N-(2-Phenylprop-1-enyl)proline Methyl Ester: Equilibrium between the Enamine and the Aza Methine Ylide form

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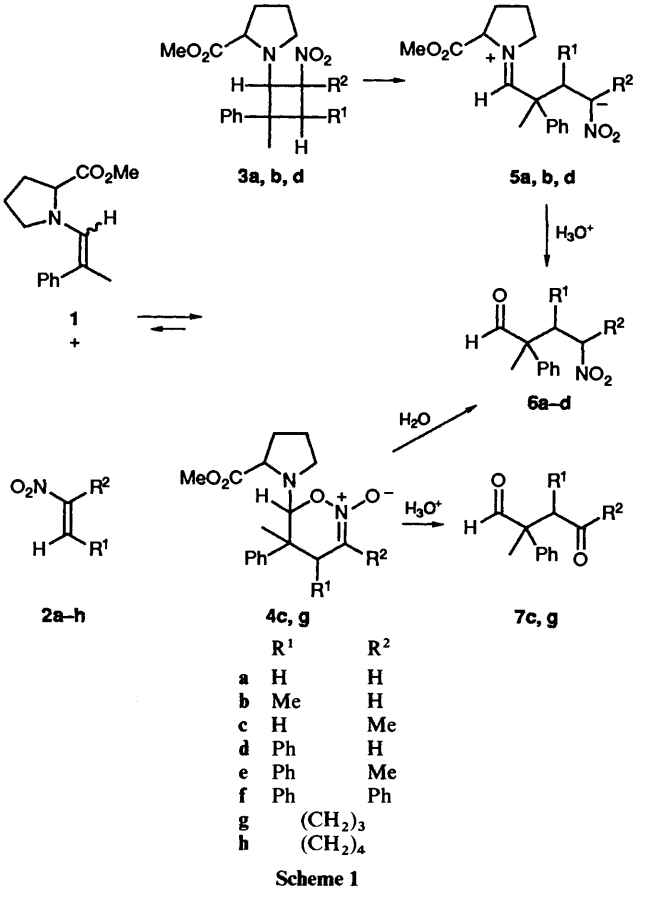
The title compound reacted with nitroolefins to give either cyclobutanes or pyrrolizidine derivatives, depending on whether it acted as an enamine or as a 1,3-dipole.

The importance of pyrrolizidine derivatives is well emphasized in a recent review covering their asymmetric synthesis.[1]

With our interest in diastereoselective syntheses of polyfunctionalized carbon–carbon single bonds starting from enamines and electrophilic olefins,[2,3] we had taken note of the potential for synthesis of compound **1** derived from 2-phenylpropanal and L-(−)-proline methyl ester.[4] By mixing the two reagents in benzene at room temperature and removing the azeotropic mixture formed under reduced pressure after 30 min we obtained crude but fairly pure enamine **1**, as a 1:1 mixture of *E* and *Z* diastereoisomers. In $CDCl_3$, however, this ratio rapidly increased to 3:1 in favour of the *E* isomer. Simultaneously, racemization occurred, the specific rotation decreasing from +72.2° ($CHCl_3$, *c* 1.28) to 0° within 2 h. The same behaviour occurred in benzene. A racemic mixture of compound **1** was, therefore, used in the reactions which were carried out in the absence of solvent and room temperature; these conditions were found to be the optimum for high yields. The nitroolefins whose reactivity we examined in the present work were nitroethylene **2a**, 1-nitropropene **2b**, 2-nitropropene **2c**, β-nitrostyrene **2d**, 2-nitro-1-phenylpropene **2e**, α-nitrostilbene **2f**, 1-nitrocyclopentene **2g** and 1-nitrocyclohexene **2h**. The course followed by the reactions depended on the electrophiles. With nitroethylene, 1-nitropropene and β-nitrostyrene the first products formed were the cyclobutanes **3a**, **3b** and **3d**, as diastereoisomeric mixtures (Scheme 1). Although too unstable to be isolated the compounds could be identified spectroscopically by the presence of nitro group absorption at 1550 cm^{-1} and the absence of absorption for double-bond stretching (corresponding to 1,2-oxazine *N*-oxide) and the parent enamine; the ^1H NMR spectra of the crude products showed signals characteristic of the cyclobutane derivatives (see Experimental section).



	R^1	R^2
a	H	H
b	Me	H
c	H	Me
d	Ph	H
e	Ph	Me
f	Ph	Ph
g	$(CH_2)_3$	
h	$(CH_2)_4$	

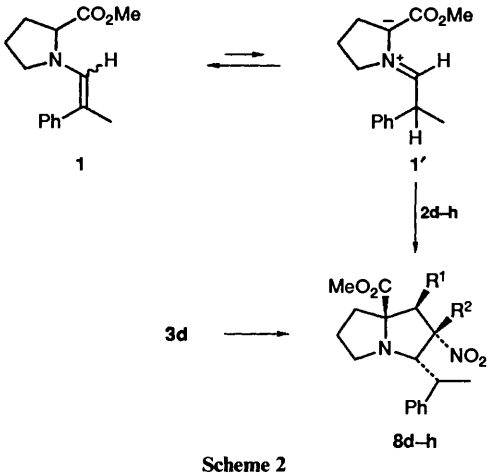
Scheme 1

The cyclobutanes **3b** and **3d** were diastereoisomeric mixtures as shown by the ^1H NMR spectra of the crude products. The diastereoisomerism, however, originated in the ring closure step, as shown by the acidic hydrolysis of the reaction mixtures which furnished the corresponding aldehydes **6b** and **6d** as the sole products. Their formation occurred as a result of nucleophilic ring-opening to give the corresponding dipolar intermediate **5**, followed by protonation of the carbanion and attack of water. Formation of cyclobutane derivatives, in fact, is known to be a reversible process.[5] It is evident that since the aldehydes **6b** and **6d** are the sole products, the initial C–C bond must be formed with a high degree of diastereoselectivity and this is of particular interest because of the quaternary nature of prochiral enamine β-carbon.

With 2-nitropropene and 1-nitrocyclopentene, the corresponding 1,2-oxazine *N*-oxide derivatives **4c** and **4g** were obtained rather than the corresponding cyclobutanes; they were identified by the presence of strong C=N–O (stretching) absorption at 1620 cm^{-1} and by the absence of NO_2 (stretching) absorptions. Unfortunately, as is usual with 1,2-oxazine *N*-oxides, they were too unstable to be analysed on the basis of NMR results, but their hydrolysis at pH 2 to the corresponding products of the Nef reaction, compounds **7c** and **7g**, gave chemical proof of their intermediacy. Exposure of compound **4c** to aerial humidity gave the nitroalkylated aldehyde **6c**.

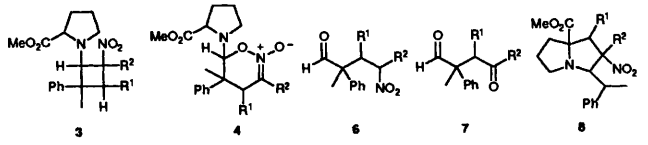
The cyclobutane **3d** when dissolved in either chloroform or methanol or when stored for a few days at room temp. was gradually converted into the corresponding pyrrolizidine derivative **8d** (Scheme 2) without by-product contamination. This transformation was slow enough to be followed by ^1H NMR spectroscopy.

The assignment was based on the analysis of the mass spectrum of **8d** and confirmed subsequently by other spectroscopic techniques. Apart from the peaks at *m/z* 394 ($C_{23}H_{26}N_2O_4$, molecular ion), at *m/z* 348 ($C_{23}H_{26}NO_2$, 348.196 34, found 348.195 97) corresponding to a loss of NO_2, and at *m/z* 335 ($C_{21}H_{23}N_2O_2$, 335.175 94, found 335.176 07) corresponding to a loss of CO_2Me, the most significant peak was that at *m/z* 289 ($C_{15}H_{17}N_2O_4$, 289.118 82, found 289.119 81) due to the loss of



Scheme 2

Table 1 Reaction products (yield, %, after purification)



R^1	R^2					
H	H	**a**		**a** (72)[a]		
Me	H	**b**		**b** (79)[a]		
H	Me		**c**	**c** (65)[a]	**c** (84)[b]	
Ph	H	**d**		**d** (80)[a]		**d** (87)
Ph	Me					**e**,**e**′ (90)
Ph	Ph					**f** (84)
$(CH_2)_3$			**g**		**g** (20)[b]	**g** (60)
$(CH_2)_4$						**h** (90)

[a] By hydrolysis of the crude. [b] By hydrolysis of the corresponding 1,2-oxaxine *N*-oxide **4**.

the fragment PhCHMe, also present in the spectrum (C_8H_9, 105.070 42, found 105.071 32). The presence of the residue PhCHMe, also confirmed by ^1H and ^{13}C NMR spectra, was proof that the reaction had proceeded to give form **1**′, derived from **1** by protonation of its β-carbon atom by 2-H of a proline ring. The substrate had, therefore, reacted as an azomethine ylide.

Substrate **1** also reacted with 2-nitro-1-phenylpropene **2e**, α-nitrostilbene **2f**, 1-nitrocyclopentene **2g** and 1-nitrocyclohexene **2h** to give the pyrrolizidines **8e**, **8f**, **8g** and **8h** respectively. These reactions, however, were too fast to allow the reaction intermediates to be observed.

In the reactions with 2-nitro-1-phenylpropene **2e** and with α-nitrostilbene **2f** the presence a small amount (7–10%) of a further diastereoisomer was noted in the ^1H NMR spectrum. In the former reaction it could be isolated and was assigned the structure, **8**′**e**, derived from **8e** by an inversion of configuration at C-2. The stereochemical assignment is in accord with the changes observed in the chemical shifts of the protons when compared with those of **8e**. The benzylic proton singlet, in fact, is shifted to highfield (3.27 ppm *vs.* 4.20 ppm) and the doublet at 3-H is shifted to lowfield (5.55 *vs.* 4.66) as a consequence of the nitro group orientation being different. Table 1 lists the products obtained, with the yields in parentheses.

The stereochemistry of the pyrrolizidine derivatives was established by means of the NOEDS technique as shown above.

Although the experimental results are clear only for the pyrrolizidines **8d**, **8e** and **8**′**e**, the same configuration was also assigned to **8f**, **8g** and **8h**, by analogy.

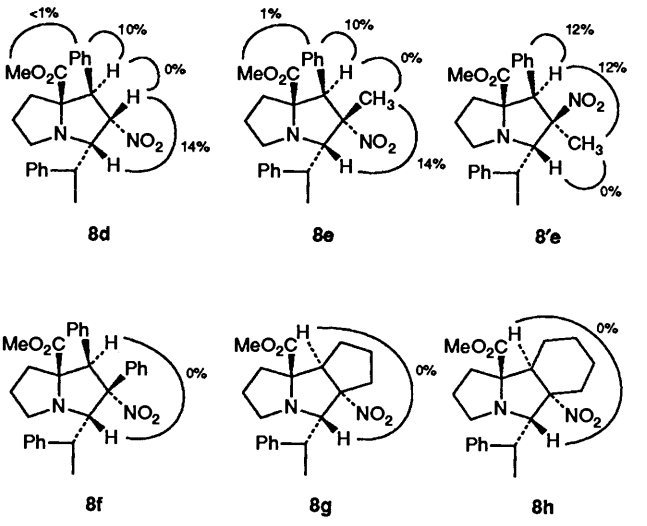
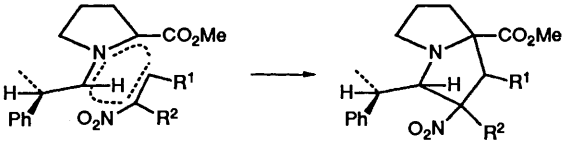


Fig. 1 NOEDS data on pyrrolizidines

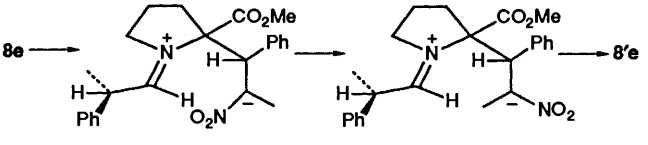
The stereochemical assignments are in accord with a reaction mechanism proposed for the intramolecular cyclization of the condensation product of proline methyl ester and *O*-prop-2-ynylsalicylaldehyde.[6] In these compounds, the phenylethyl group and the ester group are likely to be *anti*, to avoid steric interactions. As a consequence, in the interaction between the



Scheme 3

addends, the R^1 and R^2 substituents of the nitroolefin would assume an *exo* orientation with respect to the substrate, leading to the final product with a high degree of diastereoselectivity. The chiral carbon atom of the PhCHMe group has two configurations, since the substrate is now racemic. The nitroolefin attack occurs from one side only, resulting in the formation of a single diastereoisomer. From the values of the coupling constant between NCH and PhC*H*Me, which range from 10.6 to 11.3 Hz, it can be deduced that they are antiperiplanar and, therefore, the relative configuration of the two chiral centres is likely to be *erythro* (using the CIP notation).[7]

Formation of the diastereoisomer **8**′**e** can be postulated as deriving from opening of the pyrrolizidine substituted ring to give the zwitterionic intermediate **9e**, followed by recyclization at the inverted carbanion. Attack of the carbanion onto the other plane of the C=N group is unlikely to occur for steric reasons since it would be an *endo* attack of the nitroolefin onto the substrate. The intermediacy of a zwitterion has already been proposed for the reaction of β-nitrostyrene with azomethine ylides.[8]



Scheme 4

The present reactions, however, are not reversible which sets them apart from the cases studied by Tsuge. Equilibration reactions were then attempted in order to transform the pyrrolizidine derivatives. Heating with an without an acid catalyst in polar and non polar solvents had no effect. Basic

treatment with sodium methoxide in refluxing methanol for 12 h was effective only on **8e**, converting it into the minor isomer **8'e** (10%). The other pyrrolizidines, **8d** included, remained unchanged when similarly treated. Evidently they are product of thermodynamic control. Equilibration under basic conditions had been observed for pyrrolizidines obtained from dipolarophiles and azomethine ylides derived from proline by elimination of CO_2.[9,10] In that case, however, the reaction was less diastereoselective and isomerization led exclusively to the more stable product.

Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded as Nujol mulls, unless otherwise stated, on a Perkin-Elmer 1320 spectrometer. Optical rotations were determined on a Perkin-Elmer Model 241 Polarimeter. ^{1}H NMR spectra were run on the following machines: a Varian 360 A (60 MHz), a Varian VXR (300 MHz), a JEOL EX-400 (400 MHz) and a Bruker AMX (500 MHz) using deuteriochloroform as solvent, unless otherwise stated, and tetramethylsilane as internal standard; *J* Values are given in Hz. NOE measurements were performed on a Varian VXR (300 MHz). ^{13}C NMR spectra were recorded on a Bruker WP-80 instrument (20.1 MHz). Electron impact mass spectra were obtained on a VG 7070 spectrometer at 70 eV. TLC were performed on Whatman K6F silica gel plates. Flash chromatography was run on silica gel 230–400 mesh ASTM Kieselgel 60, Merck. Light petroleum refers to that fraction with b.p. 40–70 °C and ether to diethyl ether.

Synthesis of the Reactants.—N-(2-*Phenylprop*-1-*enyl*)*proline Methyl Ester* **1**. L-(−)-Proline methyl ester hydrochloride (1.5 g, 9.2 mmol) was treated with an equimolar amount of $NaHCO_3$, in benzene with magnetic stirring until CO_2 evolution was complete; 2-phenylpropionaldehyde (1.2 g, 9.2 mmol) was added and water removed by azeotropic distillation. The product **1** was either used without further purification or distilled: b.p. 118 °C at 1 mmHg; ν_{max}/cm^{-1} 1730 (CO_2Me), 1625 (C=C), 1590, 750, 690 and 680 (Ph); δ_H(60 MHz) 7.3 (5 H, m, Ph), 6.3, 6.1 (1 H, each br s, rel. intensities 4:1, C=CH), 4.1 (1 H, m, C*H*CO_2Me), 3.8 (3 H, s, CO_2Me), 3.3 (2 H, br m, NCH_2), 2.1 (3 H, s, Me), 2.0 (4 H, m, $NCH_2CH_2CH_2$): δ_C 175.0 (s), 144.1 (s), 135.9 (d), 129.3 (d), 128.9 (d), 128.6 (d), 128.3 (d), 127.7 (d), 125.2 (3), 65.7, 65.1 (2d), 53.2, 52.6 (2d), 52.0, 47.0 (2q), 30.3 (t), 24.7, 23.0 (2t), 15.8 and 14.7 (2q); *m/z* 245.140 92 (M^+, Calc. for $C_{15}H_{19}NO_2$: 245.141 57, 25%), 187 (19), 186 (100), 184 (36), 170 (15), 142 (13), 115 (17), 105 (19), 91 (10) and 77 (12).

Reaction of **1** *with Nitroethylene* **2a**.—The nitroalkene **2a** (0.2 g, 3.0 mmol) was added dropwise to the enamine **1** (0.75 g, 3.0 mmol), at −30 °C and in the absence of solvent. After 12 h at 0 °C, the compound **3a**, 1-(2-*carboxymethyl*)*pyrrolidin*-1-*yl*-2-*methyl*-4-*nitro*-2-*phenylcyclobutane* was detected in the reaction mixture as a mixture of diastereoisomers; ν_{max}/cm^{-1} 3060 (CH), 1720 (CO_2Me), 1550, 1380 (NO_2), 1600, 1490, 760 and 700 (Ph); δ_H(60 MHz) 7.3 (5 H, m, Ph), 4.38 (1 H, dt, J_1 10.0, J_2 2.0, $CHNO_2$), 3.63, 3.61 (3 H, each s, CO_2Me), 2.1–1.6 (6 H, m, $CH_2CH_2CH_2N$), 1.5, 1.4 (3 H, each s, 2-Me). Hydrolysis of the crude mixture, performed in MeOH and 10% HCl at pH 2, afforded after work-up compound **6a**, 2-*methyl*-4-*nitro*-2-*phenylbutanal* (0.45 g, 72%) as an oil; ν_{max}/cm^{-1} 2820, 2720 (CHO), 1730 (C=O), 1560, 1380 (NO_2), 1600, 1490, 770 and 700 (Ph); δ_H 9.33 (1 H, s, CHO), 7.20 (5 H, m, Ph), 4.13 (2 H, m, CH_2NO_2), 2.57, 2.40 (each 1 H, part AB of the ABXY system, J_{AB} 13.78, J_{AX}, J_{BX} 9.3, J_{AY}, J_{BY}, 6.2, CH_2C$H_2$$NO_2$) and 1.42 (3 H, s, Me); δ_C 200.2 (d), 137.6 (d), 129.6 (d), 128.4 (d), 127.0 (d), 71.9 (t), 52.5 (s), 33.6 (t) and 18.6 (q); *m/z* 178 (M − HCO^+, 6), 132 (14), 131 (100), 121 (22), 115 (22), 105 (42), 91 (67) and 77 (39).

Reaction of **1** *with* 1-*Nitropropene* **2b**.—The nitroalkene **2b** (0.18 g, 2.0 mmol) was added dropwise to the enamine **1** (0.5 g, 2.0 mmol), at −30 °C and in the absence of solvent. After 24 h at 0 °C, the compound **3b**, 1-(2-*carboxymethyl*)*pyrrolidin*-1-*yl*-2,3-*dimethyl*-4-*nitro*-2-*phenylcyclobutane* was detected in the crude as a mixture of diastereoisomers; ν_{max}/cm^{-1} 3060 (CH), 1720 (CO_2Me), 1550, 1380 (NO_2), 1600, 1490, 760 and 700 (Ph); δ_H(60 MHz) 7.4 (5 H, m, Ph), 4.8 (1 H, m, $CHNO_2$), 4.2, 4.15, 4.0 (1 H, each d, CHN), 3.8, 3.75, 3.6, 3.55 (3 H, each s, CO_2Me), 1.5, 1.4, 1.3, 1.2 (3 H, each d, 2-Me). Hydrolysis of the cyclobutanes, performed in MeOH and 10% HCl at pH 2, afforded after work-up compound **6b**, 2,3-*dimethyl*-4-*nitro*-2-*phenylbutanal* (0.35 g, 79% yield) as an oil; ν_{max}/cm^{-1} 2820, 2720 (CHO), 1720 (C=O), 1550, 1370 (NO_2), 1600, 1490, 760 and 700 (Ph); δ_H 9.6 (1 H, s, CHO), 7.5 (5 H, m, Ph), 4.61, 4.25 (2 H, dq, AB part of the $ABMX_3$ system, J_{AB} 12.0, J_{AM} 10.8, J_{BM} 3.2, CH_2NO_2), 3.2 (1 H, ddq, M part of the $ABMX_3$ system, J_{AM} 10.8, J_{BM} 3.2, J_{MX} 7.0, MeC*H*NO_2), 1.5 (3 H, s, Me) and 0.85 (d, X part of the $ABMX_3$ system, J_{MX} 7.0, 3-Me).

Reaction of **1** *with* 2-*Nitropropene* **2c**.—The nitroalkene **2c** (0.25 g, 2.0 mmol) was added dropwise to the enamine **1** (0.7 g, 2.8 mmol), −30 °C, in the absence of solvent. After 24 h at 0 °C, the compound **4c**, 6-(2-*carboxymethyl*)*pyrrolidin*-7-*yl*-3,5-*dimethyl*-5-*phenyl*-1,2-*oxazine* N-*oxide* was detected in the crude mixture; ν_{max}/cm^{-1} 3050, 3010 (CH), 1730 (CO_2Me), 1620 (C=NO), 1595, 1490, 760 and 700 (Ph). When the crude mixture was either dissolved in a solvent or left in the air for 24 h, the corresponding 2-*methyl*-4-*nitro*-2-*phenylpentanal* **6c** was formed as a 3:2 diastereoisomeric mixture, by slow hydrolysis (0.40 g, 65%) as an oil; ν_{max}/cm^{-1} 2820, 2720 (CHO), 1720 (C=O), 1550, 1370 (NO_2), 1600, 1490, 770 and 700 (Ph); δ_H 9.39 (0.4 H, s, CHO), 9.37 (0.6 H, s, CHO), 7.4, 7.2 (3 H and 2 H, each m, Ph), 4.61 (0.4 H, ddq, J_1 3.41, J_2 6.83, J_3 8.8, $CHNO_2$), 4.35 (0.6 H, ddq, J_1 3.41, J_2 6.83, J_3 8.8, $CHNO_2$), 2.77 (0.4 H, dd, J_1 15.6, J_2 8.8, C*H*$CHNO_2$), 2.68 (0.6 H, dd, J_1 15.6, J_2 8.8, C*H*$CHNO_2$), 2.32 (0.4 H, dd, J_1 15.6, J_2 C*H*$CHNO_2$), 2.21 (0.6 H, dd, J_1 15.6, J_2 3.4, C*H*$CHNO_2$), 1.53 (1.2 H, s, Me), 1.52 (1.2 H, d, *J* 6.83, Me), 1.48 (1.8 H, s, Me) and 1.39 (1.8 H, d, *J* 6.83, Me); δ_C 200.3 (s), 200.0 (s), 137.5 (s), 137.0 (s), 129.3 (d), 129.1 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.2 (d), 127.0 (d), 80.6 (d), 80.3 (d), 53.2 (s), 152.9 (s), 40.7 (t), 40.6 (t), 21.8 (q), 21.7 (q), 17.6 (q) and 17.3 (q). Hydrolysis of the crude product performed in MeOH and 10% HCl at pH 2, afforded after work-up, 2-*methyl*-4-*oxo*-2-*phenylpentanal* **7c** (0.45 g, 85%) as an oil; ν_{max}/cm^{-1} 2720 (CHO), 1710 (C=O), 1600, 1595, 1490, 760 and 700 (Ph); δ_H 9.46 (1 H, s, CHO), 7.23 (5 H, m, Ph), 3.17, 2.98 (2 H, AB system, CH_2), 2.00 (3 H, s, CH_3CO) and 1.53 (3 H, s, CH_3); δ_C 206.1(s), 201.0(s), 139.2(s), 129.1(d), 127.5(d), 126.8(d), 51.8(s), 50.4(t), 30.9(q) and 19.9(q).

Reaction of **1** *with* β-*Nitrostyrene* **2d**.—The nitroanalkene **2d** (0.6 g, 4.1 mmol) was added to the enamine **1** (1 g, 4.1 mmol), at room temp. and in the absence of solvent. After 12 h, 1-(2-*carboxymethyl*)*pyrrolidin*-1-*yl*-2-*methyl*-4-*nitro*-2,3-*diphenylcyclobutane* was detected in the crude product as a mixture of diastereoisomers; ν_{max}/cm^{-1} 3060, 3030 (CH), 1720 (CO_2Me), 1550, 1380 (NO_2), 1600 and 700 (Ph); δ_H(60 MHz) 7.3 (10 H, m, 2 Ph), 5.6, 5.5 (1 H, each dd, J_1 10.0 and 9.0, J_2 7.0 and 7.0, $CHNO_2$), 4.4, 4.2, 4.1, and 4.0 (2 H, each d, *J* 8.0, 8.0, 9.0, 9.0, CHPh and CHN), 3.7, 3.6 (3 H, each s, CO_2Me), 1.9 (4 H, m, CH_2CH_2) and 1.3, 1.2 (3 H, each s, 2-Me). Hydrolysis of the cyclobutanes, performed in MeOH and 10% HCl at pH 2, afforded after work-up 2-*methyl*-4-*nitro*-2,3-*diphenylbutanal* **6d** (0.93 g, 80% yield), m.p. 101–103 °C (Found: C, 72.1; H, 6.1; N,

4.85. $C_{17}H_{17}NO_3$ requires C, 72.07; H, 6.05; N, 4.94%); ν_{max}/cm^{-1} 2700 (CHO), 1710 (C=O), 1550, 1370 (NO_2), 1600, 760 and 700 (Ph); δ_H 9.7 (1 H, s, CHO), 7.2 (10 H, m, Ph), 5.0 (2 H, m, CH_2NO_2), 4.2 (1 H, m, C*H*Ph) and 1.5 (3 H, s, Me); δ_C 201.6 (d), 131.1 (d), 129.2 (d), 128.9 (d), 128.8 (d), 127.9 (d), 127.6 (d), 127.4 (d), 76.6 (t), 50.0 (d), 44.0 (s) and 17.2 (q); *m/z* 283 (M^+, 2.5%), 207 (M − HNO_2 − HCO^+, 7), 134 (54), 129 (14), 115 (10), 105 (73), 91 (29), 77 (29) and 32 (100). The cyclobutane derivatives when stored as a chloroform solution for 12 h were converted into *methyl 2-nitro-1-phenyl-3-(1-phenylethyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate* **8d** (1.4 g, 87% yield, after recrystallisation); m.p. 145 °C (from ethanol) (Found: C, 70.0; H, 6.7; N, 7.1. $C_{23}H_{26}N_2O_4$ requires C, 70.03; H, 6.64; N, 7.10%; ν_{max}/cm^{-1} 1725 (CO_2Me), 1600, 1590, 1490, 700 (Ph), 1545 and 1370 (NO_2); δ_H(500 MHz) 7.65 (8 H, m, ArH), 7.4 (2 H, m, *o*-ArH), 5.69 (1 H, dd, J_1 5.6, J_2 6.7, $CHNO_2$), 4.92 (1 H, dd, J_1 11.4, J_2 6.7, CHN), 4.02 (1 H, d, *J* 5.6, CHPh), 3.4 (1 H, m), 3.20 (3 H, s, CO_2Me), 3.08 (1 H, dq, J_1 7.0, J_2 11.4, PhC*H*Me), 2.53 (1 H, m), 2.45 (1 H, m), 2.26 (1 H, m), 2.10 (1 H, m), 1.32 (3 H, d, *J* 7.0, Me); δ_C 173.1 (s), 145.1 (s), 136.7 (s), 129.4 (d), 129.3 (d), 128.6 (d), 128.3 (d), 127.0 (d), 99.1 (d), 83.6 (s), 71.8 (d), 63.2 (d), 51.4 (q), 47.3 (t), 40.0 (d), 34.6 (t) and 23.4 (q and t); *m/z* 394 (M^+, 10%), 348 (M − NO_2, 10), 335 (M − CO_2Me, 8), 289 (M − PhCHMe, 19), 243 [(M − NO_2) − PhCHMe and (M − PhCHMe) − NO_2, 25], 221 (17), 184 (M − NO_2 − CO_2Me − PhCHMe, 30), 143 (19), 142 (15), 128 (25), 114 (23), 105 (PhCHMe, 100), 98 (69), 91 (63), 77 (44) and 70 (83).

Reaction of **1** *with 2-Nitro-1-phenylpropene* **2e**.—The nitroalkene **2e** (0.67 g, 4.1 mmol) was added to the enamine **1** (1 g, 4.1 mmol); after 48 h, the solidified crude was washed with ether. The product, *methyl 2-methyl-2-nitro-1-phenyl-3-(1-phenylethyl)hexahydro-1H-pyrrolizine-7a-carboxylate* was obtained as a mixture of diastereoisomers **8e** and **8′e** (ratio 9:1, by ^1H NMR spectroscopy) (1.5 g, 90% total yield); they were separated by flash chromatography using ethyl acetate–light petroleum (1:9) as eluent; **8e**, m.p. 137–138 °C (Found: C, 70.6; H, 6.8; N, 6.8. $C_{24}H_{28}N_2O_4$ requires C, 70.57; H, 6.91; N, 6.86%); ν_{max}/cm^{-1} 1720 (CO_2Me), 1530, 1360 (NO_2), 1600, 1580, 1490, 760, 710 and 700 (Ph); δ_H(400 MHz) 7.31 (8 H, m, ArH), 7.0 (2 H, m, *o*-ArH), 4.66 (1 H, d, *J* 11.1, CHN), 4.20 (1 H, s, C*H*Ph), 3.65 (3 H, s, CO_2Me), 3.56 (1 H, m), 3.14 (dq, J_1 11.1, J_2 6.5, C*H*Me), 2.60 (1 H, m), 2.39 (1 H, m), 1.95 (2 H, m), 1.73 (3 H, s, Me), 1.70 (1 H, m) and 1.16 (3 H, d, *J* 6.5, $CHCH_3$); *m/z* 362.212 54 (M − NO_2, calc. for $C_{24}H_{28}NO_2$: 362.211 97, 2.8%), 361 (M − HNO_2, 3.1), 349 (M − CO_2Me, 2.2), 305 (8), 303 (27), 301 (10), 287 (13), 258 (13), 257 (24), 245 (21), 243 (27), 224 (8), 210 (7), 198 (36), 196 (13), 186 (100), 184 (30), 182 (17), 170 (12), 140 (13), 125 (13), 118 (19), 117 (28), 116 (22), 115 (73), 105 (82), 91 (51), 86 (27), 84 (36) and 77 (30); **8′e**, m.p. 130 °C (Found: C, 70.55; H, 6.8; N, 6.9. $C_{24}H_{28}N_2O_4$ requires C, 70.57; H, 6.91; N, 6.86%); ν_{max}/cm^{-1} 1730 (CO_2Me), 1530, 1360 (NO_2), 1600, 1580, 1490, 720, 705 and 695 (Ph); δ_H 7.55–7.20 (8 H, m, ArH), 7.15 (2 H, m, *o*-ArH), 5.55 (1 H, d, *J* 11.6, CHN), 3.51 (3 H, s, CO_2Me), 3.27 (1 H, s, C*H*Ph), 3.1 (2 H, m and dq, J_1 11.6, J_2 6.7, C*H*Me and annular proton), 2.71 (1 H, m), 2.30 (1 H, m), 2.05–1.6 (6 H, m and s at 1.93 ppm, annular protons and Me), 1.11 (3 H, d, *J* 6.7, $CHCH_3$); *m/z* 362.212 54 (M − NO_2, Calc. for $C_{24}H_{28}NO_2$: 362.211 97, 5.5%), 3.61 (M − HNO_2, 7.2), 349 (2.5), 304 (19), 303 (M − PhCHMe, 75), 302 (18), 301 (22), 287 (31), 258 (33), 257 (55), 245 (18), 243 (25), 224 (22), 198 (83), 197 (20), 196 (25), 186 (79), 184 (25), 182 (18), 171 (10), 137 (16), 128 (17), 118 (23), 117 (26), 116 (21), 115 (67), 105 (100), 91 (41) and 77 (25).

Reaction of **1** *with α-Nitrostilbene* **2f**.—The nitroolefin **2f** (0.95 g, 4.1 mmol) was added at room temp. to the enamine **1** (1 g, 4.1 mmol); after 12 h, ether was added and a crystalline product was isolated and identified as *methyl 2-nitro-1,2-diphenyl-3-(1-phenylethyl)hexahydropyrrolizine-7a-carboxylate* **8f** (1.6 g, 84% yield), m.p. 138–140 °C from methanol (Found: C, 74.0; H, 6.35; N, 6.0. $C_{29}H_{30}N_2O_4$ requires C, 74.02; H, 6.43; N, 5.95%); ν_{max}/cm^{-1} 1720 (CO_2Me), 1600, 1580, 770, 760, 705, 685 (Ph), 1530, 1370 (NO_2); δ_H(200 MHz) 7.6–6.9 (13 H, m, ArH), 6.5 (2 H, bd, *o*-ArH), 5.92 (1 H, d, *J* 10.6, CHN), 5.25 (1 H, s, C*H*Ph), 3.73 (1 H, m, C*H*CO_2Me), 3.32 (3 H, s, CO_2Me), 3.17 (1 H, m), 2.96 (1 H, dq, J_1 10.6, J_2 6.6, C*H*Me), 2.45 (1 H, m), 2.35–2.12 (2 H, m), 1.66 (1 H, m), 1.27 (3 H, d, *J* 6.6, Me); δ_C 174.6 (s), 146.4 (s), 136.7 (s), 135.6 (s), 130.9 (d), 129.1 (d), 128.5 (d), 128.2 (d), 127.7 (d), 127.6 (d), 127.3 (d), 127.2 (d), 126.1 (d), 112.1 (s), 91.1 (s), 71.9 (d), 67.0 (d), 51.2 (q), 46.8 (t), 42.6 (d), 34.8 (t), 24.9 (q) and 22.7 (t); *m/z* 364.204 02 (M − NO_2 − CO_2Me − H, Calc. for $C_{27}H_{26}N$: 364.206 51, 36), 363 (18), 362 (18), 348 (28), 318 (88), 286 (32), 260 (48), 259 (36), 258 (28), 230 (9), 202 (5.5), 105 (100), 91 (6.5), 79 (7) and 77 (9).

Reaction of **1** *with 1-Nitrocyclopentene* **2g**.—The nitroalkene **2g** (0.26 g, 2.0 mmol) was added neat to the enamine **1** (0.5 g, 2.0 mmol) at 0 °C. After 24 h at 0 °C, the compound **4g**, *3-(2-carboxymethyl)pyrrolidin-1-yl-4-methyl-4-phenylcyclopent*[c][2,1]*oxazine N-oxide* was detected in the crude mixture; ν_{max}/cm^{-1} 3050, 3010 (CH), 1730 (CO_2Me), 1620 (C=N–O), 1600, 1490, 760 and 700 (Ph). Hydrolysis of the crude mixture furnished a mixture of compounds which were separated by column chromatography. Compound **8g** was isolated as major product and identified as *methyl 5a-nitro-5-(1-phenylethyl)-cyclopent*[a]*pyrrolizine-8b-carboxylate* (0.43 g, 60% yield) as an oil; ν_{max}/cm^{-1} 1730 (CO_2Me), 1600, 760, 700 (Ph), 1530 and 1350 (NO_2); δ_H(400 MHz) 7.32 (4 H, m, Ar), 7.18 (1 H, m, Ar), 4.16 (1 H, d, *J* 11.3, CHN), 3.72 (3 H, s, CO_2Me), 3.28 (1 H, dd, J_1 7.2, J_2 8.5), 3.28 (1 H, dt, J_1 8.7, J_2 7.2), 2.99 (1 H, dq, J_1 11.3, J_2 6.7, C*H*Me), 2.74, 2.49, 2.31, 2.16, 2.06 (each 1 H, each m), 1.83 (4 H, m), 1.48, 1.25 (each 1 H, m) and 1.25 (3 H, d, *J* 6.7 Hz, Me); δ_C 175.2 (s), 145.5 (s), 128.5 (d), 127.1 (d), 126.2 (d), 111.6 (s), 79.6 (d), 76.2 (d), 65.7 (d), 51.6 (q), 47.2 (t), 40.1 (d), 37.1 (t), 37.0 (t), 29.3 (t), 28.3 (t), 24.6 (t) and 23.0 (q). The other fractions were identified as the two diastereoisomers of *2-methyl-2-phenyl-3-(2-oxocyclopentyl)propanal* **7g** (0.1 g, 20% yield) as an oil; ν_{max}/cm^{-1} 2720 (CHO), 1710 (C=O), 1600, 1595, 1490, 770, 700 (Ph); δ_H 9.73 (1 H, s, CHO), 7.31 (5 H, m, Ph), 2.64 (1 H, m, CHCO), 2.26 (1 H, dd), 2.18 (1 H, m), 1.90 (2 H, m), 1.67 (4 H, m and s) and 1.52 (1 H, m); δ_C 218.2 (s), 201.7 (d), 139.3 (s), 128.7 (d), 127.6 (d), 127.4 (d), 55.5 (s), 55.4 (d), 39.3 (t), 26.6 (t), 20.6 (t) and 19.8 (q). Isomer **7′g** (0.1 g, 20% yield), oil; ν_{max}/cm^{-1} 2720 (CHO), 1710 (C=O), 1600, 1595, 1490, 770 and 700 (Ph); δ_H 9.72 (1 H, s, CHO), 7.35 (5 H, m, Ph), 3.25 (1 H, m, CHCO), 2.36 (1 H, dd), 2.05 (1 H, m), 1.95 (1 H, m), 1.80 (2 H, m), 1.55 (1 H, m) and 1.52 (3 H, s, Me); δ_C 218.1 (s), 200.7 (d), 138.0 (s), 128.9 (d), 127.5 (d), 127.1 (d), 54.7 (s), 54.1 (d), 39.0 (t), 25.5 (t), 20.5 (t) and 14.8 (q).

Reaction of **1** *with 1-Nitrocyclohexene* **2h**.—The nitroalkene **2h** (0.52 g, 4.1 mmol) was added neat to the enamine **1** at 0 °C; after 48 h the product was isolated and identified as *methyl decahydro-5a-nitro-5-(1-phenylethyl)cyclopent*[a]*isoindole-9b-carboxylate* (1.4 g, 90% yield), m.p. 123–124 °C from ethanol (Found: C, 67.8; H, 7.55; N, 7.5. $C_{21}H_{28}N_2O_4$ requires C, 67.72; H, 7.58; N, 7.52%); ν_{max}/cm^{-1} 1730 (CO_2Me), 1600, 760, 700 (Ph), 1530 and 1350 (NO_2); δ_H(400 MHz) 7.27 (5 H, s, Ph), 4.29 (1 H, d, *J* 11.2, CHN), 3.7 (3 H, s, CO_2Me), 3.29 (1 H, m), 3.10 (1 H, m), 2.92 (1 H, dq, J_1 11.2, J_2 6.6, C*H*Me), 2.45 (1 H, m), 2.32 (1 H, m), 2.08 (1 H, m), 1.92 (1 H, m), 1.8–1.2 (9 H, m) and 1.17 (3 H, d, *J* 6.6, Me); δ_C 170.3 (s), 137.0 (s), 129.0 (d), 127.7 (d), 126.6 (d), 91.7 (s), 79.1 (d), 56.7 (d), 52.1 (q), 47.2 (t), 41.9 (d), 35.0 (t), 32.2 (t), 23.7 (t), 23.3 (q), 22.4 (t), 20.6 (t) and 19.7 (t); *m/z* 372 (M^+, 1%), 356 (0.8), 326.213 28 (M − NO_2, Calc. for $C_{21}H_{28}NO_2$: 326.211 97, 6.5), 314 (10), 313 (M −

CO_2Me, 32), 268 (13), 267 (M − PhCHMe, 52), 266 (68), 264 (11), 250 (20), 245 (25), 243 (11), 222 (20), 221 (70), 220 (69), 188 (12), 187 (24), 186 (87), 184 (24), 169 (16), 163 (19), 162 (M − NO_2 − CO_2Me − PhCHMe, 100), 161 (24), 160 (40), 140 (30), 133 (30), 128 (30), 118 (62), 117 (24), 115 (22), 105 (73), 91 (33) and 77 (30).

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