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Synthesis and Reactivity of 1-Pyrroline-5-carboxylate Ester 1-Oxides

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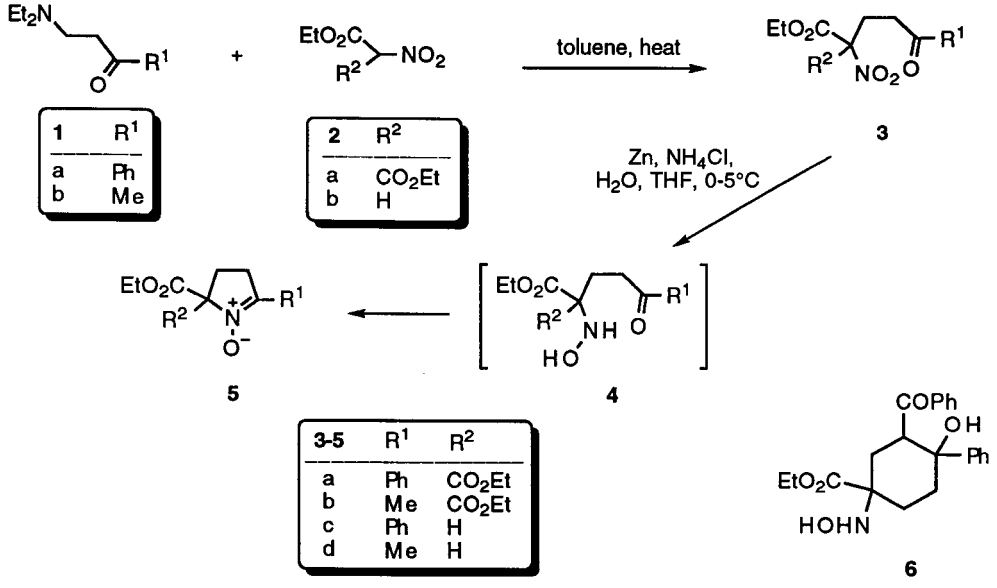
Abstract—Some C5 mono- and diester-substituted 1-pyrroline-1-oxides have been prepared via reductive cyclisation of the corresponding γ-nitro carbonyl compounds. Ethyl 2-phenyl-1-pyrroline-1-oxide-5-carboxylate **5c** was regioselectively alkylated at C5. Acylation of this molecule occurs exclusively on the nitrone oxygen and leads to C3 substituted pyrrolines as the result of a hetero-Cope rearrangement.

The cyclic nature of the 1-pyrroline-1-oxide unit imparts stability towards hydrolysis of the nitrone system.[1] The majority of experimentation on such compounds has been performed with *gem*-dimethyl substitution at C5 of the ring. Whilst this pattern of substitution provides further stability, facile chemical elaboration is disallowed at this position. We envisaged that incorporation of a single ester function at C5 would provide a means by which carbanion chemistry could be performed at this position via basic removal of the acidic proton. The synthesis of such novel nitrones and the reactivity of a representative example will be described herein.

Although new synthetic routes to cyclic nitrones continue to emerge,[2–4] the reductive cyclisation of γ-nitro carbonyl compounds is most commonly used and was our chosen strategy. The synthetic approach to the C5 monoester substituted nitrones was initially planned to proceed via overall dealkoxycarbonylation of the malonate derivatives **5a** and **5b**. To this end, requisite precursors **3a** and **3b** were



Scheme 1.

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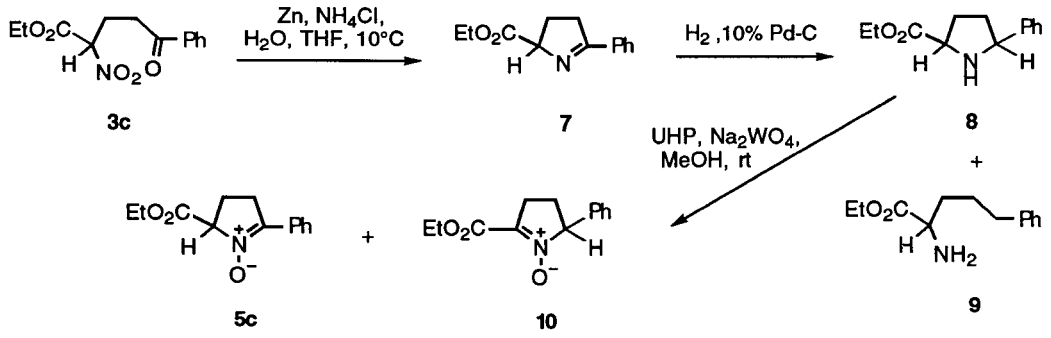


Scheme 2.

prepared by reacting diethyl nitromalonate **2a** with the Mannich bases **1a** and **1b**, respectively, in refluxing toluene. Subsequent treatment of these compounds with cold aqueous ammonium chloride and zinc dust produced the nitrones **5a** and **5b** without isolation of the intermediate hydroxylamines **4a** and **4b**. Development of the monoester derivative **5c** from the malonate compound **5a** was attempted and proved to be problematic using both Krapcho[5] and standard hydrolysis-decarboxylation-esterification methodology. This problem was circumvented by replacing malonate **2a** with ethyl nitroacetate **2b** in reaction Scheme 1. It was found that compound **2b** could be reacted with either amino ketone **1a** or **1b** to give the γ-nitro carbonyl compounds **3c** and **3d**. Reductive cyclisation of these latter derivatives gave the target C5 monoester nitrones **5c** and **5d** in 70% and 46% yield, respectively.

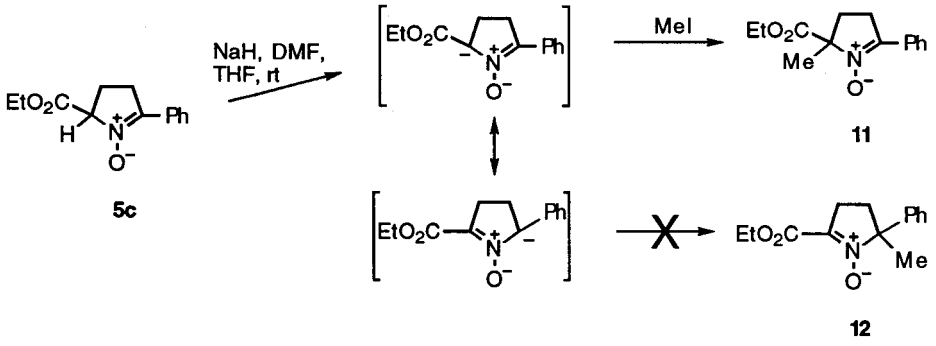
An interesting by-product, identified as hydroxylamine **6** (Scheme 1), was isolated in small yield on recrystallisation of **5c** from ethanol, and is believed to arise via trapping of the intermediate hydroxylamine **4c** by contaminant phenyl vinyl ketone.

During the reductive cyclisation of **3c** it was found that an elevated temperature of 10°C gave the corresponding pyrroline **7** in 92% yield. This subtle change in methodology produced superior results for ring formation and was not as sensitive to changes in zinc quality as was the nitrone synthesis. An alternative route to the desired nitrone system followed reduction of compound **7** to the pyrrolidine **8** and subsequent oxidation of the secondary amine to give the target molecule **5c**.

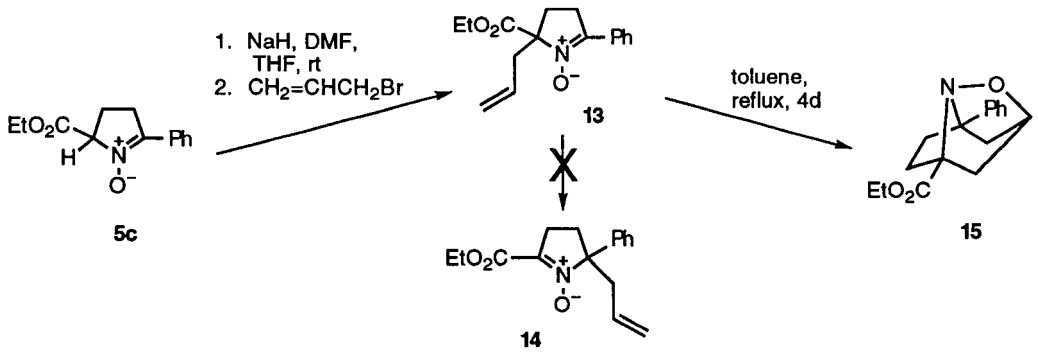
The attempted reduction of pyrroline **7** using sodium borohydride was unsuccessful, so catalytic hydrogenation was employed. Reduction at 1 atm gave the desired pyrrolidine **8** together with the amino ester **9**. Hydrogenation at 20 psi gave an 89% yield of compound **9**. Oxidation of the pyrrolidine **8** using urea hydrogen peroxide (UHP)[6] and sodium tungstate[7] gave a mixture of the two isomeric nitrones **5c** and **10** in a ratio of 3.8:1 (Scheme 2). The product ratio suggests that the nitrone is better stabilised when conjugated to the phenyl group as opposed to the ester function. This result is not surprising when considering that the nitrone carbon is somewhat cationic in nature and can be relatively destabilised by electron withdrawing groups.

The reactivity of nitrone **5c** was examined, initially with respect to removal of the acidic proton at C5. Treatment with sodium hydride followed by quenching with methyl iodide produced compound **11** exclusively, with no evidence for the formation of the isomeric compound **12** (Scheme 3), which would be formed by methylation of the alternative carbanion. This finding is consistent with the result of oxidation of pyrrolidine **8** with UHP and sodium tungstate.

It was found that nitrone **5c** could also be regioselectively alkylated at C5 with allyl bromide to give compound **13**, which on heating in refluxing toluene gave a single product **15** resulting from 1,3-dipolar cycloaddition. When compared with an earlier example of this type,[8] formation of the isomeric nitrone **14** (Scheme 4) could be expected via 3,3-Cope rearrangement of allyl nitrone **13**. Although both allylated nitrones **13** and **14** should give the same



Scheme 3.



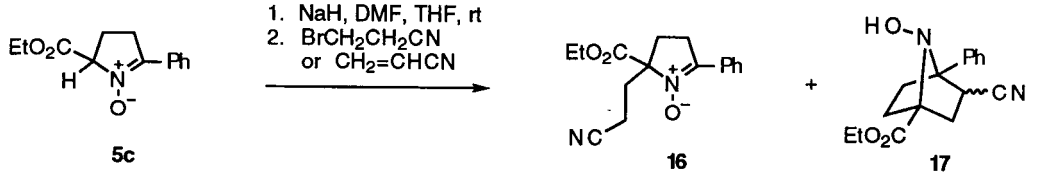
Scheme 4.

cycloaddition product **15**, monitoring of the reaction by ^{1}H NMR spectroscopy revealed that nitrone **14** was not formed at any stage.

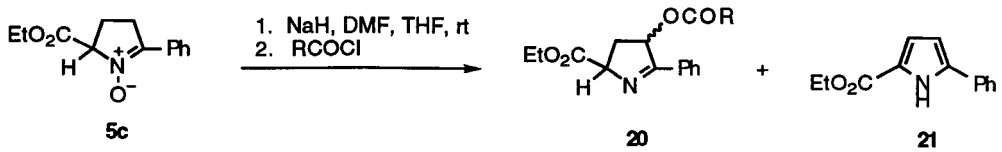
The attempted alkylation of nitrone **5c** with β-bromopropionitrile as alkylating agent gave unexpected results. Treatment with 1 equiv. of sodium hydride followed by addition of the β-halo nitrile gave quantitative recovery of **5c**. Failure of this reaction was attributed to quenching of the C5 carbanion via proton exchange with the position α- to the nitrile of the alkylating agent. When repeated with 2 equiv. of base the reaction not only gave the C5 alkylated product **16** but also the bicyclic compound **17** (Scheme 5). It is proposed that compound **17** arises through net loss of hydrogen bromide from 3-bromopropionitrile to give acrylonitrile, followed by Michael addition of the C5 carbanion of nitrone **5c** and subsequent trapping of the intermediate anion α- to the nitrile. Inferential evidence in support of this mechanism was found when treatment of nitrone **5c** with 1 equiv. of base followed by acrylonitrile gave an improved yield of hydroxylamine **17** together with some C5 alkylated compound **16**.

To test the generality of the route to 7-azabicyclo[2.2.1]heptane skeletons such as compound **17**, addition of the α,β-unsaturated carbonyl compounds chalcone and ethyl crotonate to the C5 carbanion of **5c** was carried out. However, no bicyclic compounds were isolated under these conditions and only the products **18** and **19** of Michael addition were observed. It appears that the intermediate carbanions α- to the carbonyl functions located on the acceptor during the Michael reaction are too stable, relative to that in the nitrile analogue, and do not attack the nitrone system. Indeed, treatment of compounds **18** and **19** with one molar equivalent of sodium hydride followed by aqueous workup resulted in only near quantitative recovery of starting material.

The above results argue against a [3+2] concerted cycloaddition mechanism in the formation of compound **17** from nitrone **5c** and acrylonitrile. The α,β-unsaturation in the carbonyl bearing examples is more activated and would be expected to give bicyclic compounds, at least to some extent, if a concerted process was in operation.

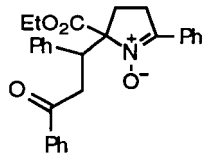


Scheme 5.



20	R	Yield % 20 *cis*	Yield % 20 *trans*	Yield % 21
a	Me	24	20	41
b	Et	22	19	33
c	$(CH_2)_2Br$	0	0	92
d	$(CH_2)_3Br$	25	22	39
e	Ph	25	35	23

Scheme 6.



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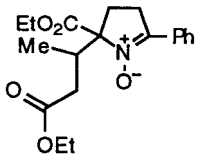

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Acylation of the C5 carbanion derived from nitrone **5c** was attempted with a variety of acid chlorides. However, electrophilic attack occurred exclusively at oxygen and not at C5 to give compounds **20a**–**e** via hetero-Cope rearrangement. These products readily lose carboxylic acid and undergo aromatisation to the pyrrole **21** (Scheme 6). This result was not entirely unexpected as it has been shown that nitrones, when treated with benzoyl chloride[9–14] or benzoic anhydride,[14] produce *O*-benzoyl imine derivatives. In a few of these previous examples small amounts of 2*H*-pyrroles have also been obtained. More recently a reliable route to these pyrroles from 1-pyrroline-1-oxides has been described.[15]

The acylation of nitrone **5c** generated both possible isomers of the compounds **20a**–**e**. The C3 ester exists both *cis* and *trans* to the C5 ethyl carboxylate and there appears to be no particular preference for the formation of either isomer. The two isomeric forms were distinguished by the observation of a 1.5 Hz 'W' type coupling between the C3 and C5 protons in the ^{1}H NMR spectrum of the *cis* compounds.

In summary, some 1-pyrroline-1-oxide-5-carboxylic esters have been synthesised by the reductive cyclisation of γ-nitro ketoesters. The carbanion of the nitrone monoester **5c** reacts with alkylating agents and Michael acceptors but not with acyl chlorides in which cases attack on the nitrone oxygen atom occurs. In connection with this work, pendant alkenyl chains have been introduced at C5 of compound **5c** and the intramolecular 3+2 cycloaddition chemistry of the resulting nitrones examined.[16] These nitrones have also been converted into the corresponding oxaziridines and their radical cyclisation chemistry investigated.[17]

Experimental

General information

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Hitachi model EPI-G instrument and refer to thin films of liquids between KBr plates or paraffin mulls of solids. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker CXP 300 instrument (300 MHz). The chemical shifts are reported in parts per million (δ) with chloroform as an internal standard. Electron ionisation mass spectra were measured at 70 eV ionising voltage using an AEI MS12 instrument with an 8000 V accelerating voltage and an ion source temperature of 200°C. Chemical ionisation mass spectra were recorded on a MEI MS902 instrument using a 450 V ionising voltage and a source temperature of 200°C at 8000 V accelerating voltage. Flash column chromatography employed Kieselgel 60 silica gel and the solvents used as eluent are quoted in the text.

Preparation of γ-nitro ketones 3a–d

A solution containing either diethyl nitromalonate **1a**[18] or ethyl nitroacetate **1b**[19] and an equimolar amount of 1-diethylaminopropiophenone **2a**[20] or 1-diethylamino-3-butanone **2b**[21] in dry toluene was gently refluxed in a nitrogen flow until diethylamine ceased to be evolved (2–6 h). The solvent was removed and the residue was purified by flash chromatography (5% methanol/chloroform) to give the pure γ-nitro ketone **3**.

Diethyl 1-nitro-4-oxo-4-phenylbutane-1,1-dicarboxylate 3a. The above procedure using malonate **1a**[18] (10.0 g, 49.0 mmol) and amino ketone **2a**[20] (10.3 g, 49.0 mmol) gave nitro ketone **3a** as a light yellow oil (16.4 g, 100%). IR ν_{max} 1770, 1690, 1570, 1450, 1375, 1090, 355, 740, 655 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.31 (6H, t, J=7.1 Hz, Me), 2.91 (2H, m, H3), 3.31 (2H, m, H2), 4.35 (4H, q, J=7.1 Hz, OCH_2), 7.46 (2H, m, ArH), 7.57 (1H, m, ArH), 7.93 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.5, 25.1, 34.0, 63.6, 76.9, 127.5, 128.4, 133.2, 137.3, 162.3, 197.3; *m*/*z* 338 (M+1, 62%), 292 (57), 173 (29), 133 (48), 105 (100). The 2,4-dinitrophenylhydrazone formed as a yellow solid, mp 156–157°C. (Found: C, 51.4; H, 4.2; N, 13.1. $C_{22}H_{23}N_5O_{10}$ requires C, 51.1; H, 4.5; N, 13.5%).

Diethyl 1-nitro-4-oxopentane-1,1-dicarboxylate 3b. The above procedure using malonate **1a**[18] (25.0 g, 0.12 mol) and amino ketone **2b**[21] (19.2 g, 0.12 mol) gave nitro ketone **3b** as a pale yellow oil (23.5 g, 70%): bp 160°C/2.5 mmHg. (Found: C, 48.4; H, 6.3; N, 5.4. $C_{11}H_{17}NO_7$ requires C, 48.0; H, 6.2; N, 5.1%). IR ν_{max} 1760, 1730, 1570, 1370, 1090, 1010 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.29 (6H, t, J=7.1 Hz, CH_2*Me*), 2.14 (3H, s, COMe), 2.71 (4H, m, H2 and H3), 4.31 (4H, q, J=7.1 Hz, OCH_2); δ_C (75.5 MHz, $CDCl_3$) 13.55, 27.52, 29.71, 37.84, 63.65, 96.89, 162.31, 205.25; *m*/*z* 276 (M+1, 9%), 230 (66), 184 (100), 173 (95), 160 (40), 141 (30), 127 (23), 111 (17).

Ethyl 2-nitro-5-oxo-5-phenylpentanoate 3c. The above procedure using acetate **1b**[19] (4.92 g, 37.0 mmol) and amino ketone **2a**[20] (7.59 g, 37.0 mmol) gave nitro ketone **3c** as a light brown oil (9.81 g, 100%). bp 250°C/110 mmHg. (Found: C, 58.6; H, 5.9; N, 5.0. $C_{13}H_{15}NO_5$ requires C, 58.9; H, 5.6; N, 5.2%). IR ν_{max} 1750, 1990, 1565, 1450, 1375, 1020, 860, 750, 695 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.30 (3H, t, J=6.0 Hz, Me), 2.70 (2H, m, H3), 3.14 (2H, m, H4), 4.30 (2H, q, J=7.1 Hz, OCH_2), 5.37 (1H, t, J=8.3 Hz, H2), 7.92 (5H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.73, 24.38, 33.52, 62.98, 86.88, 127.84, 128.62, 133.44, 136.06, 164.27, 197.36; *m*/*z* 265 (M, 15%), 264 (100), 105 (10), 52 (14).

Ethyl 2-nitro-5-oxohexanoate 3d. The above procedure using acetate **1b**[19] (4.65 g, 34.9 mmol) and amino ketone **2b**[21] (5.00 g, 34.9 mmol) gave nitro ketone **3d** as a waxy white solid [22] (4.28 g, 60%). bp 218°C/760 mmHg. (Found: C, 47.2; H, 6.5; N, 6.7. $C_8H_{13}NO_5$ requires C, 47.3; H, 6.40; N, 6.9%). IR ν_{max} 1755, 1720, 1540, 1365, 1000, 800 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, J=7.1 Hz, CH_2*Me*), 2.14 (3H, s, COMe), 2.41 (2H, m, H3), 2.58 (2H, m, H4), 4.25 (2H, q, J=7.1 Hz, OCH_2), 5.21 (1H, m, H2); *m*/*z* 203 (M, 11%), 188 (24), 157 (22), 130 (58), 84 (22).

Preparation of 1-pyrroline-1-oxides 5a–d

A cold solution of ammonium chloride in water was added to the γ-nitro ketone **3** in tetrahydrofuran. The mixture was cooled to 0°C before adding zinc powder at such a rate that the temperature was not allowed to exceed 5°C and stirring was continued for 3–5 h. The solution was filtered, evaporated under reduced pressure and the aqueous residue extracted with chloroform. The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to leave the crude product.

Diethyl 2-phenyl-1-pyrroline-5,5-dicarboxylate 1-oxide 5a. The reduction of nitro ketone **3a** (7.00 g, 20.0 mmol) in tetrahydrofuran (60 ml) used ammonium chloride (2.00 g, 37.0 mmol) in water (50 ml) and zinc powder (8.50 g). The crude product was recrystallised from 95% ethanol to give nitrone **5a** as white needles (3.50 g, 55%). mp 118–120°C. (Found: C, 63.0; H, 6.2; N, 4.6. $C_{16}H_{19}NO_5$ requires C, 63.0; H, 6.20; N, 4.6%). IR ν_{max} 1760, 1740, 1580, 1570, 1460, 1390, 1310, 1300, 1280, 1260, 1220, 1180, 1120, 1040, 760, 690, 560 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.34 (6H, t, *J*=7.1 Hz, Me), 2.36 (2H, m, H4), 3.18 (2H, m, H3), 4.37 (4H, m, OCH_2), 7.36 (3H, m, ArH), 8.4 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.86, 27.27, 29.31, 62.45, 77.90, 127.48, 129.45, 130.10, 131.00, 150.30, 167.31; *m*/*z* 305 (M, 16%), 233 (17), 232 (57), 217 (28), 216 (100), 215 (15), 171 (19), 160 (25), 156 (10), 144 (35), 143 (39), 125 (18), 105 (41), 103 (13), 77 (23).

Diethyl 2-methyl-1-pyrroline-5,5-dicarboxylate 1-oxide 5b. The reduction of nitro ketone **3b** (8.52 g, 30.9 mmol) in tetrahydrofuran (80 ml) used ammonium chloride (3.00 g, 56.0 mmol) in water (50 ml) and zinc powder (10.0 g). The crude product was distilled to give nitrone **5b** as a bright yellow oil (5.80 g, 77%). bp 165°C/3.5 mmHg. (Found: C, 54.5; H, 7.2; N, 5.4. $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.0; N, 5.8%). IR ν_{max} 1740, 1645, 1370, 1270, 1150, 1090, 1020, 860 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.23 (6H, t, *J*=7.1 Hz, CH_2*Me*), 2.10 (3H, s, 2-Me), 2.51 (2H, t, *J*=7.3 Hz, H4), 3.34 (2H, t, *J*=7.3 Hz, H3), 4.15 (4H, m, OCH_2); δ_C (75.5 MHz, $CDCl_3$) 14.01, 24.55, 28.89, 35.99, 63.71, 97.01, 150.01, 164.50; *m*/*z* 243 (M, 21%), 171 (21), 170 (100), 142 (26), 125 (13), 124 (50), 99 (47).

Ethyl 2-phenyl-1-pyrroline-5-carboxylate 1-oxide 5c. The reduction of nitro ketone **3c** (1.60 g, 6.03 mmol) in tetrahydrofuran (30 ml) used ammonium chloride (1.00 g, 18.0 mmol) in water (30 ml) and zinc powder (6.00 g). The crude product was a yellow oil which crystallised on standing to give nitrone **5c** as white needles (1.00 g, 70%). mp 140°C (dec.). (Found: C, 66.9; H, 6.5; N, 5.9. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%). IR ν_{max} 1746, 1570, 1550, 1450, 1392, 1375, 1348, 1295, 1255, 1235, 1210, 1200, 1180, 1155, 1045, 1020, 760 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.33 (3H, t, *J*=7.1 Hz, Me), 2.33 (1H, m, H4), 2.50 (1H, m, H4), 3.20 (1H, m, H3), 3.31 (1H, m, H3), 4.30 (2H, m, OCH_2), 4.90 (1H, dd, *J*=4.9, 1.3 Hz, H5), 7.45 (3H, m, ArH), 8.35 (2H, m, ArH; δ_C (75.5 MHz, $CDCl_3$) 14.11, 19.62, 30.17, 61.69, 68.13, 127.50, 128.50, 130.79, 135.80, 149.23, 169.02; *m*/*z* 233 (M, 43%), 161 (17), 105 (18), 102 (20), 91 (10), 77 (20).

Attempted recrystallisation of nitrone **5c** (0.10 g, 0.43 mmol) gave some ***ethyl 2-benzoyl-1-hydroxy-4-hydroxylamino-1-phenylcyclohexane-4-carboxylate 6*** as colourless crystals (11.0 mg, 7.0%). mp 93°C. (Found: C, 68.7; H, 6.9; N, 3.4. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.7%). IR ν_{max} 3405, 2950, 1740, 1660, 1600, 1450, 1380, 1265, 1225, 1160, 1090, 1070, 1050, 960, 920, 850, 765, 750, 705, 690 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J*=6.93 Hz, Me), 1.73 (2H, m, H6), 2.16 (2H, m, H5), 2.50 (2H, m, H3), 4.23 (2H, q, *J*=7.2 Hz, OCH_2), 4.59 (1H, dd, *J*=13.0, 3.6 Hz, H2), 7.11 (1H, t, *J*=7.2 Hz, ArH), 7.22 (2H, t, *J*=7.2 Hz, ArH), 7.54 (3H, m, ArH), 7.88 (2H, dd, *J*=8.7, 1.5 Hz, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.06, 26.29, 29.08, 35.37, 44.90, 61.61, 64.47, 74.05, 124.45, 128.20, 128.71, 135.75, 147.34, 174.45, 205.29; *m*/*z* 384 (M+1, 8%), 366 (100), 348 (12), 338 (10), 234 (24).

Ethyl 2-methyl-1-pyrroline-5-carboxylate 1-oxide 5d. The reduction of nitro ketone **3d** (3.50 g, 17.3 mmol) in tetrahydrofuran (90 ml) used ammonium chloride (2.75 g, 51.5 mmol) in water (70 ml) and zinc powder (17.0 g). The crude product was purified via flash chromatography with 5% methanol/chloroform as eluent to give nitrone **5d** as a viscous yellow oil (1.40 g, 46%). bp 165°C (dec.). (Found: C, 56.2; H, 7.3; N, 8.0. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.6; N, 8.2%). IR ν_{max} 2995, 1750, 1730, 1550, 1460, 1300, 1250, 1205, 1150, 780 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J*=7.1 Hz, CH_2*Me*), 2.07 (3H, s, 2-Me), 2.16 (1H, m, H4), 2.37 (1H, m, H4), 2.72 (1H, m, H3), 2.85 (1H, m, H3), 4.25 (2H, m, OCH_2), 4.64 (1H, m, H5); *m*/*z* 171 (M, 8%), 155 (28), 154 (34), 141 (43), 109 (56).

Ethyl 2-phenyl-1-pyrroline-5-carboxylate 7. This compound was prepared as for compounds **5a–d** using nitro ketone **3c** (7.50 g, 28.3 mmol) in tetrahydrofuran (140 ml), ammonium chloride (4.52 g, 84.5 mmol) in water (140 ml) and zinc powder (28.1 g) with a temperature increase to 10°C during and after the zinc addition. The resulting product was purified via flash chromatography to give imine **7** as a yellow oil[23] (5.70 g, 92%). bp 214°C (dec.). (Found: C, 70.3; H, 7.1; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.5%). IR ν_{max} 2910, 1735, 1575, 1445, 1370, 1340, 1260, 1185, 1035, 755, 690 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J*=7.1 Hz, Me), 2.24 (2H, m, H4), 3.02 (2H, m, H3), 4.19 (2H, q, *J*=7.1 Hz, OCH_2), 4.85 (1H, m, H5), 7.36 (3H, m, ArH), 7.83 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.11, 26.33, 35.34, 60.98, 74.56, 127.93, 128.29, 130.81, 133.75, 172.84, 175.92; *m*/*z* 217 (M, 10%), 146 (5), 145 (20), 144 (100), 117 (10), 115 (22), 91 (25), 41 (5).

Catalytic hydrogenation of 1-pyrroline 7

(i) Ethyl 2-phenyl-1-pyrroline-5-carboxylate **7** (0.25 g, 1.15 mmol) was hydrogenated in absolute ethanol (10 ml) over palladium-charcoal (0.2 g of 10%) in the Parr apparatus at 20 psi for 12 h. The reaction mixture was passed through a plug of Celite which was washed with dichloromethane and the filtrate and washings were combined. The solvent was evaporated under reduced pressure to leave a crude tan oil. The oil was purified using preparative TLC with ether/light petroleum as eluent to give ***ethyl 2-amino-5-phenylpentanoate 9*** as a tan oil (227 mg, 89%). (Found:

C, 70.0; H, 9.2; N, 6.0. $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.6; N, 6.3%). δ_H (300 MHz, $CDCl_3$) 1.35 (3H, t, J=7.2 Hz, Me), 1.78 (4H, m, H2, H3), 2.72 (2H, m, H4), 3.53 (1H, m, H1), 4.25 (2H, q, J=7.2 Hz, OCH_2), 7.27 (3H, m, ArH), 7.36 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.14, 27.28, 34.34, 35.46, 54.22, 60.70, 125.70, 128.22, 128.27, 141.83, 175.86; *m*/*z* 221 (M, 4%), 193 (14), 149 (12), 148 (62), 131 (100), 103 (39), 91 (89), 77 (26), 74 (27), 65 (22), 56 (35), 44 (19).

(ii) Ethyl 2-phenyl-1-pyrroline-5-carboxylate **7** (0.25 g, 1.15 mmol) was hydrogenated in absolute ethanol (10 ml) over palladium-charcoal (0.02 g of 10%) at 1 atm for 6 h. The reaction mixture was passed through a plug of Celite which was washed with dichloromethane and the filtrate and washings were combined. The solvent was evaporated under reduced pressure to leave a crude tan oil. The oil was purified using preparative TLC with ether/light petroleum as eluent to give α-amino ester **9** as a tan oil in 20% yield with identical spectral characteristics to those above and ***ethyl 5-phenylpyrrolidine-2-carboxylate 8*** as a pale yellow oil[23] (136 mg, 54%). (Found: C, 70.9; H, 8.0; N, 7.0. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%). δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, J=6.7 Hz, Me), 1.72 (1H, m, H4), 2.15 (3H, m, H4, H3), 2.52 (1H, bs, NH), 3.91 (1H, m, H2), 4.18 (1H, m, H5), 4.22 (2H, q, J=6.7 Hz, OCH_2), 7.23 (1H, m, ArH), 7.31 (2H, m, ArH), 7.44 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.34, 30.59, 34.09, 60.04, 60.95, 63.53, 126.68, 127.12, 128.37, 143.12, 175.03; *m*/*z* 219 (M, 1%), 218 (10), 217 (40), 145 (16), 144 (82), 143 (29), 129 (13), 117 (31), 115 (71), 105 (52), 104 (41), 103 (26), 91 (68), 89 (42), 77 (100), 76 (24), 63 (33), 57 (30), 51 (71).

Oxidation of ethyl 5-phenylpyrrolidine-2-carboxylate 8

To a solution of ethyl 5-phenylpyrrolidine-2-carboxylate **8** (75.0 mg, 0.34 mmol) in methanol (5 ml) was added sodium tungstate (5.6 mg, 0.02 mmol) and urea hydrogen peroxide (125 mg, 1.37 mmol). The reaction mixture was stirred for 3 h and the solvent evaporated under reduced pressure. The remaining residue was dissolved in dichloromethane (5 ml), filtered and the solvent evaporated under reduced pressure to leave an oil. A ^{1}H NMR spectrum of the crude reaction mixture showed only two products to be present. One of these had identical spectroscopic characteristics to 1-pyrroline-1-oxide **5c** above and the other product appeared to fit the expected ^{1}H NMR spectrum for ethyl 5-phenyl-1-pyrroline-1-oxide-2-carboxylate **10**. The latter product rapidly decomposed on attempted purification via chromatography and could not be further characterised. However, integration and comparison of both C5 proton peaks for nitrones **5c** and **10** showed that these products were in the ratio of 3.8:1.

Ethyl 5-methyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 11. Ethyl 2-phenyl-1-pyrroline-5-carboxylate 1-oxide **5c** (0.50 g, 2.15 mmol) was dissolved with stirring in dry tetrahydrofuran (10 ml). Sodium hydride (70 mg of an 80% dispersion in oil, 2.36 mmol) was added, followed after 5 min by dimethylformamide (0.5 ml). After a further 5 min methyl iodide (0.30 g, 2.15 mmol) was added slowly over 10 min. After 24 h water (1 ml) was added and the solvent evaporated under reduced pressure to leave an oily residue, which was extracted with chloroform (3×15 ml) and the combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and flash chromatographed using ether/light petroleum as eluent to give ***ethyl 5-methyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 11*** as a yellow oil (400 mg, 76%): bp 285°C. (Found: C, 68.0; H, 6.9; N, 5.7. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%). IR ν_{max} 1640, 1535, 1460, 1370, 1310, 1290, 1210, 1040, 900, 720 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.15 (3H, t, J=7.2 Hz, CH_2*Me*), 1.69 (3H, s, 5-Me), 2.02 (2H, m, H4), 3.06 (2H, m, H3), 4.13 (2H, m, OCH_2), 7.34 (3H, m, ArH), 8.27 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.85, 21.19, 28.06, 29.76, 61.19, 81.08, 127.24, 128.25, 129.05, 130.36, 140.63, 170.35; *m*/*z* 247 (M, 23%), 175 (18), 174 (100), 159 (9), 158 (54), 156 (30), 143 (11), 130 (13), 129 (18), 128 (38), 115 (72), 105 (64), 103 (58), 91 (42), 89 (16), 79 (6), 78 (20), 77 (97), 65 (17), 63 (22), 51 (42), 41 (40).

Ethyl 5-allyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 13. The reaction was performed as described for the synthesis of 1-pyrroline **11** above, replacing methyl iodide with allyl chloride (165 mg, 2.15 mmol) to give ***ethyl 5-allyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 13*** as a waxy yellow solid (390 mg, 66%): mp 46°C. (Found: C, 70.1; H, 7.1; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%). IR ν_{max} 1735, 1680, 1570, 1543, 1465, 1375, 1360, 1305, 1275, 1250, 1205, 1175, 1120, 1068, 1025, 910, 760 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.23 (3H, t, J=6.9 Hz, Me), 2.28 (2H, m, H4), 2.74 (1H, m, H3), 3.08 (3H, m, H1′, H3), 4.22 (2H, d, J=6.9 Hz, OCH_2), 5.16 (2H, m, H3′), 5.64 (1H, m, H2′), 7.42 (3H, m, ArH), 8.32 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.79, 25.21, 37.40, 61.93, 84.12, 120.45, 127.22, 128.19, 129.10, 130.30, 131.29, 162.25, 169.98; *m*/*z* 273 (M, 28%), 256 (10), 233 (11), 232 (51), 216 (12), 201 (17), 200 (100), 184 (24), 182 (51), 170 (21), 156 (36), 143 (22), 142 914), 128 912), 115 938), 103 (40), 91 (19), 80 (32), 77 (64).

Ethyl 6-phenyl-8-oxa-7-azatricyclo[4.2.1.0^{3,7}]nonane-3-carboxylate 15. A solution of ethyl 5-allyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide **13** (0.30 g, 1.09 mmol) in dry, degassed toluene (50 ml) was heated at reflux for 7 days. The solvent was evaporated under reduced pressure to leave a red–brown residue. The crude residue was chromatographed using dichloromethane as eluent to give ***ethyl 6-phenyl-8-oxa-7-azatricyclo[4.2.1.0^{3,7}]nonane-3-carboxylate 15*** as colourless crystals (237 mg, 79%): mp 98°C. (Found: C, 70.2; H, 7.2; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%). IR ν_{max} 2800, 2750, 2555, 2300, 2110, 1720, 1595, 1415, 1250, 1115, 1010, 975, 885 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.30 (3H, t, J=7.2 Hz, Me), 1.72 (1H, d, J=12.3 Hz, H9), 1.94 (1H, d, J=12.0 Hz, H2), 2.18 (2H, m, H4, H5), 2.43 (3H, m, H2, H4, H5), 2.68 (1H, m, H9), 4.24 (2H, q, J=7.2 Hz, OCH_2), 4.88 (1H, t, J=4.9 Hz, H1), 7.17 (1H, m, ArH), 7.29 (2H, m, ArH), 7.51 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.08, 30.14, 34.97, 47.23, 50.21, 62.22, 74.92, 76.32, 81.25, 125.14, 126.24, 128.24, 147.19, 173.31; *m*/*z* 273 (M, 48%), 256 (12), 233 (12), 232 (60), 210 (10), 201 (20), 200 (100), 184 (21), 182 (28), 170 (24), 156 (30), 144 (32), 143 (21), 129 (25), 115 (48), 103 (50), 91 (65), 80 (18), 77(35), 69 (11), 57 (12).

Attempted C5 alkylation of 1-pyrroline-1-oxide 5c with 3-bromopropionitrile

To a solution of ethyl 2-phenyl-1-pyrroline-5-carboxylate 1-oxide **5c** (0.25 g, 1.07 mmol) in dry tetrahydrofuran (5 ml) was added sodium hydride (33 mg of an 80% dispersion in oil, 1.12 mmol) followed after 30 min by 3-bromopropionitrile (143 mg, 1.07 mmol). Sodium hydride (33 mg of an 80% dispersion in oil, 1.12 mmol) was again added and stirring was continued for 2 h before quenching with water (1 ml). The solvent was evaporated under reduced pressure and the resulting aqueous residue was extracted with dichloromethane (3×5 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave a viscous brown oil. The oil was flash chromatographed using 30% ether/light petroleum as eluent to give: (i) ***ethyl 5-cyanoethyl-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 16*** as a yellow oil (74 mg, 24%). Due to instability of this compound, a satisfactory microanalysis could not be obtained. IR ν_{max} 2350, 1745, 1560, 1375, 1360, 1330, 1300, 1280, 1250, 1215, 1180, 1050, 1020, 910, 780, 720, 650 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J*=7.2 Hz, Me), 2.51 (6H, m, H1′, H2′, H4), 3.21 (2H, m, H3), 4.24 (2H, q, *J*=7.2 Hz, OCH_2), 7.45 (3H, m, ArH), 8.34 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 12.6, 14.34, 27.17, 28.76, 30.66, 63.02, 82.79, 119.55, 127.88, 128.04, 128.93, 131.41, 142.63, 169.58; *m*/*z* 287 (M+1, 6%), 286 (18), 234 (14), 233 (88), 216 (100), 213 (64), 197 (34), 195 (22), 188 (16), 172 (49), 156 (48), 144 (52), 128 (19), 115 (38), 105 (42), 103 (34), 77 (63), 76 (19), 51 (17) and (ii) ***ethyl 3-cyano-7-hydroxy-4-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylate 17*** as a white solid (88 mg, 29%): mp 92°C. (Found: C, 65.7; H, 6.6; N, 8.7. $C_{16}H_{18}N_2O_3.1/2H_2O$ requires C, 65.1; H, 6.4; N, 9.5%). IR ν_{max} 3390, 2950, 2150, 1745, 1445, 1235, 1090, 1010, 810, 700, 690 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, *J*=7.2 Hz, Me), 2.04 (2H, m, H5, H6), 2.20 (1H, m, H5), 2.33 (1H, dd, *J*=12.6, 5.1 Hz, H2), 2.48 (1H, m, H6), 3.02 (1H, td, *J*=12.3, 3.1 Hz, H3), 4.23 (2H, q, *J*=7.2 Hz, OCH_2), 7.35 (3H, m, ArH), 7.64 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.07, 29.79, 31.16, 33.06, 36.80, 61.43, 74.80, 77.20, 121.02, 126.59, 127.63, 130.52, 137.90, 171.02; *m*/*z* 216 (12), 160 (15), 144 (22), 143 (25), 128 (24), 116 (30), 115 (100), 103 (47), 91 (49), 77 (98), 65 (35), 51 (52).

The reaction was performed as for the synthesis of **11** above using acrylonitrile as alkylating agent to give compounds **16** and **17** in 27 and 59% yields, respectively.

Ethyl 5-(1,3-diphenyl-3-oxoprop-1-yl)-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 18. The C5 carbanion of 1-pyrroline-1-oxide **5c** was generated as above on a 1.07 mmol scale then treated with an equimolar amount of chalcone. Following workup in the usual way a white solid was produced. The crude material was purified via flash chromatography using 30% ether/light petroleum as eluent to give ***ethyl 5-(1,3-diphenyl-3-oxoprop-1-yl)-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 18*** as a white powder (350 mg, 74%): mp 115–116°C. (Found: C, 73.3; H, 6.5; N, 2.8. $C_{28}H_{27}NO_4.H_2O$ requires C, 73.2; H, 6.3; N, 3.0%). IR ν_{max} 2950, 1735, 1680, 1550, 1250, 1040 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J*=7.2 Hz, Me), 2.01 (1H, m, H4), 2.36 (2H, m, H2′), 2.80 (1H, m, H4), 3.78 (3H, m, H3, H1′), 4.32 (2H, m, OCH_2), 7.04–7.15 (3H, m, ArH), 7.37–7.52 (8H, m, ArH), 7.92–7.99 (2H, m, ArH), 8.27–8.32 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.98, 27.59, 28.16, 42.16,45.62, 62.42, 86.67, 127.40, 128.01, 128.35, 128.49, 129.11, 129.25, 129.87, 130.50, 132.81, 136.84, 138.31, 143.20, 170.07, 191.80; *m*/*z* 441 (M, 10%), 423 (13), 397 (11), 396 (28), 380 (15), 353 (18), 352 (54), 349 (74), 348 (37), 338 (32), 336 (100), 334 (32), 320 (45), 307 (45), 304 (39), 290 (30), 279 (24).

Ethyl 5-[2-(ethoxycarbonyl)-1-methylethyl]-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 19. The C5 carbanion of 1-pyrroline-1-oxide **5c** was generated as above on a 1.07 mmol scale then treated with an equimolar amount of ethyl 2-butenoate. Following workup in the usual way a white solid was produced. The crude material was partially purified via flash chromatography using 30% ether/light petroleum as eluent to give ***ethyl 5-[2-(ethoxycarbonyl)-1-methylethyl]-2-phenyl-1-pyrroline-5-carboxylate 1-oxide 19*** as an orange oil (301 mg, 81%). IR ν_{max} 1740, 1730, 1575, 1540, 1460, 1375, 1200, 1090, 1060, 1025, 850, 760, 690 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.13 (3H, d, *J*=3.2 Hz, CH*Me*), 1.18 (3H, t, *J*=7.2 Hz, CH_2*Me*), 1.23 (3H, t, *J*=7.2 Hz, CH_2*Me*), 2.17 (2H, m, H4), 2.50 (2H, m, H2′), 3.18 (3H, m, H1′, H3), 4.08 (2H, q, *J*=7.2 Hz, OCH_2), 4.22 (2H, q, *J*=7.2 Hz, OCH_2), 7.39 (3H, m, ArH), 8.32 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 13.81, 13.99, 14.23, 23.07, 28.27, 32.66, 36.05, 60.23, 62.02, 86.76, 127.27, 128.24, 128.81, 130.42, 141.39, 169.18, 171.95; *m*/*z* 347 (M, 5%), 318 (25), 274 (65).

Reaction of 1-pyrroline-1-oxide 5c with acyl chlorides

The C5 carbanion of 1-pyrroline-1-oxide **5c** (4.3 mmol) was generated as above before adding the desired acyl chloride (4.3 mmol) and stirring the reaction mixture for 4–8 h. The reaction was quenched with water (1 ml) and the solvent evaporated under reduced pressure to leave a residue which was extracted with dichloromethane (3×5 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to leave the crude product mixture. The products were separated rapidly using preparative TLC with ether/light petroleum as eluent. Satisfactory analytical data could not be obtained for the pyrrolines **20** because of trace contamination by the pyrrole **21**.

Reaction of 1-pyrroline-1-oxide 5c with acetyl chloride

The reaction was performed as described above to give: (i) **cis** ***ethyl 3-acetoxy-2-phenyl-1-pyrroline-5-carboxylate 20a*** as a waxy yellow solid (28 mg, 24%): mp 42°C. δ_H (300 MHz, $CDCl_3$) 1.31 (3H, t, *J*=7.2 Hz, CH_2*Me*), 2.06 (3H, s, COMe), 2.27 (1H, m, H4), 2.66 (1H, m, H4), 4.25 (2H, q, *J*=7.2 Hz, OCH_2), 5.08 (1H, ddd, *J*=8.2, 5.1, 1.5 Hz, H5), 6.32 (1H, ddd, *J*=7.9, 4.2, 1.5 Hz, H3), 7.46 (3H, m, ArH), 7.86 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.15, 20.93, 34.08, 34.78, 61.53, 72.84, 128.35, 128.66, 130.56, 131.44, 171.74, 174.85; *m*/*z* 275 (M, 5%), 274 (10), 260 (30), 246 (44), 142 (100), (ii) **trans** ***ethyl 3-acetoxy-2-phenyl-1-pyrroline-5-carboxylate 20a*** as a yellow oil (23 mg, 20%). δ_H (300 MHz, $CDCl_3$) 1.33 (3H, t,

J=7.2 Hz, CH_2*Me*), 2.06 (3H, s, COMe), 2.20 (1H, m, H4), 2.86 (1H, m, H4), 4.27 (2H, q, *J*=7.2 Hz, OCH_2), 4.89 (1H, dd, *J*=7.9, 4.3 Hz, H5), 6.27 (1H, dd, *J*=7.6, 5.6 Hz, H3), 7.44 (3H, m, ArH), 7.84 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.19, 20.91, 34.07, 35.01, 61.52, 71.70, 128.36, 128.64, 130.10, 131.52, 170.21, 171.35, 174.61; *m*/*z* 275 (M, 3%), 274 (15), 261 (42), 244 (16), 142 (96), 77 (100), (iii) ***ethyl 5-phenylpyrrole-2-carboxylate 21*** as a white crystalline solid[24–26] (37 mg, 41%): mp 116°C (lit.[24,25] mp 121–122°C; lit.[26] mp 115–116°C).

Reaction of 1-pyrroline-1-oxide 5c with propanoyl chloride

The reaction was performed as described above to give: (i) **cis *ethyl 2-phenyl-3-propanoyl-1-pyrroline-5-carboxylate 20b*** as a yellow oil (27 mg, 22%): bp 180°C (dec.). δ_H (300 MHz, $CDCl_3$) 1.11 (3H, t, *J*=7.0 Hz, $COCH_2$*Me*), 1.29 (3H, t, *J*=7.1 Hz, OCH_2*Me*), 2.26 (3H, m, H4, $COCH_2$; 2.66 (1H, m, H4), 4.26 (2H, q, *J*=7.1 Hz, OCH_2, 5.04 (1H, ddd, *J*=7.6, 4.1, 1.5 Hz, H5, 6.42 (1H, ddd, *J*=7.8, 4.1, 1.5 Hz, H3). 7.40 (3H, m, ArH), 7.85 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.15, 20.93, 25.19, 34.59, 48.95, 61.52, 72.84, 128.36, 128.60, 128.66, 131.44, 152.55, 171.98, 174.52; *m*/*z* 290 (M+1, 9%), 289 (4), 261 (14), 233 (48), 216 (65), 77 (100), (ii) **trans *ethyl 2-phenyl-3-propanoyl-1-pyrroline-5-carboxylate 20b*** as a yellow oil (23 mg, 19%). δ_H (300 MHz, $CDCl_3$)(1.11 (3H, t, *J*= 6.7 Hz, OCH_2Me), 1.33 (3H, t, *J*=7.7 Hz, $COCH_2$*Me*), 2.18(1H, m, H4), 2.31 (2H, q, *J*=7.7 Hz, $COCH_2$; 2.86 (1H, m, H4), 4.27 (2H, q, *J*=6.7 Hz, OCH_2), 4.86 (1H, dd, *J*=6.2, 4.1 Hz, H5), 6.28 (1H, dd, *J*=8.2, 4.6 Hz, H3), 7.41 (3H, m, ArH), 7.82 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 8.96, 14.18, 25.07, 27.55, 61.46, 71.74, 76.69, 128.29, 128.87, 131.36, 131.61, 171.45, 172.93, 173.69; *m*/*z* 290 (M+1, 6%), 289 (7), 260 (19), 233 (64), 216 (68), 143 (86), 77 (100) and (iii) ***ethyl 5-phenylpyrrole-2-carboxylate 21*** as a white crystalline solid (30 mg, 33%) with identical spectroscopic characteristics to the sample above.

Reaction of 1-pyrroline-1-oxide 5c with 3-bromopropanoyl chloride

The reaction was performed as described above to give ***ethyl 5-phenylpyrrole-2-carboxylate 21*** as a white crystalline solid (84 mg, 92%) with identical spectroscopic characteristics to the sample above.

Reaction of 1-pyrroline-1-oxide 5c with 4-bromobutanoyl chloride

The reaction was performed as described above to give: (i) **cis *ethyl 2-phenyl-3-(4′-bromobutanoyloxy)-1-pyrroline-5-carboxylate 20d*** as a tan oil (40 mg, 25%): bp 146°C (dec.). (Found: C, 53.8; H, 5.2; N, 3.4. $C_{17}H_{20}BrNO_4$ requires C, 53.4; H, 5.2; N, 3.7%). δ_H (300 MHz, $CDCl_3$) 1.30 (3H, t, *J*=7.2 Hz, Me), 2.13 (2H, quin., *J*=6.7 Hz, H3′), 2.25 (1H, m, H4), 2.48 (2H, t, *J*=7.2 Hz, H2′), 3.38 (2H, t, *J*=6.2 Hz, H4′), 4.24 (2H, q, *J*=7.2 Hz, OCH_2), 5.04 (1H, ddd, *J*=7.7, 6.2, 1.5 Hz, H5), 6.42 (1H, ddd, *J*=7.7, 3.1, 1.5 Hz, H3), 7.43 (3H, m, ArH), 7.82 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.13, 27.43, 32.25, 32.41, 34.70, 61.52, 72.98, 77.25, 128.26, 128.64, 131.49, 131.53, 171.66, 171.74, 172.79; *m*/*z* 310, 308 (5%), 233 (5), 216 (12), 215 (92), 189 (64), 169 (82), 161 (47), 143 (47), 142 (70), 115 (100), 105 (64), 104 (47), 89 (28), (ii) **trans *ethyl 2-phenyl-3-(4′-bromobutanoyloxy)-1-pyrroline-5-carboxylate 20d*** as a yellow oil (35 mg, 22%). (Found: C, 53.6; H, 5.3; N, 3.4. $C_{17}H_{20}BrNO_4$ requires C, 53.4; H, 5.2; N, 3.7%). δ_H (300 MHz, $CDCl_3$) 1.33 (3H, t, *J*=6.8 Hz, Me), 2.19 (3H, m, H4), 2.49 (2H, t, *J*=7.3 Hz, H2′), 2.84 (1H, m, H4), 3.38 (2H, t, *J*=8.7 Hz, H4′), 4.25 (2H, q, *J*=6.8 Hz, OCH_2), 4.87 (1H, dd, *J*=8.2, 5.6 Hz, H5), 6.28 (1H, dd, *J*=8.2, 5.1 Hz, H3), 7.44 (3H, m, ArH), 7.82 (2H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 14.09, 27.00, 32.18, 32.42, 33.99, 61.50, 71.77, 72.84, 127.64, 128.25, 128.92, 131.44, 171.62, 172.75, 173.48; *m*/*z* 310, 308 (10%), 233 (11), 216 (12), 215 (86), 189 (100), 169 (16), 161 (76), 151 (55), 143 (74), 142 (91), 115 (70), 105 (84), 104 (52), 77 (23), 73 (13) and (iii) ***ethyl 5-phenylpyrrole-2-carboxylate 21*** as a white crystalline solid (35 mg, 39%) with identical spectroscopic characteristics to the sample above.

Reaction of 1-pyrroline-1-oxide 5c with benzoyl chloride

The reaction was performed as described above to give: (i) **cis *ethyl 2-phenyl-3-benzoyl-1-pyrroline-5-carboxylate 20e*** as a brown oil (50 mg, 35%): bp 206°C (dec.). (Found: C, 70.2; H, 5.8; N, 3.9. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.6; N, 4.2%). δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J*=7.2 Hz, Me), 2.39 (1H, m, H4), 2.78 (1H, m, H4), 4.26 (2H, q, *J*=7.2 Hz, OCH_2), 5.13 (1H, ddd, *J*=7.7, 5.6, 1.5 Hz, H5), 6.60 (1H, ddd, *J*=7.7, 3.1, 1.5 Hz, H3), 7.49 (6H, m, ArH), 7.95 (4H, m, ArH); *m*/*z* 338 (M+1, 16%), 265 (14), 164 (62), 233 (8), 232 (54), 215 (100), 142 (92), 89 (71), 73 (48), (ii) **trans *ethyl 2-phenyl-3-benzoyl-1-pyrroline-5-carboxylate 20e*** as a brown oil (44 mg, 31%). (Found: C, 68.7; H, 5.7; N, 4.4. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.6; N, 4.2%). δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J*=7.2 Hz, Me), 2.32 (1H, m, H4), 2.98 (1H, m, H4), 4.27 (2H, q, *J*=7.2 Hz, OCH_2), 4.95 (1H, dd, *J*=8.2, 5.6 Hz, H5), 6.49 (1H, dd, *J*=8.5, 5.6 Hz, H3), 7.46 (6H, m, ArH), 7.97 (4H, m, ArH); *m*/*z* 337 (M, 2%), 336 (21), 290 (18), 232 (12), 215 (68), 189 (33), 169 (41), 115 (69), 105 (100), 104 (37), 77 (89), 51 (50) and (iii) ***ethyl 2-phenylpyrrole-5-carboxylate 21*** as a white crystalline solid (35 mg, 39%) with identical spectroscopic characteristics to the sample above.

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