Isoxazolo[2,3-d][1,4]benzoxazepine rings from 1,3-dipolar cycloaddition of [1,4]benzoxazepine *N*-oxides with acetylenic and olefinic dipolarophiles

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Dedicated to Professor Tony McKervey on his 65th birthday

(received 07 Mar 03; accepted 02 May 03; published on the web 11 May 03)

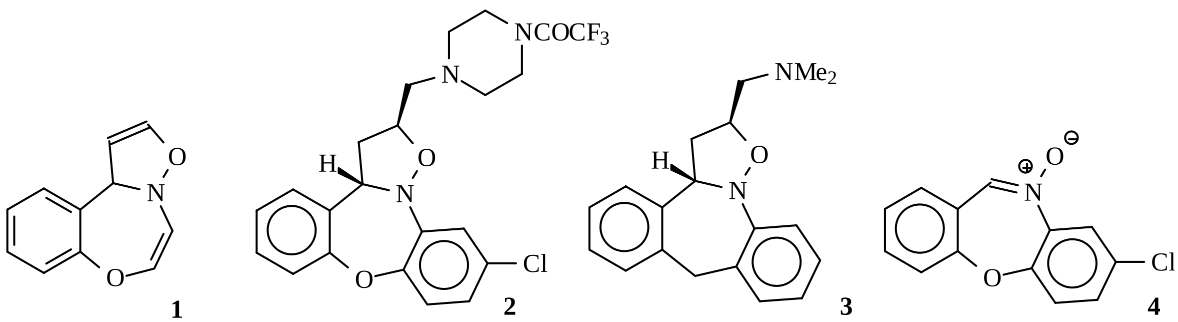
Abstract

1,3-Dipolar cycloaddition of [1,4]benzoxazepine *N*-oxides to triple and double bonded dipolarophiles affords di- and tetrahydro-isoxazolobenzoxazepines in the first reported synthesis of this tricyclic ring system. It is observed that in addition to the acetylenic dipolarophiles the diastereofacial selectivity varied both with the nature of the C-nitrone substituent as well as on the degree of substitution of the dipolarophile. Addition to alkene substrates occurred regiospecifically furnishing "5-substituted" isoxazolidine rings. For each olefinic dipolarophile the major cycloadduct arose *via* an *endo*-addition of the dipolarophile to the β-face of the dipole. Some of the new tricycles displayed sharp signals in their pmr spectra whilst signal duplication/broadening was evident for others indicating the adducts exist in solution as pairs of conformational isomers which reach coalescence at or close to room temperature. Preliminary investigations show the isoxazolidine ring of the tricycles can be cleaved under reductive and oxidative conditions affording novel benzoxazepines. The structure of the cycloadduct **6a** formed between the C-phenyl nitrone **5a** and dimethyl acetylenedicarboxylate and has been solved by single crystal xray analysis.

Keywords: Isoxazolo[2,3-d][1,4]benzoxazepine, [1,4]benzoxazepine *N*-oxide, 1,3-dipolar cycloaddition, spectroscopy, xray crystal structure

Introduction

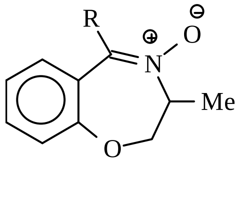
The clinical importance of the 1,4-benzodiazepine drugs makes synthesis of analogues important and derivatives with an additional heterocyclic ring fused to the "a", "c" or "d" edges have been investigated[1-4,5]. We have previously contributed to this area in the synthesis of di- and tetrahydroisoxazolo[2,3-d][1,4]benzeneodiazepinones from dipolar cycloaddition to a range of benzodiazepinone *N*-oxides[6,7]. We now report an investigation into the preparation of a related, yet hitherto unknown series of compounds *viz* tricyclic isoxazolo[2,3-d][1,4]benzoxazepines **1**. Given the structural similarity between the new tricycles and the tetracyclic isoxazolodibenzoxazepine **2** reported by Jannsen it is anticipated that the former may have interesting biological activity. Jannsen have filed a patent detailing the preparation of the tetracycle **2** by cycloaddition of the nitrone **4** to terminally unsaturated amines. The tetracycle is claimed to have biological activity – in the "elevated and illuminated plus maze test"[8]. In a second patent the same group claim preparation of azepine analogues, *e.g.* **3**, which may have application in the treatment of CNS, cardiovascular or gastrointestinal disorders[9].



1 **2** **3** **4**

Results and Discussion

The current approach to the targeted di- and tetrahydroisoxazolo[2,3-d][1,4]benzoxazepines involves 1,3-dipolar cycloaddition of the benzoxazepine nitrones **5** to acetylenic as well as olefinic dipolarophiles. We have previously reported synthesis of the bicyclic nitrones beginning from hydroxybenzophenone and hydroxyacetophenone respectively[10]. The C-phenyl nitrone **5a** reacted with dimethyl acetylenedicarboxylate ($CHCl_3$ for 32 h) to furnish a single cycloadduct, **6a** (90%). The resonance signals for **6a** ($CDCl_3$, room temperature) were sharp suggesting either that the tricyclic framework adopts a single preferred conformation or that equilibration between conformational isomers is very rapid at room temperature. This observation is in line with our earlier finding that the isoxazolobenzodiazepinones **7**[11] and the isoxazolopyrimidodiazepinone **8**[12] have sharp pmr spectral signals, on the other hand Romeo's related tricycles, *e.g.* **9** (R = Et, Me) exist as a mixture of slowly interconverting diastereomers[13,14]. The two isomeric forms, **9-f** folded and **9-e** extended, result from the flexibility of the 7-membered ring, the barrier to inversion of which is calculated at ~17 kCal mol^{-1}. One significant structural feature uniting compounds **6a**, **7** & **8** and dividing them from Romeo's adduct **9**, is the presence of a C-5 substituent, accordingly we conclude that this substituent may be important in determining the conformational preferences of the tricycle at room temperature.



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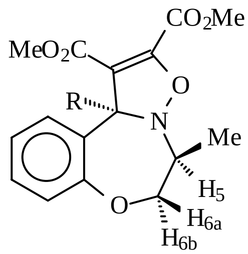
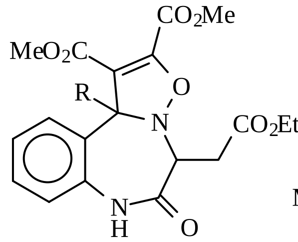
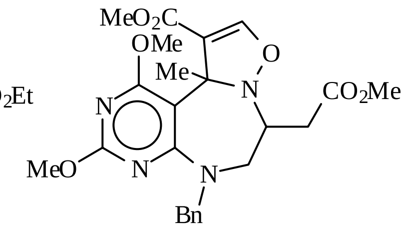
b. R = Me



6 a. R = Ph
b. R = Me



7 *e.g.* R = Me, H



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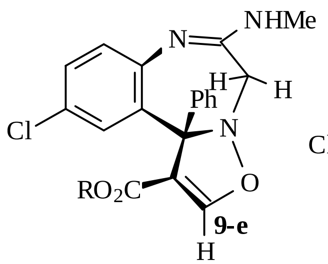
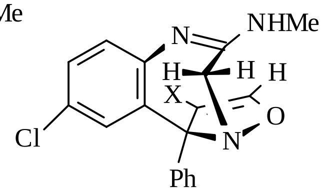
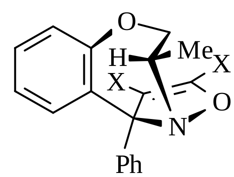


9-e



9-f

X = CO_2Me



6a-f

NOEDS data for **6a** (and all the dihydro-adducts in the series) was inconclusive, thus relative stereochemistry could not be assigned by spectral methods. However, single crystal xray structure analysis reveals **6a** to have the 3-dimensional structure shown in Figure 1[15-17]. In keeping with Romeo's terminology the tricyclic framework adopts a folded conformation in the solid state **6a-f**. The boat like conformation of the 7-membered ring is such that it would be simplistic to describe the C-11b aryl ring and the C-5 groups simply as being *cis* or *trans*. However, it is clear that in the transition state leading to **6a** that the dipolarophile must have approached the nitrone on the α–face, *i.e.* the face bearing the C-3 methyl substituent, Figure 2.

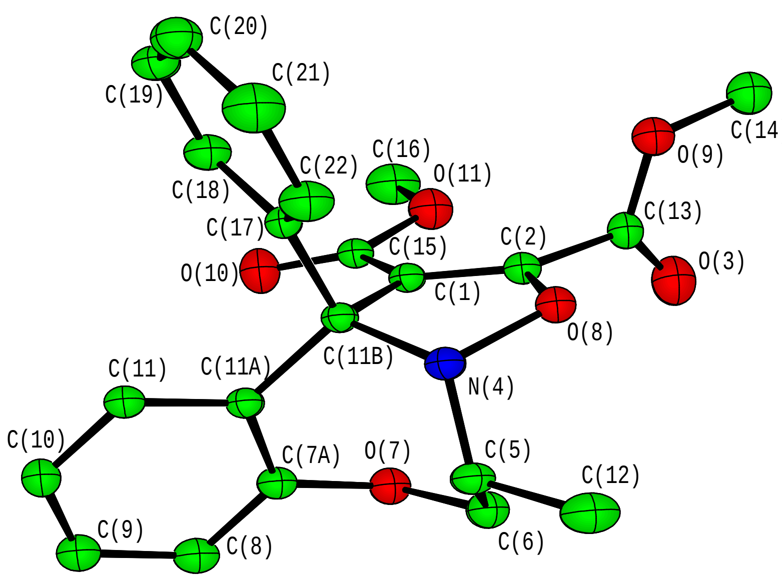


Figure 1. OSCAIL Representation of **6a**.

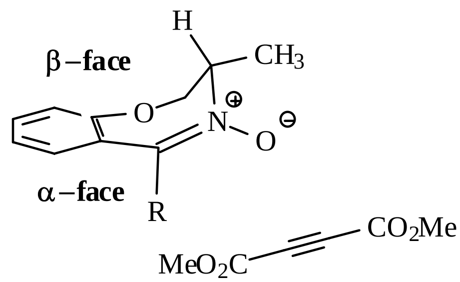
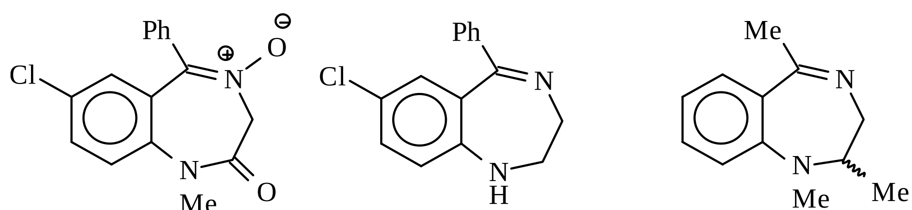


Figure 2

In attempting to account for the facial specificity of the cycloaddition we aimed firstly to establish the most likely conformation of the reacting dipole. A survey of the literature reveals that neither theoretical nor experimental data on the conformational preferences of the 2,3-dihydro-1,4-benzoxazepine system are available. Accordingly, whilst neither is an ideal model for the dipoles **5,** the closest are the diazepam-4-oxide **10**[18] and the 5-phenyl-7-chlorobenzodiazepine **11**[19]. Crystal structure data for **10** and **11** indicate that the 7-membered ring adopts a boat conformation in the solid state. Messinger and Buss in a PM3-quantum mechanical study suggest that the more sterically hindered a 2,3-dihydro-1*H*-1,4-benzodiazepine the more favoured the boat over the half-chair conformers, for example the boat conformation of the 1,2,5-trimethyl substituted bicycle **12** is estimated to be 1.39 to 3.75 kCal mol^{-1} more stable that the alternate lowest energy chair forms[20]. Following from these reports and on inspection of Dreiding scale models it is suggested that the seven membered ring of **5** also adopts a boat conformation and one diastereomeric form, with the C-3 methyl in the less sterically hindered *pseudo* equatorial[21] position, is shown in Figure 2. In some of the pmr spectra of the nitrones **5a** and **5b** (room temperature, $CDCl_3$) there is evidence for the existence of two doublets representing the C-3 methyl protons, *e.g.* a pair of doublets centered about 1.38 ppm (major, *J* 6.4) and 1.37 ppm (minor, *J* 6.6) are visible for **5b**, no duplication of other signals is observed. In other ^{1}H and in all the ^{13}C nmr spectra of the same molecule there is no signal duplication and all signals are sharp, these observations suggest that the bicyclic nitrones are present in solution as a pair of conformers which have almost reached coalescence at room temperature.



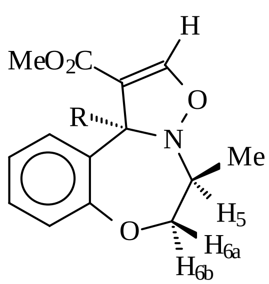
10 **11** **12**

In the transition state of a 1,3-dipolar cycloaddition the two reactants approach each other in parallel planes, the crystallographic data of **6a** indicates it arose from an approach of the dipolarophile to the face of the dipole bearing the methyl group (α-face), Figure 2. Our explanation for the observed facial preference lies with an inspection of a Dreiding scale model of **5a** which shows the *pseudo* equatorial methyl substituent to be almost co-planar with the dipolar moiety [CH_3-C3-N4-C5 dihedral angle ~15^o], thus, the steric impact of the methyl group is not significantly greater on the α-face than it is on the β-face of the 7-membered ring. Infact the β-face with the *pseudo* axial C-3 proton is more crowded. Thus, the dipolarophile adds to the α-face as it is less crowded than the β-face.

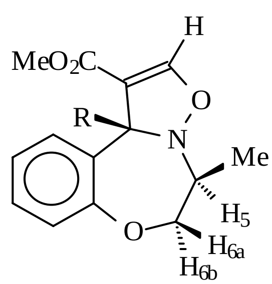
Facial specificity was lost upon reaction with methyl propiolate and the diastereomeric adducts **13a** and **14a** (~4:1) resulted after heating at reflux in $CHCl_3$ (36 h). Reaction of nitrones with electron poor acetylenic dipolarophiles is expected to yield 4-substituted isoxazolines[22]. That **13a** and **14a** have the expected regiochemistry is deduced from the resonance position of the vinylic proton which appears at 7.24 and 7.71 ppm. That cycloaddition to both the α- and the β-faces of the dipole occurs with the monosubstituted dipolarophile is likely a simple reflection of the reduced steric demands of the dipolarophile. In the transition state for the formation of the "4-substituted" isoxazolines there is no destabilising steric interaction between the dipolarophile substituent and the H/CH_3 at the C-3 position of the dipole.

It is impossible to determine the relative stereochemistry of either adduct by NOEDS analysis. However, it is possible to discriminate between **13a** and **14a** following from a comparison of the resonance positions of their ring protons [H-5 and the methylenic pair H-6a/6b] with the data obtained for **6a** where the relative stereochemistry is unambiguously known, selected data are summarised in Table 1. Thus, the resonance signals for H-5, H-6a, H-6b of the major adduct **13a** appear at similar positions to the corresponding protons in **6a**, whilst those of the minor adduct **14a** show an upfield shift, of most significant magnitude for the H-6a (Δ 0.68 ppm) and H-6b protons (Δ 0.33 ppm). It is proposed that the major adduct, **13a**, has the same relative configuration as **6a** and that the minor adduct, **14a**, has the C-11b Ph and the C-5 Me substituents of the 7-membered ring on the "same" face of the tricyclic skeleton.

It is of interest that the pmr spectral signals of the minor adduct **14a** are sharp whilst those of **13a** shows some signal duplication at room temperature, *e.g.* the signal for Me-5 is represented by overlapping doublets at 1.21 and 1.22 ppm suggesting **13a** has a higher barrier to conformational inversion than either **6a** or **14a**.

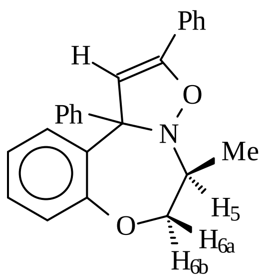


13 a. R = Ph
b. R = Me



14 a. R = Ph
b. R = Me

The same dipole reacted with an excess of phenyl acetylene (30 equivalents) affording isomeric adducts **15** (40%) and **16** (55%). The formation of regioisomers is a consequence of a delicate balance between the steric factors promoting the 5-substituted isomer and the electronic factors favouring the 4-substituted product[22]. Discrimination between the regioisomers is based on the resonance position of the vinylic proton, for **15** H-1 appears as a singlet at 5.88 ppm whist H-2 of **16** resonates together with the aryl protons (m, 7.02-7.56 ppm). There is insufficient similarity between the pmr positions for the ring protons of **15**/**16** with **6a** (Table 1) to draw any conclusions with regard to the relative stereochemistry of the regioisomeric adducts.



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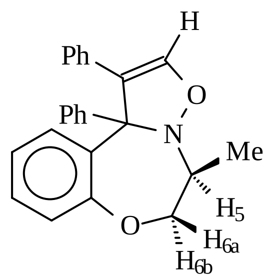

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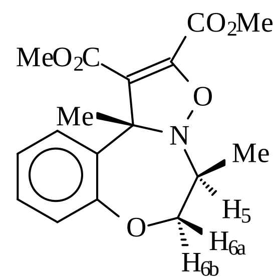


17

Cycloaddition of the C-methyl nitrone **5b** with either of the acetylenic dipolarophiles occurred, with minimal facial selectivity. Reaction with dimethyl acetylenedicarboxylate furnished the diastereomeric cycloadducts **6b** and **17** in an 11:9 ratio. It is thus apparent that the dipole C-substituent plays an important role in dictating facial preferences and with a methyl group in this position the two faces of the dipole **5b** are almost equally attractive to the approaching dipolarophile. That the major adduct **6b** has the same relative stereochemistry as **6a** is concluded on the basis of the similarity between the resonance positions of the protons of the 7-membered ring in the two adducts (Table 1). The signals for H-5, H-6a, H-6b of **17** are shifted upfield with respect to **6a** indicating **17** arises from addition to the β-face of the dipole. Both **6b** and **17** have sharp resonance signals in their pmr spectra in accordance with conformational inversion on the nmr time scale at room temperature.

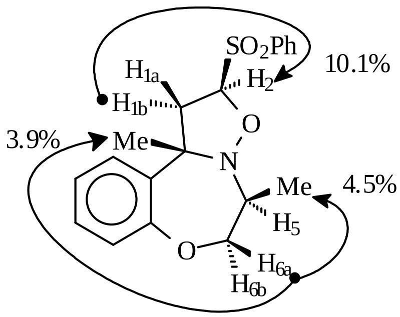
Two diastereomeric cycloadducts also resulted from addition of **5b** to methyl propiolate. For each isomer the vinylic proton resonates at ~7.5 ppm. The 6a-H and 6b-H of the minor adduct **14b** are both more shielded than the corresponding protons in **13b** thus it is concluded that the major adduct, **13b** (50%), arises from dipolarophile addition to the α-face and the minor adduct, **14b** (38%), from addition to the β-face of the nitrone.The pmr spectral signals ($CDCl_3$, room temperature) of **13b** are sharp whilst those for **14b** show some broadening and infact, two singlet signals at 7.554 and 7.549 represent the H-2 proton. These data suggest a high barrier to conformational inversion for **14b** with respect to **13b**.

Table 1. Selected pmr spectral data for adducts **6**, **13**, **14**, **15**, **16** & **17** (chemical shifts in δ units)

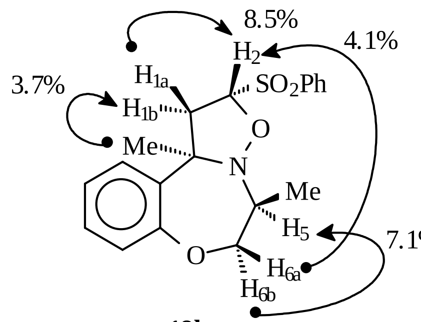
Adduct	Me-11b	Me-5	H-5	H-6b	H-6a
6a	-	1.24	3.54	3.94	4.25
13a	-	1.22 & 1.21	3.64	3.84 & 3.82	4.14 & 4.13
14a	-	1.13	3.23	3.61	3.57
15	-	1.29	3.77	3.92	4.11
16	-	1.32	3.66	4.4	
6b	2.03	1.17	3.32	4.02	4.17
17	1.92	1.14	3.31	3.73	4.18
13b	2.07	1.15	3.23	3.99	4.16
14b	1.92	1.15	3.34	3.74 (br)	4.11 (br)

Cycloaddition of the nitrones **5** to unsymmetrical olefinic dipolarophiles leaves open the possibility for the formation of regio- and diastereomeric cycloadducts. Indeed Varlamov *et al* have noted that the related nitrone, 5-methyl-4,5-dihydro-3*H*-spiro[benz-2-azepine-3,1'-cyclohexane] *N*-oxide reacts with acrylonitrile[23a] with no selectivity, but with selectivity to trimethylvinylsilane[23b] or styrene[23c]. Reaction of **5b** with each of phenyl vinyl sulfone, methyl acrylate and methyl vinyl ketone progressed slowly upon heating in boiling toluene (100 h, 110 ^{o}C, N_2). In all cases reaction occurred regiospecifically, however, facial and *exo/endo* selectivity varied with the dipolarophile. Addition to phenyl vinyl sulfone progressed with the least selectivity and addition to methyl vinyl ketone with the greatest selectivity. The major adduct in all three cases arose from an *endo* addition of the dipolarophile to the β-face of the dipole.

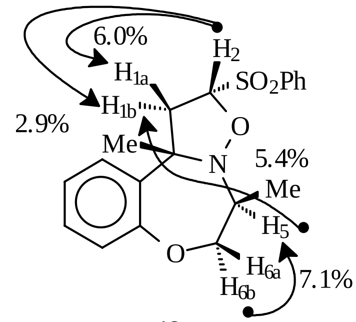
Reaction between **5b** and phenyl vinyl sulfone furnished three diastereomeric adducts **18a**, **18b** and **18c** isolated in 8, 14 and 20% yield respectively. That all adducts bear "5-substituted" isoxazolidine rings is evident from the resonance position of the H-2 proton; in the pmr spectrum of all three isomers of **18** the H-2 signal appears as a dd at ~5 ppm. The relative stereochemistry of each adduct has been assigned following analysis of NOEDS data, key enhancements are shown in Figure 3. The minor adduct arises from an *exo* addition of the dipolarophile to the β-face of the dipole and the major product from an *endo* addition to the same face. The intermediate product, **18b** is a result of an *exo* addition to the α-face of the dipole.



18a



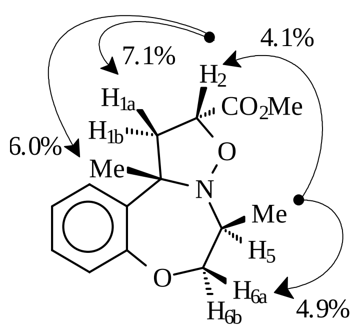
18b



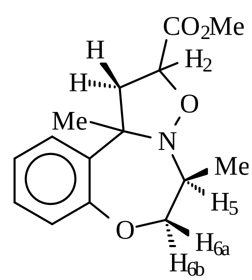
18c

Figure 3

Reaction of **5b** with methyl acrylate with furnished, following purification by flash column chromatography, diastereomeric adducts **19a** (56%) and **19b** (20%). The former was obtained as an enriched sample with a trace amount of a third diastereomer. The resonance position of the H-2 proton in **19a** and **19b** indicates they each bear a 5-substituted isoxazolidine ring. NOEDS data for the major adduct suggests it arises by way of an *endo* attack on the β-face of the dipole. NOEDS data for the minor adduct, **19b**, were inconclusive.

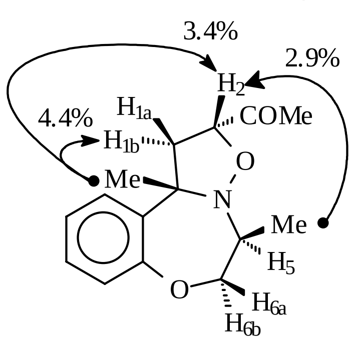


19a

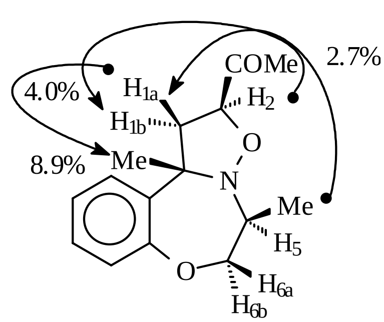


19b

The greatest facial selectivity was observed in the cycloaddition to methyl vinyl ketone and **20a**, the major product (69%), results from an *endo* addition to the β-face of the dipole. NOEDS results for are shown in the drawing. The minor adduct, **20b** (17%) arises from *exo* addition to the same face. For each adduct the H-2 proton appears in the pmr spectrum at ~4.4 ppm which characterises both the isoxazolidine rings as having a 5-substitution pattern.

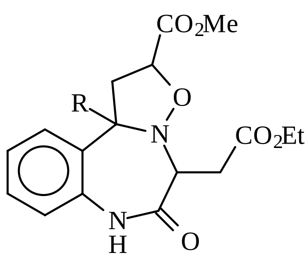


20a

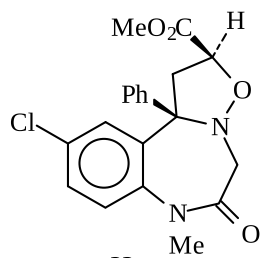


20b

It is of interest that in the pmr spectra ($CDCl_3$) of adducts, **18-20**, resulting from trapping of the benzoxazepine nitrone **5b** with olefinic dipolarophiles, only **19a** and **19b** showed any evidence for signal broadening. In each of these adducts the signals representing 5-H, 6a-H and 6b-H were slightly broad in appearance. We have previously observed that the analogous isoxazolobenzodiazepinones **21** have sharp pmr and ^{13}C nmr spectral signals at room temperature[7,11] whilst similar adducts, *e.g.* **22** from Aversa's laboratory[14] and the isoxazolopyrimidodiazepine **23** which we have recently reported[12], display signal duplication and signal broadening respectively at room temperature. Upon perusal of the pmr spectral characteristics (room temperature) of the aforementioned molecules it is apparent that the conformational freedom of the 5,7,6-tricyclic framework is not easily predictable. However, it is apparent that the following factors likely to be important: (i) the size of the C-11b substituent, [thus **13a** inverts more slowly than **13b**]; (ii) the relative configuration of the C-11b and C-5 substituents [thus **13a** inverts more slowly than **14a**]; (iii) the nature of the substituent at the C-2 position [thus **19a** inverts more slowly than **20a**]; (iv) the hybridisation state of the C-6 carbon atom [thus **19a** inverts more slowly than **21**]; (v) the degree of substitution at the C-5 position [thus the dihydro-adducts **9**, and **22** both invert slowly on the nmr time scale].



21 *e.g.* R = Me, H



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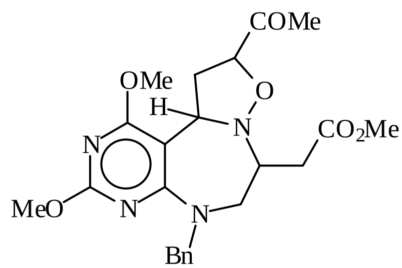

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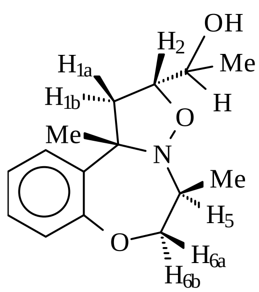
In terms of the influence of the relative stereochemistry about the 7-membered ring on the resonance position of the adjacent protons it is interesting that for both diastereomeric pairs of adducts **6b**, **17** and **13b**, **14b**, the C-11b Me protons of the adducts arising from addition to the β-face of the dipole, appear ~0.1 ppm upfield of the corresponding protons in the adduct resulting from addition to the α-face of the nitrone. The same trend is noted amongst the isomeric adducts arising from phenyl vinyl sulfone or methyl vinyl ketone addition to **5b**. Thus, the C-11b methyl protons of **18b** resonate at 1.66 ppm, 0.2 ppm downfield of the corresponding protons in **18a** and **18c**, products of addition to the β-face.

Much of the rich contribution of nitrone chemistry to synthesis lies in post cycloaddition manipulation of the isoxazolidine/isoxazoline ring and in this respect we wished to explore the potential of the new tricycles to submit to oxidative and reductive ring cleavage. The cycloadduct **20a** has two groups susceptible to reduction and on treatment with palladium (*II*) chloride under an atmosphere of H_2, reaction products varied with duration of reaction. The peripheral ketone was the most vulnerable functionality and after 6 h reaction the hydroxyethyl derivative **24** was formed in 80% yield. After 24 h duration the isoxazolidine ring had also cleaved and the diol **25** could be isolated in 95% yield. It is of interest that following cleavage of the isoxazolidine ring the pmr signals of **25**, most especially those of the seven membered ring, were very broad in their appearance. This may reflect a decrease in the rate of inversion of the seven membered ring and/or transient intramolecular H-bonding between N4 and the pendant OH groups. The cycloadduct **18c** was investigated as a test case for an oxidative ring opening of the isoxazolidine nucleus. Following exposure to chromium trioxide the [1,4]benzoxazepine *N*-oxide **26** was isolated as the only identifiable material, 36%. The presence of the additional site of unsaturation in the nitrone **26** with respect to the diol **25** is likely responsible for the conformational rigidity of the former bicycle. The ease with which the reduction of **20a** and the oxidation of **18c** occur assures the role of the new tricycles as platforms for the construction of a range of substituted benzoxazepines.



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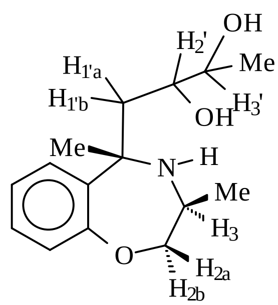
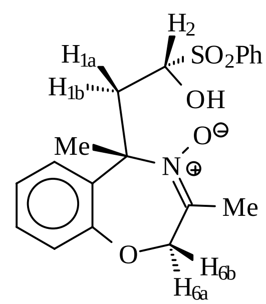


25



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Conclusions

The tricyclic isoxazolobenzoxazepine ring system has been formed for the first time following 1,3-dipolar cycloaddition to benzoxazepine *N*-oxides. The regio- and stereochemical outcome of the reactions was sensitive to both the nature of the C-nitrone substituent as well as the structure of the dipolarophile. Thus, whilst dimethyl acetylenedicarboxylate added stereospecifically to the C-phenyl nitrone there was almost no selectivity when the C-methyl nitrone was trapped by the same dipolarophile. Regiospecific cycloaddition was noted in the addition to monosubstituted dipolarophiles with 4-substituted isoxazoline rings resulting from addition to acetylenic dipolarophiles and 5-substituted isoxazolidine rings from addition to alkenic dipolarophiles. The appearance of broad pmr signals or of signal duplication in the pmr spectra for some of the new cycloadducts suggests the tricyclic ring is in a state of conformational flux which is slow on the nmr timescale. The spectral signals for other adducts are sharp suggesting rapid equilibration at room temperature. A survey of the structural features of the adducts falling into each of these divisions indicates that the factors influencing conformational mobility are many and varied and that prediction of same is likely to be very difficult. That the new cycloadducts have synthetic potential is illustrated in the oxidative and reductive ring opening to novel compounds with a benzoxazepine scaffold.

Experimental Section

General Procedures. Mps. were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. ^1H and ^{13}C NMR spectra were recorded using a JOEL EX270 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference and deuteriochloroform as solvent, *J* values are given in Hertz. Flash column chromatography was carried out on silica gel 60 (Merck 9385, 70-230 mesh) and analytical TLC plates were purchased from Merck. Samples were located by *UV* illumination using a portable Spectroline Hanovia lamp (λ, 254 nm) or by the use of iodine staining.

Dimethyl 5-methyl-11b-phenyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine-1,2-dicarboxylate (6a). Freshly recrystallised nitrone **5a** (0.40 g, 1.58 mmol) and dimethyl acetylenedicarboxylate (0.27 g, 1.90 mmol) were stirred in refluxing $CHCl_3$ (60 cm³) under N_2 for 36 h. The reaction solvent was removed under reduced pressure leaving a viscous yellow oil. Purification by flash column chromatography (Et_2O:pet. spirit, 1:5) afforded the product as an off white solid (0.57 g, 90%), which was further purified by crystallisation. **6a**, Colourless cubic crystals mp 168-170 ºC ($CHCl_3$, pet. spirit), (Found: C, 66.57; H, 5.48; N, 3.47. $C_{22}H_{21}NO_6$ requires: C, 66.84; H, 5.32; N, 3.54%). δ_H 7.59 (d, 2H, ArH, *J* 8.0) 7.34 (m, 4H, ArH) 6.96 (m, 2H, ArH) 6.61 (d, 1H, ArH, *J* 8.0) 4.25 (dd, 1H, H_{6a}, *J* 11.3 &11.3) 3.94 (dd, 1H, H_{6b}, *J* 11.3 & 4.0) 3.88 & 3.57 (2 x s, 2 x 3H, 2 x OMe) 3.54 (m, 1H, H_5) 1.24 (d, 3H, Me, *J* 7.0); δ_C 163.1 & 160.0 (2 x $\underline{C}O_2Me$) 154.7 (C_{7a}) 143.8 (C_2) 132.0-121.9 (ArC) 112.5 (C_1) 78.9 (C_{11b}) 69.3 (C_6) 56.9 (C_5) 53.2 & 51.8 (2 x OMe) 14.7 (Me).

Xray crystal determination of (6a). The structure was solved by direct methods, SHELXS-97[16], and refined by full matrix least squares using SHELXL-97[17]. SHELX operations were automated using OSCAIL which was also used to obtain the drawings[18]. The XDS program was used for data reduction and the data was corrected for Lorentz and polarization effects but not for absorption. 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. Crystal data for **6a** –Table 2.

Table 2. Crystal data and structure refinement for **6a**

Identification code	com21
Empirical formula	C22 H21 N O6
Formula weight	395.40
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 14.826(2)Å
	b = 7.586(2)Å β = 91.74(1)°
	c = 17.303(2)Å
Volume	1945.2(6) $Å^3$
Z	4
Density (calculated)	1.350 Mg/m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	832
Crystal size	0.32 x 0.38 x 0.41 mm
Theta range for data collection	2.36 to 23.97 °.
Index ranges	-2<=h<=16; -2<=k<=8; -19<=l<=19
Reflections collected	3202
Independent reflections	3040 [R(int) = 0.0340]
Reflections observed (>2σ)	1859
Data Completeness	0.999
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3040 / 0 / 265
Goodness-of-fit on F^2	1.022
Final R indices [I>2σ(I)]	R_1 = 0.0487 wR_2 = 0.1280
R indices (all data)	R_1 = 0.0891 wR_2 = 0.1539
Largest diff. peak and hole	0.222 and -0.259 e.$Å^{-3}$

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).
$w = 1/[(\sigma F_o)^2 + (0.0937*P)^2]$.
Goodness–of–fit = $[\Sigma_w(F_o{}^2 - F_c{}^2)^2/(\mathrm{Nobs}-\mathrm{Nparameters})]^{1/2}$.

Methyl 5-methyl-11b-phenyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine-1-carboxylates (13a and 14a). Freshly recrystallised nitrone **5a** (0.63 g, 2.50 mmol) and methyl propiolate (0.63 g, 7.50 mmol) were stirred in $CHCl_3$ (120 cm³) at reflux under N_2 for 36 h. The reaction solvent and unreacted dipolarophile were removed under reduced pressure leaving an orange gum, which was purified by flash column chromatography (Et_2O:pet. spirit, 1:12). Pure samples of **14a** (0.16 g, 19%) and **13a** (0.60 g, 71%) as well as unreacted nitrone (0.06 g, 9%) were obtained. **14a** Colourless rods, mp 177-179 ºC ($CHCl_3$, hex). (Found; C, 71.33; H, 5.50; N, 3.98. $C_{20}H_{14}NO_4$ requires: C, 71.22; H, 5.64; N, 4.15%). δ_H 7.41 (m, 3H, H_2 & 2xArH) 7.22 (m, 1H, ArH) 7.13 (m, 5H, ArH) 6.91 (d, 1H, ArH *J* 8.0) 3.61 (m, 1H, H_{6b}) 3.57 (dd, 1H, H_{6a}, *J* 11.0 & 11.0) 3.48 (s, 3H, OMe) 3.23 (m, 1H, H_5) 1.13 (d, 3H, Me, *J* 6.2). δ_C 163.9 ($\underline{C}O_2Me$) 153.6 (C_2) 152.4 (C_{7a}) 143.2 (C_{11}) 130.3-126.5 (ArC) 121.8 (C_1) 76.6 (C_6) 72.3 (C_{11b}) 55.8 (OMe) 51.2 (C_5) 16.0 (Me). **13a** Colourless cubic crystals mp 178-179 ºC ($CHCl_3$, hex). (Found: C, 71.34; H, 5.66; N, 3.98. $C_{20}H_{14}NO_4$ requires: C, 71.22; H, 5.64; N, 4.15%). δ_H 7.712 & 7.706 (2xs, 1H, H_2) 7.49 (m, 2H, ArH) 7.31 (m, 4H, ArH) 6.93 (m, 2H, ArH) 6.87 (d, 1H, ArH *J* 7.7) 4.14 and 4.13 (2xt, 1H, H_{6a}) 3.84 & 3.82 (2xdd, 1H, H_{6b}) 3.64 (m, 1H, H_5) 3.59 & 3.60 (2xs, 3H, OMe) 1.22 &1.21 (2xd, 3H, Me, *J* 6.6 & 7.0). δ_C 164.3 ($\underline{C}O_2Me$) 155.4 (C_2) 154.8 (C_{7a}) 144.2 (C_{11}) 133.4-123.9 (ArC) 122.0 (C_1) 78.0 (C_6) 70.2 (C_{11b}) 56.5 (C_5) 51.2 (OMe) 15.2 (Me).

5-Methyl-1,11b-diphenyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine and 5-methyl-2,11b-diphenyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepines (15 and 16). A solution of the nitrone **5a** (0.18 g, 0.7 mmol), phenylacetylene (2.40 g, 20.0 mmol) and hydroquinone (0.05 g, 0.5 mmol) in toluene (1 cm³) was stirred at 120 ºC for 8 h. After cooling to room temperature solvent and unreacted phenylacetylene were removed under reduced pressure to afford a brown solid which was taken up in $CHCl_3$ (1 cm³). After 0.5 h standing at room temperature hydroquinone precipitated and was removed by filtration. The filtrate was concentrated and the resulting crude product purified by flash column chromatography (Et_2O:pet. spirit, 1:6) to yield samples of **15** (0.10 g, 40%), and **16** (0.14 g, 55%). **15**, Colourless cubic crystals mp 130-131 ºC (benzene, pet. spirit), (Found: C, 81.29; H, 5.64; N, 3.65. $C_{24}H_{21}NO_2$ requires: C, 81.13; H, 5.92; N, 3.94%). δ_H 7.61 (m, 2H, ArH) 7.39 (m, 9H, ArH) 7.06 (m, 2H, ArH) 6.79 (m, 1H, ArH) 5.88 (s, 1H, H_1) 4.11 (dd, 1H, H_{6a} *J* 9.1 & 9.1) 3.92 (dd, 1H, H_{6b}, *J* 9.1 & 2.2) 3.77 (m, 1H, H_5) 1.29 (d, 3H, Me, *J* 6.6); δ_C 156.3 (C_{7a}) 153.2 (C_2) 144.2 ($C_{1'}$) 129.8-122.3 (ArC) 102.1 (C_1) 80.0 (C_6) 71.7 (C_{11b}) 56.6 (C_5) 15.9 (Me). **16**, Colourless plates mp 122-124 ºC. (benzene, pet. spirit), (Found: C, 81.05; H, 5.96; N, 4.15. $C_{24}H_{21}NO_2$ requires: C, 81.13; H, 5.92; N, 3.94%). δ_H 7.54, 7.32 & 7.03 (3 x m, 15H, ArH & H_2) 4.40 (m, 2H, H_{6b} & H_{6a}) 3.66 (m, 1H, H_5) 1.32 (d, 3H, Me, *J* 6.6) δ_C 168.9 (C_{7a}) 157.0 (C_2) 139.6 ($C_{1'}$) 131.6-123.8 (ArC) 121.8 (C_1) 84.0 (C_6) 76.3 (C_{11b}) 55.1 (C_5) 18.0 (Me).

Dimethyl 5,11b-dimethyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine-1,2-dicarboxylates (6b and 17). Freshly distilled nitrone **5b** (0.48 g, 2.50 mmol) and dimethyl acetylenedicarboxylate (0.40 g, 2.80 mmol) were stirred in refluxing $CHCl_3$ (80 cm³) under N_2 for 32 h. The reaction solvent was removed under reduced pressure leaving a viscous yellow oil. Purification by flash column chromatography (Et_2O:hex, 1.0:1.6) gave samples of **17** (0.375 g, 45%) and **6b** (0.45 g, 54%). **17**, Colourless rods mp 87-89 ºC ($CHCl_3$, hex). (Found: C, 61.47; H, 5.91; N, 4.31. $C_{17}H_{14}NO_6$ requires: C, 61.26; H, 5.71; N, 4.20%). δ_H 7.38 (d, 1H, ArH, *J* 8.0), 7.29 (m, 1H, ArH) 7.15 (m, 1H, ArH) 6.98 (m, 1H, ArH) 4.18 (dd, 1H, H_{6a}, *J* 11.3 & 12.0) 3.90 & 3.50 (2 x s, 2 x 3H, 2 x OMe) 3.73 (dd, 1H, H_{6b}, *J* 11.3 & 4.8) 3.31 (m, 1H, H_5) 1.92 (s, 3H, Me_{11b}) 1.14 (d, 3H, Me_5, *J* 6.6); δ_C 162.3 & 159.9 (2 x $\underline{C}O_2Me$) 154.7 (C_{7b}) 152.5 (C_2) 130.6-122.3 (ArC) 113.7 (C_1) 73.9 (C_6) 69.9 (C_{11b}) 56.4 (C_5) 53.1 & 51.5 (2 x OMe) 27.2 (Me_{11b}) 15.2 (Me_5). **6b** Colourless rods mp 101-103 ºC ($CHCl_3$, hex). (Found: C, 61.06; H, 5.64; N, 4.18. $C_{17}H_{14}NO_6$ requires: C, 61.26; H, 5.71; N, 4.20%). δ_H 7.30 (m, 1H, ArH), 7.11 (m, 2H, ArH) 6.99 (d, 1H, ArH *J* 8.0) 4.17 (dd, 1H, H_{6a}, *J* 11.3 & 12.0) 4.02 (dd, 1H, H_{6b}, *J* 11.3 & 3.3) 3.93 & 3.78 (2xs, 2x3H, 2xOMe) 3.32 (m, 1H, H_5) 2.03 (s, 3H, Me_{11b}) 1.17 (d, 3H, Me_5, *J* 6.2). δ_C 162.4 & 159.5 (2 x $\underline{C}O_2Me$) 152.4 (C_{7b}), 152.2 (C_2) 131.0-121.0 (ArC) 111.2 (C_1) 74.2 (C_6) 73.6 (C_{11b}) 56.2 (C_5) 55.6 & 51.1 (2 x OMe) 22.4 (Me_{11b}) 18.3 (Me_5).

Methyl 5,11b-dimethyl-5,6-dihydro-11b*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine-1-carboxylates (13b and 14b). Freshly distilled nitrone **5b** (0.46 g, 2.40 mmol) and methyl propiolate (0.70 g, 8.40 mmol) were stirred in $CHCl_3$ (90 cm³) at reflux under N_2 for 36 h. The reaction solvent and unreacted dipolarophile were removed under reduced pressure to give a viscous yellow oil, which was purified by flash column chromatography (Et_2O:pet. spirit, 1:5). Pure samples of **13b** (0.33 g, 50%) and **14b** (0.25 g, 38%) were obtained as well as returned nitrone (0.04 g, 9%). **13b** Colourless rods mp 55-56 ºC ($CHCl_3$, hex). (Found: C, 65.65; H, 6.38; N, 4.96. $C_{15}H_{17}NO_4$ requires: C, 65.45; H, 6.18; N, 5.09%). δ_H 7.47 (s, 1H, H_2) 7.27 (m, 1H, ArH) 7.09 (m, 1H, ArH) 7.11 (m, 2H, ArH) 4.16 (dd, 1H, H_{6a}, *J* 11.2 & 11.2) 3.99 (dd, 1H, H_{6b} 11.2 & 3.3) 3.78 (s, 3H, OMe) 3.23 (m, 1H, H_5) 2.07 (s, 3H, Me_{11b}) 1.15 (d, 3H, Me_5, *J* 6.0). δ_C (67.5MHz) 164.7 ($\underline{C}O_2Me$) 153.4 (C_{7a}) 153.1 (C_2) 131.2-124.8 (5 x ArC) 72.6 (C_6) 72.1 (C_{11b}) 56.4 (OMe) 51.3 (C_5) 25.8 (Me_{11b}) 15.8 (Me_5). **14b** A viscous pale yellow oil (R_f 0.67, Et_2O). (Found: C, 65.35; H, 6.48; N, 4.98%. $C_{15}H_{17}NO_4$ requires: C, 65.45; H, 6.18; N, 5.09%). δ_H 7.554 & 7.549 (2xs, 1H, H_2) 7.44 (d, 1H, ArH *J* 7.7) 7.29 (m, 1H, ArH) 7.15 (m, 1H, ArH) 6.98 (d, 1H, ArH) 4.11 (br t, 1H, H_{6a}) 3.74 (br dd, 1H, H_{6b}) 3.54 (s, 3H, OMe) 3.34 (m,1H, H_5) 1.92 (s, 3H, Me_{11b}) 1.15 (d, 3H, Me_5, *J* 6.6).

5,11b-Dimethyl-2-(phenylsulphonyl)-1,5,6,11b-tetrahydro-2*H*-isoxazolo[2,3-*d*][1,4]benzoxazepines (18a-c). A solution of the nitrone **5b** (1.91 g, 10 mmol) and phenyl vinyl sulfone (2.19 g, 13 mmol) in toluene (400 cm³) was stirred at reflux under N_2 for 120 h. The reaction solvent was removed under reduced pressure to afford a brown gummy residue which was purified by flash column chromatography (Et_2O:pet. spirit, 1.0:2.3). Unreacted dipolarophile and nitrone (0.87 g, 46%) were both returned. **18a** (0.29 g, 8%) and **18b** (0.50 g, 14%) coeluted and were subsequently separated by fractional crystallisation (benzene, pet. spirit). The third fraction was **18c** (0.72 g, 20%). **18a** Colourless cubic crystals (benzene, pet. spirit) mp 190-191 ºC. (Found: C, 63.75; H, 5.94; N, 3.96. $C_{19}H_{21}NSO_4$ requires: C, 63.51; H, 5.85; N, 3.90%). δ_H 7.96 (m, 2H, ArH, *J* 8.1) 7.63 (m, 1H, ArH) 7.53 (m, 2H, ArH) 7.36 (m, 2H, ArH) 7.18 (m, 1H, ArH) 6.94 (m, 1H, ArH, *J* 8.1) 5.01 (dd, 1H, H_2, *J* 7.3 & 7.3) 4.08 (m, 1H, H_{6a}) 3.52 (m, 3H, H_{6b} & H_5 & H_{1a}) 2.82 (dd, 1H, H_{1b}, *J* 7.2 & 12.5) 1.46 (s, 3H, Me_{11b}) 1.02 (d, 3H, Me_5, *J* 5.9). δ_C 158.7 (C_{7a}) 134.3 ($C_{1'}$) 133.9-121.9 (ArC) 89.6 (C_2) 75.7 (C_6) 69.2 (C_{11b}) 56.9 (C_5) 42.0 (C_1) 18.8 (Me_{11b}) 16.0 (Me_5). NOEDS results for **18a**: Irradiation of H-6a caused a 3.9% enhancement on Me-11b and a 4.5% enhancement on Me-5. Irradiation of H-1b caused a 10.1% enhancement on H-2. **18b** Colourless needles (benzene, pet. spirit) mp 64-65 ºC. (Found: C, 63.68; H, 5.79; N, 3.69. $C_{19}H_{21}NSO_4$ requires: C, 63.51; H, 5.85; N, 3.90%). δ_H 7.98 (d, 2H, 2 x ArH *J* 8.1) 7.65 (m, 1H, ArH) 7.55 (m, 2H, ArH) 7.19 (m, 4H, ArH) 6.94 (d, 1H, ArH) 4.97 (dd, 1H, H_2, *J* 8.1 & 7.3) 4.09 (dd, 1H, H_{6a} 11.0 & 11.0) 3.92 (dd, 1H, H_{6b}, *J* 11.0 & 1.2) 3.35 (dd, 1H, H_{1a}, *J* 8.1 & 14.7) 3.03 (dd, 1H, H_{1b} *J* 7.33 & 14.7) 2.92 (m, 1H, H_5) 1.66 (s, 3H, Me_{11b}) 1.01 (d, 3H, Me_5, *J* 5.9). δ_C 153.9 (C_{7a}) 136.3 ($C_{1'}$) 134.0-121.9 (ArC) 90.2 (C_2) 71.8 (C_6) 69.1 (C_{11b}) 56.4 (C_5) 42.11 (C_1) 18.6 (Me_{11b}) 16.1 (Me_5). NOEDS results for **18b**: Irradiation of H-1a caused the following enhancements H-2 (8.5%), H-6a (4.1%) and H-1b (25.1%). Irradiation of Me-11b caused a 3.7% enhancement on H-1b, and a 2.3% enhancement on H-5. Irradiation of 6a-H caused an enhancement of 4.1% on H-2, 3.6% onto H-1a and 18.1% on its partner H-6b. Irradiation of H-6b caused an enhancement of 7.1% on H-5, 4.6% onto Me-5 and 21.2% H-6a. **18c** Colourless cubic crystals (benzene, pet. spirit) mp 141-142 ºC. (Found: C, 63.48; H, 5.98; N, 4.02. $C_{19}H_{21}NSO_4$ requires: C, 63.51; H, 5.85; N, 3.90%). δ_H 7.92 (d, 2H, ArH *J* 7.3) 7.63 (m, 1H, ArH) 7.55 (m, 2H, ArH) 7.21 (m, 1H, ArH) 7.11 (m, 2H, ArH) 6.97 (d, 1H, ArH *J* 7.7) 5.05 (dd, 1H, H_2, *J* 7.3 & 9.5) 3.93 (t, 1H, H_{6a}, *J* 10.2 & 10.2) 3.78 (dd, 1H, H_{6b}, *J* 10.2 & 4.4) 3.38 (m, 1H, H_5) 3.18 (dd, 1H, H_{1a}, *J* 9.5 & 9.5) 2.98 (dd, 1H, H_{1b} *J* 7.3 & 9.5) 1.46 (s, 3H, Me_{11b}) 1.22 (d, 3H, Me_5, *J* 6.2). δ_C 157.0 (C_{7a})134.2 ($C_{1'}$) 129.5-122.4 (ArC) 92.5 (C_2) 77.8 (C_6) 69.8 (C_{11b}) 55.8 (C_5) 41.3 (C_1) 19.2 (Me_{11b}) 15.1 (Me_5). NOEDS results for **18c:** Irradiation of H-2 caused an enhancement of 6.0% on H-1a and 2.9% onto Me-11b. Irradiation of H-5 caused a 5.4% enhancement on H-1b, 6.8% enhancement on H-6b and 7.1% enhancement on Me-5. Irradiation of H-6b caused an enhancement of 7.1% on H-5 and 22.6% on its partner H-6a. Irradiation of Me-11b caused an enhancement of 3.6% on H-2 and 2.4% onto H-1a.

Methyl 5,11b-dimethyl-1,5,6,11b-tetrahydro-2*H*-isoxazolo[2,3-*d*][1,4]benzoxazepine-2-carboxylates (19a and 19b). Freshly distilled nitrone **5b** (1.63 g, 8.5 mmol) and methyl acrylate (14.34g, 0.17 mmol) were stirred in the presence of hydroquinone (0.2% $^{w}/_{v}$, 0.3 g) in toluene (150 cm³) at reflux under N_2 for 110 h (using a double sided water condenser). The reaction solvent and unreacted dipolarophile were removed under reduced pressure (100 ºC, 0.5 mm Hg) to leave a viscous yellow residue which was taken up in $CHCl_3$ (1.5 cm³). After standing at room temperature (0.5 h), the precipitated hydroquinone was removed *in vacuo*. Purification of the crude product by flash column chromatography (Et_2O:pet. spirit, 1.0:5.5) yielded, following further purification by fractional distillation **19a** as an enriched sample containing ~5% of a third isomer[24] (1.32 g, 56%) and **19b** (0.48 g, 20%) a highly viscous yellow oil which solidified upon trituration (pet. spirit). **19a** A viscous colourless oil (b.p. 155-158 ºC, 0.02 mm Hg). (Found: C, 64.79; H, 6.59; N, 4.96. $C_{15}H_{19}NO_4$ requires: C, 64.98; H, 6.86; N, 5.05%). δ_H 7.20 (m, 2H, ArH) 7.04 (m, 1H, ArH) 6.94 (d, 1H, ArH, *J* 8.1) 4.60 (dd[25], 1H, H_2) 4.14 (m, 1H, H_{6a}) 3.75 (s, 3H, OMe) 3.61 (m, 2H, H_{6b} & H_5) 3.09 (dd[25], 1H, H_{1a}) 2.74 (dd[25], 1H, H_{1b}) 1.51 (s, 3H, Me_{3a}) 1.18 (d, 3H, Me_5, *J* 2.93). NOEDS results for **19a**: Irradiation of H-2 caused enhancements on the following protons H-1a (7.1%) and Me-11b (6.0%). Irradiation of Me-5 caused a 4.1% enhancement on H-2 and a 2.6% enhancement on Me-11b and 4.9% on H-6a. Irradiation of H-1a caused an enhancement of 12.0% on H-2, 22.5% onto H-1b and 6.8% onto Me-11b. **19b** Colourless needles mp 47-49 ºC. (benzene, pet. spirit). (Found: C, 64.92; H, 6.82; N, 5.01. $C_{15}H_{19}NO_4$ requires: C, 64.98; H, 6.86; N, 5.05%). δ_H 7.24 (m, 2H, ArH) 7.06 (t, 1H, ArH, *J* 7.3) 6.98 (d, 1H, ArH, *J* 7.3) 4.67 (dd, 1H, H_2, *J* 10.2 & 4.4) 4.14 (br d, 1H, H_{6a}) 3.82 (s, 3H, OMe) 3.72 (m, 1H, H_5) 3.61 (br dd, 1H, H_{6b}) 3.33 (dd, 1H, H_{1a}, *J* 10.2 & 11.7) 2.58 (dd, 1H, H_{1b}, *J* 4.4 & 11.7) 1.54 (s, 3H, Me_{11b}) 1.20 (d, 3H, Me_5, *J* 5.90).

1-[5,11b-dimethyl-1,5,6,11b-tetrahydro-2*H*-isoxazolo[2,3-*d*][1,4]benzoxazepin-2-yl]-1-ethanones (20a and 20b). Freshly distilled nitrone **5b** (1.63 g, 8.50 mmol), methyl vinyl ketone (12.63g, 0.18 mol) and hydroquinone (0.2% $^{w}/_{v}$, 0.3 g) were stirred in toluene (150 cm³) at reflux under N_2 for 110 h (using a double sided water condenser). The reaction solvent and unreacted dipolarophile were removed under reduced pressure (100 ºC, 0.5 mm Hg) and the residue was taken up in $CHCl_3$ (2.5 cm³). After standing at room temperature (0.5 h) the precipitated hydroquinone was removed *in vacuo*. Purification of the crude products by flash column chromatography (Et_2O:pet. spirit, 1:4), yielded **20a** as a colourless oil (1.53 g, 69%) and **20b** (0.38 g, 17%) both of which were further purified by fractional distillation. **20a** A viscous colourless oil (b.p. 130-132, 0.03 mm Hg). (Found: C, 68.99; H, 7.31; N, 5.30. $C_{15}H_{19}NO_3$ requires: C, 68.97; H, 7.28; N, 5.36%). δ_H 7.21 (m, 2H, ArH), 7.06 (t, 1H, ArH, *J* 7.4) 6.96 (d, 1H, ArH, *J* 7.4) 4.34 (dd, 1H, H_2, *J* 7.3 & 8.8) 4.17 (d, 1H, H_{6a}, *J* 10.2) 3.62 (m, 2H, H_{6b}, H_5) 2.89 (dd, 1H, H_{1a}, *J* 7.3 & 11.8) 2.67 (dd, 1H, H_{1b}, *J* 8.8 & 11.8) 2.33 (s, 3H, COMe) 1.50 (s, 3H, Me_{11b}) 1.20 (d, 3H, Me_5, *J* 5.9). δ_C 213.3 (<u>C</u>OMe) 159.0 (C_{7a}) 133.6-121.9 (ArC) 78.5 (C_2) 76.0 (C_6) 68.6 (C_{11b}) 56.6 (C_5) 45.8 (C_1) 25.7 (CO<u>Me</u>) 19.1 (Me_{11b}) 16.4 (Me_5). NOEDS results for **20a**: Irradiation of Me-11b caused enhancements on the following protons H-2 (3.4%) and H-1a (4.4%). Irradiation of Me-5 caused a 2.9% enhancement on H-2, and a 2.3% enhancement on H-6b. Irradiation of H-2 caused an enhancement of 5.0% on H-1a, 2.0% onto Me-11b and 2.6% on Me-5. **20b** A viscous colourless oil (b.p. 55-60 ºC, 0.03 mm Hg). (Found: C, 69.25; H, 7.39; N, 5.56. $C_{15}H_{19}NO_3$ requires: C, 68.97; H, 7.28; N, 5.36%). δ_H 7.27-6.96 (3 x m, 4H, ArH) 4.47 (m, 1H, H_2) 4.14 (dd, 1H, H_{6s}, *J* 5.4 & 11.0) 3.65 (m, 2H, H_{6b} & H_5) 3.21 (dd, 1H, H_{1a}, *J* 11.7 & 11.7) 2.57 (m, 1H, H_{1b}) 2.34 (s, 3H, COMe) 1.40 (s, 3H, Me_{11b}) 1.21 (d, 3H, Me_5, *J* 5.9). δ_C 213.8 (<u>C</u>OMe) 158.6 (C_{7a}) 137.1-117.4 (ArC) 79.6 (C_2) 76.2 (C_6) 67.7 (C_{11b}) 56.6 (C_5) 45.2 (C_1) 26.5 (CO<u>M</u>e) 19.7 (Me_{11b}) 16.3 (Me_5)**.** NOEDS results for **20b**: Irradiation of H-1a caused an 8.9% enhancement on Me-11b. Irradiation of Me-5 caused a 2.7% enhancement on H-1a. Irradiation of H-6a caused an enhancement of 1.9% on Me-11b and 6.5% on Me-5.

1-(5,11b-Dimethyl-1,5,6,11b-tetrahydro-2*H*-isoxazolo[2,3-*d*]]1,4]benzoxazepin-2-yl)-1-ethanol (24). The cycloadduct **20a** (0.30 g, 1.15 mmol) and palladium (*II*) chloride (0.14 g, 0.8 mmol) were stirred in an ethanol (6 cm^3) and tetrahydrofuran (3 cm^3) mixture at room temperature under an atmosphere of hydrogen gas for 6 h. Filtration of the catalyst through Celite and concentration of the filtrate yielded a colourless oil, which solidified upon standing and was purified by flash column chromatography (EtOAc: EtOH, 95:1). Unchanged starting material (0.024g, 8%) and the title compound (0.24g, 80%) were returned. **24** Colourless cubic crystals mp 101-102 ºC (benzene, pet. spirit). (Found: C, 68.62; H, 8.17; N, 5.03. $C_{15}H_{21}NO_3$ requires: C, 68.44; H, 7.98; N, 5.32%). δ_H 7.14 (m, 2H, ArH) 6.96 (t, 1H, ArH, *J* 7.3) 6.83 (m, 1H, ArH *J* 7.3) 4.18 (m, 1H, H_2) 3.94 (dd, 1H, H_{6a}, *J* 11.0 & 11.0) 3.80 (dd, 1H, H_{6b}, *J* 11.0 & 5.5) 3.58 (m, 1H, C$\underline{H}$OH) 3.24 (m, 1H, H_5) 2.14 (dd, 1H, H_{1a}, *J* 5.9 & 13.2) 1.93 (dd, 1H, H_{1b}, *J* 6.6 & 13.2) 1.67 (br s, 1H, OH) 1.56 (s, 3H, Me_{11b}) 1.11 (d, 3H, CHOH$\underline{Me}$, *J* 6.6) 1.00 (d, 3H, Me_5, *J* 7.3). δ_C 154.2 (C_{7a}) 142.5 (C_{11a}) 128.3-122.9 (ArC) 73.6 (C_2) 72.5 (C_6) 66.7 ($\underline{C}$HOH) 56.2 (C_{11b}) 49.2 (C_5) 48.4 (C_1) 31.2 (Me_{11b}) 18.6 (CHOH$\underline{Me}$) 18.1 (Me_5).

1-(3,5-Dimethyl-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)-2,3-butanediol (25). The cycloadduct **20a** (0.30 g, 1.15 mmol) and palladium (*II*) chloride (0.42 g, 2.40 mmol) were stirred in an ethanol (6 cm^3) and tetrahydrofuran (3 cm^3) mixture at room temperature under an atmosphere of hydrogen for 24 h. Filtration of the catalyst through Celite and concentration of the filtrate yielded a colourless oil, which solidified upon standing. This solid was purified by flash column chromatography (EtOAc:EtOH, 6:1) to yield **25** (0.29g, 95%). **25** Clourless cubic crystals mp 225-226 ºC (EtOH, Et_2O). (Found: C, 68.22; H, 8.17; N, 5.03. $C_{15}H_{23}NO_3$ requires: C, 67.92; H, 7.92; N, 5.28%). δ_H 7.84-7.02 (3 x m, 4H, ArH) 4.46 (m, 3H, H_{2a}, $H_{2'}$ & C$\underline{H}$OH) 4.10 (dd, 1H, H_{2b}) 3.82 (m, 1H, H_3) 2.68 (m, 2H, $H_{1'a}$ & $H_{1'b}$) 2.19 (s, 3H, Me_5) 1.64 (d, 3H, CHOH$\underline{Me}$, *J* 6.60) 1.35 (d, 3H, Me_3, *J* 6.59). δ_C (67.5 MHz), (CD_3OD) 155.0 (C_{9a}) 136.2-124.7 (ArC) 81.1 ($C_{3'}$) 73.6 ($C_{2'}$) 71.2 (C_2) 66.2 (C_5) 56.3 (C_3) 49.6 ($C_{1'}$) 27.9 (Me_5) 15.2 (CHOH$\underline{Me}$) 14.9 (Me_3).

5-[2-Hydroxy-2-(phenylsulfonyl)ethyl]-3,5-dimethyl-2,5-dihydro-1,4benzoxazepin-4-ium 4-olate *N*-oxide (16). The cycloadduct **18c** (0.45 g, 1.25 mmol) and chromium trioxide (0.75 g, 7.50 mmol) were stirred in a CH_2Cl_2:HOAc mixture (1.5:1.0, 25 cm^3) for 1.75 h. The reaction was stopped by the slow addition of a sat. *aq*. $NaHCO_3$ solution (effecting a change in the pH from pH 5 to pH 7). The reaction mixture was extracted carefully with CH_2Cl_2 (4 x 100 cm^3). The combined organic layers were washed with a 10% ($^w/_v$) brine solution (2 x 100 cm^3), dried (anh. Na_2SO_4) and concentrated to yield a dark green/black solid (0.27 g). The crude mixture was separated by flash column chromatography (Et_2O:pet. spirit 5:1). The title product was the only identifiable material, (0.17 g, 36%). **26** Yellow cubic crystals mp 115-117 ºC (benzene, pet. spirit). (Found: C, 61.04; H, 5.33; N, 3.54%. $C_{19}H_{21}NO_5C$ requires: C, 60.80; H, 5.60; N, 3.73%). δ_H 7.96 (d, 1H, ArH *J* 8.1) 7.76 (d, 1H, ArH *J* 8.1) 7.68 (m, 1H, ArH) 7.54 (m, 3H, ArH) 7.19 (t, 1H, ArH, *J* 8.1) 6.94 (t, 1H, ArH *J* 7.3) 6.67 (d, 1H, ArH *J* 8.1) 6.58 (br s, 1H, OH) 4.86 (dd, 1H, $H_{2'}$, *J* 8.4 & 5.4) 4.67 (s, 2H, H_{2a} & H_{2b}) 3.46 (dd, 1H, $H_{1'b}$, *J* 8.4 & 13.3) 3.05 (d, 1H, $H_{1'a}$, *J* 5.4 & 13.3) 2.34 (s, 3H, Me_5) 1.73 (s, 3H, Me_3). δ_C 156.0 (C_{7a}) 136.7-121.6 (ArC & C_3) 111.4 (C_9) 94.8 ($C_{2'}$) 72.6 (C_2) 66.3 (C_5) 42.3 ($C_{1'}$) 26.9 (Me_3) 21.8 (Me_5).

Supporting information available online. Crystallographic Information Files (CIF) for **6b**.

Acknowledgements

This work has been supported by the chemistry departments of The National University of Ireland, Galway and The National University of Ireland, Maynooth.

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