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A New Synthesis of 3,5-Diaryl-pyrrole-2-carboxylic Acids and Esters

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Abstract—A new two-step synthesis of pyrrole-2-carboxylic acids, steps via 1,3 dipolar cycloaddition of azomethine ylides to nitro-styrenes and oxidation of the resulting pyrrolidines with alkaline hydrogen peroxide is described. The oxidation of cycloadducts **3** by the means of MnO_2 under different conditions also has been examined.

Introduction

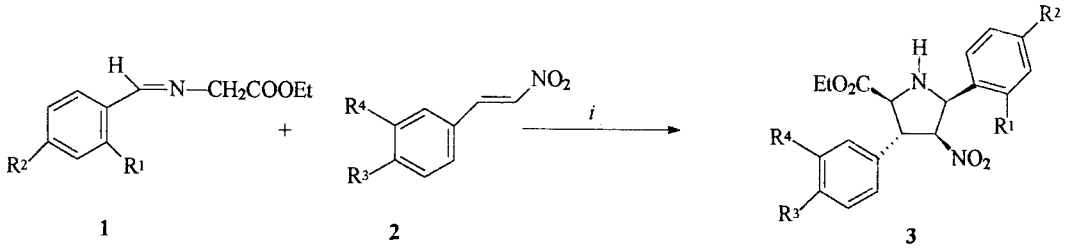
The biological importance of pyrrole-containing natural products, such as heme, chlorophyll and vitamin B_{12} has stimulated extensive research on the synthesis and reactivity of pyrrole derivatives.[1] There are many methods for the synthesis of these important heterocycles,[2] including the 1,3-dipolar cycloaddition of azomethine ylides to alkynes, followed by aromatisation of the intermediate pyrrolines.[3] However, the preparation of pyrroles by dehydrogenation of pyrrolidines has found little application due to the lack of general methods, and to the forcing conditions required in most cases.[4] We now report that a variety of substituted nitro-pyrrolidines can be converted into pyrroles using alkaline hydrogen peroxide to promote a cascade oxidation–elimination process.[5]

Results and Discussion

The highly substituted pyrrolidines were prepared in high yield by the stereoselective 1,3-dipolar cycloaddition of azomethine ylides (generated from the imines **1**) with aryl-nitrostyrenes **2** in the presence of silver acetate (Scheme 1). The stereochemistry of the exclusive *syn-endo* cycloadducts were deduced by comparison with the ^{1}H NMR data of similar compounds.[6]

We originally attempted to find a feasible method for the Nef-type conversion of highly substituted nitro-pyrrolidines, in connection with our studies on the synthesis of pyrrolidine alkaloids. After several standard methods failed in our hands we turned our attention to the oxidation of the corresponding nitronate anion by hydrogen peroxide, which was first described by Olah and co-workers.[7]

To our surprise we found that after several hours stirring at room temperature a light brown material began to precipitate from the solution which was shown to be the pyrrole derivative. In all cases the reactions, using 2 equiv. of base, were complete after stirring for 1 day, giving the diaryl-pyrrole-2-carboxylic acids **4** in virtually quantitative yield.



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Scheme 1. *Reagents and conditions:* (i) AgOAc, Et_3N, toluene, rt.

Keywords: cycloadditions; pyrrolidines; pyrroles; oxidation.

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Table 1. Conversion of 2-carboethoxy-4-nitropyrrolidines **3** into pyrrole-2-carboxylic acids using H_2O_2

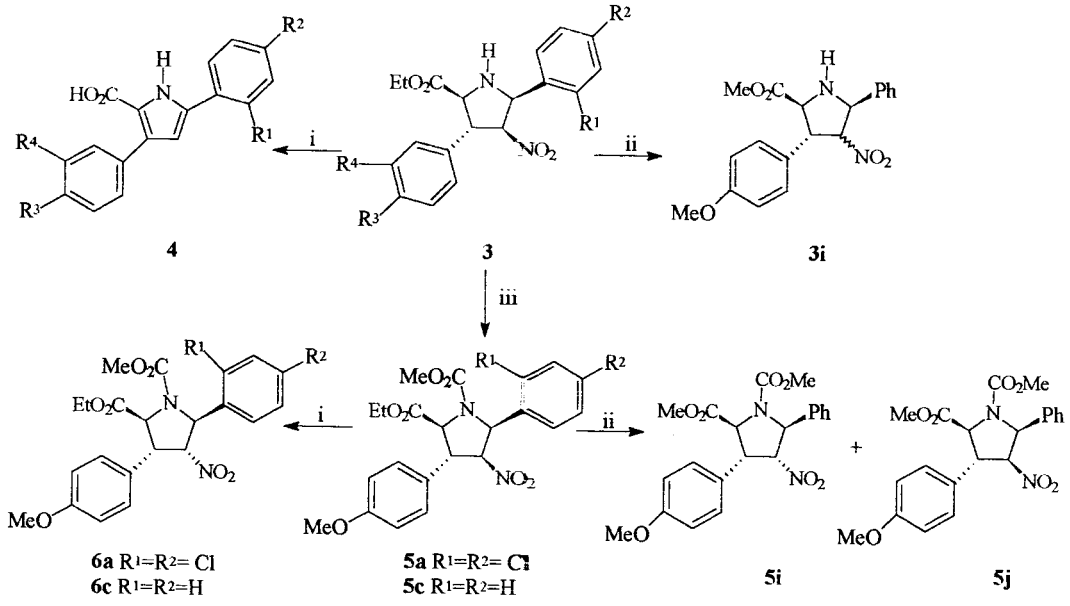
Entry	Starting material	R^1	R^2	R^3	R^4	Base	Product	Yield (%)
1	**3a**	Cl	Cl	OMe	H	2 equiv. NaOMe	**4a**	94
2	**3b**	H	H	H	H	2 equiv. NaOMe	**4b**	96
3	**3c**	H	H	OMe	H	4 equiv. K_2CO_3	**4c**	87
4	**3c**	H	H	OMe	H	–	–	0
5	**3c**	H	H	OMe	H	1 equiv. NaOMe	**4c**	32
6	**3c**	H	H	OMe	H	2 equiv. NaOMe	**4c**	95
7	**3d**	H	Me	H	H	2 equiv. NaOMe	**4d**	96
8	**3e**	H	CF_3	OMe	H	2 equiv. NaOMe	**4e**	92
9	**3e**	H	CF_3	OMe	H	4 equiv. K_2CO_3	**4e**	84
10	**3f**	H	Cl	H	H	2 equiv. NaOMe	**4f**	95
11	**3g**	H	H	OCH_2O		2 equiv. NaOMe	**4g**	92

The results are summarised in Table 1. Alternatively, it was possible to use potassium carbonate as a base, but in these cases the yield was somewhat lower (Entries 3 and 9). In the absence of base no reaction occurred (Entry 4), while in the absence of hydrogen peroxide after the work-up a 1:1 mixture of inseparable isomers **3i** was isolated, due to the strongly acidic nature of the proton adjacent to the nitro-group (Scheme 2).

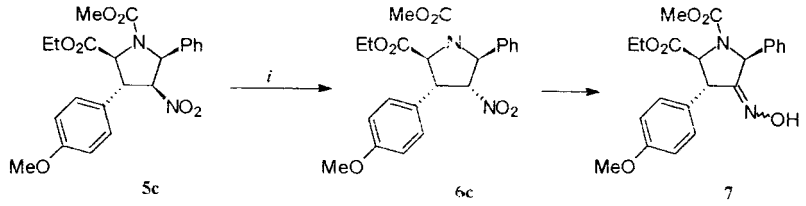
No aromatisation occurred in the case of the *N*-protected derivatives **5a** and **5c**. However, when the solution of the nitronate derived from **5c** was treated directly with acid again the 1:1 mixture of ester exchanged isomers **5i** and **5j** was obtained (these were separated by column chromatography), while after the work-up of the reaction treated with hydrogen peroxide only the corresponding single isomer of **6** was obtained. The stereochemistry of these pyrrolidines was confirmed by $^1H^1H$-COSY and NOE experiments.

This epimerisation also takes place as the first step in the reduction of the nitro-group using carbon disulphide and an excess of triethylamine at room temperature.[8] After 4 h reaction time only pyrrolidine **6c** was isolated, while after 72 h the oxime **7** was formed in good yield (Scheme 3).

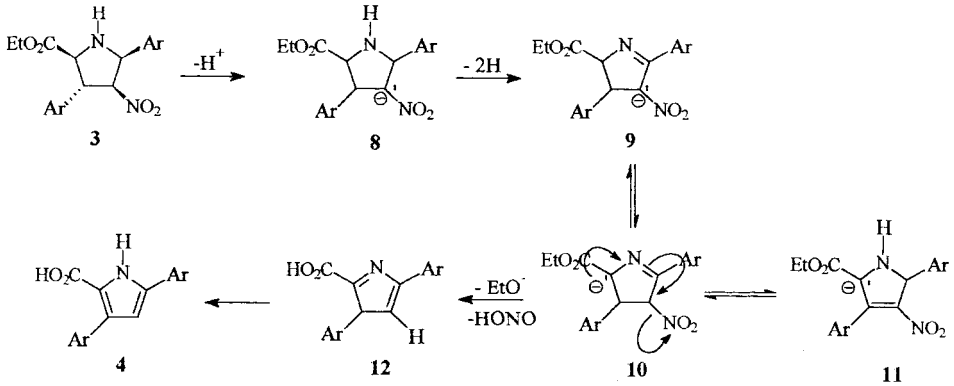
The nitro group of any nitro-alkane generally fails to serve as a leaving group in ionic base-catalysed elimination reactions since the reaction of primary and secondary nitro alkanes with base results in the formation of nitronate anions. However, with electron-withdrawing groups at the



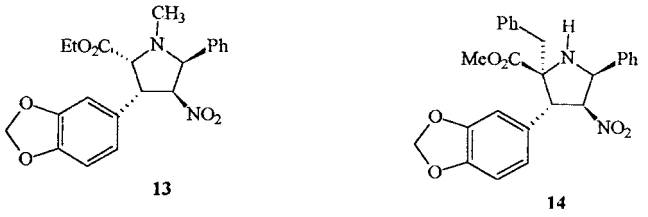
Scheme 2. *Reagents and conditions:* (i) NaOMe, MeOH, H_2O_2; (ii) (a) NaOMe, MeOH; (b) H^+; (iii) ClCOOMe, pyridine, CH_2Cl_2, rt.



Scheme 3. *Reagents and conditions:* (i) CS_2, Et_3N, CH_3CN, rt.



Scheme 4. Suggested mechanism of pyrrole formation.



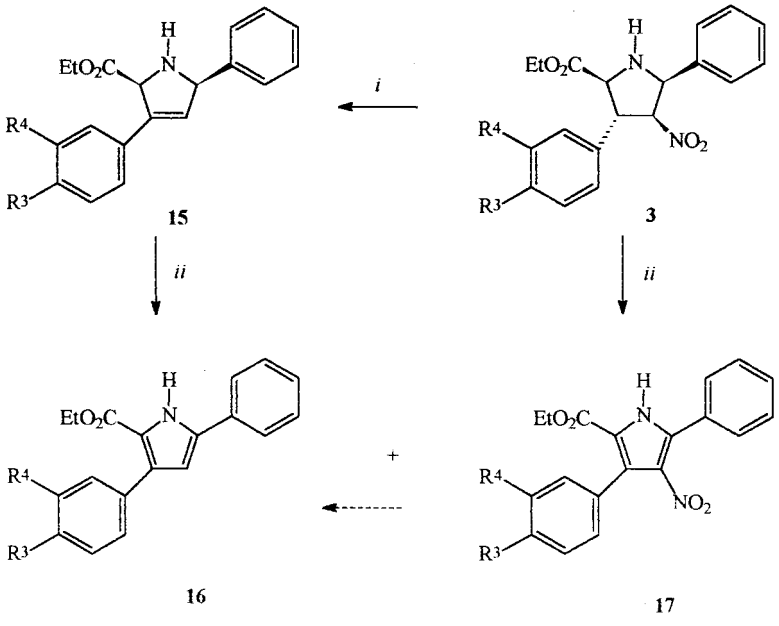
Scheme 5.

β-position to the nitro-group the base induced elimination of nitrous acid takes place smoothly to give alkenes in good yield.[9]

Our results suggest that the first step in this aromatisation is a dehydrogenation leading to the formation of the pyrroline derivative **10**. This intermediate can then eliminate a nitronate ion through a vinylogous E_{1CB} mechanism with the

Table 2. Transformation of 2-carboethoxy-4-nitropyrrolidines **3** with MnO_2

Entry	Starting material	R^2	R^3	R^4	Reaction conditions	Ratio of		
						15	**16**	**17**
1	**3b**	H	H	H	THF, rt	1	0	0
2	**3c**	H	MeO	H	THF, rt	1	0	0
4	**3g**	H	OCH_2O		THF, rt	1	0	0
3	**3h**	H	Cl	H	THF, rt	1	0	0
5	**3b**	H	H	H	THF, reflux	0	3.5	1
6	**3c**	H	MeO	H	THF, reflux	3.5	1	0
7	**3f**	Cl	H	H	THF, reflux	0	1	0
8	**3g**	H	OCH_2O		THF, reflux	0	1	1.5
9	**3h**	H	Cl	H	THF, reflux	0	1	0



Scheme 6. (i) MnO_2, THF, rt, 24 h; (ii) MnO_2, THF, reflux, 3 h.

alkaline hydrolysis of the ester group to give pyrrole-2-carboxylic acids, after aromatisation through a [1,5] sigmatropic shift of hydrogen (Schemes 4 and 5). The elimination step is similar to that proposed by Barton and co-workers[10] in their pyrrole synthesis. In the reaction of similar cycloadducts, having no carbethoxy functionality, with alkaline potassium permanganate only nitro-pyrroline formation was observed,[11] which is further support for our observations.

In order to obtain further proof for this reaction pathway we have attempted the similar oxidation of the cycloadducts **13** and **14**. As expected, the extra substituent on these pyrrolidine rings prevented the oxidation process.

Alternatively, we examined the oxidation of some of the cycloadducts **3** in the presence of manganese dioxide. At room temperature after 24 h reaction time the reaction of **3** gave rise only to the formation of pyrroline **15**. However, at reflux temperature in tetrahydrofuran the formation of different pyrroles[12] (**15**, **16** and **17**) was observed after a short reaction time in a different ratio (Table 2), depending on the substrate. Interestingly the conversion of **15** proceeded much more slowly to pyrrole **16**, than in the direct oxidation. The nitro-pyrrole **17** is quite stable under the above reaction conditions, but transforms easily to **16** during standing in $CDCl_3$ solution at room temperature (Scheme 6). We have no clear explanation for the observed product ratios. This unpredictable nature gives less synthetic value for this kind of transformation in comparison with the oxidation of nitronate anion by hydrogen peroxide.

Experimental

Methods

Column chromatography was performed using Merck Kieselgel 60, 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. IR spectra were measured on a NICOLET FT-IR and Shimadzu IR-435 instrument. Low resolution electron impact mass spectra were obtained on a Varian CH5-D and GCMS-QP5050A mass spectrometer. NMR measurements were carried out on Brucker 200, 250 and 500 instruments at 20°C. Chemical shifts are given relative to δ_{TMS}=0.00 ppm. The preparation of 3,5-diphenyl-2-ethoxycarbonyl-4-nitropyrrolidine[6c] (**3b**) 2-ethoxycarbonyl-3-(3,4-methylenedioxyphenyl)-4-nitro-5-phenylpyrrolidine[6c] (**3g**) 2-ethoxycarbonyl-1-methyl-3-(3,4-methylenedioxyphenyl)-4-nitro-5-phenylpyrrolidine[6b] (**13**) have been reported by us earlier.

1,3-Dipolar cycloadditions between ethyl (arylideneamino)acetates and aryl-nitroethylenes

General procedure: Ethyl (arylideneamino)acetate (10 mM) and aryl-nitroethylene (9 mM) were dissolved in solvent (50 mL) then AgOAc (2.5 g, 15 mM) and triethylamine (1.7 mL, 1.21 g, 12 mM) were added to the well stirred reaction mixture. After 1–3 h, when the reaction was completed (judged by TLC) 25 mL saturated aqueous ammonium chloride was added, the precipitate was filtered off and the residue was extracted with ether. The combined organic fractions were dried over magnesium sulphate, evaporated and the residue was trituated with ether.

5-(2,4-Dichlorophenyl)-2-ethoxycarbonyl-3-(4-methoxyphenyl)-4-nitropyrrolidine (3a). *syn-endo* Isomer; yield: 82%; white powder, mp 122°C; [Found: C, 54.7; H, 4.51, N, 6.41. $C_{20}H_{20}Cl_2N_2O_2$ requires C, 54.68; H, 4.59; N, 6.38%]; δ_H ($CDCl_3$, 200 MHz): 7.45 (1H, d, *J*=8.6 Hz, Ar^5-6′*H*), 7.28 (1H, dd, *J*=2.0 and 8.6 Hz, Ar^5-5′*H*), 7.22 (1H, d, *J*=2.0 Hz, Ar^5-3′*H*), 7.20 (2H, d, *J*=8.8 Hz, Ar^3-3′*H* and 5′*H*), 6.92 (2H, d, *J*=8.8 Hz, Ar^3-2′*H* and 6′*H*), 5.49 (1H, dd, *J*=3.4 and 6.3 Hz, *H*-4), 5.15 (1H, broad s, *H*-5), 4.27 (2H, q, *J*=6.1 Hz, OCH_2CH_3), 4.19 (1H, dd, *J*=3.4 and 7.9 Hz, *H*-3), 4.00 (1H, broad s, *H*-2), 3.81 (3H, s, OCH_3). 3.17 (1H, broad s, NH), 1.27 (3H, t, *J*=6.1 Hz, CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 171.0 (*C*=O), 159.3 (Ar^3-4′*C*), 135.2 (Ar^5-4′*C*), 133.7 (Ar^5-2′*C*), 130.9 (Ar^5-1′*C*), 130.6 (Ar^3-1′*C*), 129.3 (Ar^5-3′*C*), 128.6 (Ar^3-2′ and 6′*C*), 128.2 (Ar^5-6′*C*), 127.6 (Ar^5-5′*C*), 114.6 (Ar^3-3′ and 5′*C*), 94.6 (*C*-4), 67.4 (*C*-5), 65.8 (*C*-2), 61.7 (OCH_2), 55.3 (OCH_3), 54.3 (*C*-3), 14.1 (CH_3); EIMS *m/z* (rel. intensity, %): 439 (M^+, 1.3), 392 (3), 318 (20), 291 (100), 259 (17), 185 (25); IR (KBr, cm^{-1}): 3445, 2980, 2937, 1732, 1615, 1548, 1517, 1437, 1375, 1312, 1235, 1183, 1116, 1032, 826.

2-Ethoxycarbonyl-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (3c). *syn-endo* Isomer; yield: 75%; white powder, mp 120–121°C; [Found: C, 65.0; H, 6.1; N, 7.6. $C_{20}H_{22}N_2O_5$ requires C, 64.85; H, 5.99; N, 7.56%); δ_H ($CDCl_3$, 200 MHz): 7.35 (5H, s, Ph), 7.22 (2H, d, *J*=8.8 Hz, Ar-2′*H* and 6′*H*), 6.92 (2H, d, *J*=8.8 Hz, Ar-3′*H* and 5′*H*), 5.25 (1H, dd, *J*=3.4 and 6.5 Hz, *H*-4), 4.90 (1H, d, *J*=6.5 Hz, *H*-5), 4.39–4.04 (4H, m, *H*-2, *H*-3, OCH_2), 3.82 (3H, s, OCH_3), 1.26 (3H, t, *J*=7.0 Hz, CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 171.3 (*C*=O), 159.2 (Ar-4′*C*), 134.5 (Ph-1′*C*), 130.5 (Ar-1′*C*), 128.7 (Ph-3′*C* and 5′*C*), 128.65 (Ph-4′*C*), 128.6 (Ph-2′*C* and 6′*C*), 126.4 (Ar-2′*C* and 6′*C*), 114.5 (Ar-3′*C* and 5′*C*), 97.1 (*C*-4), 67.6 (*C*-5), 67.5 (*C*-2), 61.6 (OCH_2), 55.3 (OCH_3), 54.9 (*C*-3), 14.1 (CH_2CH_3); EIMS *m/z* (rel. intensity, %): 371 (MH^+, 1.2), 324 (1.8), 250 (24), 223 (100), 145 (11), 117 (24). IR (KBr, cm^{-1}): 3451, 3031, 2838, 1747, 1610, 1550, 1368, 1303, 1185, 1033.

2-Ethoxycarbonyl-5-(4-methylphenyl)-4-nitro-3-phenylpyrrolidine (3d). *syn-endo* Isomer; yield: 69%; white powder, mp 111–112°C; [Found: C, 67.9; H, 6.2; N, 7.9. $C_{20}H_{22}N_2O_4$ requires C, 67.78; H, 6.26; N, 7.90%); δ_H ($CDCl_3$, 200 MHz): 7.42–7.12 (9H, m, Ar), 5.26 (1H, dd, *J*=6.4 and 3.7 Hz, *H*-4), 4.87 (1H, d, *J*=6.4 Hz, *H*-5), 4.20 (2H, q, *J*=7.1 Hz, OCH_2), 4.18 (1H, dd, *J*=3.7 and 7.5 Hz, *H*-3), 4.07 (1H, d, *J*=7.5 Hz, *H*-2), 3.35 (1H, br s, NH), 2.31 (3H, s, Ar-CH_3), 1.23 (3H, t, *J*=7.1 Hz, CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 171.2 (*C*=O), 138.6 and 138.4 (Ar-1′*C*), 131.4 (Ar^5-4′*C*), 129.3 (Ar-3′, and 5′*C*), 129.1 (Ar-3′, and 5′*C*), 127.9 (Ar^3-4′*C*), 127.5 (Ar-2′ and 6′*C*), 126.2 (Ar-2′ and 6′*C*), 97.0 (*C*-4), 67.6 (*C*-5), 67.5 (*C*-2), 61.6 (OCH_2), 55.5 (*C*-3), 21.0 (Ar-CH_3), 14.0 (CH_3); EIMS *m/z* (rel. intensity,%): 355 (MH^+, 0.3), 308 (3), 281 (14), 234 (100), 207 (90), 131 (50), 115 (31), 91 (17), 77 (9); IR (KBr, cm^{-1}): 3340, 2986, 1732, 1604, 1552, 1499, 1457, 1371, 1130, 1033, 976.

2-Ethoxycarbonyl-4-nitro-3-phenyl-5-(4-trifluoromethylphenyl)-pyrrolidine (3e). *syn-endo* Isomer; yield: 83%; white powder, mp 105°C; [Found: C, 58.8; H, 4.6; N, 6.9. $C_{20}H_{19}F_3N_2O_4$ requires C, 58.82; H, 4.69; N, 6.86%); δ_H ($CDCl_3$, 200 MHz): 7.62 (2H, d, J=8.4 Hz, Ar^2-2′ and 6′*H*), 7.47 (2H, d, J=8.4 Hz, Ar^2-3′ and 5′*H*), 7.41–7.25 (5H, m, Ph), 5.32 (1H, dd, J=4.0 and 6.7 Hz, *H*-4), 4.96 (1H, d, J=6.7 Hz, *H*-5), 4.24 (3H, dq+dd, OCH_2+*H*-3), 4.12 (1H, d, J=7.8 Hz, *H*-2), 3.30 (1H, br s, NH), 1.25 (3H, t, J=7.1 Hz, CH_2CH_3); δ_C ($CDCl_3$, J=75 MHz): 171.0 (*C*=O), 138.8 (Ph-1′C), 138.1 (Ar-1′*C*), 130.0 (*C*F_3, quartet, J=32.5 Hz), 129.3 (Ph-2′ and 6′*C*), 128.2 (Ph-4′*C*), 127.5 (Ph-3′ and 5′*C*), 127.0 (Ar-2′, and 6′*C*), 125.0 (Ar-3′ and 5′), 96.5 (*C*-4), 67.2 (*C*-5), 66.9 (*C*-2), 61.8 (OCH_2), 55.1 (*C*-3), 14.1 (CH_3); EIMS *m*/*z* (rel. intensity, %): 409 (MH^+, 7), 362 (3), 335 (15), 288 (100), 261 (98), 185 (19), 115 (24); IR (KBr, cm^{-1}): 3457, 3296, 2988, 1738, 1547, 1367, 1329, 1192, 1164, 1114, 1071, 841.

5-(4-Chlorophenyl)-2-ethoxycarbonyl-4-nitro-3-phenylpyrrolidine (3f). *syn-endo* Isomer; yield: 75%; white powder, mp 108°C; [Found: C, 61.1; H, 5.2; N, 7.4. $C_{19}H_{19}ClN_2O_4$ requires C, 60.88; H, 5.11; N, 7.47%]; δ_H ($CDCl_3$, 200 MHz): 7.33 (9H, m, Ar), 5.28 (1H, dd, J=3.9 and 6.6 Hz, *H*-4), 4.89 (1H, d, J=6.6 Hz, *H*-5), 4.25 (2H, q, J=7.0 Hz, OCH_2), 4.20 (1H, dd, J=3.9 and 7.2 Hz, *H*-3), 4.09 (1H, d, J=7.2 Hz, *H*-2), 3.25 (1H, br s, NH), 1.25 (3H, t, J=7.0 Hz, CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 171.1 (*C*=O), 138.2 (Ar^5-4′*C*), 134.5 (Ar^5-1′*C*), 133.2 (Ar^3-1′*C*), 129.2 (Ar^5-3′ and 5′*C*), 128.9 (Ar^3-3′ and 5′*C*), 128.1 (Ar^3-4′*C*), 127.9 (Ar^5-2′ and 6′), 127.5 (Ar^3-2′ and 6′*C*), 96.6 (*C*-4), 67.2 (*C*-5), 66.8 (*C*-2), 61.7 (OCH_2), 55.1 (*C*-3), 14.1 (CH_3); EIMS *m*/*z* (rel. intensity, %): 375 (M^+, 0.8), 328 (1), 301 (4), 254 (100), 227 (40), 219 (25), 191 (13), 151 (33), 115 (38); IR (KBr, cm^{-1}): 3344, 2978, 2934, 1737, 1549, 1492, 1374, 1330, 1215, 1132.

3-(4-Chlorophenyl)-2-ethoxycarbonyl-4-nitro-3-phenylpyrrolidine (3h). *syn-endo* Isomer; yield: 77%; white powder; [Found: C, 61.0; H, 5.3; N, 7.5. $C_{19}H_{19}ClN_2O_4$ requires C, 60.88; H, 5.11; N, 7.47%); δ_H ($CDCl_3$, 250 MHz): 7.43–7.27 (7H, m, Ph and Ar), 7.23 (2H, d, J=8.4 Hz, Ar), 5.25 (1H, dd, J=6.5 and 4.0 Hz, *H*-4), 4.89 (1H, d, J=6.5 Hz, *H*-5), 4.37–4.21 (m, 2H, OCH_2), 4.17 (1H, dd, J=8.0 and 4.0 Hz, *H*-3), 4.03 (1H, d, J=8.0 Hz, *H*-2), 3.31 (1H, br s, NH), 1.25 (3H, t, J=7.1 Hz, CH_2CH_3); δ_C ($CDCl_3$, 63 MHz): 171.0 (*C*=O), 136.9 (q), 134.5 (q), 133.9 (q), 129.4 (2×CH), 129.0 (2×CH), 128.8 (CH), 128.7 (2×CH), 126.5 (2×CH), 96.7 (*C*-4), 67.5 (*C*-5), 67.3 (*C*-2), 61.8 (CH_2), 54.6 (*C*-3), 14.1 (CH_3); IR (KBr, cm^{-1}): 3934, 3030, 2982, 1734, 1551, 1530, 1494, 1452, 1371, 1258, 1200. 1137, 1088, 1030, 1014.

2-Benzyl-2-ethoxycarbonyl-3-(4-methylenedioxyphenyl)-4-nitro-5-phenylpyrrolidine (14). *syn-endo* Isomer; white powder, yield 74%; mp 158–160°C; [Found: C, 67.9; H, 5.2; N, 6.1. $C_{26}H_{24}N_2O_6$ requires C, 67.82; H, 5.25; N, 6.08%); δ_H ($CDCl_3$, 250 MHz): 7.50–7.30 (5H, m, Ar), 7.25–7.05 (5H, m, Ar), 6.85–6.70 (3H, m, Ar), 5.99 (2H, s, OCH_2O), 5.59 (1H, dd, J=7.0 and 5.2 Hz, *H*-4); 5.16 (1H, dd, J=9.3 and 7.0 Hz, *H*-5), 4.39 (1H, d, J=5.2 Hz, *H*-3), 3.73 (3H, s, OCH_3), 3.33 (1H, d, J=9.3 Hz, N*H*), 2.66 (2H, s, CH_2Ph); δ_C ($CDCl_3$, 75 MHz): 173.7 (q), 148.0 (q), 147.5 (q), 136.4 (q), 135.5 (q), 130.0 (2×CH), 128.9 (q), 128.8 (CH), 128.7 (2×CH), 128.1 (2×CH), 126.9 (2×CH), 124.1 (q), 122.6 (CH), 109.4 (CH), 108.5 (CH), 101.4 (CH_2), 96.3 (CH), 73.0 (q), 65.2 (CH), 57.6 (CH), 52.4 (CH_3), 40.8 (CH_2); EIMS *m*/*z* (rel. intensity, %): 461 (M^+, 29), 427 (20), 369 (9), 337 (8), 322(12), 296 (9), 268 (60), 237 (13), 206 (7), 178 (36), 162 (17), 135 (100), 118 (31), 106 (38); IR (KBr, cm^{-1}): 3028, 2950, 2909, 1733, 1609, 1551, 1503, 1492, 1445, 1369, 1252, 1238, 1201, 1125, 1036, 932.

Preparation of pyrrole derivatives

General procedure: The nitro-pyrrolidine derivative (1.0 mmol) was suspended in methanol (10 mL) and sodium methylate (0.108 g, 2.0 mmol) was added. When the reaction mixture became homogenous it was cooled to 0°C and 30% hydrogen peroxide solution (2 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Then the solution was acidified by dilute hydrochloric acid, and the precipitated pyrrole was filtered off. The residue was evaporated, dissolved in dichloromethane, washed with water, dried over magnesium sulphate and evaporated to yield a further crop. The yields are collected in Table 1.

5-(2,4-Dichlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (4a). Light brown powder; mp 188°C; δ_H (DMSO-d_6, 500 MHz): 12.7 (1H, broad s), 7.82 (1H, d, J=1.9 Hz, Ar^5-3′*H*), 7.57 (4H, m, Ar-*H*), 7.26 (1H, s, *H*-4), 6.94 (2H, d, J=8.7 Hz, Ar^3-3′ and 5′*H*), 3.79 (3H, s, OCH_3); δ_C ($CDCl_3$, 125 MHz): 160.0 (q), 158.4 (q), 134.7 (q), 134.6 (q), 130.2 (q), 129.7 (CH), 129.1 (q), 129.0 (CH), 128.3 (q), 127.2 (2×CH), 125.8 (q), 125.2 (CH), 116.6 (q), 114.6 (q), 113.6 (2×CH), 55.1 (CH_3); CIMS *m*/*z* (rel. intensity, %): 362 (MH^+, 8), 346 (15), 310 (100), 295 (23), 279 (25), 267 (27), 232 (14), 203 (17), 158 (24), 89 (36), 75 (40), 63 (64); IR (KBr, cm^{-1}): 3082, 3013, 2901, 2888, 1675, 1608, 1495, 1312, 1256, 1223, 1182, 1146, 1030; HRMS (EI): Found: 361.0276. $C_{18}H_{13}Cl_2NO_3$ requires 361.0272.

3,5-Diphenyl-1*H*-pyrrole-2-carboxylic acid (4b). Light brown powder; mp 171–172°C (lit.[13] 180°C) δ_H (DMSO-d_6, 200 MHz): 10.8 (1H, br s,), 8.13 (2H, d, J=7.2 Hz), 7.42 (2H, t, J=7.2 Hz, Ar), 7.35 (1H, t, J=7.2 Hz, Ar), 7.31 (2H, d, J=7.7 Hz), 7.24 (2H, t, J=7.7 Hz), 7.16 (1H, t, J=7.7 Hz), 6.81 (1H, s, H-4); δ_C ($CDCl_3$, 125 MHz): 161.0 (q), 135.4 (q), 134.0 (q), 129.5 (2×CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 128.1 (2×CH), 127.9 (2×CH), 127.4 (2×CH), 127.2 (q), 125.7 (q), 121.4 (q); EIMS *m*/*z* (rel. intensity, %): 264 (MH^+, 6), 248 (38), 231 (12), 219 (32), 189 (48), 165 (19), 139 (13), 114 (25), 102 (43), 89 (60), 77 (81), 63 (73), 51 (100); IR (KBr, cm^{-1}): 3022, 2514, 1672, 1611, 1427, 1313, 1252 1221, 1030; HRMS (EI): Found: 263.0943. $C_{17}H_{13}NO_2$ requires 263.0946.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrrol-2-carboxylic acid (4c). Light brown powder; 158°C; δ_H (DMSO-d_6, 200 MHz): 8.07 (2H, d, J=8.4 Hz, Ar), 7.85 (t, 1H, J=8.4 Hz, Ar), 7.44 (4H, m, Ar), 7.27 (2H, d, J=8.5 Hz, Ar), 6.96 (1H, s, H-4), 3.77 (3H, s, OCH_3); δ_C ($CDCl_3$,

125 MHz): 160.9 (q), 158.2 (q), 133.3 (q), 131.0 (q), 130.2 (CH), 129.9 (2×CH), 129.5 (2×CH), 129.4 (q), 128.6 (q), 128.5 (2×CH), 113.9 (q), 113.2 (2×CH), 112.6 (CH), 55.4 (CH_3); EIMS *m/z* (rel. intensity, %): 294 (MH^+, 7), 278 (52), 261 (27), 249 (11), 235 (16), 217 (20), 204 (64), 176 (53), 151 (36), 102 (54), 89 (78), 77 (100), 63 (70), 51 (80); IR (KBr, cm^{-1}): 2511, 1670, 1427, 1311, 1250, 1221, 1032; HRMS (EI): Found: 293.1048. $C_{18}H_{15}NO_3$ requires 293.1051.

5-(4-Methylphenyl)-3-phenyl-1*H*-pyrrole-2-carboxylic acid (4d). Light brown powder; 169–171°C; δ_H (DMSO-d_6, 200 MHz): 11.5 (1H, br s), 8.01 (2H, d *J*=8.0 Hz, Ar), 7.46–7.07 (7H, m, Ar) 6.96 (1H, s, *H*-4). 2.36 (3H, s, C*H*$_3$); δ_C ($CDCl_3$, 125 MHz): 160.0 (q), 138.5 (q), 138.4 (q), 130.1 (q), 129.6 (2×CH), 129.0 (2×CH), 128.8 (CH), 128.7 (CH), 128.1 (2×CH), 127.5 (2×CH), 126.2 (q), 121.3 (q), 118.4 (q), 21.0 (CH_3); MS *m/z* (rel. intensity, %): 278 (MH^+, 20), 262 (34), 245 (8), 233 (100), 217 (18), 207 (21), 189 (13), 131 (12), 116 (35), 109 (17), 91 (13), 77 (12); IR (KBr, cm^{-1}): 3036, 2797, 2517, 1673, 1610, 1428, 1319, 1237, 988. HRMS (EI): Found: 277.1102. $C_{18}H_{15}NO_2$ requires 277.1102.

5-(4-Trifluoromethylphenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid (4e). Light brown powder; mp 142°C; δ_H (DMSO-d_6, 500 MHz): 10.2 (1H, br s), 8.22 (2H, d, *J*=8.1 Hz, Ar), 7.91 (2H, d, *J*=8.1 Hz, Ar), 7.24 (2H, d, *J*=8.5 Hz, Ar), 7.16 (1H, s, *H*-4), 6.89 (2H, d, *J*=8.5 Hz, Ar), 3.81 (3H, s, OC*H*$_3$); δ_C ($CDCl_3$, 125 MHz): 159.3 (q), 158.6 (q), 133.9 (q), 130.4 (2×CH), 129.9 (q), 129.6 (2×CH), 127.5 (q), 125.4 (2×CH), 125.2 (CF_3), 125.1 (CH), 121.0 (q), 113.9 (q), 113.2 (2×CH); MS *m/z* (rel. intensity, %): 362 (MH^+, 12), 346 (100), 329 (45), 317 (7), 303 (10), 272 (13); IR (KBr, cm^{-1}): 3081, 2885, 1673, 1608, 1495, 1319, 1221, 1141, 1033; HRMS (EI): Found: 361.0926. requires 361.0925.

5-(4-Chlorophenyl)-3-phenyl-1*H*-pyrrol-2-carboxylic acid (4f). Light brown powder; mp 182°C; δ_H (DMSO-d_6, 200 MHz): 12.2 (1H, br s), 8.08 (2H, d, *J*=7.8 Hz, Ar), 7.66–7.10 (8H, m); δ_C ($CDCl_3$, 125 MHz): 160.1 (q), 138.5 (q), 134.1 (q), 131.9 (q), 129.5 (2×CH), 129.3 (2×CH), 128.4 (CH), 128.1 (q), 128.0 (2×CH), 127.6 (2×CH), 126.0 (q), 116.8 (q), 114.5 (CH); MS *m/z* (rel. intensity, %): 298 (MH^+, 14), 282 (100), 265 (26), 253 (38), 217 (44), 189 (40), 109 (34), 101 (45); IR (KBr, cm^{-1}): 3082, 3014, 2909, 2887, 1669, 1609, 1491, 1317, 1227, 1149, 1033; HRMS (EI): Found: 297.0555. $C_{17}H_{12}NO_2Cl$ requires 297.0556.

3-(3,4-Methylenedioxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylic acid (4g). Light brown powder; mp 172–175°C; δ_H (DMSO-d_6, 250 MHz): 12.79 (1H, br s,), 8.03 (2H, m, Ar), 7.54–7.37 (4H, m, Ar), 7.10 (1H, s, Ar), 6.82 (2H. m, Ar), 6.03 (2H, s, OC*H*$_2$O); δ_C ($CDCl_3$, 69 MHz): 159.1 (q), 146.7 (q), 146.4 (q), 129.9 (2×CH), 129.6 (CH), 129.0 (q), 128.6 (2×CH), 128.0 (q), 127.0 (q), 126.9 (q), 121.8 (CH), 120.8 (CH), 108.9 (CH), 107.6 (CH), 100.9 (CH_2); CIMS *m/z* (rel. intensity, %): 307 (M^+, 12), 293 (15), 279 (100), 264 (7), 104 (12); IR (nujol, cm^{-1}): 1672, 1620, 1550, 1490, 1300, 1247, 1218, 1100, 1040, 925; HRMS (EI): Found: 307.0847. $C_{18}H_{13}NO_4$ requires 307.0844.

Protection of pyrrolidine nitrogen

General procedure: The pyrrolidine derivative (10 mM) was dissolved in dry dichloromethane (30 mL) and pyridine (1 mL) was added. The solution was cooled to 0°C and then $ClCO_2Me$ (10 mM) was added slowly. The orange mixture was stirred for further 16 h, allowing the temperature to rise to the room temperature. The reaction mixture was extracted with water, dilute hydrocholric acid and aqueous sodium hydrogencarbonate, dried over magnesium sulphate, evaporated to yield the product which was purified by recrystallisation from ether.

5-(2,4-Dichlorophenyl)-2-(ethoxycarbonyl)-1-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-pyrrolidine (5a). Yield: 86%; pale yellow powder, mp 95°C; [C, 53.6; H, 4.8; N, 5.6. $C_{22}H_{22}Cl_2N_2O_7$ requires C, 53.13; H, 4.46; N, 5.63%]; δ_H ($CDCl_3$, 200 MHz): 8.10 (1H, broad d, *J*=8.0 Hz, Ar^5-6′*H*), 7.34 (2H, m, Ar^5-3′*H* and 5′*H*), 7.14 (2H, d, *J*=8.8 Hz, Ar^3-2′*H* and 6′*H*), 6.90 (2H, d, *J*=8.8 Hz, Ar^3-3′*H* and 5′*H*), 6.01 (1H, d, *J*=8.3 Hz, *H*-5), 5.45 (1H, dd, *J*=6.5 and 8.3 Hz, *H*-4), 4.67 (1H, d, *J*=6.3 Hz, *H*-2), 4.31 (3H, q+t, OC*H*$_2$+*H*-3), 3.80 (3H, s, ArOCH_3), 3.67 (3H, br s, NCOOC*H*$_3$), 1.23 (3H, t, *J*=7.2 Hz, C*H*$_3$CH$_2$); δ_C (125 MHz, $CDCl_3$): 170.3 (q), 159.8 (q), 154.8 (br, q), 135.6 (q), 133.4 (q), 127.8 (2×CH), 129.5 (CH), 129.1 (CH), 128.5 (q), 128.1 (q), 127.4 (CH), 125.2 (CH), 114.9 (2×CH), 94.3 (CH), 65.0 (br, CH), 63.7 (CH), 61.9 (CH_2), 55.3 (CH_3), 53.6 (CH_3), 49.9 (br, CH), 14.1 (CH_3); EIMS *m/z* (rel. intensity, %): 497 (M^+, 0.2), 496 (0.3), 449 (5), 414 (4), 390 (4), 376 (68), 344 (9), 318 (15), 291 (14), 145 (14), 121 (17), 59 (100); IR (KBr, cm^{-1}): 3022, 2955, 1793, 1743, 1612, 1546, 1457, 1251, 1130, 1030.

2-(Ethoxycarbonyl)-1-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (5c). Yield: 78%; white powder, mp 155°C; [Found: C, 61.7; H, 5.6; N, 6.7. $C_{22}H_{24}N_2O_7$ requires C, 61.68; H, 5.65; N, 6.54%); δ_H ($CDCl_3$, 200 MHz): 7.66 (2H, dd, *J*=1.4 and 8.1 Hz, Ph-2′ and 6′*H*), 7.35 (3H, m, Ph-3′, 4′ and 5′*H*), 7.19 (2H, d, *J*=8.7 Hz, Ar-3′ and 5′*H*), 6.87 (2H, d, *J*=8.7 Hz, Ar-2′ and 6′*H*), 5.60 (1H, broad s, *H*-5), 5.43 (1H, t, *J*=10.6 Hz, *H*-4), 4.47 (1H, d, *J*=7.0 Hz, *H*-2), 4.25 (3H, m, *H*-3+OC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 3.64 (3H, br s, CO_2CH_3), 1.21 (3H, t, *J*=7.4 Hz, CH_2CH_3); δ_C ($CDCl_3$, 75 MHz): 170.4 (q), 159.7 (q), 155.1 (br, q), 135.0 (br, q), 128.8 (3×CH), 128.7 (2×CH), 128.6 (q), 126.9 (2×CH), 114.5 (2×CH), 90.8 (br, CH), 64.2 (CH), 62.6 (br, CH), 61.6 (CH_2), 55.2 (CH_3), 53.2 (CH_3), 47.8 (CH), 14.0 (CH_3); EIMS *m/z* (rel. intensity, %): 428 (M^+, 3), 381 (17), 322 (11), 308 (100), 276 (10), 248 (8), 115 (6); IR (KBr, cm^{-1}): 3019, 2960, 1790, 1741, 1613, 1556, 1451, 1367, 1254, 1186, 1131, 1031, 774.

Reaction of 3 or 5 with NaOMe/acid

General procedure: The nitro-pyrrolidine derivative (1.0 mmol) was suspended in methanol (8 mL) and sodium methylate was added (0.108 g, 2.0 mmol). When the reaction mixture become homogenous, this solution was added dropwise to an excess of cold aqueous or methanolic solution of hydrochloric acid (≈5%). After 1 h stirring the reaction mixture was washed with dichloromethane.

The organic layer was separated, washed with brine, dried over magnesium sulphate, evaporated to yield the products.

1,2-Bis(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (5i). Separated from **5j** by column chromatography, yield: 18%; white powder, mp 132°C; [Found: C, 61.1; H, 5.5; N, 6.8. $C_{21}H_{22}N_2O_7$ requires C, 60.86; H, 5.35; N, 6.76%]; δ_H ($CDCl_3$, 200 MHz): 7.70 (2H, d, J=7.3 Hz, Ph-2′ and 6′*H*), 7.40 (3H, m, Ph-3′, 4′ and 5′*H*), 7.12 (2H, d, J=8.6 Hz, Ar^3-2′ and 6′*H*), 6.83 (2H, d, J=8.6 Hz, Ar^3-3′ and 5′*H*), 5.53 (1H, br s, *H*-5), 5.10 (1H, d, J=10.0 Hz, *H*-4), 5.02 (1H, d, J=6.7 Hz, *H*-2), 3.98 (1H, dd, J=6.7 and 10.0 Hz, *H*-3), 3.76 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.22 (3H, br s, NCO_2CH_3); EIMS *m*/*z* (rel. intensity, %): 414 (M^+, 6), 382 (9), 368 (61), 336 (72), 308 (100), 226 (27), 248 (27), 233 (36), 115 (29); IR (KBr, cm^{-1}): 3440, 2956, 2840, 1752, 1713, 1614, 1548, 1450, 1381, 1258, 1201, 1028.

1,2-Bis(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (5j). Separated from **5i** by column chromatography, yield: 32%; white powder, mp 147–148°C; [Found: C, 61.01; H, 5.29; N, 6.67. $C_{21}H_{22}N_2O_7$ requires C, 60.86; H, 5.35; N, 6.76%); δ_H ($CDCl_3$, 200 MHz): 7.63 (2H, d, J=7.2 Hz, Ph-2′ and 6′*H*), 7.35 (3H, m, Ph-3′, 4′ and 5′*H*), 7.15 (2H, d, J=8.7 Hz, Ar^3-2′ and 6′*H*), 6.83 (2H, d, J=8.7 Hz, Ar^3-3′ and 5′*H*), 5.55 (1H, br s, *H*-5), 5.39 (1H, t, J=10.6 Hz, *H*-4), 4.49 (1H, d, J=6.0 Hz, *H*-2), 4.22 (1H, broad dd, J=6.0 and 10.0 Hz, *H*-3), 3.75 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.58 (3H, br s, NCO_2CH_3); δ_C ($CDCl_3$, 125 MHz): 170.0 (q), 159.7 (q), 155.0 (br, q), 135.0 (br, q), 128.8 (3×CH), 128.7 (2×CH), 128.6 (q), 126.9 (2×CH), 114.6 (2×CH), 90.9 (br, CH), 64.1 (CH), 61.6 (br CH), 55.2 (CH_3), 53.3 (CH_3), 52.6 (CH_3), 47.7 (CH); EIMS *m*/*z* (rel. intensity, %): 414 (M^+, 12), 368 (41), 336 (100), 308 (88), 226 (21), 233 (11); IR (KBr, cm^{-1}): 2951, 1750, 1712, 1613, 1548, 1451, 1382, 1200, 1025.

Reaction of 5 with $NaOMe/H_2O_2$

General procedure: The nitro-pyrrolidine derivative (1.0 mmol) was suspended in methanol (10 mL) and sodium methylate was added (0.054 g, 1.0 mmol). When the reaction mixture become homogenous it was cooled to 0°C and 30% hydrogen peroxide solution was added dropwise. The reaction mixture was stirred at room temperature overnight. Then the reaction mixture was acidified with aqueous hydrochloric acid and extracted with a large volume of dichloromethane. The organic layer was separated, washed with brine, dried over magnesium sulphate, evaporated to yield the appropriate product.

5-(2,4-Dichlorophenyl)-2-(ethoxycarbonyl)-1-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitropyrrolidine (6a). Yield: 92%; white powder; mp 128°C; [Found: C, 53.0; H, 4.6; N, 5.6. $C_{22}H_{22}Cl_2N_2O_7$ requires C, 53.13; H, 4.46; N, 5.63%); δ_H (DMSO-d_6, 200 MHz): (mixture of two invertomers) 8.15 and 8.13 (1H, 2×d, J=8.6 Hz, Ar^5-6′*H*), 7.77 (1H, d, J=2.1 Hz, Ar^5-3′*H*), 7.64 (1H, m, Ar^5-5′*H*), 7.29 (1H, d, J=8.8 Hz, Ar^3-2′ and 6′*H*), 6.89 (1H, d, J=8.8 Hz, Ar^3-3′ and 5′*H*), 5.61 (1H, s, *H*-5), 5.51 (1H, d, J=5.3 Hz, *H*-2), 4.95 (1H, d, J=10.8 Hz, *H*-4), 4.12 (2H, m, OCH_2CH_3), 3.99 (1H, m, *H*-3), 3.74 (3H, s, OCH_3), 3.70 and 3.59 (3H, 2×br s, 3H, NCO_2CH_3), 1.04 and 1.07 (3H, 2×t, J=7.1 Hz, CH_2CH_3); δ_C (75 MHz, $DMSO_{d6}$): (mixture of two invertomers) 171.0 and 170.7 (esters), 159.4 (q), 154.6 and 154.3 (N*C*=O), 134.4 and 134.2 (q), 133.9 (q), 132.5 and 132.4, 129.3 (Ar^3-2′ and 6′*C*), 128.3 (q), 127.9 (q), 122.3 (CH), 114.0 (Ar^3-3′ and 5′*C*), 93.6 and 92.7 (*C*-4), 63.9 and 63.1 (*C*-2), 62.3 and 61.8 (*C*-5), 55.1 (OCH_3), 53.5 (OCH_3), 49.7 and 48.5 (*C*-3), 13.9 (CH_3); EIMS *m*/*z* (rel. intensity, %): 498 (MH^+, 1.7), 496 (9), 450 (43), 423 (14), 404 (71), 376 (100), 342 (56), 318 (18), 232 (25), 121 (26); IR (KBr, cm^{-1}): 2967, 2832, 1746, 1715, 1558, 1517, 1450, 1371, 1199, 1032.

2-(Ethoxycarbonyl)-1-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidine (6c). Yield: 95%; white powder; mp 132°C; [Found: C, 61.5; H, 5.5; N, 6.5. $C_{22}H_{24}N_2O_7$ requires C, 61.68; H, 5.65; N, 6.54%]; δ_H (DMSO-d_6, 200 MHz): (mixture of two invertomers) 7.69 (2H, d, J=6.4 Hz, Ph-2′ and 6′*H*), 7.42 (2H, t, J=6.4 Hz, Ph-3′, and 5′*H*), 7.35 (1H, t, J=6.4 Hz, Ph-4′*H*), 7.22 (2H, d, J=8.6 Hz, Ar^3-2′ and 6′*H*), 6.83 (2H, d, J=8.6 Hz, Ar^3-3′ and 5′*H*), 5.72 (1H, s, *H*-5), 5.82 (1H, d, J=6.0 Hz, *H*-4), 4.85 (1H, d, J=10.2 Hz, *H*-2), 4.12 (3H, q+dd, OCH_2+*H*-3), 3.72 (3H, s, OCH_3), 3.67 and 3.55 (3H, 2×br s, NCO_2CH_3), 1.06 (3H, t, J=7.1 Hz, CH_3); δ_C (75 MHz, $DMSO_{d6}$): (mixture of two invertomers) 171.0 and 170.7 (ester), 159.2 (Ar-4′*C*), 155.1 and 154.4 (N*C*=O), 138.7 and 138.5 (q), 129.2 (2×CH), 128.6 (2×CH), 127.9 (CH), 125.6 (2×CH), 122.9 (q), 114.0 (Ar-3′ and 5′*C*), 95.5 and 94.5 (*C*-4), 64.5 and 64.8 (*C*-2), 62.4 and 61.9 (*C*-5), 61.2 and 61.1 (OCH_2), 55.1 (OCH_3), 53.1 (OCH_3), 49.6 and 48.4 (*C*-3), 13.9 (CH_2CH_3); EIMS *m*/*z* (rel. intensity, %): 428 (M^+, 2), 382 (45), 355 (13), 336 (50), 308 (100), 294 (32), 276 (18), 249 (18), 232 (17), 115 (31), 59 (48); IR (KBr, cm^{-1}): 3443, 2958, 2838, 1744, 1713, 1553, 1516, 1450, 1375, 1256, 1194, 1029.

Barton method for conversion of 5c to oxime 7

To a solution of nitro-pyrrolidine **5c** (0.428 g, 1 mmol) in acetonitrile (3 mL) is added triethylamine (1.4 mL, 10 mmol) followed by carbon disulphide (0.18 mL, 3 mmol). The mixture was stirred at room temperature for 72 h, concentrated under reduced pressure and the residue purified by chromatography on silica to yield an 1:1 mixture of *syn* and *anti* oximes (**7**) as a colourless oil (0.21 g, 52%). δ_H ($CDCl_3$, 200 MHz): 7.72 (1H, d, J=8.4 Hz, Ar), 7.52 (1H, d, J=8.4 Hz, Ar), 7.30 (3H, m, Ar), 7.16 (1H, d, J=8.0 Hz, Ar), 7.08 (1H, d, J=8.0 Hz, Ar), 6.87 (1H, d, J=8.4 Hz, Ar), 6.84 (1H, d, J=8.4 Hz, Ar), 5.97 (0.5H, br s, *H*-5), 5.40 (0.5H, br s, *H*-5), 4.60 (1H, br s, *H*-2), 4.42 (0.5H, br d, J=9.9 Hz, *H*-3), 4.28 (1H, q, J=6.2 Hz, OCH_2), 4.20 (1.5H, m, OCH_2+*H*-3), 3.78 (3H, s, OCH_3), 3.58 (3H, br s, CO_2CH_3), 1.29 (1.5H, t, J=6.2 Hz, CH_2CH_3), 1.17 (1.5H, t, J=6.2 Hz, CH_2CH_3); EIMS *m*/*z* (rel. intensity, %): 412 (M^+, 36), 395 (6), 339 (100), 323 (41), 291 (14), 264 (20), 236 (52), 164 (23), 146 (29); IR (KBr, cm^{-1}): 3373, 2959, 2929, 1741, 1678, 1516, 1460, 1386, 1256, 1197, 1032; HRMS (EI): Calculated: Found: 412.1632. $C_{22}H_{24}N_2O_6$ required 412.1634.

Oxidations with MnO_2

General procedure: The appropriate cycloadduct (1 mmol) was dissolved in THF (10 mL) and manganese(IV)-oxide (0.87 g, 10 mmol) was added. The reaction mixture was stirred under the conditions given in Table 2. After the completion of the reaction (judged by TLC) all the solid was removed by filtration and the residue was evaporated. The product ratios (see Table 2) were determined from the crude reaction mixture, while the pure compounds were obtained by column chromatography.

Ethyl 3,5-diphenyl-pyrroline-2-carboxylate (15b). White powder; yield 87%; mp 105–107°C; [Found: C, 77.9; H, 6.7; N, 4.7. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77%]; δ_H ($CDCl_3$, 250 MHz): 7.40–7.29 (6H, m, Ph), 7.29–7.22 (2H, m, Ph), 7.19–7.13 (2H, m, Ph), 6.02 (1H, d, *J*=7.3 Hz, *H*-4), 5.37 (1H, dd, *J*=7.3 and 2.2 Hz, *H*-5), 5.27 (1H, s, *H*-2), 4.29 (2H, dq, *J*=7.1 and 1.4 Hz, CH_2CH_3), 1.27 (3H, t, *J*=7.1 Hz, CH_2CH_3); δ_C (63 MHz, $CDCl_3$): 168.4 (q), 160.8 (q), 134.6 (q), 133.2 (q), 129.7 (2×CH), 128.9 (CH), 128.7 (CH), 128.5 (2×CH), 127.4 (2×CH), 127.3 (2×CH), 95.0 (CH), 79.4 (CH), 62.5 (CH_2), 60.7 (CH), 13.9 (CH_3); EIMS *m*/*z* (rel. intensity, %): 292 (M^+-1, 100), 274 (5), 246 (19), 220 (7), 118 (3), 106 (4), 85 (10), 71 (7); IR (KBr, cm^{-1}): 3417, 2987, 1720, 1635, 1545, 1493, 1545, 1454, 1374, 1261, 1107, 995.

Ethyl 3-(4-methoxyphenyl)-5-phenyl-pyrroline-2-carboxylate (15c). White powder; yield 76%; mp 117–119°C; [Found: C, 74.6; H, 6.7; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55; N, 4.33%]; δ_H ($CDCl_3$, 250 MHz): 7.40–7.30 (3H, m, Ph), 7.30–7.20 (2H, m, Ph), 7.07 (2H, d, *J*=8.3 Hz, Ar), 6.90 (2H, d, *J*=8.3 Hz, Ar), 6.00 (1H, d, *J*=7 Hz, *H*-4), 5.34 (1H, d, *J*=7.0 Hz, *H*-5), 5.22 (1H, s, *H*-2), 4.30 (2H, q, *J*=7.1 Hz, CH_2CH_3), 3.78 (3H, s, OCH_3), 1.28 (t, 3H, CH_3); δ_C (63 MHz, $CDCl_3$): 168.7 (q), 160.9 (q), 159.8 (q), 133.4 (q), 128.8 (CH), 128.6 (2×CH), 128.5 (2×CH), 127.4 (2×CH), 126.3 (CH), 115.0 (2×CH), 95.1 (CH), 79.3 (CH), 62.5 (CH_2), 60.1 (CH), 55.3 (CH_3), 14.0 (CH_3); EIMS *m*/*z* (rel. intensity, %): 322 (M^+-1, 100), 304 (11), 276 (74), 250 (14), 57 (38); IR (nujol, cm^{-1}): 1722, 1627, 1602, 1581, 1512, 1302, 1250, 1165, 1112, 1029.

Ethyl 3-(3,4-methylenedioxyphenyl)-5-phenyl-pyrroline-2-carboxylate (15g). White powder; yield 63%; mp 120–122°C; [Found: C, 71.3; H, 6.0; N, 4.2. $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.68; N, 4.15%]; δ_H ($CDCl_3$, 250 MHz): 7.32 (3H, m, Ph), 7.23 (2H, m, Ph), 6.79 (1H, d, *J*=7.6 Hz, Ar), 6.61 (1H, s, Ar), 6.59 (1H, d, *J*=7.6 Hz, Ar), 5.98 (1H, d, *J*=7.4 Hz, *H*-4), 5.96 (2H, s, OCH_2O), 5.33 (1H, dd, *J*=1.9 and 7.4 Hz, *H*-5), 5.18 (1H, s, *H*-2), 4.31 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 1.31 (3H, t, *J*=7.1 Hz, CH_3); δ_C (63 MHz, $CDCl_3$): 168.4 (q), 160.8 (q), 148.7 (q), 148.0 (q), 133.2 (q), 128.9 (q), 128.5 (2×CH), 128.0 (CH), 127.4 (2×CH), 120.8 (CH), 109.1 (CH), 107.8 (CH), 101.5 (CH_2), 95.0 (CH), 79.2 (CH), 62.5 (CH_2), 60.3 (CH), 14.0 (CH_3); EIMS *m*/*z* (rel. intensity, %): 336 (M^+-1, 100), 318 (7), 290 (46), 264 99), 192 (4), 135 (5), 106 (7), 85 (14), 71 (16); IR (KBr, cm^{-1}): 3414, 1734, 1532, 1491, 1445, 1365, 1302, 1243, 1118, 1033, 929, 810.

Ethyl 3-(4-chlorophenyl)-5-phenyl-pyrroline-2-carboxylate (15h). White powder; yield 83%; mp 108–110 °C; [Found; C, 69.4; H, 5.6; N, 4.2. $C_{19}H_{18}ClNO_2$ requires C, 69.62; H, 5.53; N, 4.27%]; δ_H ($CDCl_3$, 250 MHz): 7.38–7.32 (5H, m, Ph-*H*), 7.27–7.20 (2H, m, Ar-*H*), 7.08 (2H, d, *J*=8.2 Hz, Ar-*H*), 6.01 (1H, d, *J*=7.5 Hz, *H*-4), 5.34 (1H, dd, *J*=7.5 and 2.6 Hz, *H*-5), 5.26 (1H, s, *H*-2), 4.31 (2H, q, *J*=7.1 Hz, CH_2CH_3), 1.29 (3H, t, *J*=7.1 Hz, CH_3); δ_C (63 MHz, $CDCl_3$): 167.9 (q), 160.7 (q), 134.7 (q), 133.1 (q), 133.0 (q), 129.8 (2×CH), 129.0 (CH), 128.8 (2×CH), 128.6 (2×CH), 127.4 (2×CH), 94.7 (CH), 79.4 (CH), 62.7 (CH_2), 59.9 (CH), 14.0 (CH_3); EIMS *m*/*z* (rel. intensity, %): 327 (M^+, 37), 325 (100), 279 (63), 253 (20), 216 (82), 189 (23), 117 (21), 105 (28); IR (nujol, cm^{-1}): 3315, 3062, 3025, 2985, 2960, 2902, 1743, 1652, 1554, 1490, 1450, 1367, 1301, 1259, 1197, 1126, 1087, 1014, 917, 852, 806, 754, 707, 607, 538.

Ethyl 3,5-diphenyl-1*H*-pyrrole-2-carboxylate (16b). Pale yellow powder; yield 60%; mp 138–139°C; [Found: C, 78.8; H, 5.7; N, 4.8. $C_{19}H_{17}NO_2$ requires C, 78.33; H, 5.88; N, 4.81%]; δ_H ($CDCl_3$, 250 MHz): 9.80 (1H, br s, N*H*), 7.70–7.60 (4H, m, Ph-*H*), 7.48–7.28 (6H, m, Ph-*H*), 6.60 (1H, d, *J*=3.0 Hz, *H*-4), 4.23 (2H, q, *J*=7.1 Hz, CH_2CH_3), 1.20 (3H, t, *J*=7.1 Hz, CH_2CH_3); δ_C (63 MHz, $CDCl_3$): 161.5 (q), 135.6 (q), 135.2 (q), 133.4 (q), 131.1 (q), 129.6 (2×CH), 128.9 (2×CH), 127.8 (CH), 127.6 (2×CH), 127.0 (CH), 124.9 (2×CH), 118.7 (q), 110.0 (CH), 60.5 (CH_2), 14.1 (CH_3); EIMS *m*/*z* (rel. intensity, %): 291 (M^+, 100), 275 (5), 245 (71), 217 (69), 189 (25), 175 (6), 140 (6), 115 (6), 89 (7), 77 (5); IR (KBr, cm^{-1}): 3411, 3313, 2975, 1660, 1601, 1459, 1433, 1290, 1263, 1203, 1132, 1022.

Ethyl 3-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (16c). Pale yellow powder; yield 21%; mp 132–133°C; (lit.[13] 135°C); δ_H ($CDCl_3$, 250 MHz): 9.47 (1H, s, N*H*), 7.61 (2H, d, *J*=7.5 Hz, Ph-*H*), 7.52 (2H, d, *J*=8.2 Hz, Ar-*H*), 7.38 (2H, t, *J*=7.5 Hz, Ph-*H*), 7.29 (1H, d, 7.5 Hz, Ph-H), 6.42 (2H, d, *J*=8.2 Hz, Ar-*H*), 6.57 (1H, d, *J*=1.9 Hz, *H*-4), 4.20 (2H, q, *J*=7.0 Hz, CH_2CH_3), 1.21 (3H, t, *J*=7.0 Hz, CH_2CH_3); δ_C (63 MHz, $CDCl_3$): 161.5 (q), 158.8 (q), 135.6 (q) 133.3 (q), 131.2 (q), 130.7 (2×CH), 128.9 (2×CH), 127.8 (CH), 127.6 (q), 124.9 (2×CH), 118.4 (q), 113.1 (2×CH), 109.8 (CH), 60.4 (CH_2), 55.2 (CH_3), 14.2 (CH_3); EIMS *m*/*z* (rel. intensity, %): 321 (M^+, 100), 275 (60), 247 (22), 232 (30), 204 (19), 176 (8), 137 (6), 102 (5); IR (KBr, cm^{-1}): 3440, 3310, 2934, 1675, 1527, 1452, 1191, 1171, 1248, 1178, 1029, 812, 774;

Ethyl 5-(4-chlorophenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (16f). Pale yellow powder; yield 55%; mp 180°C; (lit.[13] 185°C); [Found: C, 70.0; H, 5.2; N, 4.4. $C_{19}H_{16}ClNO_2$ requires C, 70.05; H, 4.95; N, 4.30%]; δ_H ($CDCl_3$, 250 MHz): 9.70 (1H, br s, N*H*), 7.60–7.50 (4H, m, Ph-*H*), 7.44–7.30 (5H, m, Ph-*H*), 6.59 (1H, d, *J*=2.0 Hz, Ar-*H*), 4.25 (2H, q, *J*=7.1 Hz, CH_2CH_3), 1.23 (3H, t, *J*=7.1 Hz, CH_2CH_3); δ_C (63 MHz, $CDCl_3$): 160.1 (q), 135.0 (q), 134.4 (q), 133.6 (q), 133.5 (q), 129.6 (q), 129.5 (2×CH), 129.2 (2×CH), 127.7 (2×CH), 127.2 (CH), 126.1 (2×CH), 119.0 (q), 110.3 (CH), 60.6 (CH_2), 14.1 (CH_3); EIMS *m*/*z* (rel. intensity, %): 326 (M^+, 100), 308 (14), 290 (57), 280 (89), 254 (15), 246 (17), 220 (9), 149 (5), 111 (7), 97

(25), 85 (66); IR (KBr, cm^{-1}): 3323, 3319, 2981, 2927, 1673, 1453, 1283, 1263, 1294, 1136, 1092, 1033, 1015.

Ethyl 3-(3,4-methylenedioxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (16g). Pale yellow powder; yield 13%; mp 168–169°C; [Found: C, 71.5; H, 5.5; N, 4.3. $C_{20}H_{17}NO_4$ requires C, 71.63; H, 5.11; N, 4.18%]; δ_H ($CDCl_3$, 250 MHz): 9.45 (1H, br s, N*H*), 7.59 (2H, d, *J*=7.5 Hz, Ar-*H*), 7.42 (2H, m, Ar-*H*), 7.32 (1H, m, Ar-*H*), 7.08 (2H, m, Ar-*H*), 6.84 (1H, dd, *J*=2.0 and 8.0 Hz, Ar-*H*), 6.57 (1H, d, *J*=2.0 Hz, Ar-*H*), 5.98 (2H, s, OCH_2O), 4.27 (2H, q, *J*=7.0 Hz, CH_2CH$_3$), 1.28 (3H, t, *J*=7.0 Hz, CH$_2$CH_3); δ_C (63 MHz, $CDCl_3$): 160.8 (q), 147.0 (q), 146.9 (q), 135.3 (q), 133.2 (q), 131.0 (CH), 129.0 (2×CH), 128.9 (CH), 127.9 (q), 124.7 (2×CH), 124.1 (q), 122.9 (CH), 110.3 (CH), 109.8 (CH), 107.7 (CH), 100.9 (CH_2), 60.4 (CH_2), 14.3 (CH_3); EIMS *m*/*z* (rel. intensity, %): 336 (M^+, 79), 318 (9), 290 (100), 262 (10), 97 (6), 85 (14), 79 (11), 71 (10); IR (KBr, cm^{-1}): 3306, 2973, 2884, 1667, 1467, 1449, 1290, 1265, 1243, 1204, 1120, 1096, 1034, 1017, 929.

Ethyl 3-(4-chlorophenyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (16h). Pale yellow powder; yield 50% mp 187°C; [Found: C, 69.9; H, 5.1; N, 4.2. $C_{19}H_{16}ClNO_2$ requires C, 70.05; H, 4.95; N, 4.30%]; δ_H (DMSO-d_6, 250 MHz): 12.05 (1H, br s, N*H*), 7.90 (2H, d, *J*=7.7 Hz, Ar-*H*), 7.56 (2H, d, *J*=7.7 Hz, Ar-*H*), 7.48–7.35 (4H, m, Ph-*H*), 7.35–7.24 (1H, m, Ph-*H*), 6.77 (1H, s, *H*-4), 4.19 (2H, q, CH_2CH$_3$), 1.19 (3H, t, *J*=6.9 Hz, CH_3); δ_C (63 MHz, DMSO-d_6): 160.5 (q), 135.9 (q), 134.2 (q), 131.4 (q), 131.1 (2×CH), 131.0 (q), 130.9 (q), 128.7 (2×CH), 127.6 (3×CH), 125.5 (2×CH), 118.7 (q), 109.8 (CH), 59.7 (CH_2), 14.1 (CH_3); IR (KBr, cm^{-1}): 3327, 3321, 2987, 1675, 1457, 1283, 1267, 1295, 1095, 1033, 1017.

Ethyl 3,5-diphenyl-4-nitro-1*H*-pyrrole-2-carboxylate (17b). Pale yellow powder; yield 17%; mp 182–183°C; [Found: C, 68.0; H, 4.5; N, 8.3. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.79; N, 8.33%]; δ_H ($CDCl_3$, 250 MHz): 10.16 (br s, 1H, N*H*), 7.63–7.55 (2H, m, Ph-*H*), 7.50–7.43 (3H, m, Ph-*H*), 7.43–7.31 (5H, m, Ph-*H*), 3.90 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 0.94 (t, 3H, *J*=7.1 Hz, CH$_2$CH_3); δ_C (63 MHz, $CDCl_3$): 160.9 (q), 134.7 (q), 133.3 (q), 131.4 (q), 129.9 (CH), 129.8 (2×CH), 129.0 (2×CH), 128.9 (q), 128.6 (2×CH), 127.9 (CH), 127.6 (2×CH), 127.5 (q), 118.7 (q), 61.2 (CH_2), 13.6 (CH_3); CIMS *m*/*z* (rel. intensity, %): 337 (MH^+, 100), 307 (40), 291 (16), 261 (4), 85 (9), 79 (12); IR (KBr, cm^{-1}): 3475, 3414, 3288, 1678, 1501, 1357, 1253, 1187, 1020, 697.

Ethyl 3-(3,4-methylenedioxyphenyl)-4-nitro-5-phenyl-1*H*-pyrrole-2-carboxylate (17g). Pale yellow powder; yield 24%; mp 178–180°C; [Found: C, 63.4; H, 4.4; N, 7.3. $C_{20}H_{16}N_2O_6$ requires C, 63.16; H, 4.24; N, 7.36%]; δ_H ($CDCl_3$, 250 MHz): 10.24 (1H, br s, N*H*), 7.58 (2H, m, Ar-*H*), 7.45 (3H, m, Ar-*H*), 6.81 (3H, m, Ar-*H*), 5.98 (2H, s, OCH_2O), 3.93 (2H, q, *J*=7.0 Hz, OCH_2CH$_3$), 1.01 (3H, t, *J*=7.0 Hz, CH_3); δ_C (63 MHz, $CDCl_3$): 160.0 (q), 147.4 (q), 147.0 (q), 134.8 (q), 130.2 (q), 129.8 (CH), 129.1 (2×CH), 128.8 (q), 128.6 (2×CH), 127.0 (q), 124.7 (q), 123.5 (CH), 118.8 (q), 110.6 (CH), 107.7 (CH), 101.1 (CH_2), 61.2 (CH_2), 13.7 (CH_3); CIMS *m*/*z* (rel. intensity, %): 381 (MH^+, 80), 363 (29), 351 (70), 335 (100), 305 (68), 104 (30); IR (nujol, cm^{-1}): 1669, 1499, 1293, 1243, 1187, 1032.

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References

1. Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*, Academic: London, 1977.
2. (a) Sundberg, R. J. In *Comprhensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 313. (b) Two recent examples on the synthesis of pyrrole-2-carboxylates: Uno, H.; Tanaka, M.; Inoue, T.; Ono, N. *Synthesis* **1999**, 471; Selic, L.; Stanovnik, B. *Synthesis* **1999**, 479.
3. (a) La Porta, P.; Capuzzi, L.; Bettarini, F. *Synthesis* **1994**, 287. (b) DeShong, P.; Kell, D. A.; Sidler, D. R. *J. Org. Chem.* **1985**, *50*, 2309. (c) Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801.
4. (a) Southwick, P. L.; Sapper, D. I.; Pursglove, L. A. *J. Am. Chem. Soc.* **1950**, *72*, 4940. (b) Cossy, J.; Pete, J.-P. *Tetrahedron Lett.* **1978**, 4941. (c) Cervinka, O. *Chem. Ind.* (London) **1959**, 1129. (d) Oussaid, B.; Garrigues, B.; Soufiaoui, M. *Can. J. Chem.* **1994**, *72*, 2483. (e) Bonnaud, B.; Bigg, D. C. H. *Synthesis* **1994**, 465. (f) Gupta, P.; Bhaduri, A. P. *Synth. Commun.* **1998**, *28*, 3151.
5. Part of this work has been published in preliminary form: Pak, C. S.; Nyerges, M. *Synlett* **1999**, 1271.
6. (a) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Tőke, L. *Tetrahedron Lett.* **1994**, *34*, 4413. (b) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Tőke, L. *Tetrahedron* **1995**, *51*, 11489. (c) Nyerges, M.; Rudas, M.; Tóth, G.; Herényi, B.; Bitter, I.; Tőke, L. *Tetrahedron* **1995**, *51*, 13321. (d) Ayerbe, M.; Arrieta, M.; Cossio, P. F.; Linden, A. *J. Org. Chem.* **1998**, *63*, 1795.
7. (a) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D.; Prakash, G. K. S. *Synthesis* **1980**, 662. (b) Lui, K. H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 457.
8. Barton, D. H. R.; Fernandez, I.; Richard, C. S.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 551.
9. For an excellent review on the nitro group as a leaving group, see: Ono, N. In *Nitro Compounds, Recent Advances in Synthesis and Chemistry*; Feuer, H., Nielsen, A. T., Eds.; VCH: New York, 1990.
10. Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.
11. Bajpai, K. L.; Bhaduri, A. P. *Synth. Commun.* **1998**, *28*, 181.
12. The pyrrole **17** (R^2=R^3=R^4=H) showed in vitro immunoactivty on human T lymphocytes: Birouk, M.; Harraga, S.; Panouse-Perrin, J.; Robert, J. F.; Damelincourt, M. *Eur. J. Med. Chem. Chim. Ther.* **1991**, *26*, 91.
13. Sammes, M. P.; Chung, M. W. L.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1773.