Reactivity of conjugated azoalkenes towards α-amino acid ethyl esters

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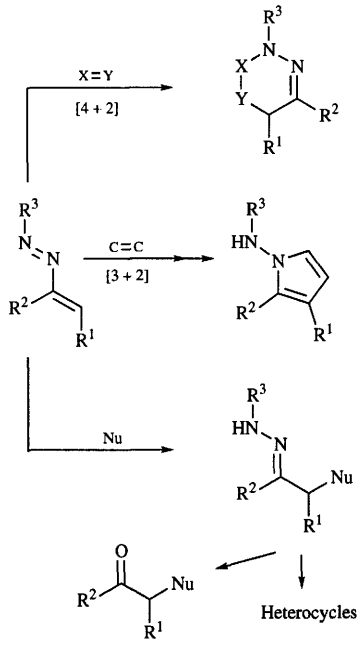
The synthesis of *Z*- and *E*-arylhydrazones by 1,4-conjugate addition of glycine, L-alanine and L-tyrosine ethyl esters to phenylazostilbene 1, *p*-nitrophenylazostilbene 2 and *p*-nitrophenylazocyclohexene 3 is described. Optically active N-functionalized 2-aminocyclohexanones 22–26 are obtained by $TiCl_3$-catalysed hydrolysis of the corresponding hydrazones. However, they have been shown to be unstable, as they undergo easy oxidation by air. X-Ray analysis of the phenylhydrazone 8a in the *Z* configuration is also reported.

Introduction

Conjugated azoalkenes are important synthetic intermediates.[1] Due to the electronic structure of the C=C–N=N system, closely related to that of nitrosoalkenes,[2] they may undergo two types of reaction: first, they can react with a wide range of dienophiles and heterodienophiles in [3 + 2] and [4 + 2] cycloadditions,[3] affording a variety of heterocyclic compounds (Scheme 1).

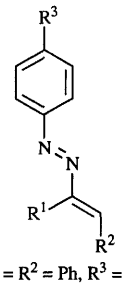


Scheme 1

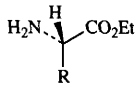
Alternatively, they are good substrates for 1,4-conjugate addition of several nucleophiles, such as Grignard reagents,[4] phenylhydrazine,[5] anionic reagents,[6] aliphatic amines,[7] phosphines[8] and activated methylene compounds.[9] These reactions constitute a valid route to functionalized hydrazones. These latter compounds can be further employed in cyclization processes, leading to various heterocycles.[10] Furthermore, carbonyl derivatives can be regenerated from the corresponding hydrazones by several methods.[1]

1,4-Additions of nucleophiles to conjugated azoalkenes have been the subject of several studies, with special care focused on the stereochemical aspects of these reactions. The hydrazone derivatives, in fact, can be obtained as *E*- and/or *Z*-isomers, depending on the nature of the reactants and the reaction conditions used. For instance, Grignard compounds furnished hydrazones in the *Z* configuration,[4] whereas anionic reagents such as sodium thiophenolate, sodium ethyl cyanoacetate, sodium malononitrile and sodium diethyl malonate gave the *E*-isomers.[6] It has also been shown that in the reactions of conjugated phenylazoalkenes with aliphatic amines, the polarity of the solvent greatly affected the *E*/*Z* ratio of the resultant hydrazone mixtures.[7] In polar protic solvents, such as methanol, the *E*-isomer was formed preferentially, whereas in apolar solvents, such as benzene, the *Z*-isomer predominated. Mixtures of diastereoisomers have been obtained in tetrahydrofuran (THF).

We have examined the behaviour of three conjugated azoalkenes in their reactions with α-amino acid ethyl esters, with the two-fold purpose of studying the influence of the N-functionalization of the amino acid residue on the geometry of the hydrazones and finding a synthetic route to N-functionalized α-amino carbonyl compounds.[11] These systems are regarded as precursors of biologically interesting 1,2-amino alcohols.[11c]



1 $R^1 = R^2 = Ph$, $R^3 = H$
2 $R^1 = R^2 = Ph$, $R^3 = NO_2$
3 $R^1R^2 = [CH_2]_4$, $R^3 = NO_2$



4 R = H
5 R = Me
6 R = *p*-$HOC_6H_4CH_2$

Results and discussion

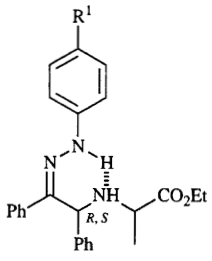
Phenylazostilbene **1**,[12] *p*-nitrophenylazostilbene **2**[12] and *p*-nitrophenylazocyclohexene **3**[13] were reacted with glycine ethyl ester **4**, L-alanine ethyl ester **5**, and L-tyrosine ethyl ester **6**. The reactions were carried out in refluxing THF for times varying from two hours to several days, as indicated in Table 1, depending on the reactivity of the reagents. In fact, the presence of the nitro group at the *para* position of the aromatic ring, as in compounds **2** and **3**, greatly enhanced the reaction rate as well as yields.

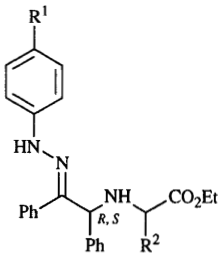
The reactions furnished the corresponding phenylhydrazones **7**–**21**, those derived from glycine ester **4** as mixtures of *Z*- and *E*-

Table 1

Reactants		Time (h)	Yield (%)	*E*:*Z*
1	**4**	100	55	1:9
1	**5**	100	40	1:9
1	**6**	100	40	1:9
2	**4**	12	98	2:3
2	**5**	12	98	1:1
2	**6**	2	98	1:1
3	**4**	3	99	4:1
3	**5**	2	99	7:3
3	**6**	2	99	9:1

diastereoisomers and those derived from L-amino esters **5** and **6** as mixtures of four diastereoisomers, namely a pair of *like* (**a**) and *unlike* (**b**) isomers for each geometric form.[14] No solvent effect was found.





7a $R^1 = R^2 = H$ **7b** $R^1 = R^2 = H$

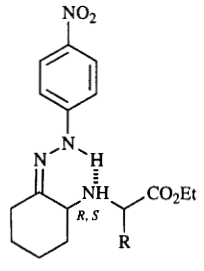
8a, 9a $R^1 = H, R^2 = Me$ **8b, 9b** $R^1 = H, R^2 = Me$

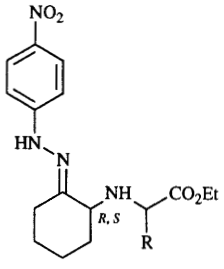
10a, 11a $R^1 = H, R^2 = p\text{-}HOC_6H_4CH_2$ **10b, 11b** $R^1 = H, R^2 = p\text{-}HOC_6H_4CH_2$

12a $R^1 = NO_2, R^2 = H$ **12b** $R^1 = NO_2, R^2 = H$

13a, 14a $R^1 = NO_2, R^2 = Me$ **13b, 14b** $R^1 = NO_2, R^2 = Me$

15a, 16a $R^1 = NO_2, R^2 = p\text{-}HOC_6H_4CH_2$ **15b, 16b** $R^1 = NO_2, R^2 = p\text{-}HOC_6H_4CH_2$





17a R = H **17b** R = H

18a, 19a R = Me **18b, 19b** R = Me

20a, 21a $R = p\text{-}HOC_6H_4CH_2$ **20b, 21b** $R = p\text{-}HOC_6H_4CH_2$

E,*Z* Diastereoisomerism in hydrazones 7–21

The *Z*- and *E*-derivatives were differentiated by the presence in the *Z*-compounds of strong intramolecular hydrogen bonding between the hydrazone NH and the nitrogen of the α-amino acid residue, as already found for the analogous derivatives obtained from secondary heterocyclic amines.[6] This hydrogen bonding was detected in the IR spectra, where an absorption between 3190 and 3100 cm^{-1} was always present, and in the ^1H NMR spectra, in which the NH proton of the hydrazone grouping resonated at very low field (δ ~11.0–13.0). Correspondingly, in the IR and ^1H NMR spectra of the *E*-isomers there was no absorption in the above regions. Also, ^{13}C NMR spectroscopy allowed a differentiation to be made between the two diastereoisomers. In accord with data reported in the literature,[15] the C-2 carbon atom was observed at higher field (δ_C 61.0–64.0) for the *Z*-arylhydrazones than for the *E*-arylhydrazones (δ_C 64.0–67.5).

The *E*,*Z*-mixtures, whose ratios are reported in Table 1, were

Table 2 Selected bond lengths for (+)-(*S*,*S*,*Z*)-**8a**

N(1)–N(2)	1.364(5)	N(3)–C(21)	1.461(5)
N(1)–C(1)	1.413(7)	C(7)–C(8)	1.466(6)
N(2)–C(7)	1.285(6)	C(7)–C(14)	1.522(6)
N(3)–C(14)	1.486(5)		

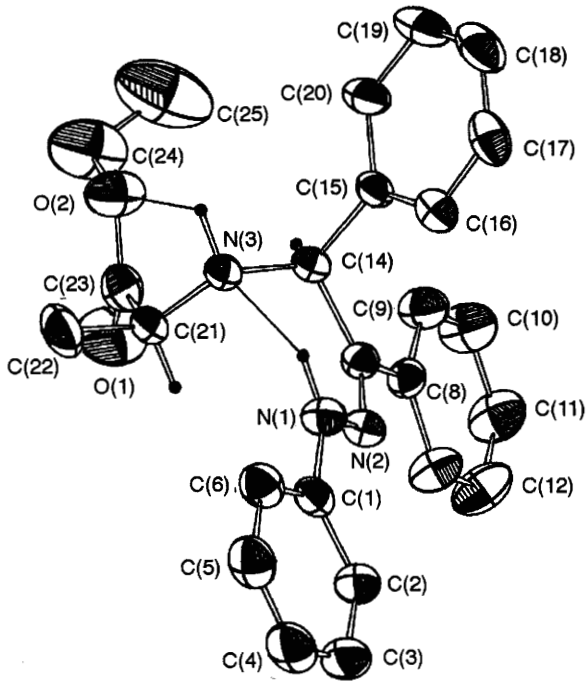


Fig. 1 X-Ray molecular structure of compound (+)-(*S*,*S*,*Z*)-**8a**, with crystallographic numbering scheme

of thermodynamic composition, as both isomers, once isolated by flash chromatography, spontaneously converted into their respective parent mixtures, even in the solid state, under nitrogen. The *Z*-isomers always predominated when the electrophilic substrate was the simple phenylazostilbene **1**, whereas with *p*-nitrophenylazocyclohexene **3** they were the minor components. In the case of *p*-nitrophenylazostilbene **2**, the *E*:*Z* ratio varied from 1:1 to 1:2, depending on the nature of the α-amino acid residue. To account for the different ratios observed, we think that in the phenylhydrazones **7**–**16** the stabilization due to the intramolecular hydrogen bonding prevailed over the destabilization caused by the steric interaction of the substituents, thus favouring the *Z* configuration. Essential in determining the prevalence of the *Z* configuration seems to be the extended electronic delocalization in the Ph–C=N–NH–Ph grouping, whose coplanarity is favoured by two intramolecular hydrogen bonds, as evidenced by the X-ray diffraction analysis of the hydrazone (+)-(*S*,*S*,*Z*)-**8a** (Fig. 1 and Table 2). The N(1)–N(3) and N(3)–O(2) distances are 2.722(6) Å and 2.761(6) Å, respectively, and the dihedral angles N(1)–N(2)–C(7)–C(8), C(1)–N(1)–N(2)–C(7), N(2)–C(7)–C(8)–C(9) and N(2)–N(1)–C(1)–C(6) are 179°, 168°, −167° and −172°, respectively.

The introduction of a nitro group at the *para* position of either phenyl ring, as in compounds **12**–**16**, slightly disfavours the *Z* configuration. This situation might be due to the preferred delocalization of the lone pair of the NH group with the *p*-nitrophenyl group, thus allowing a slight distortion of this latter grouping out of coplanarity with the Ph–C=N group.

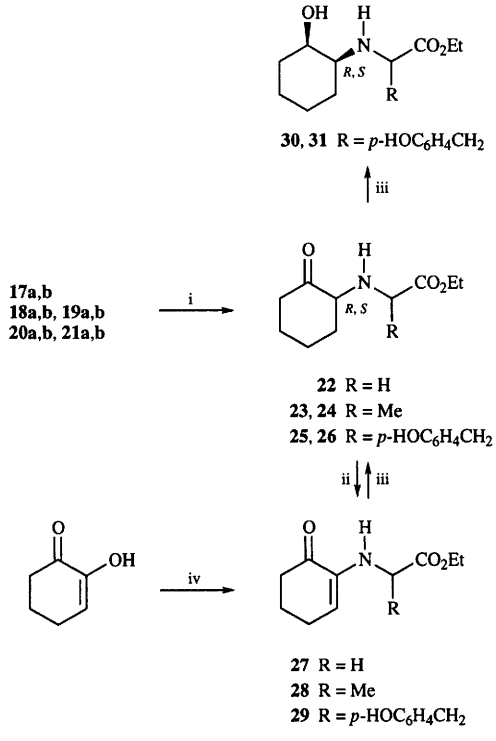
In the cyclohexanone derivatives **17**–**21**, in which two aromatic rings are replaced by a cycloalkyl group, an extended delocalization is not possible and the *E*-isomers are by far the preferred ones.

Absolute configuration of the hydrazones 8a,b and 9a,b

The absolute configuration of the *Z*-hydrazone (+)-**8a**, which was analysed by means of X-ray diffraction, is (*S*,*S*) (Fig. 1). In particular, the determination of the stereochemistry of C-2 was based on the knowledge of the absolute configuration of the natural amino acid stereocentre. The other *Z*-diastereoisomer (−)-**9a** has therefore the (*S*,*R*) configuration. As a consequence, the configuration of the *E*-stereoisomers of the L-alanine derivatives can be assigned also. In fact, (−)-(*S*,*S*,*E*)-**8b** derived from (+)-(*S*,*S*,*Z*)-**8a** and (−)-(*S*,*R*,*E*)-**9b** derived from (−)-(*S*,*R*,*Z*)-**9a**, by equilibration on silica gel. The behaviour of the four hydrazones on thin layer chromatography (TLC) was interesting. They were mobile in the order: (+)-(*S*,*S*,*Z*)-**8a** (R_f 0.65), (−)-(*S*,*R*,*Z*)-**9a** (R_f 0.60), followed by (−)-(*S*,*R*,*E*)-**9b** (R_f 0.50) and (−)-(*S*,*S*,*E*)-**8b** (R_f 0.45). An analogous order of elution on TLC and perfectly parallel relationship under equilibration was also observed for the other diastereoisomeric hydrazone pairs **10a**,**b** and **11a**,**b**, **13a**,**b** and **14a**,**b**, **15a**,**b** and **16a**,**b**. Although the absolute configuration of these latter compounds was not determined, a tentative attribution was made in analogy with that found for the L-alanine derivatives **8a**,**b** and **9a**,**b**.

Hydrolysis of hydrazones

The hydrazones **7**–**21** were treated under various hydrolysis conditions (10% nitric acid,[16] sodium periodate,[16] magnesium monoperoxyphthalate,[17] boron trifluoride–diethyl ether,[18] hydrogen peroxide–potassium carbonate[19] and titanium trichloride[20]). Whereas the hydrazones **7**–**16** did not react under any conditions to give the corresponding amino-substituted deoxybenzoins, the compounds **17**–**21** furnished the expected 2-aminocyclohexanones **22**–**26** in satisfactory yield only by the reductive procedure which makes use of titanium trichloride in acetone–water[20c] (Scheme 2).



Scheme 2 *Reagents and conditions:* i, aq. $TiCl_3$, acetone, 25 °C; ii, O_2; iii, H_2/Pd–C, EtOH, 25 °C, 40 psi; iv, **4**, **5** or **6**, benzene, reflux

The hydrolyses of compounds **17**–**21** have been carried out separately on each diastereoisomer **a** and **b**. Therefore a single α-amino ketone was obtained in each case, namely compounds **22**–**26**. Their absolute configuration, however, was not determined as yet. When the α-amino ketones possessing two chiral centres, namely mixtures **23**/**24** and **25**/**26** were kept in chloroform solution for 48 h, each of them converted into a 1 : 1 mixture of *like* and *unlike* stereoisomers. On the other hand, when left in the air in the absence of solvent, competition between the equilibration reaction and an oxidation reaction occurred, leading to the corresponding αβ-unsaturated ketones **28** and **29** (Scheme 2). The same oxidation was also observed for the ketone **22** which gave the αβ-unsaturated ketone **27**. In solution, the oxidation reaction was accelerated by bubbling oxygen.

The αβ-unsaturated ketones **27**–**29** were prepared, for comparison, from cyclohexane-1,2-dione and the corresponding α-amino acid ethyl esters, by azeotropic condensation in toluene.[21]

Particular instability was also observed for the pair of *Z*-hydrazones **18**/**19** derived from L-alanine, which directly afforded the αβ-unsaturated ketone **28** when chromatographed on silica gel. Interestingly, this behaviour was not observed for the *E*-stereoisomers. A tentative explanation is that the *Z*-hydrazones are hydrolysed on the column into the corresponding α-amino ketones **23**/**24**, which are then oxidized by air. In fact, by bubbling oxygen into a chloroform solution of **18**/**19**, in the presence of a small amount of silica gel, the pair of *Z*-hydrazones underwent a more rapid transformation into compound **28**. Correspondingly, the *E*-isomers remained stable for several hours.

Hydrogenation of the αβ-unsaturated ketones and α-amino ketones

The αβ-unsaturated ketones **27**–**29** were hydrogenated in ethanol on 5% Pd on carbon at room temperature. Interestingly, whereas compounds **27** and **28** furnished the corresponding α-aminocyclohexanones **22**, and **23**/**24**, respectively, hydrogenation of the tyrosine derivative **29** proceeded further to afford a mixture of two *cis*-1,2-amino alcohols **30** and **31** in quantitative yield. The hydroxy group in fact was axial in both isomers, as indicated by the w_H values of their respective hydroxy protons (11.0 Hz and 14.0 Hz), while the α-amino group was always equatorial (2-H: w_H 20.3 and 20.0 Hz). This is a consequence of a highly stereoselective hydrogenation of the cyclohexanone intermediates **25**/**26** (>98% de), occurring from the less hindered side of the molecule. This stereochemical result was also obtained starting from the corresponding α-amino ketones **25**/**26** and parallels those found by Sharpless[22] for the vicinal oxyamination of cyclic olefins, leading only to *cis*-1,2-aminocyclohexanols.

Experimental

Mps were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded for Nujol mulls, unless otherwise described, on a Perkin-Elmer 1320 spectrometer. ^1H and ^{13}C NMR spectra were scanned on a JEOL EX400 (400 MHz for proton and 100.4 MHz for carbon) using deuteriochloroform as solvent and tetramethylsilane as internal standard. *J* Values are given in Hz. Optical rotation values (*c*/g 100 cm^{-3}) were determined on a Perkin-Elmer Model 241 Polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Electron-impact HRMS data were obtained on a VG 7070 spectrometer at 70 eV. TLC was performed on Merck silica gel 60 F_{254} plates. Flash chromatography was run on Merck silica gel 230–400 mesh ASTM. Light petroleum refers to that fraction boiling in the range 40–70 °C, ether to diethyl ether. Diethyl ether was dried over Na wire. THF was distilled from sodium benzophenone ketyl.

Synthesis of reactants

Phenylazostilbene **1**[12] and *p*-nitrophenylazocyclohexene **3**[13] were prepared in accordance with the literature. *p*-Nitrophenylazostilbene **2** was prepared as follows: 2-oxo-1,2-diphenyl ethyl

acetate (6.0 g, 23 mmol) and *p*-nitrophenylhydrazine (7.0 g, 46 mmol) were dissolved in THF (120 cm^3) and the solution was set aside at room temperature. After 3 days, the solvent was removed *in vacuo*, the crude residue was dissolved in methylene dichloride, and the solution was washed first with 5% aq. HCl, then with water, and dried (Na_2SO_4). After evaporation of the solvent, the residue was treated with a little NaH in refluxing benzene for 7 h. Removal of the solvent left an oily residue, which was purified by flash chromatography, using a mixture of light petroleum and ethyl acetate in the ratio 4:1 as the eluent, to yield compound **2** (2.3 g, 30%), mp 131–133 °C (from MeOH) (Found: C, 72.8; H, 4.5; N, 12.9. $C_{20}H_{15}N_3O_2$ requires C, 72.94; H, 4.59; N 12.76%); ν_{max}/cm^{-1} 1600, 1580, 755, 720, 690 (Ar), 1510 and 1320 (NO_2); δ_H 8.31 (2 H, d, *J* 9.3, *p*-$O_2NC_6H_4$ *m*-H), 7.91 (1 H, s, C=CH), 7.85 (2 H, d, *J* 9.3, *p*-$O_2NC_6H_4$ *o*-H), 7.46 (4 H, m, ArH) and 7.22 (6 H, m, ArH); δ_C 149.8 (s), 148.2 (s), 146.1 (d), 139.6 (s), 134.6 (s), 133.8 (s), 130.9 (d), 129.9 (d), 129.7 (d), 128.8 (d), 128.5 (2d), 124.6 (d) and 123.1 (d); *m/z* 329 ($M^{\bullet+}$, 93%), 328 (26), 252 (19), 199 (32), 180 (16), 179 (90), 178 (61), 152 (26), 105 (45), 78 (100) and 77 (32).

Reactions between the azoalkenes and the α-amino acid ethyl esters. General procedure

The azoalkenes **1–3** (2.5 mmol) were reacted with a slight excess of the α-amino acid ethyl esters **4–6** (2.75 mmol) in refluxing, stirred, anhydrous THF (20 cm^3) for times varying from 1 h to several days (Table 1). Glycine ethyl ester **4** and L-alanine ethyl ester **5** were used as hydrochloride salts, in the presence of an equimolar amount of sodium hydrogen carbonate. When the reaction was complete, water was added (20 cm^3), and the solution was extracted three times with methylene dichloride (10 cm^3). The combined organic layers were washed with brine and dried with sodium sulfate. Evaporation of the solvents to dryness left an orange-red oily residue, which was analysed by ^1H NMR spectroscopy and chromatographed on silica gel, with light petroleum–ethyl acetate mixtures as eluent, in the ratios indicated below.

Reaction of the azoalkene 1 with glycine ethyl ester 4. (*Z*)- and (*E*)-*N*-(2-Oxo-1,2-diphenylethyl)glycine ethyl ester phenylhydrazone 7a, 7b. Compounds **1** (0.71 g, 2.5 mmol) and **4** (0.55 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave the (Z)-*isomer* **7a**, R_f 0.60 (light petroleum–ethyl acetate, 4:1), as a solid (0.47 g, 49%), mp 93–95 °C (from light petroleum) (Found: C, 74.3; H, 6.6; N, 10.8. $C_{24}H_{25}N_3O_2$ requires C, 74.4; H, 6.6; N, 10.8%); ν_{max}/cm^{-1} 3320 (NH), 3170 (bonded NH), 1730 (CO_2Et), 1600 (C=N), 1580, 1560, 1500, 1490, 750 and 690 (Ph); δ_H 11.95 (1 H, s, bonded NH), 7.66 (2 H, m, ArH), 7.47 (2 H, m, ArH), 7.28 (8 H, m, ArH), 7.14 (2 H, m, ArH), 6.83 (1 H, m, ArH), 5.39 (1 H, s, C*H*Ph), 4.19 (2 H, q, EtO), 3.62 and 3.56 (2 H, pseudo-q, AB system, J_{AB} 18, CH_2CO_2Et), 2.34 (1 H, br s, NH) and 1.23 (3 H, t, EtO); δ_C 171.8 (s), 145.2 (s), 139.2 (s), 138.0 (s), 137.5 (s), 129.1 (d), 128.2 (d), 127.8 (d), 127.4 (d), 125.7 (d), 119.6 (d), 112.7 (d), 64.1 (d), 61.2 (t), 48.6 (t) and 14.1 (q); *m/z* 387 ($M^{\bullet+}$, 2%) 284 (M − $NH_2CH_2CO_2Et$, 44), 283 (27), 207 (10), 192 (32), 180 (17), 179 (100), 178 (44), 118 (39), 105 (37), 93 (17), 78 (10) and 65 (23).

The (E)-*isomer* **7b** was isolated as a yellow oil (0.06 g, 6%), R_f 0.30; ν_{max}(neat)/cm^{-1} 3330 (NH), 1735 (CO_2Et), 1600 (C=N), 1500, 750, 705 and 695 (Ph); δ_H 7.35 (3 H, m, ArH), 7.31 (1 H, br s, NH), 7.23 (7 H, m, ArH), 7.00 (2 H, m, ArH), 6.97 (2 H, m, ArH), 6.83 (1 H, m, ArH), 4.72 (1 H, s, C*H*Ph), 4.20 (2 H, q, CH_3CH_2O) 3.51 and 3.49 (2 H, pseudo-q, AB system, *J* 17.4, CH_2CO_2Et), 2.05 (1 H, br s, NH) and 1.27 (3 H, t, CH_3CH_2O); δ_C 172.2 (s), 146.1 (s), 144.8 (s), 139.1 (s), 132.6 (s), 129.1 (d), 128.9 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.5 (d), 119.8 (d), 112.7 (d), 67.5 (d), 60.7 (t), 48.6 (t) and 14.2 (q); *m/z* 387 ($M^{\bullet+}$, 0.5%), 284 (M − $NH_2CH_2CO_2Et$, 16), 283 (11), 221 (13), 180 (10), 179 (43), 178 (28), 165 (10), 149 (43), 118 (30), 105 (63), 93 (35), 78 (11), 77 (100) and 65 (33) (Found: $M^{\bullet+}$, 387.194 51. $C_{24}H_{25}N_3O_2$ requires *M*, 387.194 68).

Reaction of the azoalkene 1 with L-alanine ethyl ester 5. (+)-(*S,S,Z*)-, (−)-(*S,R,Z*)-, (−)-(*S,S,E*)- and (−)-(*S,R,E*)-*N*-(2-Oxo-1,2-diphenylethyl)alanine ethyl ester phenylhydrazone 8a, 9a, 8b and 9b. Compounds **1** (0.71 g, 2.5 mmol) and **5** (0.55 g, 2.75 mmol) were reacted as indicated above. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave four diastereoisomers. The (S,S,Z)-*isomer* **8a**, R_f 0.65 (light petroleum–ethyl acetate, 4:1), was obtained as pale yellow crystals (0.16 g, 16%), mp 115–117 °C (from light petroleum) (Found: C, 74.7; H, 6.8; N, 10.5. $C_{25}H_{27}N_3O_2$ requires C, 74.8; H 6.8; N 10.5%); $[\alpha]_D^{28}$ +126.1 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3310 (NH), 3160 (bonded NH), 1725 (CO_2Et), 1600 (C=N), 1575, 1560, 1500, 1490, 750 and 690 (Ph); δ_H 12.10 (1 H, br s, bonded NH), 7.53 (2 H, m, ArH), 7.37 (2 H, m, ArH), 7.15 (8 H, m, ArH), 7.04 (2 H, m, ArH), 6.73 (1 H, m, ArH), 5.21 (1 H, s, C*H*Ph), 4.08 (2 H, q, CH_3CH_2O), 3.40 (1 H, q, *J* 7.3, $CHCH_3$), 2.30 (1 H, br s, NH), 1.24 (3 H, d, *J* 7.3, CH_3CH) and 1.09 (3 H, t, CH_3CH_2O); δ_C 175.4 (s), 145.2 (s), 140.0 (s), 138.2 (s), 137.7 (s), 129.4 (d), 129.3 (d), 128.3 (d), 128.0 (d), 127.5 (d), 125.7 (d), 119.6 (d), 112.6 (d), 63.5 (d), 61.2 (t), 54.8 (d), 19.6 (q) and 14.2 (q); *m/z* 401 ($M^{\bullet+}$, 8%), 328 (M − CO_2Et, 42), 286 (31), 285 [M − $CH_3CH(NH)CO_2Et$, 70], 284 (18), 208 (21), 206 (16), 193 (11), 189 (61), 179 (100), 105 (38), 91 (10), 77 (79) and 57 (13).

The (S,R,Z)-*isomer* **9a**, R_f 0.60, was separated as a yellow powder (0.16 g, 16%), mp 121–123 °C (from light petroleum) (Found: C, 74.4; H, 6.4; N, 10.8%); $[\alpha]_D^{28}$ −84.8 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3310 (NH), 3160 (bonded NH), 1725 (CO_2Et), 1600 (C=N), 1575, 1560, 1500, 1490, 750 and 690 (Ph); δ_H 11.60 (1 H, br s, bonded NH), 7.57 (2 H, m, ArH), 7.30 (2 H, m, ArH), 7.10 (10 H, m, ArH), 6.70 (1 H, m, ArH), 5.28 (1 H, s, C*H*Ph), 4.00 (2 H, q, CH_3CH_2O), 3.39 (1 H, q, *J* 7.3, $CHCH_3$), 2.50 (1 H, br s, NH), 1.31 (3 H, d, *J* 7.3, CH_3CH) and 1.05 (3 H, t, CH_3CH_2O); δ_C 174.5 (s), 145.1 (s), 139.3 (s), 138.8 (s), 137.8 (s), 129.0 (d), 128.9 (d), 128.1 (d), 127.9 (d), 127.7 (d), 127.3 (d), 125.9 (d), 119.5 (d), 112.6 (d), 61.5 (d), 61.0 (t), 53.8 (d), 18.1 (q) and 14.0 (q); *m/z* 402 (MH^+, 11%), 401 ($M^{\bullet+}$, 10), 328 (M − CO_2Et, 37), 286 (40), 285 [M − $CH_3CH(NH)CO_2Et$, 88], 235 (24), 208 (10), 206 (16), 193 (16), 179 (100), 105 (31), 91 (15) and 77 (35).

The (S,S,E)-*isomer* **8b**, R_f 0.45, was separated as pale yellow crystals (0.02 g, 2%), mp 138–140 °C (from light petroleum) (Found: C, 74.4; H, 6.5; N, 10.8%); $[\alpha]_D^{28}$ −21.2 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3340 (NH), 3155 (NH), 1720 (CO_2Et), 1595 (C=N), 1495, 1490, 750, 705 and 690 (Ph); δ_H 7.34 (4 H, m and s, ArH and NH), 7.23 (8 H, m, ArH), 7.01 (3 H, m, ArH), 6.83 (1 H, m, ArH), 4.75 (1 H, s, C*H*Ph), 4.16 (2 H, q, CH_3CH_2O), 3.59 (1 H, q, *J* 7.3, $CHCH_3$), 2.3 (1 H, br s, NH), 1.39 (3 H, d, *J* 7.3, CH_3CH) and 1.26 (3 H, t, CH_3CH_2O); δ_C 175.2 (s), 146.2 (s), 144.9 (s), 140.0 (s), 132.7 (s), 129.2 (d), 129.0 (d), 128.9 (d), 128.31 (d), 128.26 (d), 128.0 (d), 127.4 (d), 119.8 (d), 112.7 (d), 66.5 (d), 60.7 (t), 54.1 (d), 19.1 (q) and 14.3 (q); *m/z* 402 (MH^+, 4%), 401 ($M^{\bullet+}$, 5), 329 (31), 328 (M − CO_2Et, 49), 285 [M − $CH_3CH(NH)CO_2Et$, 81], 208 (15), 206 (11), 193 (166), 189 (100), 105 (22), 91 (20), 77 (49) and 57 (13).

The (S,R,E)-*isomer* **9b**, R_f 0.50, was isolated as a yellow solid, (0.02 g, 2%) mp 110–112 °C (from pentane) (Found: C, 74.3; H, 6.45; N, 10.9%); $[\alpha]_D^{28}$ −57.3 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3330 (NH), 3150 (NH), 1720 (CO_2Et), 1595 (C=N), 1495, 1490, 750, 705 and 690 (Ph); δ_H 7.33 (3 H, m and s, ArH and NH), 7.23 (8 H, m, ArH), 6.98 (4 H, m, ArH), 6.82 (1 H, m, ArH), 4.70 (1 H, s, C*H*Ph), 4.17 (2 H, q, CH_3CH_2O), 3.40 (1 H, q, *J* 7.3, $CHCH_3$), 2.30 (1 H, br s, NH), 1.37 (3 H, d, *J* 7.3, CH_3CH) and 1.26 (3 H, t, CH_3CH_2O); δ_C 175.3 (s), 146.4 (s), 144.9 (s), 140.0 (s), 132.7 (s), 129.12 (d), 129.08 (d), 128.9 (d), 128.3 (d), 127.4 (d), 119.8 (d), 112.8 (d), 66.2 (d), 60.7 (t), 54.1 (d), 19.1 (q) and 14.3 (q); *m/z* 401 ($M^{\bullet+}$, 0.3%), 328 (M − CO_2Et, 8), 286 (10), 285

[M − $CH_3CH(NH)CO_2Et$, 60], 208 (28), 193 (16), 179 (63), 149 (13), 105 (13), 91 (28), 77 (30) and 57 (100).

Reaction of the azoalkene 1 with L-tyrosine ethyl ester 6. (−)-(*S*,*S*,*Z*)-, (−)-(*S*,*R*,*Z*)-, (−)-(*S*,*S*,*E*)- and (−)-(*S*,*R*,*E*)-*N*-(2-Oxo-1,2-diphenylethyl)tyrosine ethyl ester phenylhydrazone 10a, 11a, 10b, 11b. Compounds **1** (0.71 g, 2.5 mmol) and **6** (0.57 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave four diastereoisomers. The (S,S,Z)-*isomer* **10a**, R_f 0.70 (7:3 light petroleum–ethyl acetate), was obtained as a yellow solid (0.2 g, 16%), mp 188–190 °C (from pentane) (Found: C, 75.5; H, 6.2; N, 8.6. $C_{31}H_{31}N_3O_3$ requires C, 75.4; H, 6.3; N, 8.5%); $[\alpha]_D^{28}$ −103.1 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3400 (OH), 3280 (NH), 3180 (bonded NH), 1725 (CO_2Et), 1600 (C=N), 1575, 1560, 1510, 1490, 750 and 695 (Ph); δ_H 11.09 (1 H, br s, bonded NH), 7.64 (2 H, m, ArH), 7.21 (11 H, m, ArH and OH), 7.02 (4 H, m, ArH), 6.79 (1 H, m, ArH), 6.76 (2 H, d, ArH), 5.29 (1 H, s, C*H*Ph), 4.13 (2 H, q, CH_3CH_2O), 3.62 (1 H, dd, X part of an ABX system, J_{AX} 7.8, J_{BX} 5.1, C*H*CH_2), 3.09 and 2.88 (2 H, 2 pseudo-q, AB part of an ABX system, J_{AB} 14.2, J_{AX} 7.8, J_{BX} 5.1, CH_2CH), 2.30 (1 H, br s, NH) and 1.17 (3 H, t, CH_3CH_2O); δ_C 173.9 (s), 155.1 (s), 145.2 (s), 139.9 (s), 137.6 (s), 131.0 (s), 130.5 (d), 129.1 (d), 129.0 (d), 128.3 (d), 128.0 (d), 127.7 (d), 127.5 (d), 126.3 (d), 119.7 (d), 115.8 (d), 112.9 (d), 62.0 (d), 61.3 (t), 60.2 (d), 39.4 (t) and 14.1 (q); *m*/*z* 493 ($M^{\bullet+}$, 0.6%), 298 (19), 286 (10), 285 (39), 284 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 67], 283 (32), 207 (11), 182 (14), 180 (19), 179 (100), 178 (62), 117 (10), 105 (22), 91 (29), 77 (74) and 65 (15).

The (S,R,Z)-*isomer* **11a**, R_f 0.65, was isolated as a yellow solid (0.2 g, 16%), mp 121–122 °C (from pentane) (Found: C, 75.4; H, 6.4; N, 8.5%); $[\alpha]_D^{28}$ −17.1 (c 0.1, 95% EtOH); ν_{max}/cm^{-1} 3400 (OH), 3300 (NH), 3190 (bonded NH), 1725 and 1710 (CO_2Et), 1600 (C=N), 1580, 1560, 1555, 1510, 1490, 750 and 695 (Ph); δ_H 11.60 (1 H, br s, bonded NH), 7.62 (2 H, m, ArH), 7.40 (2 H, m, ArH), 7.26 (8 H, m, ArH and OH), 6.98 (3 H, m, ArH), 6.92 (2 H, d, ArH), 6.82 (1 H, m, ArH), 6.62 (2 H, d, ArH), 5.32 (1 H, s, C*H*Ph), 4.11 (2 H, q, CH_3CH_2O), 3.69 (1 H, br m, C*H*CH_2), 2.93 (2 H, m, $CHCH_2$), 2.30 (1 H, br d, NH) and 1.11 (3 H, t, CH_3CH_2O); δ_C 174.3 (s), 154.7 (s), 144.9 (s), 139.3 (s), 137.7 (s), 137.6 (s), 130.2 (s, d), 129.1 (d), 129.0 (d), 128.2 (d), 128.1 (d), 127.7 (d), 127.4 (d), 125.6 (d), 119.5 (d), 115.5 (d), 112.6 (d), 62.5 (d), 61.1 (t), 60.5 (d), 39.1 (t) and 14.0 (q); *m*/*z* 493 ($M^{\bullet+}$, 0.4%), 285 (15), 284 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 26], 283 (13), 207 (10), 193 (14), 182 (14), 180 (18), 179 (92), 178 (58), 117 (11), 105 (29), 91 (38), 77 (100) and 65 (24).

The (S,S,E)-*isomer* **10b**, R_f 0.45, was separated as a pale yellow solid (0.02 g, 2%), mp 163–165 °C (from hexane) (Found: C, 75.4; H, 6.4; N, 8.5%); $[\alpha]_D^{28}$ −9.9 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3580, 3420 (OH), 3340 (NH), 3150 (NH), 1720 (CO_2Et), 1600 (C=N), 1580, 1550, 1510, 1500, 750 and 695 (Ph); δ_H 7.36 (1 H, s, NH), 7.23–7.13 (11 H, m, ArH and OH), 7.09 (2 H, d, ArH), 7.00 (1 H, m, ArH), 6.91 (3 H, m, ArH), 6.79 (1 H, m, ArH), 6.79 (2 H, d, ArH), 4.69 (1 H, s, C*H*Ph), 4.14 (2 H, q, CH_3CH_2O), 3.37 (1 H, dd, X part of an ABX system, J_{BX} 8.3, J_{AX} 5.4, C*H*CH_2), 3.03 and 2.91 (2 H, 2 pseudo-q, AB part of an ABX system, J_{AB} 13.6, J_{AX} 5.4, J_{BX} 8.3, CH_2CH), 1.6 (1 H, br s, NH) and 1.21 (3 H, t, CH_3CH_2O); δ_C 174.1 (s), 156.7 (s), 146.2 (s), 144.8 (s), 139.4 (s), 132.8 (s), 130.6 (s), 129.1 (d), 129.05 (d), 129.0 (d), 128.9 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.4 (d), 119.7 (d), 115.4 (d), 112.7 (d), 65.9 (d), 60.7 (t), 59.5 (d), 38.7 (t) and 14.2 (q); *m*/*z* 285 (14%), 284 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 33], 283 (29), 207 (14), 193 (10), 181 (42), 180 (57), 178 (65), 177 (64), 152 (27), 136 (34), 108 (56), 104 (79), 95 (47), 93 (38) and 77 (100).

The (S,R,E)-*isomer* **11b**, R_f 0.50, was separated as a yellow solid (0.02 g, 2%), mp 142–144 °C (from hexane) (Found: C, 75.4; H, 6.3; N, 8.6%); $[\alpha]_D^{28}$ −8.8 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3580, 3420 (OH), 3330 (NH), 3140 (NH), 1725 (CO_2Et), 1600 (C=N), 1580, 1550, 1510, 1500, 750 and 695 (Ph); δ_H 7.82 (1 H, br s, NH), 7.63 (2 H, m, ArH), 7.53–6.62 (18 H, m, ArH and OH), 4.65 (1 H, s, C*H*Ph), 4.08 (2 H, q, CH_3CH_2O), 3.79 (1 H, dd, X part of an AMX system, J_{AX} 7.7, J_{MX} 5.4, C*H*CH_2), 2.93 (2 H, m, CH_2CH), 1.7 (1 H, br s, NH) and 1.18 (3 H, t, CH_3CH_2O); δ_C 174.4 (s), 154.5 (s), 144.8 (s), 137.7 (s), 132.4 (s), 130.9 (s), 130.7 (d), 129.2 (d), 129.1 (d), 128.9 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.4 (d), 119.7 (d), 115.3 (d), 112.7 (d), 66.8 (d), 61.0 (t), 60.7 (d), 39.0 (t) and 14.2 (q); *m*/*z* 285 (10%), 284 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 40], 283 (32), 207 (32), 193 (11), 182 (23), 180 (61), 178 (89), 177 (79), 153 (11), 108 (50), 104 (45), 93 (21) and 177 (100).

Reaction of the azoalkene 2 with glycine ethyl ester 4. (*Z*)- and (*E*)-*N*-(2-Oxo-1,2-diphenylethyl)glycine ethyl ester *p*-nitrophenylhydrazone 12a, 12b. Compounds **2** (0.82 g, 2.5 mmol) and **4** (0.55 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave the (Z)-*isomer* **12a**, R_f 0.80 (light petroleum–ethyl acetate, 4:1), as a pale yellow solid (0.7 g, 64%), mp 176–178 °C (from pentane) (Found: C, 66.7; H, 5.5; N, 12.85. $C_{24}H_{24}N_4O_4$ requires C, 66.65; H, 5.6; N, 12.95%); ν_{max}/cm^{-1} 3340 (NH), 3100 (bonded NH), 1725 (CO_2Et), 1590 (C=N), 1565, 1500, 1490, 765, 750 and 695 (Ph); δ_H 12.88 (1 H, br s, bonded NH), 8.14 (2 H, d, ArH), 7.67 (2 H, m, ArH), 7.45–7.13 (10 H, m, ArH), 5.46 (1 H, s, C*H*Ph), 4.21 (2 H, q, CH_3CH_2O), 3.56 (2 H, s, $NHCH_2$), 2.48 (1 H, br s, NH) and 1.25 (3 H, t, CH_3CH_2O); δ_C 171.4 (s), 150.0 (s), 143.0 (s), 139.8 (s), 138.0 (s), 137.0 (s), 129.3 (d), 128.6 (d), 128.5 (d), 128.3 (d), 127.6 (d), 126.1 (d), 126.0 (d), 111.6 (d), 64.6 (d), 61.3 (t), 48.4 (t) and 14.0 (q); *m*/*z* 432 ($M^{\bullet+}$, 3%), 330 (17), 329 (M − $NH_2CH_2CO_2Et$, 57), 328 (27), 295 (13), 193 (17), 192 (40), 180 (17), 179 (100), 178 (53), 118 (22), 91 (20) and 77 (15).

The *isomer* **12b**, R_f 0.60, was isolated as a yellow solid (0.37 g, 34%), mp 137–139 °C (from pentane–ether) (Found: C, 66.6; H, 5.6; N, 13.0%); ν_{max}/cm^{-1} 3300, 3290 (NH), 1715 (CO_2Et), 1595 (C=N), 1510, 1500, 750 and 700 (Ph); δ_H 8.10 (2 H, d, ArH), 7.38–7.25 (8 H, m, ArH), 7.02 (2 H, d, ArH), 6.97 (2 H, m, ArH), 7.78 (1 H, br s, bonded NH), 4.77 (1 H, s, C*H*Ph), 4.19 (2 H, q, CH_3CH_2O), 3.47 (2 H, pseudo-q, AB system, J_{AB} 17.6, CH_2CO), 2.81 (1 H, br s, NH) and 1.26 (3 H, t, CH_3CH_2O); δ_C 172.0 (s), 151.0 (s), 149.6 (s), 140.1 (s), 138.7 (s), 131.5 (s), 129.5 (d), 129.2 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.8 (d), 125.9 (d), 111.8 (d), 67.5 (d), 60.8 (t), 48.4 (t) and 14.1 (q); *m*/*z* 432 ($M^{\bullet+}$, 1%), 330 (10), 329 (M − $NH_2CH_2CO_2Et$, 38), 328 (14), 295 (17), 193 (26), 192 (57), 180 (10), 179 (71), 178 (43), 138 (48), 118 (43), 110 (100), 91 (45), 77 (33) and 65 (69).

Reaction of the azoalkene 2 with L-alanine ethyl ester 5. (−)-(*S*,*S*,*Z*)-, (−)-(*S*,*R*,*Z*)-, (+)-(*S*,*S*,*E*)- and (−)-(*S*,*R*,*E*)-*N*-(2-Oxo-1,2-diphenylethyl)alanine ethyl ester *p*-nitrophenylhydrazone 13a, 14a, 13b, 14b. Compounds **2** (0.82 g, 2.5 mmol) and **5** (0.55 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave four diastereoisomers. The (S,S,Z)-*isomer* **13a**, R_f 0.70 (light petroleum–ethyl acetate, 4:1), was obtained as a yellow-orange solid (0.28 g, 25%), mp 105–107 °C (from pentane) (Found: C, 67.3; H 5.8; N 12.5. $C_{25}H_{26}N_4O_4$ requires C, 67.25; H, 5.9; N, 12.55%); $[\alpha]_D^{28}$ −32.0 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3310 (NH), 3160 (bonded NH), 1725 (CO_2Et), 1595 (C=N) 1560, 1500, 1490, 750 and 695 (Ph); δ_H 13.09 (1 H, br s, bonded NH), 8.16 (2 H, m, ArH), 7.64 (2 H, m, ArH), 7.45 (2 H, m, ArH), 7.32 (6 H, m, ArH), 7.13 (2 H, m, ArH), 5.37 (1 H, s, C*H*Ph), 4.23 (2 H, q, CH_3CH_2O), 3.51 (1 H, br q, *J* 6.8, C*H*CH_3), 2.49 (1 H, br s, NH), 1.38 (3 H, d, *J* 6.8, CH_3CH) and 1.24 (3 H, t, CH_3CH_2O); δ_C 174.7 (s), 149.8 (s), 143.2 (s), 139.8 (s), 138.0 (s), 137.1 (s), 129.3 (d), 128.6 (d), 128.5 (d), 128.3 (d), 127.6 (d), 126.1 (d), 125.9 (d), 111.4 (d), 63.9 (d), 61.3 (t), 54.8 (d), 19.4 (q) and 14.0 (q); *m*/*z* 446 ($M^{\bullet+}$, 1%), 331 (12), 330 (18), 329 (45) 328 (M − $NH_2CHMeCO_2Et$, 22), 309 (12), 206 (38),

194 (12), 193 (26), 180 (18), 170 (100), 105 (28), 91 (46) and 77 (360).

The (S,R,Z)-isomer **14a**, R_f 0.65, was separated as a yellow-orange solid (0.28 g, 25%), mp 158–160 °C (from light petroleum) (Found: C, 67.3; H, 5.9; N, 12.5%); $[\alpha]_D^{28}$ −57.1 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3310 (NH), 3160 (bonded NH), 1725 (CO_2Et), 1595 (C=N), 1560, 1500, 1490, 750 and 695 (Ph); δ_H 12.67 (1 H, br s, bonded NH), 8.13 (2 H, m, ArH), 7.62 (2 H, m, ArH), 7.32 (8 H, m, ArH), 7.12 (2 H, m, ArH), 5.42 (1 H, s, C*H*Ph), 4.15 (2 H, q, CH_3CH_2O), 3.50 (1 H, br q, *J* 6.8, C*H*CH_3), 2.20 (1 H, br s, NH), 1.47 (3 H, d, *J* 6.8, CH_3CH) and 1.19 (3 H, t, CH_3CH_2O); δ_C 174.2 (s), 150.0 (s), 144.5 (s), 139.8 (s), 137.8 (s), 137.2 (s), 129.3 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.7 (d), 126.4 (d), 126.0 (d), 111.7 (d), 62.3 (d), 61.4 (t), 54.1 (d), 18.1 (q) and 14.1 (q); *m*/*z* 446 ($M^{\bullet+}$, 2%), 330 (23), 329 (55), 328 (M − $NH_2CHMeCO_2Et$, 31), 309 (12), 206 (34), 193 (21), 180 (19), 179 (100), 178 (57), 105 (17), 91 (10) and 77 (17).

The (S,S,E)-*isomer* **13b**, R_f 0.35, was separated as a yellow solid (0.27 g, 24%), mp 128–130 °C (Found: C, 67.2; H, 6.0; N, 12.5%); $[\alpha]_D^{28}$ +155.6 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3320, 3300sh (NH), 1730 (CO_2Et), 1595 (C=N), 1515, 1325 (NO_2), 1500, 750, 740 and 700 (Ar); δ_H 8.09 (2 H, d, ArH), 7.35 (3 H, m, ArH), 7.23 (5 H, m, ArH), 7.02 (2 H, d, ArH), 6.95 (2 H, m, ArH), 7.86 (1 H, br s, NH), 4.78 (1 H, s, C*H*Ph), 4.15 (2 H, q, CH_3CH_2O), 3.56 (1 H, q, *J* 6.8, CH_3CH), 2.80 (1 H, br s, NH), 1.39 (3 H, d, *J* 6.8, CH_3CH) and 1.26 (3 H, t, CH_3CH_2O); δ_C 174.9 (s), 150.9 (s), 149.5 (s), 139.8 (s), 138.9 (s), 131.6 (s), 129.3 (d), 128.9 (d), 128.2 (d), 127.8 (d), 127.7 (d), 127.6 (d), 125.7 (d), 111.6 (d), 66.3 (d), 60.6 (t), 53.8 (d), 18.9 (q) and 14.0 (q); *m*/*z* 446 ($M^{\bullet+}$, 10%), 335 (38), 331 (23), 330 (10), 329 (M − $NH_2CHMeCO_2Et$, 21), 328 (14), 309 (29), 206 (32), 193 (14), 179 (11), 132 (29), 105 (10), 91 (9) and 77 (10).

The (S,R,E)-*isomer* **14b**, R_f 0.40, was isolated as a yellow-orange solid (0.27 g, 24%), mp 137–139 °C (from pentane) (Found: C, 67.3; H, 6.0, N, 12.5%); $[\alpha]_D^{28}$ −229.2 (*c* 0.1, 95% EtOH); ν_{max}($CHCl_3$)/cm^{-1} 3320, 3300 (NH), 1730 (CO_2Et), 1590 (C=N), 1510, 1500 and 690 (Ar); δ_H 8.11 (2 H, d, ArH), 7.40 (3 H, m, ArH), 7.26 (5 H, m, ArH), 7.01 (2 H, d, ArH), 6.99 (2 H, m, ArH), 7.82 (1 H, br s, NH), 4.77 (1 H, s, C*H*Ph), 4.20 (2 H, q, CH_3CH_2O), 3.40 (1 H, q, *J* 6.8, C*H*CH_3), 3.00 (1 H, br s, NH), 1.40 (3 H, d, *J* 6.8, CH_3CH) and 1.29 (3 H, t, CH_3CH_2O); δ_C 175.2 (s), 151.3 (s), 149.6 (s), 139.8 (s), 139.1 (s), 131.6 (s), 129.3 (d), 129.1 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.6 (d), 125.8 (d), 111.7 (d), 66.3 (d), 60.6 (t), 53.9 (d), 19.1 (q) and 14.1 (q); *m*/*z* 446 ($M^{\bullet+}$, 2%), 331 (16), 330 (41), 329 (M − $NH_2CHMeCO_2Et$, 41), 328 (16), 309 (30), 206 (100), 194 (18), 193 (64), 180 (16), 132 (73), 105 (23), 91 (23) and 77 (30).

Reaction of the azoalkene 2 with L-tyrosine ethyl ester 6. (−)-(*S*,*S*,*Z*)-, (−)-(*S*,*R*,*Z*)-, (−)-(*S*,*S*,*E*)- and (−)-(*S*,*R*,*E*)-*N*-(2-Oxo-1,2-diphenylethyl)tyrosine ethyl ester *p*-nitrophenylhydrazone 15a, 16a, 15b, 16b. Compounds **2** (0.82 g, 2.5 mmol) and **6** (0.58, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave an inseparable mixture of the (*Z*)-isomers **15a** and **16a**, R_f 0.60 (light petroleum–ethyl acetate 4:1) isolated as a yellow-orange powder (0.67 g, 50%), mp 148–150 °C (from light petroleum) (Found: C, 69.2; H, 5.6; N, 10.5. $C_{31}H_{30}N_4O_5$ requires C, 69.1; H, 5.6; N, 10.4%); $[\alpha]_D^{28}$ of the mixture −193.8 (*c* 0.05, 95% EtOH); ν_{max}/cm^{-1} 3410 (OH), 3280 (NH), 3180 (bonded NH), 1725 (CO_2Et), 1590 (C=N), 1515, 1320 (NO_2), 1560, 1490, 750 and 700 (Ar); δ_H(of the mixture) 12.12 and 12.00 (each 0.5 H, each br s, bonded NH), 8.10 (2 H, m, ArH), 7.62 (2 H, m, ArH), 7.40 (10 H, m, ArH), 7.09, 6.96, 6.84 and 6.63 (each 1 H, each m, ArH), 5.59 and 5.40 (each 0.5 H, each br s, OH), 5.37 and 5.33 (each 0.5 H, each s, C*H*Ph), 4.18 (2 H, m, CH_3CH_2O), 3.67 (1 H, m, NHC*H*CH_2), 3.17 (0.5 H, dd, J_1 4.9, J_2 14.2, CHCH_2), 3.00 (0.5 H, dd, J_1 5.4, J_2 14.2, CHCH_2), 2.87 (0.5 H, dd, J_1 8.8, J_2 14.2, CHCH_2), 2.82 (0.5 H, dd, J_1 8.8, J_2 14.2, CHCH_2), 2.39 (0.5 H, br d, *J* 12.7, NH), 2.34 (0.5 H, d, *J* 10.7, NH) and 1.21 and 1.16 (3 H, 2 t, CH_3CH_2O); δ_C(of the mixture) 174.1 (s), 173.6 (s), 155.2 (s), 155.0 (s), 149.8 (s), 149.4 (s), 145.0 (s), 143.1 (s), 139.8 (2 s), 138.2 (s), 137.9 (s), 136.8 (s), 136.5 (s), 130.4 (d), 130.1 (d), 129.3 (d), 129.0 (d), 128.6 (d), 128.55 (d), 128.52 (d), 128.44 (d), 128.41 (d), 128.3 (d), 127.53 (d), 127.48 (d), 126.6 (d), 126.0 (d), 125.9 (d), 115.8 (d), 115.7 (d), 111.8 (d), 62.8 (d), 62.6 (d), 61.5 (t), 61.4 (t), 60.9 (d), 59.8 (d), 39.1 (t), 38.2 (t), 14.14 (q) and 14.08 (q); *m*/*z* 538 ($M^{\bullet+}$, 1%), 330 (33), 329 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 67], 328 (28), 193 (10), 180 (14), 179 (100), 178 (76), 136 (13), 91 (10) and 77 (17).

The (S,S,E)-*isomer* **15b**, R_f 0.3 (light petroleum–ethyl acetate, 4:1), was separated as a yellow-orange solid (0.64 g, 24%), mp 158–160 °C (from pentane–ether) (Found: C, 69.1; H, 5.65; N, 10.5); $[\alpha]_D^{28}$ −260.0 (*c* 0.1, 95% EtOH); ν_{max}/cm^{-1} 3400 (OH), 3320 (NH), 1725 (CO_2Et), 1590 (C=N), 1515, 1325 (NO_2), 1500, 845, 750 and 710 (Ar); δ_H 8.05 (2 H, d, ArH), 7.27 (4 H, m, ArH and OH), 7.13 (4 H, m, ArH), 6.99 (2 H, d, ArH), 6.90 (2 H, m, ArH), 6.83 (2 H, m, ArH), 6.78 (3 H, m, ArH), 7.58 (1 H, s, NH), 4.67 (1 H, s, C*H*Ph), 4.09 (2 H, 2 q, CH_3CH_2O), 3.28 (1 H, dd, X part of an ABX system, J_{AX} 8.8, J_{BX} 5.4, C*H*CH_2), 2.97 and 2.81 (2 H, 2 pseudo-q, AB part of an ABX system, J_{AB} 13.7, J_{AX} 8.8, J_{BX} 5.4, CHCH_2), 2.1 (1 H, br s, NH) and 1.15 (t, 3 H, CH_3CH_2O); δ_C 174.0 (s), 155.0 (s), 151.0 (s), 149.6 (s), 140.0 (s), 138.5 (s), 131.8 (s), 130.6 (d), 129.3 (d), 129.1 (d), 128.4 (d), 128.2 (d), 127.9 (d), 127.8 (d), 126.0 (d), 115.4 (d), 111.8 (d), 65.8 (d), 60.8 (t), 59.0 (d), 38.7 (t) and 14.3 (q); *m*/*z* 538 ($M^{\bullet+}$, 1%), 330 (32), 329 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 24], 194 (10), 179 (83), 178 (74), 107 (100), 91 (26) and 77 (43).

The (S,R,E)-*isomer* **16b**, R_f 0.4 (light petroleum–ethyl acetate 4:1), was a yellow solid (0.64 g, 24%), mp 115–117 °C (from pentane–ether) (Found: C, 69.1; H, 5.6; N, 10.4%); $[\alpha]_D^{28}$ −132.2 (*c* 0.05, 95% EtOH); ν_{max}/cm^{-1} 3400 (OH), 3320 (NH), 1725 (CO_2Et), 1595 (C=N), 1515, 1325 (NO_2), 1500, 845, 750 and 710 (Ar); δ_H 8.03 (2 H, d, ArH), 7.23 (3 H, m, ArH), 7.13 (4 H, m, ArH and OH), 7.08 (2 H, m, ArH), 7.00 (2 H, d, ArH), 6.80 (2 H, d, ArH), 6.67 (4 H, m, ArH), 7.58 (1 H, s, NH), 4.58 (1 H, s, C*H*Ph), 4.03 (2 H, q, CH_3CH_2O), 3.66 (1 H, dd, X part of an ABX system, J_{AX} 8.3, J_{BX} 5.4, C*H*CH_2), 2.94 and 2.81 (2 H, 2 pseudo-q, AB part of an ABX system, J_{AB} 13.7, J_{AX} 8.3, J_{BX} 5.4, CH_2CH), 2.1 (1 H, br s, NH) and 1.12 (3 H, t, CH_3CH_2O); δ_C 174.4 (s), 154.7 (s), 151.0 (s), 149.5 (s), 140.1 (s), 139.3 (s), 131.4 (s), 130.7 (d), 129.4 (d), 129.1 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.7 (d), 126.0 (d), 115.4 (d), 111.8 (d), 67.0 (d), 61.1 (d), 60.9 (t), 39.0 (t) and 14.2 (q); *m*/*z* 538 ($M^{\bullet+}$, 1%), 329 [M − $NH_2CH(CH_2C_6H_4OH)CO_2Et$, 13], 193 (22), 180 (13), 179 (100), 178 (93), 136 (28), 107 (83), 91 (30) and 77 (43).

Reaction of the azoalkene 3 with glycine ethyl ester 4. (*Z*)- and (*E*)-*N*-(2-Oxocyclohexyl)glycine ethyl ester *p*-nitrophenylhydrazone 17a, 17b. Compounds **3** (1.10 g, 2.5 mmol) and **4** (0.55 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave the Z-*isomer* **17a** R_f 0.4 (light petroleum–ethyl acetate 1:1), as a yellow solid (0.16 g, 19%), mp 100–102 °C (from ether) (Found: C, 57.5; H, 6.8; N, 16.8. $C_{16}H_{22}N_4O_4$ requires C, 57.5; H, 6.7; N, 16.8%); ν_{max}/cm^{-1} 3370 (NH), 3240 (bonded NH), 1730, 1705 (CO_2Et), 1595 (C=N), 1510, 1320 (NO_2), 1500, 755 and 695 (Ar); δ_H 11.53 (1 H, s, NH), 8.09 (2 H, d, *J* 9.3, NO_2Ar *o*-H), 7.3 (2 H, d, *J* 9.3, NO_2-Ar *m*-H), 4.60 (1 H, br s, NH), 4.25 (2 H, q, CH_3CH_2O), 3.65 (1 H, dd, J_1 6.9, J_2 4.9, C*H*NH), 3.50 (2 H, pseudo-q, AB system, *J* 18.0, CH_2CO_2Et), 2.37 (2 H, m), 1.80 (6 H, m) and 1.29 (3 H, t, CH_3CH_2O); δ_C 172.1 (s), 151.4 (s), 150.9 (s), 139.0 (s), 126.2 (d), 110.9 (d), 60.2 (t), 57.1 (d), 48.1 (t), 33.8 (t), 31.3 (t), 26.3 (t), 22.2 (t) and 14.1 (q); *m*/*z* 334 ($M^{\bullet+}$, 0.3%), 193 (7), 179 (10), 138 (71), 110 (41), 108 (27), 92 (46), 91 (10), 83 (29), 81 (25) and 65 (100).

The diastereoisomer **17b**, R_f 0.2, was separated as a yellow-orange solid (0.67 g, 80%), mp 103–105 °C (from light petroleum) (Found: C, 57.4; H, 6.6; N, 16.8%); ν_{max}/cm^{-1} 3340

(NH), 1710, (CO_2Et), 1595 (C=N), 1520, 1320 (NO_2), 1500, 755 and 695 (Ar); δ_H 8.04 (2 H, d, NO_2Ar *o*-H), 7.91 (1 H, br s, NH), 7.03 (2 H, d, NO_2Ar *m*-H), 4.18 (2 H, q, CH_3CH_2O), 3.48 (2 H, pseudo-q, AB system, J_{AB} 17.0, CH_2CO_2Et), 3.32 (1 H, dd, J_1 7.1, J_2 5.4, CHNH), 2.2–1.5 (9 H, m) and 1.25 (3 H, t, CH_3CH_2O); δ_C 172.6 (s), 152.8 (s), 150.5 (s), 139.8 (s), 125.9 (d), 111.4 (d), 110.9 (d), 60.7 (t), 60.3 (d), 48.6 (t), 33.9 (t), 25.7 (t), 23.8 (t), 22.5 (t) and 14.0 (q); *m*/*z* 334 ($M^{\bullet+}$, 0.9%), 231 (M − $NH_2CH_2CO_2Et$, 23), 197 (10), 183 (10), 138 (11), 123 (50), 110 (18), 92 (16), 81 (100), 79 (29) and 65 (25).

Reaction of the azoalkene 3 with L-alanine ethyl ester 5. (*S*,*S*,*Z*)-, (*S*,*R*,*Z*)-, (*S*,*S*,*E*)- and (*S*,*R*,*E*)-*N*-(2-Oxocyclohexyl)-alanine ethyl ester *p*-nitrophenylhydrazone 18a, 19a, 18b, 19b. Compounds **3** (1.10 g, 2.5 mmol) and **5** (0.55 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave an inseparable mixture of the *Z*-isomers **18a** and **19a**, R_f 0.65 (light petroleum–ethyl acetate 1:1), identified in the crude reaction mixture (10%) by their characteristic signals in the ^1H NMR spectrum (bonded NH at δ_H 12.98 and 12.22) and in the IR spectrum (3280 cm^{-1}, bonded NH). The (*S*,*S*,*E*)-*isomer* **18b**, R_f 0.25, was separated as a yellow solid (0.38 g, 44%), mp 121–123 °C (from pentane) (Found: C, 58.5; H, 6.9; N, 16.1. $C_{17}H_{24}N_4O_4$ requires C, 58.6; H, 6.9; N, 16.1%); $[\alpha]_D^{28}$ −57.5 (*c* 0.15, 95% EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3370, 3340 (NH), 1725 CO_2Et), 1595 (C=N), 1510, 1325 (NO_2), 1500 and 695 (Ar); δ_H 8.13 (2 H, d, *J* 9.3, NO_2Ar *o*-H), 7.84 (s, 1 H, NH), 7.05 (2 H, d, *J* 9.3, NO_2Ar *m*-H), 4.12 and 4.02 (2 H, 4 pseudo-q, part AB of an ABX_3 system, J_{AB} 11, ^3J 7.3, CH_3CH_2O), 3.38 (1 H, q, *J* 6.8, CH_3CH), 3.26 (1 H, dd, J_1 4.4, J_2 7.3, CHNH), 2.62 (1 H, m), 2.26 (1 H, br s, NH), 2.08 (2 H, m), 2.05–1.45 (5 H, m), 1.36 (3 H, d, *J* 6.8, CH_3CH) and 1.18 (3 H, t, *J* 7.3, CH_3CH_2O); δ_C 175.9 (s), 152.8 (s), 150.5 (s), 139.7 (s), 126.0 (2 d), 111.5 (2 d), 60.8 (t), 59.0 (d), 54.3 (d), 33.9 (t), 25.5 (t), 23.9 (t), 22.5 (t), 19.6 (q) and 14.1 (q); *m*/*z* 348 ($M^{\bullet+}$, 4%), 237 (10), 233 (15), 232 (15), 231 [M − $NH_2CH(Me)CO_2Et$, 26], 211 (21), 149 (10), 138 (100), 137 (32), 124 (28), 108 (20), 92 (17), 81 (80) and 65 (37).

The (S,R,E)-*isomer* **19b** R_f 0.30 (light petroleum–ethyl acetate 1:1), was then isolated as yellow crystals (0.38 g, 44%), mp 150–151 °C (from pentane–ether) (Found: C, 58.6; H, 6.95; N, 16.1%); $[\alpha]_D^{28}$ −2.45 (*c* 0.2, 95% EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3370, 3340 (NH), 1725 (CO_2Et), 1595 (C=N), 1510, 1325 (NO_2), 1500 and 695 (Ar); δ_H 8.14 (2 H, d, *J* 9.3, NO_2Ar *o*-H), 7.70 (1 H, s, NH), 7.03 (2 H, d, *J* 9.3, NO_2Ar *m*-H), 4.20 (2 H, q, CH_3CH_2O), 3.46 (1 H, q, *J* 6.8, CH_3CH), 3.32 (1 H, dd, J_1 4.1, J_2 7.1, CHNH), 2.56 (1 H, m), 2.4 (1 H, br s, NH), 2.17 (1 H, m), 2.01–1.85 (4 H, br m), 1.69 (2 H, br m), 1.31 (3 H, d, *J* 6.8, CH_3CH) and 1.28 (3 H, t, CH_3CH_2O); δ_C 176.0 (s), 153.5 (s), 150.4 (s), 139.7 (s), 125.9 (2 d), 111.4 (2 d), 61.3 (t), 61.2 (d), 55.9 (d), 34.8 (t), 26.0 (t), 23.5 (t), 22.2 (t), 19.4 (q) and 14.1 (q); *m*/*z* 348 ($M^{\bullet+}$, 4%), 237 (14), 233 (17), 232 (17), 231 [M − $NH_2CH(Me)CO_2Et$, 32], 211 (19), 197 (10), 149 (10), 138 (100), 137 (39), 124 (28), 108 (39), 92 (31) and 65 (69).

Reaction of the azoalkene 3 with L-tyrosine ethyl ester 6. (*S*,*S*,*Z*)-, (*S*,*R*,*Z*)-, (*S*,*S*,*E*)- and (*S*,*R*,*E*)-*N*-(2-Oxocyclohexyl)-tyrosine ethyl ester *p*-nitrophenylhydrazone 20a, 21a, 20b, 21b. Compounds **3** (1.10 g, 2.5 mmol) and **6** (0.58 g, 2.75 mmol) were reacted as indicated in the general procedure. Work-up and chromatography (light petroleum–ethyl acetate, gradient from 100% light petroleum up to 4:1) gave an inseparable mixture of the *Z*-isomers **20a** and **21a**, R_f 0.60 (light petroleum–ethyl acetate, 1:1) (10%), identified in the ^1H NMR spectrum of the crude reaction mixture (bonded NH at δ_H 13.10 and 11.35 and in the IR spectrum (3260 cm^{-1}, bonded NH). The (S,S,E)-*isomer* **20b**, R_f 0.3, was separated as a yellow solid (0.48 g, 44%), mp 140–141 °C (Found: C, 62.7; H, 6.4; N, 12.7. $C_{23}H_{28}N_4O_5$ requires C, 62.7; H, 6.4; N, 12.7%); $[\alpha]_D^{28}$ −61.4 (*c* 0.13 95% EtOH); ν_{max}/cm^{-1} 3330 (OH), 3260 (NH), 1740 (CO_2Et), 1595 (C=N), 1515, 1320 (NO_2), 1500 and 695 (Ar); δ_H 8.41 (1 H, br s, NH), 8.09 (2 H, d, NO_2Ar *o*-H), 7.61 (1 H, s, ArO*H*), 7.10 (2 H, d, OHAr *o*-H), 7.04 (2 H, d, NO_2Ar *m*-H), 6.81 (2 H, d, OHAr *m*-H), 4.04 and 3.96 (2 H, 4 pseudo-q, part AB of an ABX_3 system, ^2J 11.0, ^3J 7.2, OCH_2CH_3), 3.63 (1 H, dd, part X of an ABX system, J_{AX} 6.35, J_{BX} 6.35, $CHCO_2Et$), 3.26 (1 H, dd, J_1 6.3, J_2 4.5, CHNH), 2.94 (2 H, 2 pseudo-q, part AB of an ABX system, J_{AB} 13.6, J_{AX} 6.35, J_{BX} 6.35, CH_2CHCO_2Et), 2.80 (1 H, br s, NH), 2.37 (2 H, m), 2.17–1.49 (6 H, multiplets, ring protons) and 1.09 (3 H, t, *J* 7.2, CH_3CH_2O); δ_C 174.8 (s), 155.4 (s), 153.1 (s), 150.7 (s), 139.2 (s), 130.2 (d), 128.4 (s), 125.7 (d), 115.0 (d), 111.2 (d), 60.6 (d), 60.4 (t), 58.9 (d), 38.9 (t), 34.5 (t), 25.7 (t), 25.3 (t), 23.1 (t), 21.7 (t) and 14.0 (q); *m*/*z* 231 [M − $NHCH(CH_2C_6H_4OH)CO_2Et$, 23%], 230 (3), 207 (42), 135 (100), 133 (76), 120 (32), 107 (54), 106 (55), 101 (42), 81 (35), 77 (76) and 65 (49).

The (S,R,E)-*isomer* **21b**, R_f 0.4, was isolated as a yellow solid (0.48 g, 44%) mp 165–167 °C (from pentane) (Found: C, 62.7; H, 6.4; N, 12.7%); $[\alpha]_D^{28}$ +86.2 (*c* 0.15, 95% EtOH); ν_{max}/cm^{-1} 3330 (OH), 3260 (NH), 1740 (CO_2Et), 1595 (C=N), 1515, 1320 (NO_2), 1500 and 695 (Ar); δ_H 8.13 (2 H, d, NO_2Ar *o*-H), 7.84 (1 H, s, ArOH), 7.56 (1 H, br s, NH), 7.05 (2 H, d, OHAr *o*-H), 6.92 (2 H, d, NO_2Ar-H), 6.74 (2 H, d, OHAr *m*-H), 4.17 (2 H, q, CH_3CH_2O), 3.49 (1 H, dd, part X of an AMX system, J_{AX} 8.3, J_{MX} 5.4, $CHCO_2Et$), 3.26 (1 H, dd, J_1 6.1, J_2 4.1, CHNH), 2.92 and 2.80 (2 H, ddd, part AM of an AMX system, J_{AM} 13.7, J_{AX} 8.3, J_{MX} 5.4, CH_2CHCO_2Et), 2.30 (1 H, br s, NH), 2.21–1.54 (8 H, multiplets, ring protons) and 1.23 (3 H, t, CH_3CH_2O); δ_C 175.4 (s), 157.0 (s), 155.3 (s), 152.7 (s), 140.1 (s), 131.5 (d), 129.9 (s), 126.7 (d), 115.0 (d), 112.4 (d), 61.5 (d), 60.9 (t), 59.8 (d), 39.9 (t), 35.6 (t), 30.5 (t), 27.1 (t), 23.9 (t), 22.2 (t) and 14.8 (q); *m*/*z* 231 [M − $NHCH(CH_2C_6H_4OH)CO_2Et$, 48%], 207 (31), 135 (100), 133 (83), 121 (12), 120 (32), 107 (24), 106 (13), 101 (66), 81 (49), 77 (12), 73 (24) and 65 (48).

Hydrolysis of the hydrazones 17–21

Hydrolysis of compounds **17a**,**b**–**21a**,**b** was performed following the procedure by McMurry,[20a] to afford the corresponding ketones **22**–**26**.

(±)-*N*-(2-Oxocyclohexyl)glycine ethyl ester 22. The ketone **22** (0.21 g, 70%) which was obtained from the hydrazones **17a** and **17b** (0.5 g, 1.5 mmol) after purification by chromatography, as a pale yellow oil, ν_{max}/cm^{-1} 3340 (NH), 1735 (CO_2Et) and 1715 (CO); δ_H 4.14 (2 H, q, CH_3CH_2O), 3.42 (2 H, pseudo-q, AB system, J_{AB} 18.3, CH_2CO_2Et), 3.26 (1 H, ddd, $^4J_{aa}$ 1.22, $^3J_{ae}$ 5.8, $^3J_{aa}$ 11.9, CHNH), 2.55 (1 H, br s, NH), 2.47 (1 H, m), 2.29 (2 H, m), 2.04 (1 H, m), 1.89 (1 H, m), 1.64 (2 H, m), 1.45 (1 H, m) and 1.24 (3 H, m, CH_3CH_2O); δ_C 210.1 (s), 172.2 (s), 65.3 (d), 60.7 (t), 48.6 (t), 40.9 (t), 35.0 (t), 27.6 (t), 24.2 (t) and 14.2 (q).

(−)-(*S*,*S* or *S*,*R*)-*N*-(2-Oxocyclohexyl)alanine ethyl ester 23. Hydrolysis of hydrazone **18b** (0.5 g, 1.4 mmol) furnished the corresponding ketone **23** (0.18 g, 62%) as a pale yellow oil, R_f 0.60 (4:1 light petroleum–ethyl acetate); $[\alpha]_D^{25}$ −25.6 (*c* 0.5, MeOH); ν_{max}/cm^{-1} 3320 (NH), 1735 (CO_2Et) and 1715 (CO); δ_H 4.14 (2 H, 2 q, CH_3CH_2O), 3.40 (1 H, q, *J* 7.0, $CHCH_3$), 3.20 (1 H, ddd, $^4J_{aa}$ 1.3, $^3J_{ae}$ 5.8, $^3J_{aa}$ 11.8), 2.48 (1 H, m), 2.28 (2 H, m), 2.06 (1 H, m), 1.85 (1 H, m), 1.63 (1 H, m), 1.31 (3 H, d, *J* 7.0, CH_3CH) and 1.25 (3 H, t, CH_3CH_2O); δ_C 209.3 (s), 175.4 (s), 64.0 (d), 60.7 (t), 53.9 (d), 40.8 (t), 34.7 (t), 27.3 (t), 254.0 (t), 19.3 (q) and 14.2 (q).

(−)-(*S*,*R* or *S*,*S*)-*N*-(2-Oxocyclohexyl)alanine ethyl ester 24. Hydrolyses of compound **19b** (0.5 g, 1.4 mmol) furnished the corresponding ketone **24** (0.18 g, 60%) as a pale yellow oil, R_f 0.40 (4:1 light petroleum–ethyl acetate); $[\alpha]_D^{25}$ −27.5 (*c* 0.2, MeOH); ν_{max}/cm^{-1} 3330 (NH), 1735 (CO_2Et) and 1710 (CO); δ_H 4.14 (2 H, 2 q, CH_3CH_2O), 3.44 (1 H, q, *J* 7.0, $CHCH_3$), 3.28 (1 H, ddd, $^4J_{aa}$ 1.5, $^3J_{ae}$ 5.8, $^3J_{aa}$ 11.8), 2.50 (1 H, m), 2.31 (3 H, m), 2.05 (1 H, m), 1.88 (1 H, m), 1.66 (2 H, m), 1.33 (3 H, d, *J* 7.0, CH_3CH) and 1.24 (3 H, t, CH_3CH_2O); δ_C 210.8 (s), 175.4 (s), 64.7 (d), 60.7 (t), 55.2 (d), 41.1 (t), 36.2 (t), 27.9 (t), 24.3 (t), 19.0 (q) and 14.2 (q).

(−)-(*S,S* or *S,R*)-*N*-(2-Oxocyclohexyl)tyrosine ethyl ester 25. Hydrolysis of compound **20b** (0.5 g, 1.13 mmol) furnished the corresponding ketone **25** (0.22 g, 65%), R_f 0.8 (light petroleum–ethyl acetate 4:1); $[\alpha]_D^{25}$ −21.1 (*c* 0.1, MeOH); ν_{max}/cm^{-1} 3400 (NH), 1735 (CO_2Et), 1715 (CO), 1600 and 1510 (Ar); δ_H 7.05 (2 H, d, ArOH *o*-H), 6.72 (2 H, d, ArOH *m*-H), 4.07 (2 H, d, CH_3CH_2O), 3.48 (1 H, t, *J* 6.4, $CHCO_2Et$), 3.13 (1 H, ddd, $^4J_{aa}$ 1.42, $^3J_{ae}$ 4.9, $^3J_{aa}$ 12.9, *CH*NH), 2.88 (2 pseudo-q, part AB of an ABX system, *J* 13.8 and 6.4, CH_2CHCO_2Et), 2.46 (1 H, m), 2.38–2.25 (3 H, m), 2.03 (1 H, m), 1.83 (1 H, m) and 1.16 (3 H, t, CH_3CH_2O); δ_C 209.4 (s), 174.2 (s), 154.4 (s), 130.4 (d), 128.6 (s), 115.2 (d), 64.2 (d), 60.5 (t), 60.4 (d), 40.7 (t), 39.2 (t), 34.5 (t), 29.7 (t), 27.2 (t), 23.9 (t) and 14.2 (q).

(−)-(*S,R* or *S,S*)-*N*-(2-Oxocyclohexyl)tyrosine ethyl ester 26. Hydrolysis of compound **21b** (0.5 g, 1.13 mmol) furnished the corresponding ketone **26**, R_f 0.70 (light petroleum–ethyl acetate 4:1) as a pale yellow oil (0.22 g, 65%); $[\alpha]_D^{25}$ −32.1 (*c* 0.5, MeOH); ν_{max}/cm^{-1} 3350 (NH), 1735 (CO_2Et), 1710 (CO), 1595 and 1500 (Ar); δ_H 7.06 (2 H, d, ArOH *o*-H), 6.74 (2 H, d, ArOH *m*-H), 4.17 (2 H, q, CH_3CH_2O), 3.56 (1 H, dd, *J* 6.7 and 7.3, $CHCO_2Et$), 3.22 (1 H, ddd, $^4J_{aa}$ 1.4, $^3J_{ae}$ 4.9, $^3J_{aa}$ 13.1, *CH*NH), 2.92 (2 pseudo-q, part AB of an ABX system, *J* 13.8 and 6.4, CH_2CHCO_2Et), 2.66 (1 H, br s NH), 2.48–2.25 (4 H, m), 2.06 (2 H, m), 1.83 (1 H, m), 1.61 (1 H, m), and 1.18 (3 H, t, CH_3CH_2O); δ_C 211.2 (s), 173.3 (s), 154.5 (s), 130.4 (d), 128.7 (s), 115.2 (d), 64.7 (d), 61.6 (d), 60.6 (t), 40.9 (t), 39.1 (t), 36.3 (t), 29.5 (t), 27.7 (t), 24.1 (t) and 14.2 (q).

When left in the air for at least 3–5 h, or when dissolved in $CHCl_3$ and the solution bubbled with oxygen for 2 h, the α-amino ketones **22**–**26** were converted into the corresponding αβ-unsaturated ketones **27**–**29**.

***N*-(6-Oxocyclohex-1-enyl)glycine ethyl ester 27.** The *αβ-unsaturated ketone* **27** was obtained from the ketone **22** as a yellow oil (Found: $M^{\bullet+}$, 197.107 21. $C_{10}H_{15}NO_3$ requires M, 197.105 18); ν_{max}(neat)/cm^{-1} 3400 (NH), 1740 (CO_2Et), 1670 (CO) and 1630 (C=C), δ_H 5.34 (1 H, t, *J* 4.6, C=CH), 4.73 (1 H, br s, NH), 4.18 (2 H, 2 q, *J* 7.0, CH_3CH_2O), 3.64 (2 H, br s, CH_2NH), 2.45 (2 H, t, CH_2), 2.33 (2 H, q, CH_2), 1.93 (2 H, m, CH_2) and 1.25 (3 H, t, *J* 7.0, CH_3CH_2O); δ_C 195.1 (s), 170.5 (s), 139.8 (s), 111.8 (d), 61.0 (t), 45.1 (t), 37.7 (t), 24.3 (t), 23.3 (t) and 14.1 (q); *m/z* 197 ($M^{\bullet+}$, 12%), 168 (5), 151 (3), 140 (1), 125 (10), 124 (100), 96 (7), 95 (6), 67 (9) and 55 (10).

(−)-(*S*)-*N*-(6-Oxocyclohex-1-enyl)alanine ethyl ester 28. The *αβ-unsaturated ketone* **28** was obtained from the ketones **23** and **24** as a yellow oil (Found: $M^{\bullet+}$ 211.121 37. $C_{11}H_{17}NO_3$ requires M, 211.120 83); $[\alpha]_D^{28}$ −66.2 (*c* 0.1, MeOH); ν_{max}(neat)/cm^{-1} 3390 (NH), 1735 (CO_2Et), 1670 (CO) and 1630 (C=C); δ_H 5.33 (1 H, dd, J_1 4.9, J_2 3.2, C=CH), 4.5 (1 H, br s, NH), 4.10 (2 H, q, CH_3CH_2O), 3.9 (1 H, q, *J* 8, CH_3CH), 2.40 (2 H, m), 2.27 (2 H, m), 1.87 (2 H, m), 1.34 (3 H, d, *J* 8, CH_3CH) and 1.18 (3 H, t, CH_3CH_2O); δ_C 195.3 (s), 174.0 (s), 139.3 (d), 112.4 (d), 60.8 (t), 51.4 (t), 37.7 (t), 29.6 (t), 24.3 (t), 23.2 (t), 18.3 (q) and 14.0 (q); *m/z* 211 ($M^{\bullet+}$, 48%), 182 (1), 165 (1), 154 (7), 139 (14), 138 (M − CO_2Et, 100), 67 (9) and 55 (10).

(−)-(*S*)-*N*-(6-Oxocyclohex-1-enyl)tyrosine ethyl ester 29. The *αβ-unsaturated ketone* **29** was obtained from the ketones **25** and **26** as pale yellow crystals, mp 71–73 °C (from hexane) (Found: $M^{\bullet+}$: 303.148 40. $C_{17}H_{21}NO_4$ requires M, 303.147 05); $[\alpha]_D^{28}$ −7.7 (*c* 0.3, MeOH); ν_{max}(neat)/cm^{-1} 3400 (NH and OH), 1730 (CO_2Et), 1670 (CO), 1626 (C=C), 1610, 1590, 1510 and 1480 (Ar); δ_H 7.02 (2 H, d, *J* 8.5, ArH), 6.74 (2 H, d, *J* 8.5, ArH), 6.41 (1 H, br s, OH), 5.43 (1 H, t, *J* 4.6, C=CH), 4.68 (1 H, d, *J* 7.0, NH), 4.10 (2 H, 2 q, *J* 7.1, CH_3CH_2O), 3.9 (1 H, q, *J* 7, CH_2CH), 2.97 (2 H, part AB of an ABX system, J_{AB} 13.7, $CHCH_2$), 2.45 (2 H, m, CH_2), 2.31 (2 H, m, CH_2), 1.87 (2 H, m, CH_2) and 1.18 (3 H, t, *J* 7.1, CH_3CH_2O); δ_C 195.8 (s), 173.1 (s), 155.2 (s), 139.1 (s), 130.2 (d), 127.8 (s), 115.4 (d), 113.1 (d), 61.0 (t), 57.5 (d), 37.6 (2), 24.3 (t), 23.1 (t) and 14.1 (q); *m/z* 304 (MH^+, 100%), 303 (12), 230 (M − CO_2Et, 23), 196 (25), 122 (36), 107 (23), 91 (5), 77 (9) and 55 (10).

Catalytic hydrogenation of ketones 25 and 26

Ketones **25** and **26** (0.5 g, 1.6 mmol) were separately hydrogenated in a Parr apparatus, in absolute ethanol (100 cm^3) with 5% Pd on C (60 mg), at 40 psi, for 40 min, to give the alcohols **30** and **31**, respectively, in quantitative yields.

(−)-(*SS* or *SR*)-*cis*-*N*-(2-Hydroxycyclohexyl)tyrosine ethyl ester 30. The alcohol **30** was obtained from the ketone **25** as an oil, $[\alpha]_D^{25}$ −14.7 (*c* 0.15, MeOH); ν_{max}/cm^{-1} 3600–3400 br (NH and OH), 1735 (CO_2Et), 1600 and 1495 (Ar); δ_H 7.03 (2 H, d, C_6H_4OH *o*-H), 6.69 (2 H, d, $ArCH_2$ *o*-H), 4.20 (2 H, 2 q, CH_3CH_2O), 3.80 (1 H, br s, OH), 3.56 (1 H, m, w_H 11.0, *CH*OH), 3.41 (1 H, dd, part X of an AMX system, J_{AX} 10.4, J_{MX} 4.3, $CHCO_2Et$), 2.96 (dd, part M of an AMX, J_{AM} 13.8, J_{MX} 4.3, $CHCHCO_2Et$), 2.17 (1 H, dd, part A of an AMX, J_{AM} 13.8, J_{AX} 10.4, $CHCHCO_2Et$), 2.39 (1 H, m, w_H 20.3, *CH*NH), 1.80 (1 H, m), 1.67–1.45 (2 H, m), 1.43 (3 H, m) and 1.29 (5 H, m and t, ring protons and CH_3CH_2O); δ_C 175.2 (s), 155.5 (s), 130.1 (d), 128.8 (s), 115.4 (d), 65.2 (d), 61.0 (t), 60.2 (d), 57.1 (d), 39.3 (t), 29.3 (t), 27.5 (t), 23.8 (t), 19.6 (t) and 14.2 (q); *m/z* 305 ($M^{\bullet+}$, 8%), 288 (8), 232 (33), 215 (11), 198 (32), 107 (21), 91 (12), 77 (15) and 55 (10) (Found: $M^{\bullet+}$, 305.148 40, $C_{17}H_{23}NO_4$ requires *M*, 305.146 70).

***(SR* or *SS*)-*cis*-*N*-(2-Hydroxycyclohexyl)tyrosine ethyl ester 31.** Oil, $[\alpha]_D^{25}$ −9.2 (*c* 0.1, MeOH); ν_{max}/cm^{-1} 3600 br (NH and OH), 1735 (CO_2Et), 1600 and 1495 (Ar); δ_H 7.04 (2 H, d, C_6H_4OH *o*-H), 6.76 (2 H, d, C_6H_4OH *m*-H), 4.15 (2 H, q, CH_3CH_2O), (1 H, br s, OH), 3.64 (1 H, m, w_H 14.0, *CH*OH), 3.53 (1 H, dd, part X of an AMX system, J_{AX} 7.9, J_{MX} 5.8, $CHCO_2Et$), 2.97 (dd, part M of an AMX, J_{AM} 13.7, J_{AX} 5.8 $CHCHCO_2Et$), 2.80 (1 H, dd, part A of an AMX, J_{AM} 13.7, J_{AX} 7.9, $CHCHCO_2Et$), 2.55 (1 H, m, w_H 20.0, *CH*NH), 2.32 (1 H, br s, OH), 1.80 (1 H, m) and 1.74–1.24 (10 H, m and t, ring protons and CH_3CH_2O); δ_C 174.9 (s), 154.7 (s), 130.3 (d), 128.9 (s), 115.5 (d), 68.0 (d), 60.1 (t), 59.8 (d), 57.7 (d), 38.7 (t), 30.2 (t), 29.8 (t), 26.4 (t), 22.7 (t) and 14.1 (q); *m/z* 305 ($M^{\bullet+}$, 3%), 288 (18), 232 (M − CO_2Et, 34), 230 (8), 215 (18), 198 (22), 107 (100), 91 (19), 77 (9) and 55 (21).

X-Ray crystal structure determination of compound (*S,S,Z*)-8a

Crystals of compound (*S,S,Z*)-**8a** were grown by slow evaporation of methanol solutions. A crystal of 0.20 mm × 0.30 mm × 0.80 mm was mounted on a glass fibre on an Enraf-Nonius CAD4 diffractometer, and the lattice parameters were obtained by a least-squares refinement of 25 accurately centred reflections in the range 15° < θ < 18°.

No significant changes in intensities, due to crystal decay, were noticed throughout the data collection. Systematic absences and symmetry equivalent intensities indicated the monoclinic space group $P2_1$. The structure was solved by direct methods using the MULTAN 80 suite of programs[23] and conventional Fourier syntheses. 2012 Reflections having intensities > 3σ(*I*) were used in the refinements. After anisotropic refinement, a three-dimensional Fourier-difference synthesis revealed that the calculated positions of the H-atoms occurred in the positive regions of the electron density map. The final anisotropic least-squares refinement, including the fixed contribution of H-atoms (d_{C-H} = 0.95 Å), gave an *R*-factor = 0.061. Scattering factors were those of Cromer.[24] The final Fourier-difference map did not reveal chemically significant residual electron density (± 0.2 e $Å^{-3}$). All calculations were carried out using the MOLEN program package,[25] on a VAX 2000 computer.†

Crystal data. $C_{25}H_{27}N_3O_2$, *M* = 401.51, monoclinic, space group $P2_1$, *a* = 9.969(2), *b* = 9.477(2), *c* = 12.227(3) Å, β =

† Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/27.

99.48(9)°, $V = 1139.3$ Å^3, $Z = 2$, $D_c = 1.17$ g cm^{-3}, μ(Mo-Kα) = 0.7 cm^{-1}, $F(000) = 428$, λ(Mo-Kα) = 0.710 69.

Data collection. $2.0 < 2\theta < 60.0°$, scan width = 0.6 + 0.350 tan θ, scan speed 1.0–8.0° min^{-1}, scan type ω–2θ, number of data collected 3640, number of unique data 3470, number with $I \geqslant 3\sigma(I)$ 2012, $T = 294$ K.

Structure refinement. Number of parameters, $p = 270$; $R = [\Sigma||F_o| - |F_c||/\Sigma|F_o|] = 0.061$; $R_w = \Sigma[w(|F_o| - |F_c|^2)/\Sigma w(|F_o|)^2]^{\frac{1}{2}} = 0.062$.

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