Use of highly stereospecific 1,3-dipolar cycloadditions of cyclic nitrones with acetylenes in the preparation of novel heterocyclic ring systems

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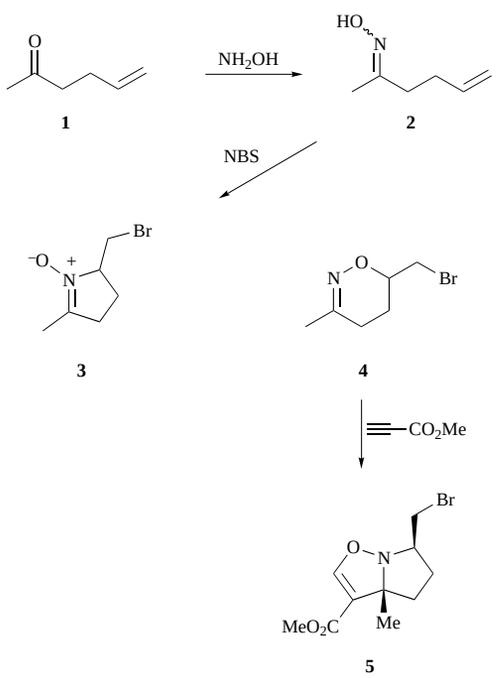
Cyclic nitrones with substituents *α* to the nitrogen atom undergo 1,3-dipolar cycloadditions in a stereo- and regio-specific manner with acetylenes. The nitrone 3 reacts with methyl propiolate, methyl phenylpropiolate and methyl acetylpropiolate to give the corresponding pyrrolo[1,2-*b*]isoxazoles 5, 8 and 13 respectively. Compound 13 reacts with 4-chlorophenylhydrazine to afford the pyrazolo[4,3-*a*]-pyrrolizine 15 by a novel rearrangement. The nitrone 18 undergoes a 1,3-dipolar cycloaddition with methyl propiolate in a stereo- and regio-specific manner to give the isoxazolo[2,3-*a*]pyridine 19. The nitrone 18, when reacted with methyl acetylpropiolate, gives a mixture of regioisomers in a ratio of 3:2. The major regioisomer 21 reacts with 4-chlorophenylhydrazine to afford the novel pyrazolo[4,3-*a*]-indolizine ring system 23. The bicyclic nitrone 26 reacts with methyl propiolate and methyl acetylpropiolate to give the cycloadducts 27 and 28 respectively; both these compounds contain the novel isoxazolo[3,2-*i*]indole ring system.

1,3-Dipolar cycloadditions between nitrones and alkynes have been used extensively for the preparation of isoxazoles.[1] Cyclic nitrones are especially useful for the formation of nitrogen containing polycycles. Recently Grigg and co-workers reported a novel method for the generation of cyclic nitrones by intramolecular conjugate addition of oximes (1,3-azaprotio cyclotransfer reaction) to electron deficient[2] or activated alkenes.[3] In this paper, as part of studies involving the synthesis of novel heterocycles for biological evaluation, this method has been applied to prepare cyclic nitrones with pendant electronegative groups. These nitrones were reacted with mono- and di-substituted alkynes to afford novel heterocycles in a stereo- and regio-selective fashion. Three cyclic nitrones **3**, **18** and **26** were used in this work.

The cyclic nitrone **3** was prepared from the alkenyl ketone **1** which reacts with hydroxylamine to give a 1:2 mixture of *anti* and *syn* oximes **2**. The mixture of oximes readily reacts intramolecularly with the alkene group when treated with *N*-bromosuccinimide in dichloromethane at 20 °C to afford a 2:1 mixture of the nitrone **3** and the oxazine **4**.[3] This mixture was reacted with methyl propiolate at 20 °C to give a single cycloadduct **5** (Scheme 1) as deduced from the ^{1}H NMR spectrum of the crude reaction mixture. Compound **5** was obtained as an oil, in 30% yield based on the nitrone **3**, by flash chromatography.

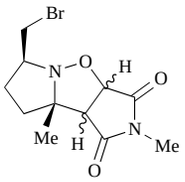
It was not possible to determine the exact stereochemistry of **5** by NOE difference spectroscopy because of overlapping signals in the ^{1}H NMR spectrum. However the stereochemistry assigned to **5** is supported by the structure of the pyrazole **15** determined by X-ray crystallography (see later) and by literature references.[2–4] Grigg *et al.*[3] reported the same *cis* relationship for the bromomethyl group and ring junction methyl group when they reacted the nitrone **3** with *N*-methylmaleimide to give the cycloadduct **6** as a mixture of *exo* and *endo* isomers. Tiecco *et al.*[4] reported the preparation of the cycloadduct **7**, which had a *cis* relationship between the phenylselenyl group and the ring junction methyl group. Cycloadduct **7** was prepared from the oxime **2** using benzeneselenenyl bromide instead of *N*-bromosuccinimide to activate the alkene function. A possible explanation for the observed stereochemistry is that the electronegative bromine atom interacts electrostatically with the positively charged nitrogen atom of the dipole to shield one face of the nitrone. MM2 molecular models show the ring in the nitrone **3** to be essentially planar, so the addition of the methyl propiolate would occur from the opposite face to that containing the bromomethyl group, *i.e.* steric hindrance could also account for the observed selectivity.



Scheme 1

The reaction of the nitrone **3** with methyl phenylpropiolate also gave a single cycloadduct **8** in 57% yield based upon the nitrone, again as an oil. The stereo- and regio-chemistry of the cycloadduct **8** are assumed to be the same as the cycloadduct **5**.

The regioselectivity of these cycloadditions is in accord with predictions based upon molecular orbital theory. In cycloadditions of this type the relatively electron rich nitrone and the



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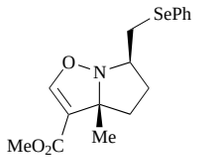

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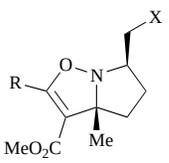


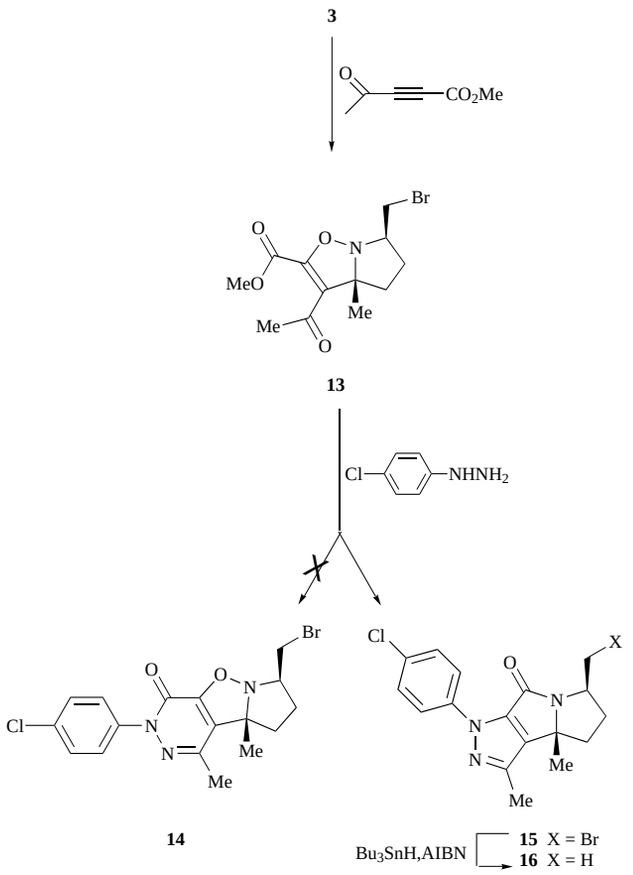
8 R = Ph, X = Br
9 R = H, X = SMe
10 R = Ph, X = SMe
11 R = H, X = H
12 R = Ph, X = H

electron deficient methyl propiolate result in a strongly dominant HOMO (nitrone)–LUMO (propiolate) interaction, this electronic effect favours the formation of isoxazole regioisomers substituted in the 4-position.[5]

The bromine atom in both **5** and **8** proved difficult to displace by an S_N2 type process. Treatment of the cycloadducts **5** or **8** with sodium methoxide or diethylamine at room temperature gave no reaction, while under more forcing conditions only intractable mixtures were recovered. Molecular models show that attack on the rear face of the bromine group is hindered by the ring junction methyl group. The bromine could be displaced with sodium methanethiolate in *N*,*N*-dimethylformamide at room temperature to give the sulfide derivatives **9** and **10** in 45 and 43% yield respectively. However, this transformation may be occurring by a single electron mechanism and is therefore not influenced by the steric requirement for S_N2 displacement. The bromine atom was removed by reduction with tributyltin hydride under free radical conditions to give the 3-methyl compounds **11** and **12** in 58 and 41% yields respectively.

To our surprise, reaction between the nitrone **3** and methyl acetylpropiolate gave a single cycloadduct **13** in 77% yield (Scheme 2). When this acetylene was used previously in reactions with simple nitrile oxides or simple nitrones a 1 : 1 mixture of regioisomers was usually obtained.[6] The cycloadduct **13** gave a complex mixture of products when it was reduced with tributyltin hydride under free radical conditions. When **13** was then treated with two equivalents of 4-chlorophenylhydrazine in refluxing glacial acetic acid, a single product was isolated in 26% yield, which was not the expected pyridazinone **14** (Scheme 2). The mass spectrum suggested that the isoxazole oxygen was missing; this loss of oxygen was confirmed by combustion analysis. An amide carbonyl was indicated by the IR spectrum, and the ^{1}H NMR spectrum indicated the presence of an α-imine methyl group and an aromatic ring. However, the spectra could be consistent with the expected product **14** or the pyrazole **15**. The structure was determined by single crystal X-ray crystallography, the product was shown to be the pyrazole **15** (Fig. 1).

The relative stereochemistry of the bromomethyl group and the ring junction methyl group in **15** was *cis*, supporting our earlier assignments. A possible mechanism for the formation of this product (see Scheme 3) involves an interesting rearrangement and reduction, which requires initial attack by the hydrazine on the acetyl group followed by Michael addition of a second molecule of the hydrazine. Elimination of this second hydrazine group followed by ring opening gives an intermediate oxalate which cyclises to give the lactam ring present in **15**. Finally, condensation of the hydrazino group with the ketone affords the pyrazole **15**. The actual sequence of events may differ from that shown.



Scheme 2

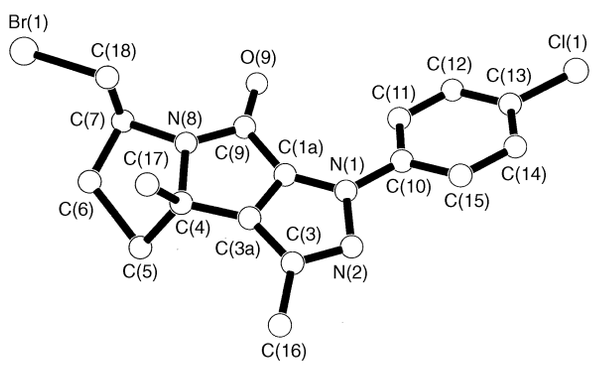
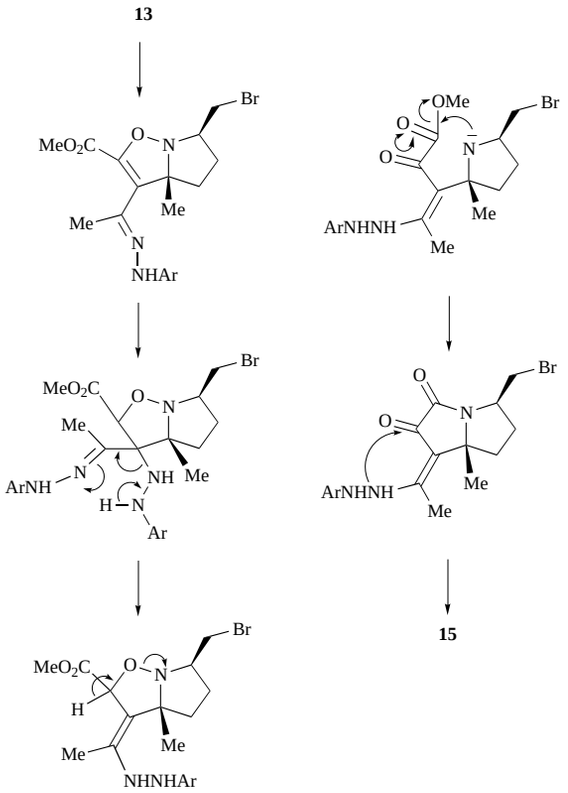


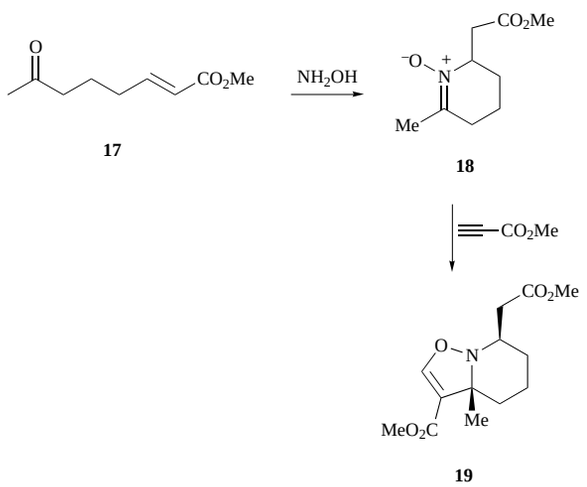
Fig. 1 Molecular structure of the pyrazolo[4,3-*a*]pyrrolizine **15** with atom numbering

This mechanism can only be applied to one of the two regioisomers which are possible from the cycloaddition, *i.e.* **13**. Reduction of the bromomethyl group of the pyrazole **15** with tributyltin hydride gave the methyl derivative **16** in 62% yield.

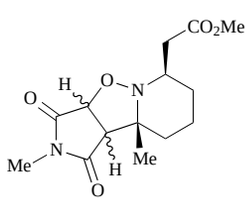
Cycloadditions of the six membered ring nitrone **18** were then studied. The methyl ketone **17** was prepared by the method described by Grigg *et al*. and reacted with hydroxylamine to give the nitrone **18** by a 1,3-azaprotio cyclotransfer reaction.[2] The nitrone **18** was reacted with methyl propiolate to give a single cycloadduct **19** in 46% yield as a colourless oil (Scheme 4). The *cis* stereochemistry of the cycloadduct **19** could not be conclusively assigned by NOE difference spectroscopy because of overlapping signals in the ^{1}H NMR spectrum. This assignment is supported in the literature; Grigg *et al*.[2] reported the same *cis* stereochemistry for the methoxycarbonyl and ring junction methyl groups when the nitrone **18** was reacted with *N*-methylmaleimide to give the cycloadduct **20** as a mixture of *exo* and *endo* isomers.



Scheme 3

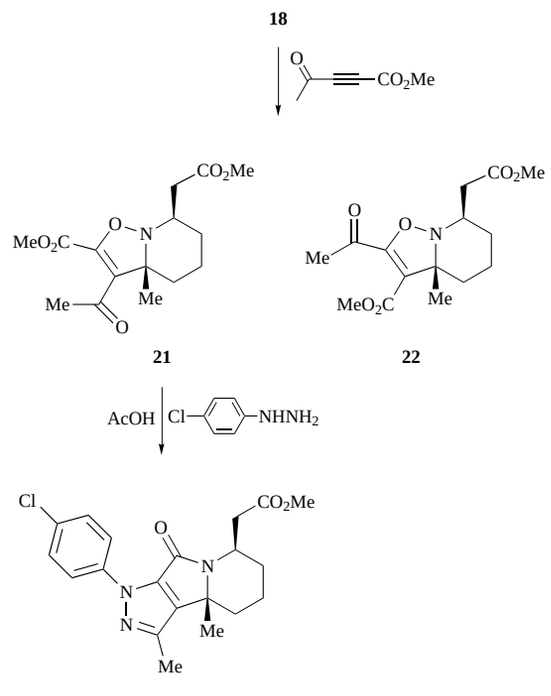


Scheme 4

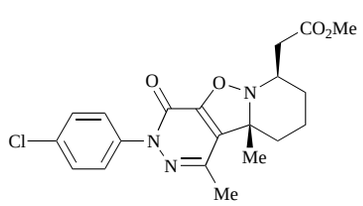


A similar effect to that observed with nitrone **3** may be occurring in this cycloaddition. An electrostatic attraction between the positive charge on the nitrogen of the dipole and the carbonyl group of the ester would shield one face of the dipole from attack by methyl propiolate. This would result in the *cis* stereochemistry as shown. Likewise MM2 molecular models show the ring of this nitrone to be essentially planar, so the side chain ester could also be exerting a steric effect by forcing the cycloaddition onto the opposite face.

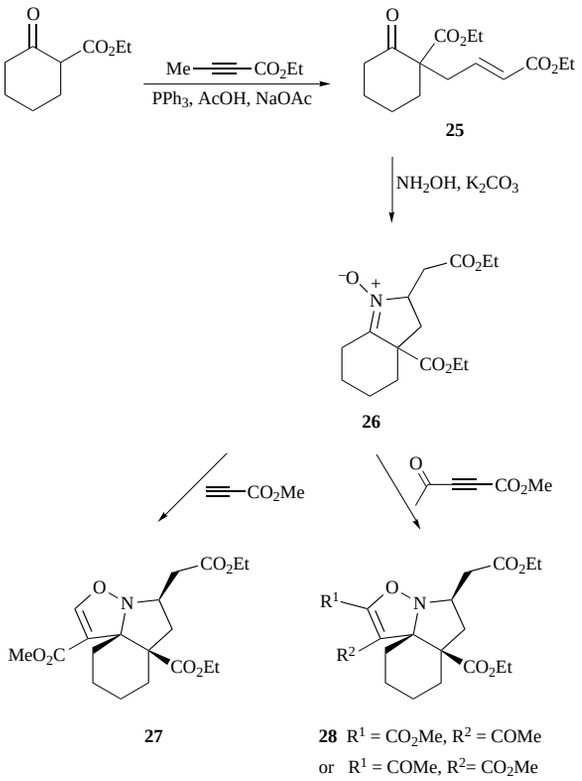
Cyclisation of the nitrone **18** with methyl acetylpropiolate yielded a separable mixture of regioisomers **21** and **22** in a ratio of 3:2. The major regioisomer **21** was reacted with 4-chlorophenylhydrazine in refluxing glacial acetic acid to give a product which from the fragmentation pattern in the mass spectrum showed the isoxazole oxygen to be absent; this loss of oxygen from the expected product **24** was confirmed by combustion analysis. The ^{1}H NMR and IR spectra were consistent with the pyrazole **23**, a structure which is supported by the structurally related pyrazole **15**. None of the expected pyridazinone **24** was isolated. The minor isomer **22** gave a complex mixture of products, none of which corresponded to the expected pyridazinone, when reacted with 4-chlorophenylhydrazine under similar conditions (Scheme 5).



Scheme 5



The bicyclic nitrone **26** which contains two pendant ester groups was studied. The precursor **25** to the bicyclic nitrone **26** was synthesized from ethyl 2-oxocyclohexanecarboxylate by the method described by Trost and Li.[7] The nitrone **26** was reacted with methyl propiolate to give the tricyclic adduct **27** as the major diastereoisomer along with trace amounts of two other diastereoisomers. The stereochemistry of the major diastereoisomer has been assigned by assuming that methyl propiolate approaches from the opposite face of the nitrone **26** to that containing the two ester groups. The nitrone **26** was reacted with methyl acetylpropiolate to give the tricyclic adduct **28** as a mixture of two isomers in a ratio of 2:1 (Scheme 6). The reaction of nitrone **26** with methyl propiolate gave a major diastereoisomer and only one regioisomer would have been predicted by MO theory for this acetylene. In this reaction, however, two regioisomers would have been predicted by MO theory. It therefore seems more likely



Scheme 6

that the two isomers obtained are regioisomers rather than diastereoisomers.

Our studies have shown that cycloadditions between nitrones and acetylenes can be regioselective and that pendant side chains on the nitrones give *cis* stereoselectivity. The stereoselectivity is possibly explained by the use of electronegative groups or atoms which can interact with positively charged centres on 1,3-dipoles and/or steric hindrance thereby forcing the cycloaddition to occur on the opposite face.

Experimental

General

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba 1106/1 elemental analyser. IR spectra were recorded on a Unicam FT IR 3020 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 and AM360 spectrometers using tetramethylsilane as the internal standard in deuteriochloroform unless otherwise stated. *J* Values are given in Hz. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer. All flash chromatography was carried out using Sorbsil silica gel (40–60 μm). Light petroleum refers to the bp 40–60 °C fraction.

General procedure for the preparation of nitrone 3

A mixture of hex-5-en-2-one **1** (10 g, 0.1 mol), hydroxylamine hydrochloride (7.1 g, 0.1 mol) and sodium carbonate (5.4 g, 0.05 mol) in water (100 cm^3) was stirred at room temperature for 1 h under nitrogen. The reaction mixture was then extracted with dichloromethane and the combined extracts were washed with water, dried and evaporated to dryness to give a mixture of the corresponding oximes **2** (11.3 g, 0.1 mol). The mixture of oximes was then dissolved in dichloromethane (200 cm^3) and cooled to 0 °C. *N*-Bromosuccinimide (17.8 g, 0.1 mol) was added portionwise over 15 min and the resultant solution stirred for 2 h at room temperature, by which time TLC analysis showed the absence of the two starting oximes. This solution of the nitrone **3** was then used in the next stage without further purification.

Methyl 6-bromomethyl-3a-methyl-3a,4,5,6-tetrahydropyrrolo-[1,2-*b*]isoxazole-3-carboxylate 5

Methyl propiolate (3.36 g, 3.55 cm^3, 0.04 mol) was added dropwise to a solution of the nitrone **3** (0.04 mol) in dichloromethane (200 cm^3) and the resultant solution was stirred for 16 h at room temperature. The reaction mixture was then evaporated to dryness and the brown oily residue was purified by flash chromatography eluting with light petroleum–ethyl acetate 5:1 to give the titled compound **5** as an oil (3.32 g, 30%); ν_{max}/cm^{-1} 1706; δ_H(360 MHz) 1.45 (3 H, s, 3a-Me), 1.70 (1 H, m, CH_2), 2.05 (2 H, m, CH_2), 2.30 (1 H, m, CH_2), 3.40 (1 H, dd, *J* 15.4 and 8.2, CH_2Br), 3.45 (1 H, m, 6-H), 3.65 (1 H, dd, *J* 15.4 and 4.3, CH_2Br), 3.75 (3 H, s, CO_2Me) and 7.25 (1 H, s, 2-H) (Found: M$^+$, 277.0137. $C_{10}H_{14}BrNO_3$ requires *M*, 277.0137); *m/z* 275 and 277 (M$^+$, 7%) and 168 (100).

Methyl 6-bromomethyl-3a-methyl-2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate 8

Methyl 3-phenylpropiolate (14.7 g, 0.09 mol) was added dropwise to a solution of the nitrone **3** (0.09 mol) in toluene (200 cm^3) and the resultant mixture was stirred and heated for 4 h under reflux. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography eluting with dichloromethane–ethyl acetate 50:1 to give the titled compound **8** as a colourless oil (18.2 g, 57%); ν_{max}/cm^{-1} 1715; δ_H(250 MHz) 1.55 (3 H, s, 3a-Me), 1.70 (1 H, m, CH_2), 2.10 (2 H, m, CH_2), 2.40 (1 H, m, CH_2), 3.45 (1 H, dd, *J* 15.4 and 8.2, CH_2Br), 3.50 (1 H, m, 6a-H), 3.70 (3 H, s, CO_2Me), 3.75 (1 H, dd, *J* 15.4 and 4.3, CH_2Br) and 7.3–7.7 (5 H, m, Ar-H); *m/z* (CI, C_4H_{10}) 352, 354 (M + H$^+$).

Methyl 3-acetyl-6-bromomethyl-3a-methyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-2-carboxylate 13

Methyl 3-acetylpropiolate[8] (5.44 g, 0.04 mol) was added dropwise to a solution of the nitrone **3** (0.04 mol) in dichloromethane (200 cm^3) and the resultant solution was stirred for 16 h at room temperature. The reaction mixture was evaporated to dryness and the brown oily residue purified by flash chromatography eluting with light petroleum–ethyl acetate 3:1 to give the titled compound **13** as a colourless oil (9.8 g, 77%); ν_{max}/cm^{-1} 1745 and 1710; δ_H(250 MHz) 1.45 (3 H, s, 3a-Me), 1.70 (1 H, m, CH_2), 2.05 (2 H, m, CH_2), 2.30 (1 H, m, CH_2), 2.35 (3 H, s, MeCO), 3.40 (1 H, dd, *J* 15.4 and 8.2, CH_2Br), 3.45 (1 H, m, 6-H), 3.65 (1 H, dd, *J* 15.4 and 4.3, CH_2Br) and 3.90 (3 H, s, CO_2Me); *m/z* (CI, C_4H_{10}) 317, 319 (M + H$^+$).

Methyl 3a-methyl-6-methylthiomethyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate 9

A mixture of the cycloadduct **5** (5.1 g, 0.02 mol) and sodium methanethiolate (1.94 g, 0.028 mol) in dimethylformamide (DMF) (100 cm^3) was stirred at room temperature under nitrogen for 3 h. The reaction mixture was then diluted with diethyl ether and the organic layer washed with water and dried. The organic layer was evaporated to dryness to give a brown oily residue. Purification by flash chromatography eluting with dichloromethane–ethyl acetate 3:1 gave the titled compound **9** as a colourless oil (2.2 g, 45%) (Found: C, 54.3; H, 7.2; N, 12.8. $C_{11}H_{17}NSO_3$ requires C, 54.3; H, 7.0; N, 13.2%); ν_{max}/cm^{-1} 1707; δ_H(360 MHz) 1.45 (3 H, s, 3a-Me), 1.65 (1 H, m, CH_2), 2.05 (2 H, m, CH_2), 2.15 (3 H, s, SMe), 2.25 (1 H, m, CH_2), 2.65 (1 H, dd, *J* 13.2 and 8.4, CH_2SMe), 2.85 (1 H, dd, *J* 15.4 and 4.3, CH_2SMe), 3.35 (1 H, m, 6-H), 3.75 (3 H, s, CO_2Me) and 7.25 (1 H, s, 2-H); *m/z* 243 (M$^+$, 64%) and 154 (81).

Methyl 3a-methyl-6-methylthiomethyl-2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate 10

A mixture of the cycloadduct **8** (2.57 g, 7.3 mmol) and sodium

methanethiolate (0.77 g, 10 mmol) in DMF (80 cm^3) was stirred at room temperature under nitrogen for 2 h. The reaction mixture was then diluted with diethyl ether and the organic layer washed with water and dried. The organic layer was evaporated to dryness and the resulting brown oily residue was purified by flash chromatography eluting with dichloromethane–ethyl acetate 3:1 to give the titled compound **10** as a colourless oil (1.0 g, 43%) (Found: C, 64.0; H, 6.95; N, 4.3; S, 10.2. $C_{17}H_{21}NSO_3$ requires C, 63.9; H, 6.6; N, 4.4; S, 10.0%); ν_{max}/cm^{-1} 1714; δ_H(250 MHz) 1.55 (3 H, s, 3a-Me), 1.70 (1 H, m, CH_2), 2.05 (2 H, m, CH_2), 2.15 (3 H, s, SMe), 2.40 (1 H, m, CH_2), 2.70 (1 H, dd, *J* 13.0 and 8.3, CH_2SMe), 2.95 (1 H, dd, *J* 15.4 and 4.3, CH_2SMe), 3.40 (1 H, m, 6-H), 3.65 (3 H, s, CO_2Me), 7.40 (3 H, m, Ar-H) and 7.65 (2 H, m, Ar-H); *m/z* (CI, C_4H_{10}) 320 ($M + H^+$).

Methyl 3a,6-dimethyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]-isoxazole-3-carboxylate 11

A mixture of the cycloadduct **5** (3.9 g, 0.014 mol), tributyltin hydride (3.8 cm^3, 0.014 mol) and azoisobutyronitrile (AIBN) (6.83 g) in toluene (200 cm^3) was stirred and heated at 50 °C under nitrogen for 2 h. The reaction mixture was then allowed to cool and evaporated to dryness. The residue was purified by flash chromatography eluting with light petroleum–ethyl acetate 10:1 to give the titled compound **11** as a colourless oil (1.21 g, 44%) (Found: C, 60.6; H, 7.8; N, 6.8. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.6; N, 7.1%); ν_{max}/cm^{-1} 1709; δ_H(250 MHz) 1.25 (3 H, d, *J* 7, 6-Me), 1.45 (3 H, s, 3a-Me), 1.50 (1 H, m, CH_2), 1.90 (2 H, m, CH_2), 2.20 (1 H, m, CH_2), 3.20 (1 H, m, 6-H), 3.75 (3 H, s, CO_2Me) and 7.25 (1 H, s, 2-H); *m/z* 197 (M^+, 48%) and 142 (100).

Methyl 3a,6-dimethyl-2-phenyl-3a,4,5,6-tetrahydropyrrolo-[1,2-*b*]isoxazole-3-carboxylate 12

A mixture of the cycloadduct **8** (5 g, 0.014 mol), tributyltin hydride (3.8 cm^3, 0.014 mol) and AIBN (6.83 g) in toluene (200 cm^3) was stirred and heated at 50 °C under nitrogen for 4 h. The reaction mixture was then allowed to cool and evaporated to dryness. The residue was purified by flash chromatography eluting with dichloromethane–ethyl acetate 99:1 to give a solid which was recrystallised from hexane to give the titled compound **12** as a colourless solid (1.58 g, 41%); mp 54–56 °C (Found: C, 69.8; H, 7.2; N, 5.3. $C_{16}H_{19}NO_3$ requires C, 70.2; H, 7.0; N, 5.1%); ν_{max}/cm^{-1} 1688; δ_H(360 MHz) 1.35 (3 H, d, *J* 7, 6-Me), 1.50 (1 H, m, CH_2), 1.55 (3 H, s, 3a-Me), 1.85 (1 H, m, CH_2), 2.00 (1 H, m, CH_2), 2.30 (1 H, m, CH_2), 3.30 (1 H, m, 6-H), 3.65 (3 H, s, CO_2Me), 7.40 (3 H, m, Ar-H) and 7.65 (2 H, m, Ar-H); *m/z* 273 (M^+, 30%).

6-Bromomethyl-1-(4-chlorophenyl)-3,3b-dimethyl-3b,4,5,6-tetrahydro-1*H*-pyrazolo[4,3-*a*]pyrrolizin-8-one 15

The cycloadduct **13** (15 g, 0.047 mol) and 4-chlorophenylhydrazine (14.8 g, 0.104 mol) were dissolved in glacial acetic acid (200 cm^3) and heated under reflux for 3 h under nitrogen. The reaction mixture was then concentrated to give a brown oily residue which was partitioned between ethyl acetate and 2 M hydrochloric acid. The organic layer was separated and washed with 2 M hydrochloric acid and brine, dried and evaporated to dryness to give a brown oil. The oil was purified by flash chromatography eluting with light petroleum–ethyl acetate 6:1 to afford a brown solid which was recrystallised from ethanol to give the titled compound **15** as light brown crystals (4.8 g, 26%); mp 142–144 °C (Found: C, 51.9; H, 4.3; N, 10.6; Cl, 18.0. $C_{17}H_{17}BrClN_3O$ requires C, 51.7; H, 4.3; N, 10.6; Cl, 18.0%); ν_{max}/cm^{-1} 1691; δ_H(250 MHz) 1.60 (3 H, s, 3b-Me), 1.70 (1 H, m, CH_2), 2.15 (1 H, m, CH_2), 2.35 (1 H, m, CH_2), 2.40 (3 H, s, 3-Me), 2.65 (1 H, m, CH_2), 3.45 (1 H, dd, *J* 10.0 and 8.3, CH_2Br), 3.75 (1 H, dd, *J* 10.0 and 4.2, CH_2Br), 4.15 (1 H, m, 6-H), 7.40 (2 H, d, *J* 8, Ar-H) and 8.15 (2 H, d, *J* 8, Ar-H); *m/z* 393, 395 and 397 (M^+, 67, 80, 21%) and 300 (100).

1-(4-Chlorophenyl)-3,3b,6-trimethyl-3b,4,5,6-tetrahydro-1*H*-pyrazolo[4,3-*a*]pyrrolizin-8-one 16

The pyrazole **15** (1.61 g, 4 mmol), tributyltin hydride (1.2 g, 4 mmol) and AIBN (2.3 g) were dissolved in toluene (100 cm^3) and stirred and heated to 110 °C for 4 h under nitrogen. The reaction mixture was evaporated to dryness to give a brown solid which was purified by flash chromatography. Elution with dichloromethane–ethyl acetate 98:2 gave the titled compound **16** as a colourless solid which was recrystallised from ethanol (0.78 g, 62%); mp 122 °C (Found: C, 64.75; H, 5.8; N, 12.95; Cl, 11.3. $C_{17}H_{18}ClN_3O$ requires C, 64.6; H, 5.7; N, 13.3; Cl, 11.25%); ν_{max}/cm^{-1} 1695; δ_H(250 MHz) 1.45 (3 H, s, 6-Me), 1.60 (3 H, s, 3b-Me), 1.60 (1 H, m, CH_2), 2.10 (2 H, m, CH_2), 2.35 (3 H, s, 3-Me), 2.60 (1 H, m, CH_2), 4.00 (1 H, m, 6-H), 7.40 (2 H, d, *J* 8, Ar-H) and 8.20 (2 H, d, *J* 8, Ar-H); δ_C(62.90 MHz) 12.28 (CH_3), 23.09 (CH_3), 23.81 (CH_3), 34.92 (CH_2), 37.09 (CH_2), 51.98 (CH), 65.49 (C-3b), 120.66 (CH_2), 121.37 (quat.), 129.13 (CH_2), 131.54 (quat.), 137.78 (quat.), 141.20 (quat.), 141.65 (quat.) and 161.70 (C-8); *m/z* 315 and 317 (M^+, 63, 21%) and 300 (100).†

Methyl 7-methoxycarbonylmethyl-3a-methyl-4,5,6,7-tetrahydro-3a*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate 19

A mixture of methyl 7-oxooct-2-enoate[2] **17** (10.61 g, 0.062 mol), hydroxylamine hydrochloride (6.5 g, 0.093 mol) and sodium carbonate (4.8 g, 0.047 mol) in water (100 cm^3) was stirred at room temperature for 6 h under nitrogen. The reaction mixture was then extracted with dichloromethane and the combined extracts were washed with water, dried and evaporated to dryness to give the nitrone **18** as a colourless oil (4.48 g, 39%) which was used in the next stage without further purification.

Methyl propiolate (2 g, 0.024 mol) was added dropwise to the above nitrone **18** in toluene (100 cm^3) and the resultant solution was stirred for 4 h at room temperature under nitrogen. TLC analysis showed the reaction to be complete. The reaction mixture was evaporated to dryness and the residue purified by flash chromatography eluting with light petroleum–ethyl acetate 5:1 to give the titled compound **19** as a colourless oil (3 g, 18% from **17**) (Found: C, 58.3; H, 7.5; N, 5.0. $C_{13}H_{19}NO_5$ requires C, 58.0; H, 7.1; N, 5.2%); ν_{max}/cm^{-1} 1710 and 1735; δ_H(250 MHz) 1.1–1.9 (5 H, m, 4-H_2, 5-H_2 and 6-H), 1.25 (3 H, s, 3a-Me), 2.45 (1 H, dd, *J* 15.4 and 8.2, CH_2CO_2Me), 2.75 (1 H, m, 6-H), 2.86 (1 H, dd, *J* 15.4 and 4.3, CH_2CO_2Me), 3.10 (1 H, ddd, *J* 15.4, 8.2 and 4.3, 7-H), 3.65 (3 H, s, CO_2Me), 3.75 (3 H, s, CO_2Me) and 7.35 (1 H, s, 2-H); *m/z* 269 (M^+, 7%) and 254 (100).

Methyl 3-acetyl-7-methoxycarbonylmethyl-3a-methyl-4,5,6,7-tetrahydro-3a*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate 21 and 2-acetyl-7-methoxycarbonylmethyl-3a-methyl-4,5,6,7-tetrahydro-3a*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate 22

A mixture of methyl 7-oxooct-2-enoate[2] **17** (2.87 g, 0.017 mol), hydroxylamine hydrochloride (1.8 g, 0.026 mol) and sodium carbonate (1.4 g, 0.013 mol) in water (50 cm^3) was stirred at room temperature for 6 h under nitrogen. The reaction mixture was then extracted with dichloromethane and the combined extracts were washed with water, dried and evaporated to dryness to give the nitrone **18** as a colourless oil (2.96 g, 94%) which was used in the next stage without further purification.

Methyl 3-acetylpropiolate (2 g, 0.016 mol) was added dropwise to the above nitrone **18** in toluene (50 cm^3) and the resultant solution was stirred for 4 h at room temperature under nitrogen. The reaction mixture was evaporated to dryness and the brown oily residue was purified by flash chromatography eluting with light petroleum–ethyl acetate 4:1 to give the compound **22** as a colourless oil (0.52 g, 10%); ν_{max}/cm^{-1} 1720 and 1710; δ_H(250 MHz) 1.10–1.90 (5 H, m, 4-H_2, 5-H_2 and 6-H),

† Quat. = quaternary carbon.

1.35 (3 H, s, 3a-Me), 2.45 (3 H, s, MeCO), 2.45 (1 H, dd, *J* 15.4 and 8.2, CH_2CO_2Me), 2.75 (1 H, m, 6-H), 2.86 (1 H, dd, *J* 15.4 and 4.3, CH_2CO_2Me), 3.15 (1 H, ddd, *J* 15.4, 8.2 and 4.3, 7-H), 3.65 (3 H, s, CO_2Me) and 3.75 (3 H, s, CO_2Me) (Found: M^+, 311.1365. $C_{15}H_{21}NO_6$ requires *M*, 311.1350); *m/z* 311 (M^+, 6%) and 296 (100). Further elution gave compound **21** as a colourless oil (0.77 g, 15%); ν_{max}/cm^{-1} 1720 and 1695; δ_H(250 MHz) 1.1–1.9 (5 H, m, 4-H_2, 5-H_2 and 6-H), 1.35 (3 H, s, 3a-Me), 2.35–2.50 (2 H, m, CH_2CO_2Me and CH_2), 2.45 (3 H, s, MeCO), 2.90 (1 H, dd, *J* 15.4 and 4.3, CH_2CO_2Me), 3.15 (1 H, ddd, *J* 15.4, 8.2 and 4.3, 7-H), 3.67 (3 H, s, CO_2Me) and 3.89 (3 H, s, CO_2Me) (Found: M^+, 311.1359. $C_{15}H_{21}NO_6$ requires *M*, 311.1350); *m/z* 311 (M^+, 5%) and 296 (100).

7-Methoxycarbonylmethylene-1-(4-chlorophenyl)-3,3b-dimethyl-4,5,6,7-tetrahydro-1*H*,3b*H*-pyrazolo[4.3-*a*]indolizin-9-one 23

The cycloadduct **22** (0.2 g, 0.6 mmol) and 4-chlorophenylhydrazine (0.23 g, 1 mmol) in glacial acetic acid (25 cm^3) were stirred and heated under reflux for 5 h under nitrogen. The reaction mixture was evaporated to dryness to give a brown oily residue which was partitioned between ethyl acetate and 2 M hydrochloric acid. The organic layer was separated and washed with 2 M hydrochloric acid and brine, dried and evaporated to dryness to give a brown oil. The oil was purified by flash chromatography eluting with light petroleum–ethyl acetate 5:1 to afford a beige solid which was recrystallised from ethanol to give the title compound **23** as colourless crystals (0.12 g, 51%); mp 105–106 °C (Found: C, 61.65; H, 5.7; N, 10.6; Cl, 9.05. $C_{20}H_{22}ClN_3O_3$ requires C, 61.9; H, 5.7; N, 10.8; Cl, 9.2%); ν_{max}/cm^{-1} 1740; δ_H(250 MHz) 1.30–2.00 (5 H, m, CH_2), 1.60 (3 H, s, 3b-Me), 2.20 (1 H, br dt, *J* 12 and 3, CH_2), 2.35 (3 H, s, 3-Me), 2.75 (2 H, m, CH_2CO_2Me), 3.70 (3 H, s, CO_2Me), 5.10 (1 H, br q, *J* 7, 7-H), 7.40 (2 H, d, *J* 8, Ar-H) and 8.25 (2 H, d, *J* 8, Ar-H); *m/z* 387, 389 (M^+, 44, 12%) and 314 (100).

Reaction between cycloadduct 21 and 4-chlorophenylhydrazine

The cycloadduct **21** (0.2 g, 0.6 mmol) and 4-chlorophenylhydrazine (0.23 g, 1 mmol) in glacial acetic acid (25 cm^3) were stirred and heated under reflux for 3 h under nitrogen. The reaction mixture was then worked up the same as for compound **22** to give a dark brown oil which proved to be a complex mixture by TLC analysis.

Ethyl 4-(2-oxo-1-ethoxycarbonylcyclohexyl)but-2-enoate 25

A mixture of ethyl but-2-ynoate (20 g, 0.18 mol), ethyl 2-oxocyclohexanecarboxylate (30 g, 0.18 mol), triphenylphosphine (2.36 g, 0.09 mol), acetic acid (5.4 g, 0.09 mol) and sodium acetate (7.4 g, 0.09 mol) in toluene (200 cm^3) was heated at 80 °C for 20 h under nitrogen. After cooling, the reaction mixture was filtered and the solid washed with diethyl ether. The combined organic fractions were evaporated to dryness and the residue purified by flash chromatography eluting with light petroleum–ethyl acetate 10:1 to give the title compound **25** as a yellow oil (21.44 g, 42%); ν_{max}/cm^{-1} 1718; δ_H(250 MHz) 1.25 (6 H, 2 × t, OCH_2CH_3), 1.40–1.80 (4 H, m, cyclohexyl CH_2), 1.95 (1 H, m, cyclohexyl H), 2.45 (3 H, m, cyclohexyl CH_2), 4.20 (4 H, 2 × q, OCH_2CH_3), 4.75 (2 H, dd, *J* 4.6 and 2.0, $CH_2CH{=}CH$), 6.0 (1 H, dt, *J* 15.7 and 2.0, $CH_2CH{=}CH$) and 6.95 (1 H, dt, *J* 15.7 and 4.6, $CH_2CH{=}CH$); *m/z* (CI, C_4H_{10}) 283 ($M + H^+$).

General procedure for the preparation of nitrone 26

A mixture of **25** (10 g, 0.04 mol) and sodium carbonate (3.2 g, 0.03 mol) was dissolved in water (100 cm^3) and stirred for 4 h at room temperature under nitrogen. The reaction mixture was extracted with dichloromethane and the combined organic extracts were washed with water and dried. The organic extracts were evaporated to dryness to give the nitrone **26** as a pale yellow oil. This oil was used in the next stage without further purification.

Ethyl 6a-ethoxycarbonyl-1-(methoxycarbonyl)-6,6a,7,8,9,10-hexahydro-5*H*-isoxazolo[3,2-*i*]indole-5-acetate 27

The nitrone **26** (10 g, 34 mmol) and methyl propiolate (2.9 g, 34 mmol) were dissolved in toluene (100 cm^3) and stirred at room temperature under nitrogen for 24 h. The reaction mixture was evaporated to dryness to give a brown oily residue which was purified by flash chromatography eluting with light petroleum–ethyl acetate 5:1. The title compound **27** was isolated as a pale yellow oil (2.43 g, 19%), attempts to crystallise this oil failed (Found: C, 60.0; H, 7.1; N, 3.6. $C_{19}H_{27}NO_7$ requires C, 59.8; H, 7.1; N, 3.7%); ν_{max}/cm^{-1} 1730; δ_H(360 MHz) peaks corresponding to the major isomer, 1.25 (6 H, 2 × t, OCH_2CH_3), 1.50–1.90 (10 H, m, CH_2), 2.20 (1 H, dd, *J* 15.0 and 8.0, $CHHCO_2Et$), 2.50 (1 H, dd, *J* 15.0 and 5.0, $CHHCO_2Et$), 2.85 (1 H, dd, *J* 8.0 and 5.3, $NCHCH_2$), 3.67 (3 H, s, CO_2Me), 4.10 and 4.15 (4 H, 2 × q, OCH_2CH_3) and 7.24 (1 H, s, olefinic H); *m/z* 381 (M^+, 23%) and 105 (100).

Ethyl 1(2)-acetyl-6a-ethoxycarbonyl-2(1)-(methoxycarbonyl)-6,6a,7,8,9,10-hexahydro-5*H*-isoxazolo[2,3-*i*]indole-5-acetate 28

The nitrone **26** (6.80 g, 20 mmol) and methyl 3-acetylpropiolate (2.9 g, 20 mmol) were dissolved in toluene (80 cm^3) and stirred at room temperature under nitrogen for 4 h. The reaction mixture was evaporated to dryness to give a brown oily residue which was purified by flash chromatography eluting with light petroleum–ethyl acetate 3:1. The title compound **28**, a mixture of regioisomers, was isolated as a yellow oil (6.0 g, 71%), attempts to crystallise this oil failed (Found: C, 59.25; H, 6.95; N, 3.15. $C_{21}H_{29}NO_8$ requires C, 59.6; H, 6.90; N, 3.3%); ν_{max}/cm^{-1} 1732 and 1640; δ_H(250 MHz) mixture of regioisomers in a ratio of 2:1, part spectrum, 1.25 (6 H, m, OCH_2CH_3), 2.36 and 2.39 (3 H, 2 × s, $COCH_3$), 2.60 (1 H, m, $CHHCO_2Et$), 2.95 (1 H, m, $NCHCH_2$), 3.70 and 3.86 (3 H, 2 × s, CO_2CH_3) and 4.05 and 4.15 (4 H, 2 × m, OCH_2CH_3); *m/z* 423 (M^+, 6%) and 380 (24).

X-Ray crystallographic analysis of 15

Crystal data: single crystals of **15** suitable for X-ray crystallography were grown from ethanol. $C_{17}H_{17}N_3OClBr$, $M = 394.7$, orthorhombic, $a = 16.197(7)$, $b = 21.837(4)$, $c = 9.764(5)$ Å, $U = 3453(2)$ $Å^3$, space group *Pbca*, $Z = 8$, $D_c = 1.52$ g cm^{-3}. A clear plate, dimensions 0.15 × 0.20 × 0.40 mm, μ(Cu-Kα) = 47 cm^{-1}, $F(000) = 1600$. 2939 Independant reflections were collected on a Rigaku AFC7S diffractometer, ω scan method, $5 < 2\theta < 120°$, graphite monochromated Cu-Kα radiation ($\lambda = 1.541\,78$ Å) with 1582 observed [$I > 3.00\sigma(I)$] and corrected for Lorentz and polarisation factors. An empirical absorption correction was applied (transmission factors 0.7614–1.000). The structure was solved by the heavy atom method, and the non-hydrogen atoms refined anisotropically. High thermal motion and disorder was observed in the region of C(6), C(7) and C(18). This could not be resolved into discrete sites. The hydrogen atoms were idealised. Refinement was by full-matrix least-squares to give $R = 0.074$, $R_w = 0.054$ [$w^{-1} = \sigma^2(F_o)$]. The maximum residual electron density in the final ΔF map was 1.17 e $Å^{-3}$ and the maximum shift/error in the final refinement was 0.53. All calculations were carried out using the TEXSAN[9] crystallographic software package of Molecular Structure Corporation.‡

‡ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/70.

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