponding proton in **17a** and **17b**. Analysis of NOEDS data indicates the relative stereochemistry of these adducts to be as shown in the drawings, thus, the major adducts **17a** (*endo*-) and **17b** (*exo*-) are products of addition to the least hindered face of the dipole whilst **17c** and **17d** result, respectively, from *exo*- and *endo*-addition to the β-face of the dipole. Indeed it may be the case that a downfield resonance for 6b-H characterises adducts in this series which result from dipolarophile addition to the more hindered face of the nitrone.

Reaction between methyl vinyl ketone and the *C*-phenyl nitrone **1b** in boiling toluene (100 h) gave samples of all possible diastereoisomeric cycloadducts. Separation by flash chromatography yielded a pure sample of the major adduct only **18a** (67%) with the remaining diastereomers **18b** (12%), **18c** (7%) and **18d** (2%) being obtained as enriched mixtures. NOEDS studies on the major adduct **18a** indicate that it arises from an *endo*-approach of the dipolarophile to the α-face of the dipole. The complete relative stereochemistry of all the minor products remains unknown hence no comment can be made concerning their origin.

**Table 2** Crystal data and structure refinement for **16a**

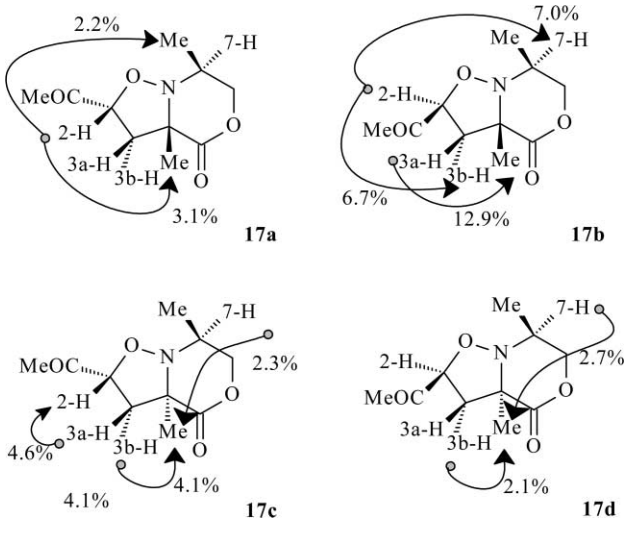
| Identification code | fh1 |
|---|---|
| Empirical formula | $C_{14}H_{17}NO_5S.1/2(C_6H_6)$ |
| Formula weight | 350.40 |
| Temperature/K | 293(2) |
| Wavelength/Å | 0.71069 |
| Crystal system | Monoclinic |
| Space group | *P*21/*c* |
| Unit cell dimensions/Å | *a* = 9.286(2)<br>*b* = 18.246(2) $\beta$ = 90.77(2)°<br>*c* = 10.204(2) |
| Volume/Å$^3$ | 1728.7(5) |
| *Z* | 4 |
| Density (calculated)/Mg m$^{-3}$ | 1.346 |
| Absorption coefficient/mm$^{-1}$ | 0.213 |
| F(000) | 740 |
| Crystal size/mm | 0.39 × 0.35 × 0.22 |
| Theta range for data collection/° | 2.19 to 27.97 |
| Index ranges | 0<=*h*<=12; −10<=*k*<=24;<br>−13<=*l*<=13 |
| Reflections collected | 4975 |
| Independent reflections | 4154 [*R*(int) = 0.0531] |
| Reflections observed (>2$\sigma$) | 3062 |
| Data Completeness | 1.000 |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 4154/0/219 |
| Goodness-of-fit on $F^2$ | 1.035 |
| Final *R* indices [$I>2\sigma(I)$] | $R_1$ = 0.0696 $wR_2$ = 0.1830 |
| *R* indices (all data) | $R_1$ = 0.0856 $wR_2$ = 0.1956 |
| Largest diff. peak and hole/e Å$^{-3}$ | 0.680 and −0.878 |

*R* indices; $R_1 = [\Sigma\,||F_o| - |F_c||]/\Sigma\,|F_o|$ (based on *F*), $wR_2 = [[\Sigma_w\,(|F_o{}^2 - F_c{}^2|)^2]/[\Sigma_w\,(F_o{}^2)^2]]^{1/2}$ (based on $F^2$). $w = 1/[(\sigma F_o)^2 + (.1501*P)^2]$. Goodness-of-fit = $[\Sigma_w\,(F_o{}^2 - F_c{}^2)^2/(N\text{obs} - N\text{parameters})]^{1/2}$

**Table 3** Crystal data and structure refinement for **16c**

| Identification code | jf1 |
|---|---|
| Empirical formula | $C_{15}H_{19}NO_5S$ |
| Formula weight | 325.37 |
| Temperature/K | 293(2) |
| Wavelength/Å | 0.71069 |
| Crystal system | Orthorhombic |
| Space group | *P*212121 |
| Unit cell dimensions/Å | a = 8.3850(10)<br>b = 11.2710(10)<br>c = 16.603(2) |
| Volume/Å$^3$ | 1569.1(3) |
| *Z* | 4 |
| Density (calculated)/Mg m$^{-3}$ | 1.377 |
| Absorption coefficient/mm$^{-1}$ | 0.229 |
| *F*(000) | 688 |
| Crystal size/ mm | 0.45 × 0.32 × 0.28 |
| Theta range for data collection/° | 2.18 to 21.17 |
| Index ranges | −8<=*h*<=8; −11<=*k*<=11;<br>−16<=*l*<=16 |
| Reflections collected | 6779 |
| Independent reflections | 1683 [*R*(int) = 0.0241] |
| Reflections observed (>2$\sigma$) | 1641 |
| Data Completeness | 0.976 |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 1683/0/202 |
| Goodness-of-fit on $F^2$ | 0.859 |
| Final *R* indices [$I>2\sigma(I)$] | $R_1$ = 0.0256 $wR_2$ = 0.0667 |
| *R* indices (all data) | $R_1$ = 0.0283 $wR_2$ = 0.0680 |
| Absolute structure parameter | −0.02(8) |
| Largest diff. peak and hole/e Å$^{-3}$ | 0.200 and −0.289 |

*R* indices; $R_1 = [\Sigma\,||F_o| - |F_c||]/\Sigma\,|F_o|$ (based on *F*), $wR_2 = [[\Sigma_w\,(|F_o{}^2 - F_c{}^2|)^2]/[\Sigma_w\,(F_o{}^2)^2]]^{1/2}$ (based on $F^2$). $w = 1/[(\sigma F_o)^2 + (.0579*P)^2 + .41*P)]$. Goodness-of-fit = $[\Sigma_w\,(F_o{}^2 - F_c{}^2)^2/(N\text{obs} - N\text{parameters})]^{1/2}$.



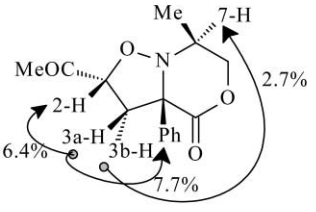

The rate and the selectivity of the cycloaddition between **1** and methyl acrylate in boiling toluene varied significantly with the substitution pattern on the dipole. Thus, reaction of **1g**,[2] carrying a $^t$Bu substituent at the C-2 position progressed slowly (110 h) to afford the *exo*-adduct **19** (68%). The preference for the *exo*-approach is likely a reflection of the steric bulk of the $^t$Bu substituent in **1g**, this hypothesis is supported by the finding that the C-2 unsubstituted analogue **1b**, displays *endo*-selectivity with **20a** being isolated in 67% yield. A second diastereoisomer, **20b** was found in 22% yield. NOEDS data failed to afford reliable information on the relative stereochemistry of the minor adduct.

The *C*-methyl nitrone **1a**, like **1b** has its C-2 position unsubstituted, it reacted rapidly with methyl acrylate (45 h) and the diastereomeric adducts **21a**,**b**,**c** were found in, 39, 25 and 7% yield respectively. NOEDS data for the minor adduct **21c** were inconclusive, however, following a comparison of $^1$H NMR data with that of the adducts **17** the significant deshielding of the axial methylene proton 6b-H (4.96 ppm) characterises the adduct as arising from an attack of the dipolarophile to the β-face of the nitrone. NOE data for the adducts **21a** ($C_6D_6$) and **21b** indicate they arise, respectively, from an *endo*- and *exo*-addition of the dipolarophile to the α-face of the dipole.

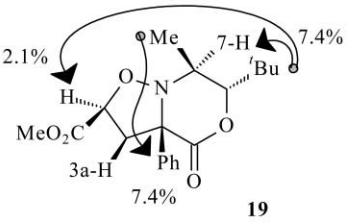
Nitrone **10a** with a bulky 1-(phenylselenyl)ethyl substituent at the C-3 position failed to react with olefinic substrates and it was only following heating with dimethyl acetylenedicarboxylate (72 h) that any products were isolated. The trimethoxypyrrolo-fused adduct **23** was found in 45% yield, it likely arises by rearrangement of the primary cycloadduct **22**. We have previously noted thermal lability of C-7 methyl analogues, *e.g.* **24**, and we propose that **23** arises from **22** by a mechanism parallel to that suggested earlier.[1]

## Conclusion

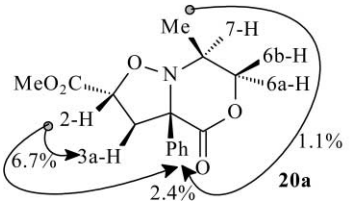
In conclusion efforts to prepare variously substituted oxazin-2-one nitrones by cyclization of a series of δ-alkenyl and δ-alkynyl α-oximino esters were somewhat thwarted by an allylic transposition which conspired to reduce the number of available precursors. Not with standing this complication nitrones carrying a Me or $^t$Bu substituent at C-2 or a 1-(phenylselenyl)ethyl substituent at C-3 have been synthesised. 1,3-Dipolar cycloaddition of the oxazinone *N*-oxides **1** to olefinic dipolarophiles proceeded regiospecifically and only 5-substituted isoxazolidine rings were formed. The facial selectivity was for addition of the dipolarophile to the least hindered (α-)face of the dipole. *Endo–exo* selectivity varied with the choice of dipolarophile with *endo*-specificity being observed with phenyl vinyl sulfone and a strong *exo*-selectivity with styrene. In the cases of methyl vinyl ketone and methyl acrylate both *endo*- and *exo*-adducts resulted and minor products arising from addition to the β-face of the dipole were observed. The steric bulk of nitrone substituents was also important in controlling



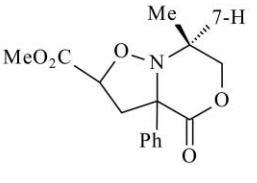

**18a**



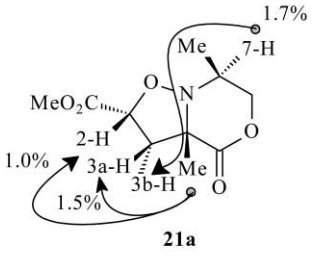

**19**



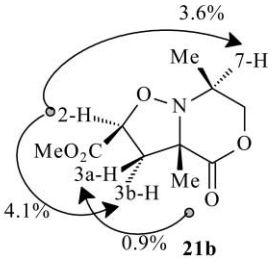

**20a**



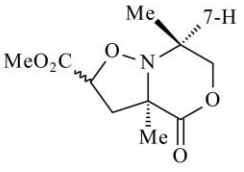

**20b**



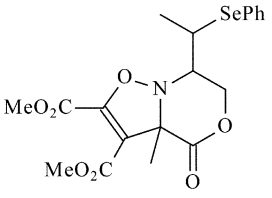

**21a**



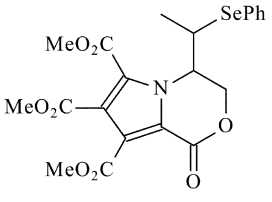

**21b**



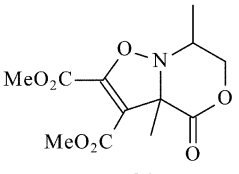

**21c**




**22**




**23**




**24**

diastereoselectivity, in particular a C-2 $^{t}$Bu substituent on **1g** directed cycloaddition to occur by an *exo*-attack whilst the preference for *endo*-selectivity observed for **1b** was retained with the C-2 methyl substituted dipole **1d**. Synthetic manipulation of the new cycloadducts, *viz*. reductive cleavage of the isoxazolidine ring and hydrolysis of the lactone moiety potentially provides access to unusual *N*,α-bis(2-hydroxyethyl) α-amino acids which may serve as novel chelating agents.

## 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. IR spectra (nujol mull and liquid film) were measured on a Perkin Elmer 1600 series (FT) or a Perkin Elmer 983G spectrometer. NMR spectra were recorded using a JOEL EX270 FT NMR spectrometer or a JOEL JNM-LA400 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference and deuteriochloroform as solvent, *J* values are given in Hertz. DEPT 135 assignments, where presented, immediately follow individual $^{13}$C resonance signals as positive signals (+, CH or $CH_3$), negative signals (−, $CH_2$) or absent signals (abs., quaternary carbon). 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, 254nm) or by the use of iodine staining. Crotyl alcohol was obtained from Aldrich Chemical Company as a mixture of isomers and was used as such.

### 1-Methyl-2-propenyl 2-oxo-2-phenylacetate 6b

Benzoylformic acid (5.02 g, 33.5 mmol) and 3-buten-2-ol (2.93 g, 40.7 mmol) were heated for 7 h at reflux in $C_6H_6$ (120 cm$^3$) in the presence of a catalytic amount of *p*-TsOH (0.33 g, 1.74 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 100 cm$^3$) and then with water (2 × 100 cm$^3$). The organic layers were collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product as a yellow mobile oil (5.58 g, 82%) which was not purified further. Compound **6b** (59%) obtained as an enriched mixture with **7b** (23%). Spectral data reported for **6b** only; $R_f$ 0.8 $Et_2O$; $\delta_H$ (400 MHz) 1.47 (3H, d, *J* 6.3, Me), 5.25 (1H, d, *J* 10.3, $=CH_2$), 5.38 (1H, d, *J* 17.1, $=CH_2$), 5.65 (1H, m, OCH), 5.94 (1H, m, CH=), 7.49 (2H, m, 2 × ArH), 7.65 (1H, m, ArH), 7.97 (2H, m, 2 × ArH).

### 3-Phenyl-2-propenyl 2-oxopropanoate (from α-vinylbenzyl alcohol) 7c and dicinnamyl ether 8

Pyruvic acid (0.44 g; 5.0 mmol) and α-vinylbenzyl alcohol (1.0 g, 7.5 mmol) were heated at reflux for 75 min in $C_6H_6$ (20 cm$^3$) in the presence of a catalytic amount of *p*-TsOH (0.05 g; 0.26 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 10 cm$^3$) and then with water (2 × 10 cm$^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product, a viscous orange oil. Purification by column chromatography ($Et_2O$ : petroleum ether; 1 : 10) yielded two major products; dicinnamyl ether **8** (158 mg; 15.8%) and the ester **7c**, a yellow mobile oil (310 mg; 31%) which was not purified further.

**8** $\delta_H$ (400 MHz) 4.22 (4H, dd, *J* 1.5 and 5.9, $OCH_2$), 6.31 (2H, dt, *J* 5.9 and 16.0, C*H*=CH–Ph), 6.63 (2H, d, *J* 16.0, CH=C*H*–Ph), 7.21–7.40 (10H, 10 × ArH); $\delta_C$ (100 MHz) 70.72 (−ve) ($OCH_2$), 125.96 (+ve) (ArC), 126.46 (+ve) (ArC), 127.65 (+ve) (*C*H=CH–Ph), 128.50 (+ve) (ArC), 132.58 (+ve) (CH=*C*H–Ph), 136.65 (abs.) (*n*-ArC).

**7c** $\delta_H$ (400 MHz) 2.49 (3H, s, Me), 4.90 (2H, d, *J* 6.6, $OCH_2$), 6.31 (1H, dt, *J* 6.6 and 15.7, $OCH_2CH$=), 6.73 (1H, d, *J* 15.7, C*H*–Ph), 7.33 (m, 5 × ArH).

### 3-Phenyl-2-propenyl 2-oxo-2-phenylacetate (from α-vinylbenzyl alcohol) 7d

Benzoylformic acid (0.49 g; 3.27 mmol) and α-vinylbenzyl alcohol (0.53 g; 3.99 mmol) were heated at reflux in $C_6H_6$ (10 $cm^3$) for 90 min in the presence of a catalytic amount of *p*-TsOH (0.03 g; 0.158 mmol) using a Dean–Stark trap. The reaction mixture was allowed to cool to rt and was washed with sat. $NaHCO_3$ (3 × 10 $cm^3$) and water (2 × 10 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to afford the crude product, an orange oil. Purification by column chromatography ($Et_2O$ : petroleum ether; 1 : 3) afforded **7d**, a colourless mobile oil (245 mg, 37%) (Found: C, 77.30; H, 5.23. $C_{17}H_{14}O_3$ requires: C, 76.69; H, 5.26%); $\delta_H$ (400 MHz) 4.96 (2H, dd, *J* 1.1 and 6.6, $OCH_2$), 6.30 (1H, dt, *J* 6.6 and 15.9, $OCH_2CH$=), 6.70 (1H, d, *J* 15.9, CH–Ph), 7.23 (3H, m, 3 × ArH), 7.35 (2H, m, 2 × ArH), 7.44 (2H, m, 2 × ArH), 7.57 (1H, m, 1 × ArH), 7.95 (2H, m, 2 × ArH); $\delta_C$ (100 MHz) 66.68 (−ve) ($OCH_2$), 121.50 (+ve) (CH=), 126.76 (+ve) (CH–Ph), 128.42, 128.67, 128.93, 130.07, 134.96, 135.98, (+ve) (10 × ArC), 132.45 (abs.) (*n*-ArC), 135.81 (abs.) (*n*-ArC), 163.53 (abs.) (C=O, ester), 185.95 (abs.) (C=O, ketone).

### 3-Phenyl-2-propenyl 2-oxopropanoate (from cinnamyl alcohol) 7c

Pyruvic acid (3.16 g, 35.9 mmol) and cinnamyl alcohol (5.77 g, 43.1 mmol) were heated for 4 h at reflux in $C_6H_6$ (120 $cm^3$) in the presence of a catalytic amount of *p*-TsOH (0.34 g, 1.80 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 100 $cm^3$) and then with water (2 × 100 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product, a complex mixture 5.71 g, 78%, which was purified by flash column chromatography (petroleum ether) to yield **7c** as a colourless mobile oil (0.219 g, 3%), much decomposed material was also obtained. Spectral data as reported above.

### 2-Butenyl 2-oxopropanoate 7a

Pyruvic acid (6 g, 68.2 mmol) and crotyl alcohol (5.89 g, 81.9 mmol) were heated for 5 h at reflux in $C_6H_6$ (200 $cm^3$) in the presence of a catalytic amount of *p*-TsOH (0.65 g, 3.41 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 100 $cm^3$) and then with water (2 × 100 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product as a yellow mobile oil (7.51 g, 93%) which was not purified further. $\delta_H$ (400 MHz) 1.65 (3H, d, *J* 6.6, $CH_3$), 2.36 (3H, s, $CH_3$), 4.57 (2H, d, *J* 6.6, $OCH_2$), 5.55 (1H, m, C*H*=CH–$CH_3$), 5.81 (1H, m, CH=C*H*–$CH_3$).

### 2-Butenyl 2-oxo-2-phenylacetate 7b

Benzoylformic acid (6 g, 40 mmol) and crotyl alcohol (3.46 g, 48 mmol) were heated for 6 h at reflux in $C_6H_6$ (120 $cm^3$) in the presence of a catalytic amount of *p*-TsOH (0.38 g, 2 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 100 $cm^3$) and then with water (2 × 100 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product as a colourless mobile oil (6.57 g, 81%) which was not purified further. **7b** (72%) obtained as an enriched mixture with **6b** (9%). Spectral data reported for **7b** only. $\delta_H$ (400 MHz) 1.75 (3H, d, *J* 6.1, Me), 4.80 (2H, d, *J* 6.8, $OCH_2$), 5.70 (1H, m, C*H*=CH–$CH_3$), 5.92 (1H, m, CH=C*H*–$CH_3$), 7.34 (2H, m, 2 × *o*-ArH), 7.63 (1H, m, 1 × *p*-ArH), 7.99 (2H, d, *J* 4.9, 2 × *p*-ArH)

### 2-Propynyl 2-oxopropanoate 9a

Pyruvic acid (3.00 g, 34.1 mmol) and propargyl alcohol (2.29 g, 40.9 mmol) were heated for 4 h at reflux in $C_6H_6$ (120 $cm^3$) in the presence of a catalytic amount of *p*-TsOH (0.32 g, 1.7 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 100 $cm^3$) and then with water (2 × 100 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product as an odourless mobile yellow oil (2.08 g, 49%) which was not purified further. $\delta_H$ (400 MHz) 2.39 (3H, s, $CH_3$), 2.51 (1H, t, *J* 2.5, CH), 4.73 (2H, d, *J* 2.5, $CH_2$).

### 2-Propynyl 2-oxo-2-phenylacetate 9b

Benzoylformic acid (3 g, 20 mmol) and propargyl alcohol (1.34 g, 24 mmol) were heated for 5 h at reflux in $C_6H_6$ (72 $cm^3$) in the presence of a catalytic amount of *p*-TsOH (0.19 g, 0.1 mmol) using a Dean–Stark apparatus. The reaction was allowed to cool to rt and was washed with sat. $NaHCO_3$ (2 × 50 $cm^3$) and then with water (2 × 50 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to yield the crude product as a viscous non-mobile yellow oil (2.61 g, 69%) which was not purified further (Found: C, 69.77; H, 4.51. $C_{11}H_8O_3$ requires: C, 70.21; H, 4.26%); $\delta_H$ (400 MHz) 2.54 (1H, t, *J* 2.4, CH), 4.87 (2H, d, *J* 2.4, –$CH_2$–), 7.42 (2H, m, 2 × *o*-ArH), 7.57 (1H, m, *p*-ArH), 7.91 (2H, m, *m*-ArH); $\delta_C$ (100 MHz) 53.18 (−ve) (–$CH_2$–), 76.19 (abs.) (*C*≡CH), 128.21 (+ve) (C≡*C*H), 128.84 (+ve) (ArC), 129.95 (+ve) (ArC), 132.07 (abs.) (*n*-ArC), 135.08 (ArC), 162.64 (abs.) (C=O, ester), 185.10 (abs.) (C=O).

### 1-Methyl-2-propenyl 2-(hydroxyimino)-2-phenylacetates *E*- and *Z*-4b

α-Keto ester **6b** (as a mixture with **7b**, 2.5 : 1) (3.20 g, 15.7 mmol), $NH_2OH$·HCl (1.64 g, 23.6 mmol) and pyridine (1.86 g, 23.6 mmol) were stirred in EtOH (170 $cm^3$) at rt for 15 h. The mixture was concentrated, taken up in $CH_2Cl_2$ (200 $cm^3$) and washed with water (2 × 100 $cm^3$). The organic layer was collected, dried ($Na_2SO_4$ anh.), filtered and concentrated to afford the crude product as a mixture of *Z*-**4b** : *E*-**4b** : *Z*-**5b** : *E*-**5b** (ratio by $^1$H NMR spectral analysis 18 : 4 : 6 : 1). Purification by column chromatography afforded *Z*-**4b** as an inseparable mixture with *Z*-**5b** [1.75 g, 51% – combined yield, *Z*-**4b** : *Z*-**5b** 3 : 1] and *E*-**4b** as an inseparable mixture with *E*-**5b** [0.62 g, 18% – combined yield, *E*-**4b** : *E*-**5b** 3 : 1].

*Z*-**4b** a colourless mobile oil (Found: C; 65.75, H; 6.06, N; 6.36. $C_{12}H_{13}NO_3$ requires: C; 65.74, H; 5.98, N; 6.39%.); $\delta_H$ (400 MHz) 1.47 (3H, d, *J* 6.8, Me), 5.23 (1H, d, *J* 10.7, =$CH_2$), 5.40 (1H, d, *J* 17.1, =$CH_2$), 5.72 (1H, m, OCH), 5.93 (1H, m, CH=), 7.41 (3H, m, *o*- & *p*-ArH), 7.69 (2H, m, *m*-ArH), 9.63 (1H, br s, OH); $\delta_C$ (100 MHz) 19.94 (+ve) (Me), 73.39 (+ve) (OCH), 117.21 (−ve) (=$CH_2$), 126.29 (+ve) (ArC), 128.84 (+ve) (ArC), 130.03 (abs.) (*n*-ArC), 130.50 (+ve) (ArC), 136.53 (+ve) (CH=), 151.73 (abs.) (C=N), 163.11 (abs.) (C=O).

*E*-**4b** a white powder mp 115–116 °C (from benzene–hexane) (Found: C; 65.04, H; 6.03, N; 6.31. $C_{12}H_{13}NO_3$ requires: C; 65.74, H; 5.98, N; 6.39%.); $\delta_H$ (400 MHz) 1.38 (3H, d, *J* 6.8, Me), 5.16 (1H, d, *J* 10.7, =$CH_2$), 5.28 (1H, d, *J* 17.6, =$CH_2$), 5.52 (1H, m, OCH), 5.84 (1H, m, C*H*–Ph), 7.44 (3H, br m, 3 × ArH), 7.52 (2H, br s, 2 × ArH), 10.6 (1H, br s, NOH); $\delta_C$ (100 MHz) 19.81 (Me), 73.35 (OCH), 116.95 (=$CH_2$), 127.91 (ArC), 128.50 (*n*-ArC), 129.39 (ArC), 129.73 (ArC), 136.74 (CH=), 149.05 (C=N), 162.60 (C=O).

### 3-Phenyl-2-propenyl-2-(hydroxyimino)propanoate 5c

α-Keto acid **7c** (0.64 g, 3.15 mmol), $NH_2OH$·HCl (0.39 g, 4.73 mmol) and pyridine (0.37 g, 4.73 mmol) were stirred in EtOH (50 $cm^3$) at rt for 15 h. The mixture was concentrated, taken up in $CHCl_3$ (60 $cm^3$) and washed with water

(2 × 20 $cm^3$). The organic layer was dried ($Na_2SO_4$ anh.), filtered and concentrated to afford the crude product, which crystalised to colourless cubic crystals (0.306 g; 44%), mp 116–118°C (from $CHCl_3$–hexane) (Found: C, 65.62; H, 6.18; N, 6.10. $C_{12}H_{13}NO_3$ requires: C, 65.75; H, 5.94; N, 6.39%); $\delta_H$ (400 MHz) 2.12 (3H, s, Me), 4.91 (2H, dd, *J* 1.1 and 6.6, $OCH_2$), 6.33 (1H, dt, *J* 6.6 and 15.7, C*H*=CH–Ph), 6.71 (1H, d, *J* 15.7, CH=C*H*–Ph), 7.41 (5H, m, ArH), 9.84 (1H, br s, N–OH); $\delta_C$ (100 MHz) 10.55 (+ve) ($CH_3$), 66.34 (−ve) ($OCH_2$), 122.22 (+ve) ($OCH_2CH$), 126.68, 128.21, 128.59, 135.13 (+ve) (5 × ArC and *C*HPh), 136.02 (abs.) (*n*-ArC), 149.52 (abs.) (C=N), 163.36 (abs.) (C=O).

### 1-Phenyl-2-propenyl-2-(hydroxyimino)-2-phenylacetates, *E*- and *Z*-5d

α-Keto ester **7d** (0.15 g, 0.56 mmol), $NH_2OH{\cdot}HCl$ (0.067 g, 0.85 mmol) and pyridine (0.061 g, 0.85 mmol) were stirred in EtOH (9 $cm^3$) at rt for 2.5 h. The mixture was concentrated, taken up in $CHCl_3$ (20 $cm^3$), and washed with water (2 × 10 $cm^3$). The organic layer was collected, dried ($Na_2SO_4$ anh.), filtered and concentrated to afford the crude products. Separation by column chromatography ($Et_2O$ : petroleum ether; 1 : 3) afforded *Z*-**5d** (0.065 g, 41%) and *E*-**5d** (46 mg; 29%).

*Z*-**5d** a yellow viscous oil (Found: C, 72.27; H, 5.51; N, 4.48. $C_{17}H_{15}NO_3$ requires: C, 72.58; H, 5.37; N, 4.98%); $\delta_H$ (400 MHz) 4.96 (2H, dd, *J* 1.3 and 6.5, $OCH_2$), 6.28 (1H, dt, *J* 6.5 and 15.9, $OCH_2CH$), 6.67 (1H, d, *J* 15.9, C*H*Ph), 7.26 (8H, m, ArH), 7.49 (2H, m, ArH), 8.92 (1H, s, OH); $\delta_C$ (100 MHz) 66.43 (−ve) ($OCH_2$), 121.84 (+ve) ($OCH_2CH$), 126.42, 126.72, 128.29, 128.59, 128.80, 129.22, 130.50 (+ve) (10 × ArC), 130.07 (abs.) (*n*-ArC), 135.42 (+ve) (*C*HPh), 135.89 (abs.) (*n*-ArC), 151.60 (abs.) (C=N), 163.36 (abs.) (C=O), *m*/*z* 219, 133 ($^+OCH_2CH$=CHPh), 117 ($^+CH_2CH$=CHPh).

*E*-**5d** colourless plates, mp 175–177 °C (from $CHCl_3$–hexane) (Found: C, 72.19; H, 4.84; N, 5.34. $C_{17}H_{15}NO_3$ requires: C, 72.58; H, 5.37; N, 4.98%); $\delta_H$ (400 MHz) 4.92 (2H, dd, *J* 0.9 and 6.5, $OCH_2$), 6.30 (1H, dt, *J* 15.7 and 6.5, $OCH_2CH$), 6.68 (1H, d, *J* 15.7, C*H*Ph), 7.30 (5H, m, 5 × ArH), 7.42 (3H, m, 3 × ArH), 7.52 (2H, m, 2 × ArH), 10.03 (1H, br s, OH); $\delta_C$ (100 MHz) 66.60 (−ve) ($OCH_2$), 122.01(+ve) ($OCH_2CH$), 126.68, 127.99, 128.16, 128.55, 129.27, 129.82 (+ve) (10 × ArC), 128.33 (abs.) (*n*-ArC), 135.21 (+ve) (*C*HPh), 135.93 (abs.) (*n*-ArC), 149.26 (abs.) (C=N), 163.06 (abs.) (C=O).

### 2-Butenyl 2-(hydroxyimino)propanoate 5a

α-Keto ester **7a** (3 g, 21.13 mmol), pyridine (2.51 g, 31.7 mmol) and $NH_2OH{\cdot}HCl$ (2.30 g, 31.7 mmol) were stirred in EtOH (250 $cm^3$) at rt for 15 h. The mixture was concentrated, taken up in $CH_2Cl_2$ (200 $cm^3$) and washed with $H_2O$ (2 × 150 $cm^3$). The organic layer was collected, dried (anh. $Na_2SO_4$), filtered and concentrated to afford the crude product. Purification by column chromatography (petroleum ether with $Et_2O$ 1% gradient) afforded **5a** (2.66 g, 80%) which crystalised to colourless plates, mp 42–45 °C (from $Et_2O$–petroleum ether), $R_f$ 0.7 ($Et_2O$) (Found: C, 53.91; H, 7.04; N, 8.79. $C_7H_{11}NO_3$ requires: C, 53.50; H, 7.01; N, 8.92%); $\delta_H$ (400 MHz) 1.72 (3H, d, *J* 6.2, $CH_3$), 2.10 (3H, s, $CH_3$), 4.67 (2H, d, *J* 6.2, $CH_2$), 5.64 (1H, m, C*H*=CH–$CH_3$), 5.84 (1H, m, CH=C*H*–$CH_3$), 10.18 (1H, br s, OH); $\delta_C$ (100 MHz) 10.47 (+ve) (Me), 17.73 (+ve) (=CHC$H_3$), 66.43 (−ve) ($CH_2$), 124.30 (+ve) (CH=*C*H-$CH_3$), 132.45 (+ve) (*C*H=CH–$CH_3$), 149.39 (abs.) (C=N), 163.49 (abs.) (C=O).

### 2-Butenyl 2-(hydroxyimino)-2-phenylacetate 5b

α-Keto ester **7b** (as a mixture with **6b**, 8 : 1) (2.2 g, 10.78 mmol), $NH_2OH{\cdot}HCl$ (1.12 g, 16.2 mmol) and pyridine (1.28 g, 16.2 mmol) were stirred at rt in EtOH (200 $cm^3$) for 16 h. The mixture was concentrated, taken up in $CH_2Cl_2$ (200 $cm^3$) and washed with water (2 × 200 $cm^3$). The organic layer was dried ($Na_2SO_4$ anh.), filtered and concentrated to afford the crude product. Examination of the $^1H$ NMR spectral data of the crude reaction mixture indicated a *Z*-**5b** : *E*-**5b** : *Z*-**4b** : *E*-**4b** ratio of 12 : 5 : 3.5 : trace. Purification by flash column chromatography (petroleum ether with $Et_2O$, 1% gradient) afforded *Z*-**5b** as an inseparable mixture with *Z*-**4b** (1.75 g, 74% – combined yield, *Z*-**5b** : *Z*-**4b**, 7 : 2) and *E*-**5b** (0.26 g, 11%). Spectral data reported for title compounds only. Data for *Z*-**4b** matches that as previously reported.

*Z*-**5b** a colourless, odourless, mobile oil, [$R_f$ 0.9 ($Et_2O$), 0.28 ($Et_2O$ : petroleum ether; 1 : 1)] (Found: C, 65.49; H, 6.16; N, 6.59. $C_{12}H_{13}NO_3$ requires: C, 65.75; H, 5.94; N, 6.39%); $\delta_H$ (400 MHz) 1.75 (3H, d, *J* 5.9, Me), 4.85 (2H, d, *J* 6.4, $CH_2$), 5.70 (1H, m, C*H*=CH–$CH_3$), 5.93 (1H, m, CH=C*H*–$CH_3$), 7.41 (3H, m, *o*- & *p*-ArH), 7.58 (2H, m, *m*-ArH), 9.45 (1H, br s, OH); $\delta_C$ (100 MHz) 17.77 (+ve) ($CH_3$), 66.64 (−ve) ($CH_2$), 123.92 (+ve) (*C*H-$CH_3$), 126.34 (+ve) (*C*H=CH–$CH_3$), 128.76 (+ve) (ArC), 129.99 (abs.) (*n*-ArC), 130.46 (+ve) (ArC), 133.00 (+ve) (ArC), 151.60 (abs.) (C=N), 163.49 (abs.) (C=O), $\nu_{max}/cm^{-1}$ 3427 (OH), 1733 (C=O).

*E*-**5b** fine colourless needles, mp 121–123 °C (from $C_6H_6$–petroleum ether) (Found: C, 65.55; H, 5.59; N, 6.15. $C_{12}H_{13}NO_3$ requires: C, 65.75; H, 5.94; N, 6.39%); $\delta_H$ (400 MHz) 1.70 (3H, d, *J* 5.4, $CH_3$), 4.70 (2H, d, *J* 6.4, $CH_2$), 5.63 (1H, m, C*H*=CH–$CH_3$), 5.85 (1H, m, CH=C*H*–$CH_3$), 7.39–7.53 (5H, m, 5 × ArH), 10.05 (1H, br s, NOH); $\delta_C$ (100 MHz) 17.73 (+ve) ($CH_3$), 66.77 (−ve) ($CH_2$), 124.17 (+ve) (CH=*C*H–$CH_3$), 127.95 (+ve) (*C*H=CH–$CH_3$), 128.46 (abs.) (*n*-ArC), 129.31 (+ve) (ArC), 129.78 (+ve) (ArC), 132.75 (+ve) (ArC), 149.26 (abs.) (C=N), 163.15 (abs.) (C=O), $\nu_{max}/cm^{-1}$ 3240 (OH), 1723 (C=O), 1677 (C=N), 1462, 1546, 684, 617 (mono sub. aryl ring).

### 2-Propynyl 2-(hydroxyimino)propanoate 9c

α-Keto ester **9a** (1.5 g, 11.9 mmol), pyridine (1.41 g, 17.85 mmol) and $NH_2OH{\cdot}HCl$ (1.24 g, 17.85 mmol) in EtOH (190 $cm^3$) were stirred at rt for 15 h. The reaction mixture was concentrated, taken up in $CHCl_3$ (200 $cm^3$) and washed with water (2 × 100 $cm^3$). The organic layer was collected, dried (anh. $Na_2SO_4$), filtered and concentrated to afford the crude product (1.14 g, 68%) which crystalised to fine colourless needles, mp 92–94 °C (from $C_6H_6$–petroleum ether) ($R_f$ 0.8 $Et_2O$) (Found: C, 51.21; H, 4.95; N, 9.58. $C_6H_7NO_3$ requires: C, 51.06; H, 5.00; N, 9.93%); $\delta_H$ (400 MHz) 2.12 (3H, s, $CH_3$), 2.51 (1H, t, *J* 2.4, CH), 4.83 (2H, d, *J* 2.4, $CH_2$); $\delta_C$ (100 MHz) 10.47 (+ve) ($CH_3$), 53.05 (−ve) ($CH_2$), 75.51 (+ve) (CH), 148.76 (abs.) (C=N), 162.81 (abs.) (C=O); *m*/*z* 142 ($M^+ + 1$), 96, 86, 68, 58.

### 2-Propynyl 2-(hydroxyimino)-2-phenylacetate 9d

α-Keto ester **9b** (3 g, 15.9 mmol), pyridine (1.89 g, 23.9 mmol) and $NH_2OH{\cdot}HCl$ (1.66 g, 23.9 mmol) were stirred in EtOH (240 $cm^3$) at rt for 15 h. The mixture was concentrated, taken up in $CH_2Cl_2$ (300 $cm^3$), and washed with water (2 × 150 $cm^3$). The organic layer was collected, dried (anh. $Na_2SO_4$), filtered and concentrated to afford crude product. Purification by column flash chromatography ($Et_2O$–petroleum ether; 1 : 5) afforded *E*-**9d** (2.77 g, 86%) and *Z*-**9d** (0.43 g, 13%).

*E*-**9d** a colourless viscous odourless oil ($R_f$ 0.5, $Et_2O$) (Found: C, 64.78; H, 4.37; N, 6.99. $C_{11}H_9NO_3$ requires: C, 65.02; H, 4.43; H, 6.90%); $\delta_H$ (400 MHz) 2.48 (1H, t, *J* 2.4, CH), 4.87 (2H, d, *J* 2.4, $CH_2$), 7.30 (3H, m, *o*- and *p*-ArH), 7.46 (2H, m, *m*-ArH), 9.23 (1H, s, NOH); $\delta_C$ (100 MHz) 53.39 (−ve) ($CH_2$), 76.36 (+ve) (CH), 76.75 (abs.) (*C*≡CH), 126.55 (+ve) (ArC), 129.14 (+ve) (ArC), 129.82 (abs.) (*n*-ArC), 130.97 (+ve) (ArC), 151.26 (abs.) (C=N), 163.06 (abs.) (C=O).

*Z*-**9d** colourless plates, mp 124–127 °C ($Et_2O$–petroleum ether) (Found: C, 64.93; H, 4.18; N, 6.45. $C_{11}H_9NO_3$ requires: C, 65.02; H, 4.46; N, 6.89%); $\delta_H$ (400 MHz) 2.42 (1H, t, *J* 2.4, CH), 4.78 (2H, d, *J* 2.4, $CH_2$), 7.37 (3H, m, *o*- and *p*-ArH), 7.45

(2H, m, *m*-ArH); $\delta_C$ (100 MHz) 53.41 (−ve) ($CH_2$), 75.83 (+ve) (CH), 77.40 (abs.) (C≡CH), 128.09 (+ve) (ArC), 129.41 (+ve) (ArC), 130.09 (+ve) (ArC), 132.20 (abs.) (*n*-ArC), 148.86 (C=N), 162.61 (C=O).

### Attempted cyclisation of oximes 2a, 9a and 9c by heating under pressure

(i) A solution of oxime **2a** (0.05 g, 0.35 mmol) in toluene (10 $cm^3$) was heated at 210 °C in a sealed tube for 16 h. The reaction was allowed to cool to rt and the solvent removed. $^1$H NMR analysis of the crude mixture showed nitrone **1a**[2] together with starting oxime in a 2 : 1 ratio.

(ii) A solution of oxime *E*-**5a** (0.05 g, 0.35 mmol) in toluene (10 $cm^3$) was heated at 190 °C in a sealed tube for 24 h. The reaction was allowed to cool to rt and the solvent removed. $^1$H NMR analysis of the crude mixture showed returned starting material only.

(iii) A solution of oxime **9c** (0.05 g, 0.34 mmol) in toluene (10 $cm^3$) was heated at 210 °C in a sealed tube with times varying from 1 to 9.5 h. The reaction was allowed to cool to rt and the solvent removed. $^1$H NMR analysis of the crude mixture showed returned starting material only.

### Attempted electrophile induced cyclisation of oximes 5a and 9c

**(i) Procedure employing $I_2$.** Oxime *E*-**5a** (0.1 g, 0.64 mmol) and $I_2$ (0.16 g, 0.64 mmol) were stirred in $CH_2Cl_2$ anh. (10 $cm^3$) at rt for 5 min. Anhydrous $K_2CO_3$ (0.10 g, 0.701 mmol) was added whereupon the colour of the reaction mixture turned from purple to a brown. The mixture stirred at rt for a further 2 h, filtration and concentration afforded the crude product. $^1$H NMR spectral analysis of which showed returned starting oxime. The reaction was repeated varying iodine concentration (0.56–2.0 mol eq.) and reaction time following addition of base (2–15 h). $^1$H NMR spectral analysis of the crude reaction mixtures showed returned starting material when less than a one mole eq. of $I_2$ is employed, with an excess of $I_2$, mixtures were returned in which the starting oxime is the major component.

**(ii) Procedure employing *N*-bromosuccinimide (NBS).** Oxime *E*-**5a** (0.05 g, 0.32 mmol) and NBS (0.017 g, 0.1 mmol) were stirred in anh. $CH_2Cl_2$ (5 $cm^3$) at rt for 2 h. The reaction mixture was concentrated to afford the crude product. $^1$H NMR spectral analysis of the crude reaction mixture showed returned oxime. The reaction was repeated varying duration between 5 min and 8 h with NBS concentration over the range 0.18–1 molar. $^1$H NMR spectral analysis of the crude reaction mixtures showed that with less than one equivalent of NBS the starting material is returned. Complex mixtures of an undetermined nature resulted when molar equivalents of NBS were employed.

**(iii) Procedure employing $AgBF_4$.** Oxime **9c** (0.20 g, 1.42 mmol) and a catalytic amount of $AgBF_4$ (0.014 g, 0.07 mmol) were stirred in $CH_2Cl_2$ (5 $cm^3$) for 6 h. The reaction mixture was washed with $H_2O$ (2 × 5 $cm^3$) and the water washings extracted with $CH_2Cl_2$ (3 × 5 $cm^3$). The combined organic layers were washed with brine (5 $cm^3$). The organic layer was collected and dried (anh. $Na_2SO_4$), filtered and concentrated to afford the crude product which was shown by $^1$H NMR spectral analysis to comprise starting material. The above reaction was repeated at rt for 24 h and at reflux temperature for 6 h, however only starting material was returned.

**(iv) Procedure employing PhSeBr.** A solution of the oxime *E*-**5a** (0.10 g, 0.637 mmol) and PhSeBr (0.15 g, 0.634 mmol) were stirred at rt in either $CH_3CN$ or $CH_2Cl_2$ (5 $cm^3$) for 3 h. $K_2CO_3$ (0.10 g, 0.70 mmol) was added and the reaction mixture was stirred for a further 15 h. The crude reaction mixture was filtered and solvent was removed under reduced pressure to afford the crude product which was shown by $^1$H NMR spectral analysis to comprise starting material. When the reaction was repeated on the same scale in $CH_2Cl_2$ at reflux temperature, a complex mixture resulted.

### Preparation of 5-methyl-6-oxo-3-[1-(phenylselenyl)ethyl]-3,6-dihydro-2*H*-1,4-oxazin-4- ium-4-olate 10a

PhSeBr (0.75 g, 3.18 mmol) and $AgBF_4$ (0.62 g, 3.18 mmol) were stirred in $CH_2Cl_2$ anh. (25 $cm^3$) in the dark at 0 °C, for 10 min. Oxime *E*-**5a** (0.50 g, 3.18 mmol) was added at 0 °C and the mixture was stirred for 3 h. $K_2CO_3$ (0.48 g, 3.50 mmol) was added and stirring continued at rt for a further 15 h, after which time the mixture was filtered with suction. The inorganic residue was extracted several times [$CH_2Cl_2$] and the organic layers collected. The solvent was removed from the combined organic layers under reduced pressure, to yield the crude product as a blue–green oil. Purification by column chromatography ($Et_2O$–petroleum ether, 1 : 2) afforded **10a** (0.66 g, 67%) as a viscous yellow oil ($R_f$ 0.3 $Et_2O$), which solidified on standing in the cold to a yellow amorphous solid, mp 48–51 °C (Found: C, 49.80; H, 4.78; N, 4.80. $C_{13}H_{15}NO_3Se$ requires: C; 50.00, H; 4.81, N; 4.49%); $\delta_H$ (400 MHz) 1.55 (3H, d, *J* 7.3, Me), 2.17 (3H, s, 5-Me), 3.75 (1H, m, 1 : -H), 4.02 (1H, m, 3-H), 4.60 (1H, dd, *J* 2.3 and 12.3, 2b-H), 4.86 (1H, d, *J* 12.3, 2a-H), 7.30 (3H, m, 3 × ArH), 7.55 (2H, m, 2 × ArH); $\delta_C$ (100 MHz) 11.78 (+ve) (5-Me), 19.68 (+ve) (Me), 36.75 (+ve) (*C*HSePh), 64.64 (−ve) (2-C), 72.33 (+ve) (3-C), 127.02 (abs.) (*n*-ArC), 128.67 (+ve) (ArC), 129.39 (+ve) (ArC), 135.38 (+ve) (ArC), 135.93 (abs.) (5-C), 159.07 (abs.) (6-C); *m*/*z* 314 ($M^+$ + 2), 312 ($M^+$). NOEDS: irradiation of 3-H caused an enhancement the signals representing 2b-H (2.8%) and 1′-H (1.5%). Irradiation of 2b-H caused the following enhancements 3-H (4.5%) and 2a-H (26.7%).

### 6-Oxo-5-phenyl-3-[1-(phenylselenyl)ethyl]-3,6-dihydro-2*H*-1,4-oxazin-4-ium-4-olate 10b

PhSeBr (0.058 g, 0.245 mmol) and $AgBF_4$ (0.052 g, 0.268 mmol) were stirred at 0 °C in $CH_2Cl_2$ (5 $cm^3$) in the dark for 10 min. Oxime *E*-**5b** (0.05 g, 0.242 mmol) was added and the reaction mixture stirred for 3 h in the dark at 0 °C. $K_2CO_3$ (0.042 g, 0.313 mmol) was added and the reaction stirred at rt for a further 15 h. The reaction mixture was filtered with suction and the inorganic residue was extracted several times with $CH_2Cl_2$. The organic layers were collected and the solvent was removed under reduced pressure, to yield the crude product as a blue–green oil. Purification by flash column chromatography ($Et_2O$–petroleum ether; 1 : 2) afforded **10b** (0.052 g, 57%) as a fluffy white solid, mp 119–120 °C, ($C_6H_6$–petroleum ether) (Found: C, 57.47; H, 4.47; N, 3.68. $C_{18}H_{17}NO_3Se$ requires: C, 57.75; H, 4.55; N, 3.74%); $\delta_H$ (400 MHz) 1.65 (3H, d, *J* 7.3, Me), 3.79 (1H, m, H), 4.11 (1H, m, 3-H), 4.75 (1H, dd, *J* 12.5 and 3.2, 2b-H), 4.98 (1H, d, *J* 12.5, 2a-H), 7.31–7.67 (10H, m, 10 × ArH); $\delta_C$ (100 MHz) 19.74 (+ve) (Me), 36.56 (+ve) (*C*HSePh), 64.56 (−ve) (2-C), 74.40 (+ve) (3-C), 126.72 and 127.15 (abs.) (2 × *n*-ArC), 127.91, 128.86, 129.52, 130.08, 130.28, 135.68 (+ve) (10 × ArC), 135.05 (abs.) (5-C), 158.61 (abs.) (6-C), $\nu_{max}$ $cm^{-1}$ 1712 (C=O), *m*/*z* 374 ($M^+$), 376 ($M^+$ + 2).

### 2,3-Dimethyl-6-oxo-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-4-ium-4-olates 1e and 1f and 4-methyl-6a-phenyltetrahydro-3*H*,6*H*-furo[3,4-*c*]isoxazol-6-ones 11(i), 11(ii) and 11(iii)

α-Keto oxime *Z*-**4b** (as an enriched mixture with *Z*-**5b** [3 : 1]) (1 g, 4.56 mmol) was heated at reflux in xylene (300 $cm^3$) in the presence of hydroquinone (1%, $^w/_v$, 3 g) under $N_2$ for 30 h. The reaction mixture was allowed to cool to rt and the precipitated hydroquinone was filtered off with suction. The filtrate was concentrated, taken up in $CHCl_3$ (10 $cm^3$) and further hydroquinone which precipitated was again removed by filtration.

The filtrate was concentrated to yield the crude product, which was purified by flash chromatography ($Et_2O$–petroleum ether, 1 : 10) to afford a pure sample of *Z*-**5b** (12%) – all other products were obtained as enriched mixtures – **1e** (19%), **11(i)** (11%), **1f** (3%), **11(ii)** (20%) and **11(iii)** (17%).

*Z*-**5b** spectral data as previously reported, all other returned products obtained as mixtures.

**1e** ($^1$H NMR data taken from an enriched sample of **1e** with **11 (i)**, 4 : 1); $\delta_H$ (400 MHz) 1.58 (3H, d, *J* 6.6, 2-Me), 1.60 (3H, d, *J* 6.6, 3-Me), 4.09 (1H, m, 3-H), 4.60 (1H, m, 2-H), 7.37–7.70 (5H, m, 5 × ArH).

**11(i)** ($^1$H NMR data taken from a fraction composed of **11(i)** : **1e**; 1 : 4); $\delta_H$ (400 MHz) 1.36 (3H, d, *J* 6.2, Me), 3.09 (1H, br m, 3a-H), 4.39 (2H, m, 3-H and 3′-H), 4.54 (1H, m, 4-H), 6.12 (1H, br s, NH), 7.37–7.70 (5H, m, 5 × ArH).

**1f** ($^1$H NMR data taken from a sample comprising **11(ii)** : **1e** : **11(i)** : **1f**; 1.2 : 1.3 : 2.1 : 1.1); $\delta_H$ (400 MHz) 1.48 (3H, d, *J* 7.0, 2-Me), 1.52 (3H, d, *J* 6.6, 3-Me), 4.11 (1H, m, 3-H), 5.00 (1H, m, 2-H), 7.38–7.72 (5H, m, 5 × ArH).

**11(ii)** ($^1$H NMR data taken from a fraction containing trace amounts of **1f** and **11(i)**); $\delta_H$ (400 MHz) 1.52 (3H, d, *J* 6.6, Me), 3.44 (1H, br m, 3a-H), 4.00 (1H, m, 3-H), 4.46 (1H, m, 3′-H), 4.85 (1H, m, 4-H), 7.43 (3H, m, 3 × ArH), 7.55 (2H, m, 2 × ArH).

**11(iii)** ($^1$H NMR data taken from a fraction comprising **11(ii)** : **11(iii)**; 5 : 3); $\delta_H$ (400 MHz) 1.44 (3H, d, *J* 6.2, Me), 3.23 (1H, br m, 3a-H), 4.12 (1H, m, 3-H), 4.28 (1H, m, 3′-H), 4.59 (1H, m, 4-H), 5.80 (br s, NH), 7.41–7.60 (5H, m, 5 × ArH).

### 3,6a-Diphenyltetrahydro-3*H*,6*H*-furo[3,4-*c*]isoxazol-6-one 13

(i) *Z*-**5d** (0.367 g; 1.30 mmol) was heated at reflux in xylene (80 cm$^3$) in the presence of hydroquinone (1% $^w/_v$, 0.8 g) under a nitrogen atmosphere for 24 h. The mixture was allowed to cool to rt and concentrated. The residue was taken up in $CHCl_3$ (5 cm$^3$) and the hydroquinone which precipitated was removed with suction, concentration of the filtrate afforded the crude product. Purification by flash column chromatography ($Et_2O$–petroleum ether, 1 : 3) afforded **13** (0.303 g; 83%) which crystalised to colourless needles (0.270 g; 74%), mp 94–95.5 °C (from $CHCl_3$–petroleum ether) (Found: C, 72.37; H, 4.91; N, 4.90. $C_{17}H_{15}NO_3$ requires: C, 72.60; H, 5.34, N, 4.98%); $\delta_H$ (400 MHz) (rt) 3.67 (1H, br s, 3a-H), 4.62 (2H, m, 4-H and 4′-H), 5.25 (1H, br s, 3-H), 6.30 (1H br s, NH), 7.32–7.50, 10 H, m, 10 × ArH); $\delta_H$ (400 MHz) (50 °C) 3.64 (1H, slightly (sl.) br. t, *J* 4.8, 3a-H), 4.62 (2H, m, 4-H and 4′-H), 5.22 (1H, sl. br d, *J* 4.8, 3-H), 6.33 (br s, NH), 7.32–7.50 (10H, m, 10 × ArH); $\delta_C$ (100 MHz) 58.92 (+ve) (3a-C), 68.13 (−ve) (4-C), 76.20 (abs.) (6a-C), 89.96 (+ve) (3-C), 126.43, 126.64, 127.75, 128.00, 128.21, 128.42, 128.81, 128.89, 129.15 (+ve) (10 × ArC), 135.69 (abs.) (*n*-ArC), 139.08 (abs.) (*n*-ArC), 176.11 (abs.) (6-C); *m*/*z* M$^+$ 281.

(ii) The above reaction was repeated on one third the scale with *E*-**5d**, $^1$H NMR spectral analysis of the crude reaction mixture indicated **13** as the only reaction product with much decomposed material, purification by flash chromatography afforded **13** (36%), physical and spectral data as previously reported.

### 2,3,6,7-Tetrahydro-3,7-dimethyl-2-phenyl-3a*H*-isoxazolo-[3,2-*c*]-[1,4]oxazin-4-one 14a

Nitrone **1a** (1.0 g, 7.0 mmol) and hydroquinone (0.15g, 1.40 mmol), were stirred in deoxygenated styrene (15 cm$^3$) at 100 °C, under a constant flow of $N_2$ gas. After 5.5 h the reaction mixture was cooled to rt and excess styrene was removed under high vacuum (100 °C, 0.20 mmHg). The yellow solid residue was, with the aid of sonication, taken up in $CHCl_3$ (1 cm$^3$), this solution was allowed to stand at rt (0.5 h), and the precipitated hydroquinone was removed by vacuum filtration and washed with petroleum ether (20 cm$^3$). The filtrate and washings were combined and concentrated. Chromatography of the yellow solid residue on $SiO_2$ with $Et_2O$-petroleum ether (1 : 3) as eluant gave the title adduct as a white solid (1.56 g, 90%).

**14a** Colourless plates, mp 90–92 °C (benzene–petroleum ether) (Found: C, 68.11; H, 7.01; N, 5.89. $C_{14}H_{17}NO_3$ requires C, 68.02; H, 6.88; N, 5.67%); $\delta_H$ (270 MHz) 1.22 (3H, d, *J* 6.2, 7-Me), 1.68 (3H, s, 3a-Me), 2.35 (1H, dd, *J* 13.2 & 8.2, 3a-H), 3.18 (1H, dd, *J* 8.2 & 13.2, 3b-H), 3.29 (1H, m, 7-H), 4.02 (1H, dd, *J* 11.0 & 11.0, 6b-H), 4.20 (1H, dd, *J* 3.1 & 11.0 6a-H), 5.16 (1H, dd, *J* 8.1 & 8.1, 2-H), 7.36 (5H, m, ArH); $\delta_C$ (67.5 MHz) 15.2 (7-Me), 28.4 (3a-Me), 49.8 (3-C), 53.2 (7-C), 69.8 (3a-C), 70.7 (6-C), 78.0 (2-C), 126.9–138.8 (4 × Ar–C), 172.9 (4-C). NOEDS results: irradiation of 2-H caused the following enhancements 3b-H (6.4%), 7-H (7.0%), ArH (6.3%). Irradiation of 3a-Me caused 1.0% enhancement on 2-H, 1.1% on 6b-H and 2.8% on 3a-H.

### 2,3,6,7-Tetrahydro-7-methyl-2,3a-diphenyl-3a*H*-isoxazolo[3,2-*c*]-[1,4]oxazin-4-one 14b and 2,3,6,7-tetrahydro-7-methyl-2,3a-diphenyl-3a*H*-isoxazolo[3,2-*c*][1,4]oxazin-4-one 15

Freshly recrystallised nitrone **1b** (0.45 g, 2.20 mmol) and hydroquinone (0.20 g, 18.0 mmol) were stirred in deoxygenated styrene (6 cm$^3$) at 110 °C under a constant flow of $N_2$. After 8 h heating the reaction mixture was cooled to rt, and excess styrene was removed under reduced pressure (100 °C, 0.50 mmHg). The residue was taken up in $CHCl_3$ (1 cm$^3$) and allowed to stand at rt for 15 min, the precipitated hydroquinone was filtered *in vacuo*. The filtrate was collected and concentrated. Flash chromatography with $Et_2O$–petroleum ether (1 : 5) as the eluant yielded a pure sample of **14b** (0.58 g, 86%) **15** was obtained as an enriched mixture (0.07 g, 10%).

**14b** Colourless cubic crystals, mp 94–96 °C (benzene–petroleum ether) (Found: C, 74.01; H, 6.10; N, 4.72. $C_{19}H_{19}NO_3$ requires C, 73.79; H, 6.15; N, 4.53%); $\delta_H$ (270 MHz) 1.34 (3H, d, *J* 6.2, Me), 2.55 (1H, dd, *J* 12.7 & 7.2, 3a-H), 3.52 (1H, m, 7-H), 3.74 (1H, dd, *J* 12.7 & 8.3 3b-H), 3.90 (1H, dd, *J* 11.4 & 11.4 6b-H), 4.13 (1H, dd, *J* 11.4 & 3.7, 6a-H), 5.12 (1H, dd, *J* 7.2 & 8.3, 2-H), 7.37–7.25 (8H, 2 × m, ArH), 7.73 (d, 2H, 3a-ArH); $\delta_C$ (67.5 MHz) 16.5 (Me), 52.6 (3-C), 56.8 (7-C), 68.2 (6-C), 77.9 (3a-C), 78.9 (2-C), 140.0–126.3 (8 × Ar–C), 171.1 (4-C). NOEDS results: irradiation of 2-H caused the following enhancements 3b-H (8.5%), 7-H (8.8%), 6a-H (1.8%). Irradiation of 3a-H caused 3.7% enhancement on 3a-ArH, 2.8% on 2-H, 3.4% on the 2-ArH/3a-ArH multiplet and 25.2% on its partner 3b-H. Irradiation of 3b-H caused 8.9% enhancement on 2-H, 3.2 % on 6a-H and 27.9% on its partner 3a-H.

**15**; $\delta_H$ (270 MHz) 1.30 (3H, d, *J* 6.8, Me), 2.88 (1H, dd, *J* 5.9 & 13.0 3-H), 3.20 (1H, dd, *J* 10.6 & 13.0, 3-H), 3.48 (1H, m, 7-H) 4.25 (1H, dd, *J* 11.2 & 5.0 6a-H), 4.85 (1H, dd, *J* 11.2 & 11.9 6b-H,), 4.92 (1H, dd, *J* 10.6 & 5.9 2-H), 7.51–7.25 (10H m, ArH).

### 2,3,6,7-Tetrahydro-3a,7-dimethyl-2-phenylsulfonyl-3a*H*-isoxazolo[3,2-*c*][1,4]oxazin-4-one 16a

Freshly distilled nitrone **1a** (0.5 g, 3.50 mmol) and phenyl vinyl sulfone (0.74 g, 4.40 mmol) were stirred in xylene (100 cm$^3$) at reflux under $N_2$ for 36 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure (100 °C, 0.2 mmHg). Chromatography of the yellow gummy residue [$Et_2O$–petroleum ether, 1 : 1] gave the title compound (0.92 g, 85%), unreacted nitrone (8%) was returned.

**16a** Colourless needles, mp 170–172 °C (benzene–hexane) (Found; C, 53.94; H, 5.64; N, 4.61. $C_{14}H_{17}NO_5S$ requires C, 54.0; H, 5.47; N, 4.50%); $\delta_H$ (270 MHz) 1.27 (3H, d, *J* 5.9, 7-Me), 1.56 (3H, s, 3a-Me), 2.84 (1H, dd, *J* 7.7 & 13.6 3a-H), 3.21 (1H, dd, *J* 9.0 & 13.6, 3b-H), 3.61 (1H, m, 7-H), 4.00 (1H, dd, *J* 11.1 & 11.1, 6b-H), 4.24 (1H, dd, *J* 3.3 & 11.1, 6a-H), 5.05 (1H, dd, *J* 9.0 & 7.7, 2-H), 7.27 (2H, m, 2 × *m*-ArH), 7.74 (1H, m, *p*-ArH), 7.89 (2H, m, 2 × *o*-ArH); $\delta_C$ (67.5 MHz) 14.4

(7-Me), 24.9 (3a-Me), 39.7 (3-C), 55.0 (7-C), 69.4 (3a-C), 70.2 (6-C), 92.7 (2-C), 136.9–128.8 (4 × Ar–C), 170.1 (4-C). NOEDS results: irradiation of 2-H caused the following enhancements 3a-H (8.1%), 3a-Me (2.4%) and ArH (3.3%). Irradiation of 3b-H caused 3.7% enhancement on 2-H, 25.1% on 3a-H and 9.7% on 7-H. Irradiation of 3a-H caused 28.8% enhancement on 3b-H, 10.6% on 2-H and 4.2% on 3a-Me.

**Crystal structure determination for 16a †**

The structure was solved by direct methods, SHELXS-97,[31] and refined by full matrix least squares using SHELXL-97.[32] SHELX operations were automated using OSCAIL which was also used to obtain the drawings.[30] The XDS program was used for data reduction and the data was corrected for Lorentz and polarization effects but not for absorption.[33] Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC.

**2,3,6,7-Tetrahydro-7-methyl-3a-phenyl-2-phenylsulfonyl-3a*H*-isoxazolo[3,2-*c*][1,4]oxazin-4-one 16b.** Freshly recrystallised nitrone **1b** (2.0 g, 10.0 mmol), and phenyl vinyl sulfone (2.10 g, 12.5 mmol) were stirred in xylene (250 $cm^3$) at reflux under a $N_2$ atmosphere. After 42 h the reaction solvent was removed under reduced pressure. Chromatography of the yellow solid residue with $Et_2O$–petroleum ether, (10 : 19) as eluant yielded the title compound **16b** (1.60 g, 44%), unreacted nitrone **1b** was returned (0.96 g, 48%).

**16b** Cubic crystals, mp 119–121 °C (benzene–hexane) (Found; C, 60.94; H, 5.25; N, 3.64; $C_{19}H_{19}NO_5S$ requires C, 61.13; H, 5.09; N, 3.75%); $\delta_H$ (270 MHz) 1.39 (3H, d, *J* 6.0 Me), 3.52 (2H, m, 3a-H & 3b-H), 3.84 (1H, m, 7-H), 4.11 (1H, dd, *J* 10.6 & 11.5, 6b-H), 4.28 (1H, dd, *J* 3.1 & 11.5, 6b-H), 4.71 (1H, dd, *J* 7.9 & 8.6, 2-H), 7.35 (3H, m, ArH), 7.70–7.58 (3H, ArH), 7.83 (2H, m, ArH), 7.92 (2H, m, ArH); $\delta_C$ (67.5 MHz), 15.9 (Me), 42.0 (3-C), 56.7 (7-C), 71.6 (6-C), 75.8 (3a-C), 93.4 (2-C), 138.4–128.3 (8 × Ar–C), 169.8 (4-C).

**3a,6,7-Trimethyl-2-(phenylsulfonyl)tetrahydroisoxazolo-[3,2-*c*]-[1,4]oxazin-4-(2*H*)-one 16c.** Nitrone **1c** (0.10 g, 0.637 mmol) and phenyl vinyl sulfone (0.128 g, 0.764 mmol) were stirred in toluene (60 $cm^3$) at reflux under $N_2$ for 72 h. The reaction mixture was allowed to cool to rt, concentrated and purified by flash chromatography ($Et_2O$–petroleum ether; 1 : 2) yielding **16c** (63 mg, 30%) and returned dipole (59.5 mg, 60%).

**16c** Colourless needles, mp 182–183 °C (from $Et_2O$–petroleum ether) (Found: C, 55.29; H, 5.78; N, 3.92. $C_{15}H_{19}NO_5S$ requires: C, 55.38; H, 5.85; N, 4.31%); $\delta_H$ (400 MHz) 1.27 (3H, d, *J* 5.9, 7-Me), 1.42 (3H, d, *J* 6.4, 6-Me), 1.55 (3H, s, 3a-Me), 2.82 (1H, dd, *J* 13.6 and 7.8, 3a-H), 3.19 (1H, dd, *J* 13.6 and 9.2, 3b-H), 3.26 (1H, m, 7-H), 4.16 (1H, m, 6-H), 5.03 (1H, dd, *J* 9.2 and 7.8, 2-H), 7.62 (2H, m, 2 × ArH), 7.73 (1H, m, 1 × ArH), 7.94 (2H, m, 2 × ArH); $\delta_C$ (100 MHz) 14.76 (7-Me), 17.43 (6-Me), 24.82 (3a-Me), 39.81 (3-C), 61.12 (7-C), 69.15 (3a-C), 78.06 (6-C), 92.79 (2-C), 128.88 (ArC), 129.52 (ArC), 134.57 (ArC), 137.12 (*n*-ArC), 169.94 (4-C).

Crystal structure determination for **16c** as for **16a**

**3a,6,7-Trimethyl-2-(phenylsulfonyl) tetrahydroisoxazolo-[3,2-*c*]-[1,4] oxazin-4-(2*H*)-one 16d.** Nitrone **1d** (0.04 g, 0.26 mmol) and phenyl vinyl sulfone (0.05 g, 0.31 mmol) were stirred in toluene (25 $cm^3$) at reflux under $N_2$ for 192 h. The mixture was allowed to cool to rt, concentrated and purified by flash chromatography ($Et_2O$–petroleum ether, 1 : 1) yielding **16d** (25 mg, 29%) and returned dipole (23 mg, 56%).

† CCDC reference numbers 213558 and 213559. See http://www.rsc.org/suppdata/ob/b3/b307077h/ for crystallographic data in .cif or other electronic format.

**16d** Fine colourless needles, mp 178–179 °C (from $Et_2O$–petroleum ether), $R_f$ 0.7 ($Et_2O$, 100%) (Found: C, 55.37; H, 5.78; N, 4.56. $C_{15}H_{19}NO_5S$ requires: C, 55.38; H, 5.85; N, 4.31%); $\delta_H$ (400 MHz) 1.31 (3H, d, *J* 6.4, 7-Me), 1.37 (3H, d, *J* 6.8, 6-Me), 1.55 (3H, s, 3a-Me), 2.80 (1H, dd, *J* 13.7 and 7.8, 3a-H), 3.19 (1H, dd, *J* 13.7 and 9.0, 3b-H), 3.60 (1H, m, 7-H), 4.51 (1H, m, 6-H), 5.04 (1H, dd, *J* 9.0 and 7.8, 2-H), 7.61 (2H, m, 2 × ArH), 7.72 (1H, m, 1 × ArH), 7.94 (2H, m, 2 × ArH); $\delta_C$ (100 MHz) 15.16 (7-Me), 24.50 (6-Me), 29.55 (3a-Me), 40.00 (3-C), 57.23 (7-C), 69.25 (3a-C), 78.25 (6-C), 92.73 (2-C), 128.82 (ArC), 129.54 (ArC), 134.55 (ArC), 137.18 (*n*-ArC), 170.26 (4-C). NOEDS results: irradiation of 3a-H caused the following enhancements 3a-Me (2.0%), 3b-H (28.4%), 2-H (10.6%). Irradiation of 3b-H caused 7.5% enhancement on 7-H and 23.4% on 3a-H. Irradiation of 7-H caused 7.9% enhancement on 3b-H and 9.3% on 6-H.

**2-Acetyl-3a,7-dimethyltetrahydroisoxazolo[3,2-*c*][1,4]-oxazine-4(2*H*)-ones 17a–d.** Freshly distilled nitrone **1a** (0.97 g, 6.80 mmol) and methyl vinyl ketone (6 $cm^3$, 5.05 g, 72.0 mmol), were stirred in the presence of hydroquinone (2% $^w/_v$, 4.0 g) in xylene (200 $cm^3$) at reflux under $N_2$ for 32 h (using a double sided water condenser). The reaction mixture was allowed to cool to rt, both the reaction solvent and excess dipolarophile were removed under reduced pressure (100 °C, 0.5 mmHg). The brown gummy residue was taken up in $CHCl_3$ (2.5 $cm^3$) and allowed to stand at rt (0.5 h), the precipitated hydroquinone was filtered off (*in vacuo*). Purification of the crude products by flash chromatography ($Et_2O$ : petroleum ether, 1.3 : 1.0), yielded **17d**, a yellow oil (0.073 g, 5%) which solidified upon standing and was crystallised ($Et_2O$–hexane) to give colourless needles; **17b** an off white solid (0.17 g, 12%); **17a** a white solid (0.55 g, 38%); **17c** off white solid (0.15 g, 10%). Following a strip of the column ($Et_2O$) unreacted dipole (0.23 g, 24%) was obtained.

**17d** Colourless needles, mp 96–98 °C ($Et_2O$–hexane) (Found: C, 56.45; H, 6.94; N, 6.37. $C_{10}H_{15}NO_4$ requires: C, 56.34; H, 7.04; N, 6.57%); $\delta_H$ (270 MHz) 1.34 (3H, d, *J* 6.6, 7-Me), 1.50 (3H, s, 3a-Me), 2.31 (3H, s, COMe), 2.57 (1H, dd, *J* 4.2 & 13.4, 3b-H), 3.09 (1H, dd, *J* 9.5 & 13.2, 3a-H), 3.56 (1H, m, 7-H), 4.24 (2H, m, 2-H & 6a-H), 4.76 (1H, dd, *J* 11.4 & 11.4, 6b-H); $\delta_C$ (67.5 MHz) 14.6 (7-Me), 22.6 (3a-Me), 25.4 (CO*Me*), 44.1 (3-C), 49.1 (7-C), 66.6 (3a-C), 69.0 (6-C), 78.4 (2-C), 173.3 (4-C), 211.1 (*C*OMe). NOEDS results: irradiation of 7-H caused the following enhancements 2- & 6a-H (3.9%), 3a-Me (2.7%), 7-Me (6.3%) and 6b-H (1.8%). Irradiation of 3b-H caused 23.0% enhancement on its partner 3a-H, 2.6% enhancement on 6b-H and 2.1% on 3a-Me.

**17b** Colourless needles, mp 93–94 °C ($Et_2O$, hexane) (Found: C, 56.59; H, 7.21; N, 6.64. $C_{10}H_{15}NO_4$ requires: C, 56.34; H, 7.04; N, 6.57%); $\delta_H$ (270 MHz) 1.23 (3H, d, *J* 5.9, 7-Me), 1.48 (3H, s, 3a-Me), 2.30 (3H, s, COMe), 2.60 (1H, dd, *J* 13.4 & 5.1, 3a-H), 2.87 (1H, dd, *J* 13.4 & 9.8, 3b-H), 3.13 (1H, m, 7-H), 4.01 (1H, dd, *J* 11.5 & 10.1, 6b-H), 4.23 (1H, dd, *J* 11.5 & 3.5, 6a-H), 4.49 (1H, dd, *J* 9.8 & 5.1, 2-H); $\delta_C$ (67.5 MHz) 14.7 (7-Me), 26.4 (3a-Me), 27.4 (CO*Me*), 42.7 (3-C), 53.5 (7-C), 68.3 (3a-C), 70.1 (6-C), 80.6 (2-C), 171.8 (4-C), 206.6 (*C*OMe). NOEDS results: irradiation of 3a-H caused 15.4% enhancement on its partner 3b-H and 12.9% on 3a-Me. Irradiation of 2-H caused 6.7% enhancement on 3b-H and 7.0% on 7-H. Irradiation of 6b-H caused 2.7% enhancement on 7-H, 15.0% on 6a-H, 3.6% on 7-Me and 2.2% on 3a-Me. Irradiation of 6a-H caused 7.6% enhancement on 7-H, 18.8% on 6b-H and 3.3% on 7-Me. Irradiation of 7-H caused 5.1% enhancement on 2-H, 4.9% on 3b-H and 5.4% on 7-Me.

**17a** Colourless plates, mp 100–101 °C ($CHCl_3$–hexane) (Found: C, 56.24; H, 6.89; N, 6.29. $C_{10}H_{15}NO_4$ requires: C, 56.34; H, 7.04; N, 6.57%); $\delta_H$ (270 MHz) 1.25 (3H, d, *J* 5.9, 7-Me), 1.60 (3H, s, 3a-Me), 2.30 (3H, s, COMe), 2.62 (1H, dd, *J* 13.0 & 8.4, 3a-H), 2.72 (1H, dd, *J* 12.8 & 8.8, 3b-H), 2.96 (1H, m, 7-H), 3.99 (1H, dd, *J* 11.5 & 10.4, 6b-H), 4.18 (1H, dd, *J* 11.5

& 3.3, 6a-H), 4.60 (1H, dd, *J* 8.8 & 8.8, 2-H); $\delta_C$ (67.5 MHz) 14.4 (7-Me), 25.1 (3a-Me), 27.4 (CO*Me*), 41.1 (3-C), 54.5 (7-C), 69.5 (3a-C), 70.0 (6-C), 81.7 (2-C), 171.3 (4-C), 205.7 (*C*OMe). NOEDS results: irradiation of 2-H caused 6.8% enhancement on 3a-H, 3.1% on 3a-Me and 2.2% on 7-Me. Irradiation of 3a-Me caused an enhancement on 2-H (2.1%) and 7-Me (1.1%). Irradiation of 7-H caused 2.1% enhancement on 3b-H, 3.4% on 6a-H and 8.6% on 7-Me. Irradiation of 3a-H caused an enhancement on 2-H (5.0%), 3b-H (10.9%) and 3a-Me (7.4%).

**17c** Colourless needles, mp 92–93 °C ($CHCl_3$, hexane) (Found: C, 56.30; H, 7.09; N, 6.49. $C_{10}H_{15}NO_4$ requires: C, 56.34; H, 7.04; N, 6.57%); $\delta_H$ (270 MHz) 1.29 (3H, d, *J* 6.6, 7-Me), 1.55 (3H, s, 3a-Me), 2.16 (3H, s, COMe), 2.53 (1H, dd, *J* 13.6 & 9.9, 3b-H), 2.85 (1H, dd, *J* 13.6 & 6.5, 3a-H), 3.53 (1H, m, 7-H), 4.25 (1H, dd, *J* 11.3 & 4.4, 6a-H), 4.39 (1H, dd, *J* 9.1 & 6.6, 2-H), 4.83 (1H, dd, *J* 11.3 & 11.3, 6b-H); $\delta_C$ (67.5 MHz) 14.7 (7-Me), 22.8 (3a-Me), 26.3 (CO*Me*), 44.0 (3-C), 49.6 (7-C), 66.6 (3a-C), 69.2 (6-C), 79.4 (2-C), 172.8 (4-C), 205.6 (*C*OMe). NOEDS results: irradiation of 7-H caused 2.3% enhancement on 3a-Me, 2.3% on 6b-H, 1.8% on 6a-H and 10.9% on 7-Me. Irradiation of 3a-Me caused 1.7% enhancement on 3b-H and 2.4% on 6b-H. Irradiation of 3a-H caused 13.1% enhancement on its partner 3b-H and 4.6% on 2-H. Irradiation of 3b-H caused an enhancement on 2-H (2.3%), 3a-H (19.1%) and 3a-Me (4.1%).

**2-Acetyl-7-methyl-3a-phenyltetrahydroisoxazolo[3,2-*c*][1,4]-oxazine-4(2*H*)-ones 18a–d.** Nitrone **1b** (0.30 g, 1.46 mmol) and methyl vinyl ketone (3.26 g, 46.5 mmol) were stirred in toluene (50 $cm^3$) in the presence of hydroquinone (0.1%, $^w/_v$, 0.05 g) at reflux under $N_2$ for 100 h (using a double sided water condenser). The mixture was allowed to cool to rt and the solvent and excess dipolarophile were removed under reduced pressure leaving a viscous brown oil which was taken up in $CHCl_3$ and allowed to stand at rt for 0.5 h. The precipitated hydroquinone was removed by filtration with suction and the filtrate concentrated, yielding the crude product. $^1$H NMR analysis of the crude reaction mixture indicated a 33 : 6 : 4 : 2 mixture of **18a** : **18b** : **18c** : **18d**. Purification by flash chromatography ($Et_2O$–petroleum ether; 1 : 4), afforded, as enriched mixtures, **18d** (0.006 g, 2%), **18c** (0.030 g, 7%), **18b** (0.047 g, 12%) and as a pure sample, **18a** (0.269 g, 67%).

**18d** $\delta_H$ (400 MHz) 1.23 (3H, d, *J* 6.3, 7-Me), 1.75 (3H, s, COMe), 3.41 (1H, m, 7-H), 3.63 (1H, dd, *J* 12.0 and 11.7, 6b-H), 4.04 (2H, m, 3-H/6a-H), 4.36 (1H, dd, *J* 9.0 and 8.3, 3-H), 4.47 (1H, dd, *J* 8.3 and 7.2, 2-H), 7.36 (3H, m, *o*- & *p*-ArH), 7.54 (2H, m, *m*-ArH).

**18c** A colourless, mobile oil. $\delta_H$ (400 MHz) 1.26 (3H, d, *J* 6.8, 7-Me), 2.23 (3H, s, COMe), 2.85 (1H, dd, *J* 13.4 and 10.1, 3-H), 3.25 (1H, dd, *J* 13.4 and 6.1, 3-H), 3.48 (1H, m, 7-H), 4.28 (1H, dd, *J* 11.4 and 4.9, 6a-H), 4.62 (1H, dd, *J* 10.1 and 6.1, 2-H), 4.85 (1H, dd, *J* 11.5 and 11.4, 6b-H), 7.35 (3H, m, *o*- & *p*-ArH), 7.52 (2H, m, *m*-ArH).

**18b** A colourless mobile oil. $\delta_H$ (400 MHz) 1.32 (3H, d, *J* 6.4, Me), 2.23 (3H, s, COMe), 2.79 (1H, dd, *J* 4.2 and 13.3, 3-H), 3.52 (1H, m, 7-H), 3.56 (1H, dd, *J* 9.2 and 13.3, 3-H), 3.80 (1H, dd, *J* 11.7 and 11.7, 6b-H), 4.15 (1H, dd, *J* 4.2 and 11.7, 6a-H), 4.38 (1H, dd, *J* 4.2 and 9.2, 2-H), 7.33 (3H, m, *o*- & *p*-ArH), 7.53 (2H, m, *m*-ArH).

**18a** A colourless mobile oil (Found: C, 65.39; H, 6.09; N, 5.01. $C_{15}H_{17}NO_4$ requires: C, 65.46; H, 6.18; N, 5.09%); $\delta_H$ (400 MHz) 1.32 (3H, d, *J* 6.4, 7-Me), 2.22 (3H, s, COMe), 2.93 (1H, dd, *J* 7.8 and 13.1, 3a-H), 3.15 (1H, dd, *J* 9.1 and 13.1, 3b-H), 3.40 (1H, m, 7-H), 3.91 (1H, dd, *J* 11.6 and 11.2, 6b-H), 4.13 (1H, dd, *J* 11.6 and 3.7, 6a-H), 4.35 (1H, dd, *J* 7.8 and 9.1, 2-H), 7.34 (3H, m, *o*- & *p*-ArH), 7.74 (2H, m, *m*-ArH); $\delta_C$ (100 MHz) 15.43 (+ve) (7-Me), 26.73 (+ve) (COMe), 44.01 (−ve) (3-C), 56.49 (+ve) (7-C), 69.40 (−ve) (6-C), 73.99 (abs.) (3a-C), 81.33 (+ve) (2-C), 126.55, 128.50, 128.76 (+ve) (5 × ArC), 138.40 (abs.) (*n*-ArC), 170.24 (abs.) (C=O), 205.44 (abs.) (*C*OMe). NOEDS results: irradiation of 3a-H caused the following enhancements 3a-Ph (7.8%), 3b-H (24.5%), 2-H (6.4%). Irradiation of 3b-H caused 2.7% enhancement on 7-H and 20.9% on 3a-H. Irradiation of 7-H caused 1.7% enhancement on 3b-H, 4.4% on 7-Me and 3.5% on 6a-H.

**2-Methyloxycarbonyl-6-*tert*-butyl-2,3,6,7-tetrahydro-7-methyl-3a-phenyl-3a*H*-isoxazolo[3,2-*c*][1,4]oxazin-4-one 19.** Freshly recrystallised nitrone **1g** (0.21 g, 0.81 mmol), methyl acrylate (2.25 $cm^3$, 2.15 g, 25.00 mmol) and hydroquinone (0.10% $^w/_v$, 0.03 g) were stirred in toluene (30 $cm^3$) at reflux under $N_2$ for 110 h (using a double sided water condenser). The reaction mixture was allowed to cool to rt, both the reaction solvent and excess dipolarophile were removed under reduced pressure (100 °C, 0.50 mmHg). The highly viscous residue was taken up in chloroform and allowed to stand at rt for 0.5 h, the precipitated hydroquinone material was filtered off *in vacuo* and the filtrate was concentrated. Purification of the crude mixture by flash chromatography ($Et_2O$ : petroleum ether, 1 : 2) yielded **19** as a highly viscous colourless oil (0.19 g, 68%), unchanged dipole was returned (0.05 g, 24%).

**19** Bp 90–94 °C, 0.025 mmHg (Found: C, 65.86; H, 7.28; N, 3.89. $C_{19}H_{25}NO_5$ requires: C, 65.71; H, 7.21; N, 4.04%); $\delta_H$ (270 MHz) 1.01 (9H, s, $Me_3C$), 1.42 (3H, d, *J* 5.9, Me), 2.93 (1H, dd, *J* 13.2 & 8.1, 3b-H), 3.38 (1H, dd, *J* 13.2 & 7.3, 3a-H), 3.52 (1H, m, 7-H), 3.58 (d, 1H, *J* 11.0, 6-H), 3.77 (3H, s, OMe), 4.51 (1H, dd, *J* 8.1 & 7.3, 2-H), 7.35 (3H, m, ArH), 7.28 (2H, ArH); $\delta_C$ (67.5 MHz) 18.1 (Me), 26.6 (3 × Me), 34.5 ($CMe_3$), 46.7 (3-C), 52.5 (OMe), 60.4 (7-C), 68.6 (6-C), 75.2 (3a-C), 86.8 (2-C), 138.5–126. (4 × ArC), 170.5 (*C*$O_2$Me), 171.3 (4-C). NOEDS results: irradiation of the signal representing the $CMe_3$ protons caused the following enhancements 2.1% on 2-H, 1.2% on 3a-H, 7.4% on 7-H and 1.2% on *o*-ArH. Irradiation of 7-Me caused an enhancement on 7-H (10.4%), on 6-H (2.3%) and 7.4% on *o*-ArH. Irradiation of 2-H caused 5.9% enhancement on 3b-H and 4.2% on $CMe_3$. Irradiation of 3a-H caused an enhancement on 3b-H (32.1%) and ArH (6.2%).

**Methyl 3a-methyl-7-phenyl-4-oxohexahydroisoxazolo[3,2-*c*]-[1,4]oxazine-2-carboxylates 20a & 20b.** Freshly recrystallised nitrone **1b** (1.12 g, 5.50 mmol), methyl acrylate (15 $cm^3$, 14.34 g, 0.17 mol) and hydroquinone (0.10% $^w/_v$, 0.20 g) were stirred in toluene (200 $cm^3$) at reflux under $N_2$ for 110 h (using a double sided water condenser). The reaction mixture was allowed to cool to rt, and the reaction solvent and excess dipolarophile were removed under reduced pressure (100 °C, 0.50 mmHg). The highly viscous residue was taken up in $CHCl_3$ and allowed to stand at rt for 0.5 h, the precipitated hydroquinone was filtered off *in vacuo* and the filtrate was concentrated. Purification of the crude products by flash chromatography ($Et_2O$ : petroleum ether, 1.0 : 1.3) yielded **20a** (1.06 g, 67%) and **20b** (0.35 g, 22%) both as highly viscous colourless oils, unreacted dipole (0.08 g, 7%) was returned.

**20a** Bp 154–156 °C, 0.03 mmHg (Found: C, 61.82; H, 5.80; N, 4.79. $C_{15}H_{17}NO_5$ requires: C, 61.86; H, 5.84; N, 4.81%); $\delta_H$ (270 MHz) 1.35 (3H, d, *J* 5.9, Me), 3.13 (1H, dd, *J* 13.2 & 8.1, 3b-H), 3.25 (1H, dd, *J* 13.2 & 8.1, 3a-H), 3.63 (1H, m, 7-H), 3.76 (3H, s, OMe), 3.96 (1H, dd, *J* 11.5 & 11.0, 6b-H), 4.16 (1H, dd, *J* 11.5 & 3.3, 6a-H), 4.40 (1H, dd, *J* 8.1 & 8.1, 2-H), 7.36 (3H, m, ArH), 7.77 (2H, d, ArH); $\delta_C$ (67.5 MHz) 15.1 (Me), 45.4 (OMe), 56.2 (7-C), 52.56 (3-C), 69.7 (6-C), 74.2 (3a-C), 75.6 (2-C), 138.4–126.7 (4 × Ar–C), 169.9 (*C*$O_2$Me), 171.5 (4-C). NOEDS results: irradiation of 2-H caused 6.7% enhancement on 3a-H and 2.4% on ArH. Irradiation of 3a-H caused an enhancement on 2-H (2.3%), 3b-H (8.5%) and ArH (3.9%). Irradiation of Me caused the following enhancements 6b-H (6.5%), 6a-H (4.1%), 7-H (15.2%) and ArH (1.1%). Irradiation of 6b-H caused 14.6% enhancement on 6a-H, 6.8% on 7-H and 2.5% on ArH.

**20b** (Found: C, 61.99; H, 5.72; N, 4.96. $C_{15}H_{17}NO_5$ requires: C, 61.86; H, 5.84; N, 4.81%); $\delta_H$ (270 MHz) 1.31 (3H, d, *J* 6.6,

Me), 2.90 (1H, dd, *J* 13.2 & 5.1, 3-H), 3.45 (1H, m, 7-H), 3.57 (1H, m, 3-H), 3.61 (3H, s, OMe), 3.82 (1H, dd, *J* 11.7 & 11.0, 6b-H), 4.11 (1H, dd, *J* 11.7 & 3.7, 6a-H), 4.64 (1H, dd, *J* 8.8 & 5.1, 2-H), 7.34 (3H, m, ArH), 7.65 (2H, d, ArH); $\delta_C$ (67.5 MHz) 16.0 (Me), 46.0 (OMe), 52.3 (3-C), 56.8 (7-C), 68.7 (6-C), 73.6 (3a-C), 74.5 (2-C), 138.1–126.4 (4 × Ar–C), 169.7 ($CO_2Me$), 170.6 (4-C).

**Methyl 3a,7-dimethyl-4-oxohexahydroisoxazolo[3,2-*c*][1,4]-oxazine-2-carboxylates 21a, 21b & 21c.** Nitrone **1a** (0.27 g; 1.9 mmol) and methyl acrylate (2.88 g; 33.5 mmol) were stirred in toluene (100 $cm^3$) in the presence of hydroquinone (0.1% $^w/_v$, 0.1 g) at reflux under $N_2$ for 45 h (using a double sided water condenser). The reaction mixture was allowed to cool to rt and was concentrated under reduced pressure leaving a brown gummy residue, which was taken up by $CHCl_3$ (5 $cm^3$) and allowed to stand at rt for 0.5 h, the precipitated hydroquinone was removed by filtration with suction and the filtrate concentrated. Purification by flash chromatography ($Et_2O$–petroleum ether, 1.5 : 1.0), afforded **21a** (0.169 g, 39%), **21b** (0.105 g, 25%), **21c** (0.029 g, 7%) and returned dipole (0.097 g, 36%).

**21a** Colourless needles, mp 90–93 °C (from $Et_2O$–hexane) (Found: C, 52.58; H, 6.73; N, 6.09. $C_{10}H_{15}NO_5$ requires: C, 52.43; H, 6.55; N, 6.11%); $\delta_H$ (400 MHz) 1.26 (3H, d, *J* 6.1, 7-Me), 1.57 (3H, s, 3a-Me), 2.76 (2H, d, *J* 8.6, 3a-H/3b-H), 3.23 (1H, m, 7-H), 3.78 (3H, s, OMe), 4.02 (1H, dd, *J* 11.4 and 10.7, 6b-H), 4.20 (1H, dd, *J* 11.4 and 3.2, 6a-H), 4.62 (1H, t, *J* 8.6, 2-H); $\delta_H$ ($C_6D_6$, 400 MHz) 0.97 (3H, d, *J* 6.1, 7-Me), 1.37 (3H, s, 3a-Me), 2.22 (1H, dd, *J* 12.9 and 8.7, 3a-H), 2.43 (1H, dd, *J* 12.9 and 8.7, 3b-H), 2.84 (1H, m, 7-H), 3.21 (3H, s, OMe), 3.38 (2H, m, 6a/6b-H), 4.10 (1H, t, *J* 8.7, 2-H); $\delta_C$ ($C_6D_6$, 100 MHz) 14.22 (7-Me), 24.84 (3a-Me), 43.44 (3-C), 51.84 (OMe), 54.30 (7-C), 69.76 (3a-C), 70.01 (6-C), 75.79 (2-C), 170.43 and 172.21 ($CO_2Me$ and C=O). NOEDS results ($C_6D_6$): irradiation of 3a-Me caused the following enhancements 3a-H (1.5%) and 2-H (1.0%). Irradiation of 7-H caused 1.7% enhancement on 3b-H. Irradiation of 2-H caused 1.1% enhancement on 3a-H.

**21b** A white crystalline solid, mp 97–99 °C (from $Et_2O$–petroleum ether) (Found: C, 52.65; H, 6.79; H, 5.89. $C_{10}H_{15}NO_5$ requires: C, 52.40; H, 6.55; N, 6.11%); $\delta_H$ (400 MHz) 1.24 (3H, d, *J* 6.1, 7-Me), 1.62 (3H, s, 3a-Me), 2.66 (1H, dd, *J* 13.4 and 5.3, 3a-H), 2.97 (1H, dd, *J* 13.4 and 10.0, 3b-H), 3.05 (1H, m, 7-H), 3.82 (3H, s, OMe), 4.03 (1H, dd, *J* 11.2 and 10.9, 6b-H), 4.22 (1H, dd, *J* 11.2 and 3.2, 6a-H), 4.67 (1H, dd, *J* 10.0 and 5.3, 2-H); $\delta_C$ (100 MHz) 14.37 (7-Me), 25.88 (3a-Me), 43.88 (3-C), 52.71 (OMe), 53.14 (7-C), 68.89 (3a-C), 69.70 (6-C), 74.07 (2-C), 170.32 and 171.47 ($CO_2Me$ and C=O). NOEDS results: irradiation of 2-H caused 4.1% enhancement on 3b-H and 3.6% on 7-H. Irradiation of 3a-Me gave a 0.9% enhancement on 3a-H.

**21c** Fine yellow crystals, mp 76–78 °C (from $Et_2O$–petroleum ether). Microanalytical data and $^{13}C$ NMR spectral data were obtained as a mixture of **21c** with **21b** [1 : 1.4]) (Found: C, 52.16; H, 6.42; N, 5.78. $C_{10}H_{15}O_5N$ requires: C, 52.40; H, 6.55; N, 6.11%); $\delta_H$ (400 MHz) 1.29 (3H, d, *J* 7.0, 7-Me), 1.56 (3H, s, 3a-Me), 2.60 (1H, dd, *J* 13.3 and 10.0, 3b-H), 2.99 (1H, dd, *J* 13.3 and 4.6, 3a-H), 3.56 (1H, m, 7-H), 3.75 (3H, s, OMe), 4.21 (1H, dd, *J* 11.0 and 4.4, 6a-H), 4.53 (1H, dd, *J* 10.0 and 4.6, 2-H), 4.96 (1H, dd, *J* 11.4 and 11.0, 6b-H); $\delta_C$ (100 MHz) 14.50 (7-Me), 22.78 (3a-Me), 45.50 (3-C), 49.87 (OMe), 52.37 (7-C), 68.93 (6-C), 72.63 (3a-C), 170.71 and 172.45 ($CO_2Me$ and C=O). NOEDS results: irradiation of 2-H caused 2.7% enhancement on 3b-H.

**Trimethyl 1-oxo-4-[1-(phenylselenyl)ethyl]-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-6,7,8-tricarboxylate 23.** Nitrone **10a** (0.10 g, 0.32 mmol) and dimethyl acetylenedicarboxylate (0.068 g, 0.48 mmol) were heated at reflux in $CHCl_3$ (10 $cm^3$) under $N_2$ for 72 h. The mixture was allowed to cool to rt and the solvent removed under reduced pressure. Purification by column chromatography ($Et_2O$–petroleum ether, 1 : 1) returned unreacted dipole and the adduct **23** (0.0704 g, 45%) together with a complex mixture of compounds.

**23**, A viscous yellow oil, $R_f$ 0.2 ($Et_2O$). $\delta_H$ (400 MHz) 1.38 (3H, d, *J* 7.6, Me), 3.60 (1H, quintet, *J* 7.3, CH-Se), 3.78, 3.86, 3.91 (3 × 3H, 3 × s, 3 × OMe), 4.61 (1H, dd, *J* 12.5 and 2.7, 4-H), 5.03 (1H, d, *J* 12.7, 3a-H), 5.21 (1H, dd, *J* 8.3 and 2.9, 3b-H), 7.30 (3H, m, *o*- & *p*-ArH), 7.47 (2H, m, 2 × *m*-ArH), $\delta_C$ (100 MHz) 19.23 ($CH_3$), 39.01 (CH-Se), 39.10 (4-C), 52.69 (2 × OMe), 57.10 (OMe), 67.63 (3-C), 120.88 (C=N), 122.15, 123.68, 127.24 (6-C, 7-C, 8-C), 128.43, 129.24, 135.10 (ArC), 155.10, 159.51, 162.40, 163.42 (3 × $CO_2Me$ and C=O); *m*/*z* 495 (M + 1), 493, 306, 236, 184 ($CH(CH_3)SePh$), 182, 156, 105.

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