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Ethyl *N*-(Diphenylmethylene)glycinate as Anionic Glycine Equivalent. Monoalkylation, Dialkylation and Michael Additions under Solid-Liquid Phase-Transfer Catalysis.

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Abstract: Ethyl *N*-(diphenylmethylene)glycinate, **1**, undergoes monoalkylations, dialkylations and Michael additions to ethylenic and acetylenic acceptors under appropriate solid-liquid phase transfer catalysis conditions. Further transformations of the α-disubstituted ketimines lead to α-alkylated aspartic and glutamic acid derivatives **10**, **15**, **19** and **26**, to bicyclic amino acids or derivatives featuring pyrazolone and isoxazolone moieties **30** and **33**, and to α-substituted (*E*)-3,4-dehydroglutamic acids. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Aldimines and ketimines of glycine esters are useful anionic synthons for the preparation of amino acids.[1] Strong bases such as LDA or *t*-BuOK were initially used for the formation of their conjugate bases.[2] Ketimines such as ethyl *N*-(diphenylmethylene)glycinate, **1**, offer advantages due to its superior stability and commercial availability when compared with aldimines. O'Donnell has reported[3] that mono- and dialkylations of aldimines and monoalkylations (but not dialkylations) of ketimines can be carried out under several phase-transfer catalysis (PTC) conditions.[4] This differential reactivity has been attributed to the decreased acidity of the monoalkylated ketimines **2**, thus preventing the required second ionization step.[5] These studies were based on benzyl bromide as alkylating agent. The same group has extended the method and enantiomeric excesses have been obtained when chiral phase transfer catalysts based on cinchonine and cinchonidine alkaloids were used.[6] Other authors have also chosen O'Donnell's method for the alkylation of Schiff bases.[7]

In sharp contrast with the general statement established by O'Donnell, a French group has reported the arylation of aldimines and ketimines of glycine, alanine and leucine under PTC conditions by using fluorobenzenetricarbonylchromium complexes,[8] and we have also described in a preliminary communication the controlled mono- and dialkylation of ethyl *N*-(diphenylmethylene)glycinate, **1**, under solid-liquid phase transfer catalysis.[9] The succesful dialkylation of **1** with 2,3-dibromopropene followed by transition metal mediated cyclisation procedures has allowed us the preparation of bicyclic and tricyclic α,α-disubstituted α-amino acids and derivatives.[10]

On the other hand, Michael additions of glycine and alanine aldimines under solid-liquid phase-transfer catalysis have been carried out by a Chinese group[7a] and recently a Spanish group has published the

diastereoselective synthesis of substituted glutamic acid derivatives via Michael additions of *N*-[bis(methylthio)methylene]glycinates under solid-liquid phase transfer catalysis.[11]

We wish to present here our full results from the reactions of the ketimine **1** and several active halides and ethylenic and acetylenic Michael acceptors under solid-liquid phase transfer catalysis conditions. By this way several α-substituted aspartic and glutamic acids, α-substituted (*E*)-3,4-dehydroglutamic acid precursors and bicyclic α,α-disubstituted α-amino acids bearing pyrazolone and isoxazolone rings have been synthesized.

Non-proteinogenic α,α-disubstituted α-amino acids bearing a second acidic functional group somewhere in the molecule have received considerable attention as potential agonists or antagonists in the excitatory amino acid neurotransmission field.[12] Particular interest has aroused the synthesis of conformationally rigid analogues and homologues of the neurotransmitters glutamic and aspartic acids.[13]

Some heterocyclic amino acids presenting activity in neurotransmission processes contain a 3-hydroxyisoxazole moiety in their structure, i.e. ibotenic acid ((*RS*)-2-amino-2-(3-hydroxyisoxazol-5-yl)acetic acid),[12c] and AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid.[12c] Analogues of these compounds have been synthesized for testing as neurotransmitters.[14] The 5-isoxazolone ring is also present in some amino acids with agonist activity in glutamate receptors[15] and 5-pyrazolone containing amino acids have been prepared as potential agonists or antagonists in glutamate receptors.[16] Moreover, bicyclic compounds with partial structures of 3-hydroxyisoxazole, 5-isoxazolone and 3- or 5-pyrazolone have been described and evaluated as conformationally restricted analogues of ibotenic acid, AMPA, NMDA (*N*-methyl-*D*-aspartic acid), 2-aminoadipic acid or GABA (γ-aminobutyric acid).[12c,14b,f-g,17]

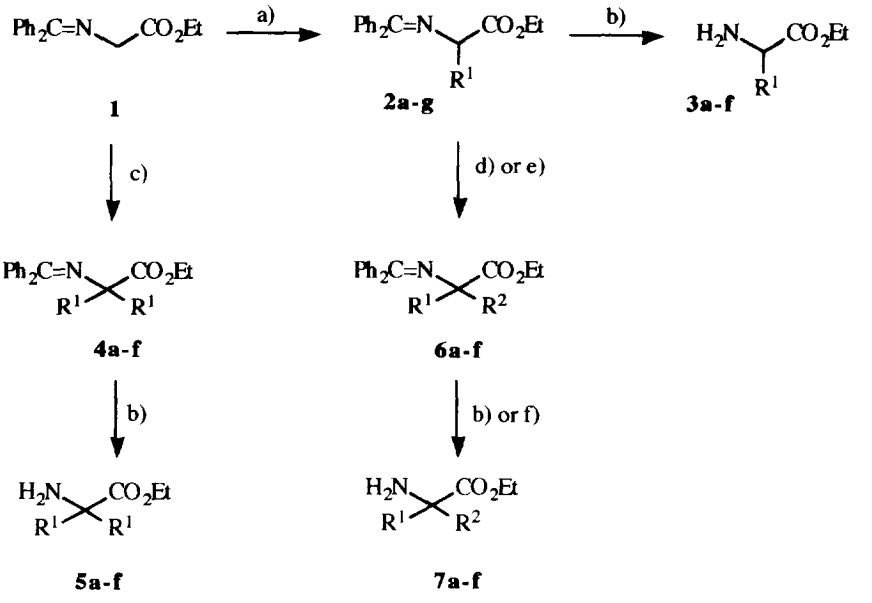
On the other hand, α,α-disubstituted glycines play an important biological role due to their ability to induce and stabilise different types of secondary structures when incorporated into small- to medium-size peptides.[18] These modified peptides show an increased stability towards biological and chemical degradation.[19] For this reason, the synthesis of α-substituted aspartic and glutamic acids and derivatives and, in general, the preparation of acyclic α,α-disubstituted unnatural amino acids has received considerable attention in the chemical literature.[20]

RESULTS

Our results concerning monoalkylation and dialkylation of ketimine **1** under solid-liquid phase transfer catalysis conditions are summarized in Scheme 1 and Tables 1 and 2. They include one-pot dialkylation with two equivalents of the same active organic halide and sequential dialkylation with two different active halides.

Monoalkylation reactions of ketimine **1** with benzylic, allylic and propargylic bromides and ethyl α-bromoacetate were achieved in refluxing acetonitrile in the presence of powdered potassium carbonate as indicated in Scheme 1 and Table 1. This base has been used before for ketimine **1** monoalkylation but in the presence of a phase transfer catalyst.[3f] However, we have found that the catalyst has only an influence on the reaction times and it is not essential for the preparation of monoalkylated ketimines **2**. These compounds were not purified but the crude mixtures were subjected to mild hydrolytic conditions to give amino esters **3**. Compound **2g** was not hydrolyzed but used for a subsequent alkylation.

Treatment of **1** with two equivalents of active bromides in acetonitrile at 0°C in the presence of powdered (a simple coffe-mill was used) potassium hydroxide afforded the dialkylated ketimines **4b-c**, **4e-f** (see Scheme 1 and Table 1). Dialkylation of **1** with benzyl bromide under the aforementioned conditions failed, according to O'Donnell's findings, but the reaction of **1** with 5.0 equivalents of benzyl bromide and 10.0 equivalents of powdered potassium hydroxide at room temperature and in the absence of any solvent yielded **4a**. Crude reaction mixtures containing dialkylated ketimines **4** were stirred at room temperature with 1M hydrochloric acid in diethyl ether to give the corresponding amino esters **5**. Product **5a** was contaminated with the corresponding benzyl ester. The excess of benzyl bromide reacts with potassium hydroxide to give benzyl alcohol, which, as its alkoxide, consumes more benzyl bromide to give dibenzyl ether, compound which could be detected by MS. This alkoxide probably also causes the formation of the transesterified product. Transesterification was also observed in the preparation of the diallyl derivative **5c**.



a) R^1-Br, K_2CO_3, refl. CH_3CN. For the preparation of **2d** and **2g** 10% $BrNBu_4$was added. b) 1M HCl, Et_2O, rt. c) R^1-Br, KOH, $BrNBu_4$, CH_3CN, 0°C, stirring. For the synthesis of **4a** the reaction was run at rt, without solvent, in the presence of excess of benzyl bromide (5.0 eq). d) R^2-Br, KOH, $BrNBu_4$,CH_3CN, 0°C, stirring. e) R^2-Br, NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. Conditions used for the preparation of **6f**. f) 15% Citric acid, Et_2O, rt. Conditions used for the preparation of **7a**.

SCHEME 1

Table 1.- Alkylation of ketimine **1**.

R^1	**2**	**3** (%)[a]	**4**	**5** (%)[a]
Ph-CH_2-	**2a**	**3a** (52)	**4a**	**5a** (24)[b]
Ph-CH=CH-CH_2-	**2b**	**3b** (59)	**4b**	**5b** (34)
CH_2=CH-CH_2-	**2c**	**3c** (33)	**4c**	**5c** (37)[c]
HC-C-CH_2-	**2d**	**3d** (46)	---	---
4-O_2N-Ph-CH_2-	**2e**	**3e** (92)	**4e**	**5e** (19)
CH_2=CBr-CH_2-	**2f**	**3f** (51)	**4f**	**5f** (72)
EtO_2C-CH_2-	**2g**[d]	---	---	---

a) Overall yields from **1** refer to isolated pure compounds. b) Benzyl 2-benzylphenylalaninate was also isolated. Dibenzyl ether was characterized by MS. c) GC-MS characterization in a mixture containing allyl 2-allylglycinate (5 %). d) 75% yield.

Two different chains can also be introduced by sequential dialkylation of **1**. Thus the monoalkylated ketimines **2d**, **2f** and **2g** were treated with a second active organic bromide under the conditions indicated in

Scheme 1. Dialkylated ketimines **6a-f** were obtained, which were converted to the corresponding amino esters **7a-f** (see Scheme 1 and Table 2).

Table 2.- Alkylation of ketimines **2d**, **2f** and **2g**.

R^1	R^2	Starting material	**6**	**7** (%)[a]
$HC\text{-}C\text{-}CH_2$-	$CH_2=CH\text{-}CH_2$-	**2d**	**6a**	**7a** (65)[b]
$CH_2=CBr\text{-}CH_2$-	Ph-CH_2-	**2f**	**6b**	**7b** (33)
$CH_2=CBr\text{-}CH_2$-	Ph-$CH=CH\text{-}CH_2$-	**2f**	**6c**	**7c** (25)
$CH_2=CBr\text{-}CH_2$-	$CH_2=CH\text{-}CH_2$-	**2f**	**6d**	**7d** (23)
$CH_2=CBr\text{-}CH_2$-	$HC\text{-}C\text{-}CH_2$-	**2f**	**6e**	**7e** (40)
$EtO_2C\text{-}CH_2$-	Ph-$CH=CH\text{-}CH_2$-	**2g**	**6f**[c]	**7f** (35)

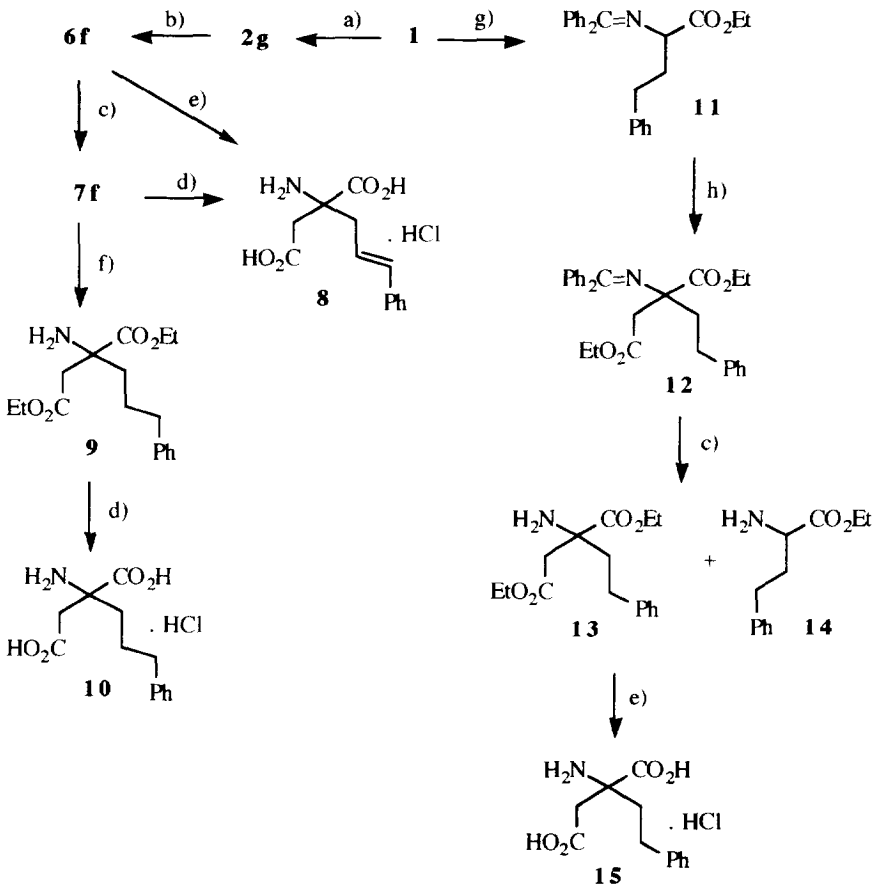
a) Overall yields from **1** refer to isolated pure compounds. b) GC-MS characterization in a mixture containing allyl 2-allyl-2-propargylglycinate (3 %). c) 59% yield from **2g**.

Exceptionally, the monoalkylated ketimine **2g** and the dialkylated ketimine **6f** could be crystallized and the corresponding yields determined. The presence of small amounts of benzophenone arising from the imino group hydrolysis prevented them to give correct analytical data. Compound **7a** was also accompanied by a small quantity (3 %) of the transesterification product allyl 2-allyl-2-propargylglycinate. The formation of this compound could be avoided by using solid sodium ethoxide as base instead of potassium hydroxide. However, when **2d** was treated with allyl bromide, excess sodium ethoxide, and a catalytic amount of tetrabutylammonium bromide in acetonitrile at 0ºC a very complex mixture was obtained. In the same way, an attempted preparation of the same compound **7a** by treatment of monoalkylated ketimine **2c** with propargyl bromide, excess sodium ethoxide and the phase transfer catalyst in acetonitrile at 0ºC also failed. In our hands, the success of the conversion of **2d** into **7a** seems to be very sensitive to the reaction conditions: extremely anhydrous medium and inert atmosphere is required. A solution of **2d** and allyl bromide in acetonitrile must be slowly added over a suspension of the base and catalyst in acetonitrile. Nevertheless, sodium ethoxide has proven to be a good base to attain the alkylation of **2g** with cinnamyl bromide to afford **6f**. As we will see later on, it is also a good base to achieve Michael additions with monoalkylated ketimines. In any case, the mixed ether arising from reaction of ethoxide anion with the organic bromide or the Michael acceptor appears as a side product. Consequently, excess of base and electrophile must be used. These side products are easily separated from the amino esters in the treatment of the Schiff base hydrolysis reactions.

Next, we decided to apply our methodology to the preparation of α-alkylated glutamic and aspartic acid derivatives. Our results about the synthesis of aspartic acid derivatives are summarized in Scheme 2. Ester group hydrolysis (conditions d) of diethyl 2-cinnamylaspartate, **7f**, afforded the hydrochloride of 2-cinnamylaspartic acid, **8**, in 61 % yield. No products from addition of hydrochloric acid to the carbon-carbon double bond were observed. The simultaneous hydrolysis of the Schiff base and ester groups was performed by treatment of ketimine **6f** with 6M hydrochloric acid at reflux temperature (conditions e) (43% yield of **8**). As **6f** was not easily solubilized in acidic aqueous medium, addition of tetrahydrofuran as cosolvent was tested, but opening of the heterocyclic ring under these conditions was observed. Catalytic hydrogenation of **7f** gave diethyl 2-(3-phenylpropyl)aspartate, **9** (92% yield), which was converted to the hydrochloride of 2-(3-phenylpropyl)aspartic acid, **10** (69%).

The introduction of the 2-phenylethyl group in the α-carbon of **1** is not possible under phase-transfer catalysis conditions. Thus the synthesis of monoalkylated ketimine **11** (Scheme 2) was achieved using Stork's methodology[2] (potassium *tert*-butoxide in tetrahydrofuran at room temperature). Some experimentation was needed to find the conditions required to alkylate **11** with ethyl α-bromoacetate or ethyl α-iodoacetate. No succesful results were obtained with potassium *tert*-butoxide, lithium diisopropylamide, lithium

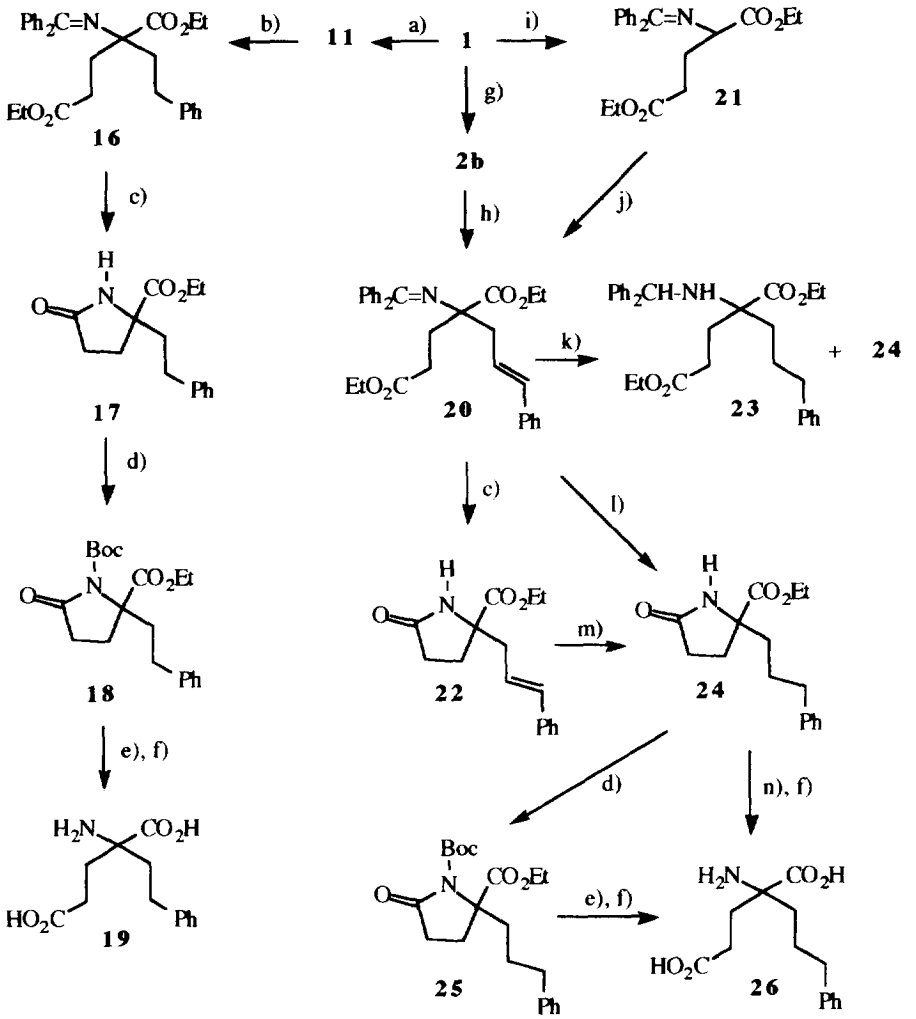
hexamethyldisilazane or our standard solid-liquid phase-transfer catalysis method (potassium hydroxide or sodium ethoxide and tetrabutylammonium bromide). Alternatively, the attempted alkylation of **2g** with 1-iodo-2-phenylethane also failed. Finally, the treatment of **11** with ethyl 2-iodoacetate, solid sodium ethoxide, a catalytic amount of tetrabutylammonium fluoride in acetonitrile at room temperature, followed by Schiff base hydrolysis of the crude mixture containing the dialkylated ketimine **12**, afforded diethyl 2-(2-phenylethyl)aspartate, **13**, in 34% isolated yield. Some ethyl 2-(2-phenylethyl)glycinate, **14**, was recovered (42%). The hydrochloride of 2-(2-phenylethyl)aspartic acid, **15**, was obtained in 92% yield from **13**.



a) Ethyl bromoacetate, K_2CO_3, $BrNBu_4$, refl. CH_3CN. b) Cinnamyl bromide, NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. c) 1M HCl, Et_2O, rt. d) 6M HCl, 70°C. e) 6M HCl, refl. f) H_2 (1 atm), 10% Pd-C, EtOH, rt. g) $PhCH_2CH_2I$, KO^{t}Bu, THF, rt. h) Ethyl iodoacetate, NaOEt, $FNBu_4$, CH_3CN, rt, stirring.

SCHEME 2

Our results concerning the preparation of glutamic acid derivatives are summarized in Scheme 3. The introduction of 2-carboxyethyl group in the α carbon of **1** could be achieved by Michael addition to ethyl acrylate and subsequent ester group hydrolysis.



a) $PhCH_2CH_2I$, KO^tBu, THF, rt. b) Ethyl acrylate, NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. c) 15% Citric acid, THF, rt. d) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, rt. e) 6M HCl, refl. f) Propylene oxide, MeOH, rt. g) Cinnamyl bromide, K_2CO_3, $BrNBu_4$, refl. CH_3CN. h) Ethyl acrylate, KOH or NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. i) Ethyl acrylate, K_2CO_3, $BrNBu_4$, CH_3CN, rt. j) Cinnamyl bromide, KOH or NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. k) H_2 (2 atm), 10% Pd-C, EtOH, rt. l) H_2 (3 atm), 10% Pd-C, EtOH, rt. m) H_2 (1 atm), 10% Pd-C, EtOH, rt. n) 6M HCl, 70°C.

SCHEME 3

The reaction of monoalkylated ketimine **11** (which bears a 2-phenylethyl group) with ethyl acrylate under solid-liquid phase transfer catalysis, using solid sodium ethoxide as a base, afforded the ketimine **16**, which was subjected to mild acidic conditions (15% citric acid, THF, rt) to give the alkylated pyroglutamate derivative **17** (33% overall yield from **1**), arising from the spontaneous cyclisation of the corresponding acyclic amino diester. Lactam hydrolysis to the corresponding acyclic ω-amino acids have been described in the literature by treatment of *N-tert*-butoxycarbonyl derivatives of these lactams with acids and bases.[21]

Accordingly to these precedents we prepared the *N*-protected derivative **18** (84% yield) by reaction of **17** with di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and triethylamine in dichloromethane at room temperature. Treatment of **18** with 6M hydrochloric acid at reflux temperature afforded 70% yield of a very hygroscopic amino acid hydrochloride. The free α-amino acid 2-(2-phenylethyl)glutamic acid, **19**, was obtained in 90% yield by subsequent reaction with propylene oxide in metanol at room temperature.

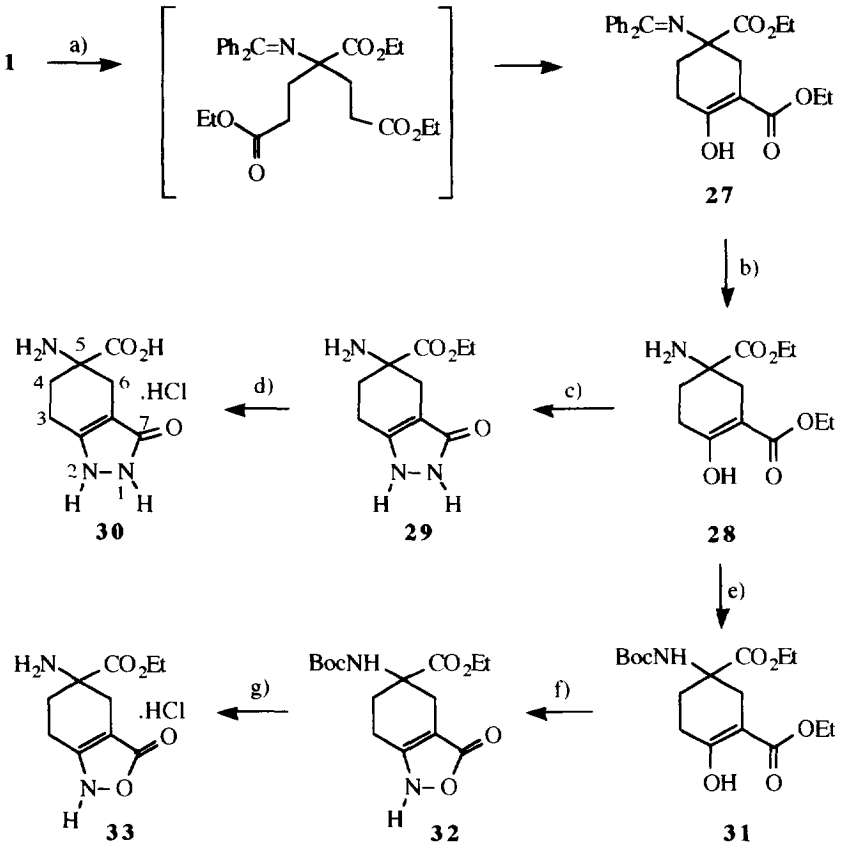
On the other hand, the Michael addition of monoalkylated ketimine **2b** (which bears a cinnamyl group) to ethyl acrylate under solid-liquid phase transfer conditions (potassium hydroxide and sodium ethoxide gave similar results) afforded the ketimine **20**, which was hydrolyzed to the pyroglutamate derivative **22** (28-31% overall yield from **1**) (see Scheme 3). Alternatively, the same compound **22** (33-34% overall yield from **1**) was also obtained by a reversed dialkylation sequence. Thus Michael addition of **1** to ethyl acrylate, using potassium carbonate as base and a phase transfer catalyst in acetonitrile at room temperature gave the ketimine **21**, which was subsequently alkylated with cinnamyl bromide. Potassium hydroxide and sodium ethoxide can be used indistinctly. Catalytic hydrogenation of **22** gave **24** (98%), which was also obtained directly from **20** in low yield (22%) by treatment with hydrogen (3 atm) and 10% Pd-C in ethanol. The cyclisation reaction of the acyclic amino diester takes place spontaneously, even in neutral medium. Lowering the hydrogen pressure to 2 atmospheres resulted in partial hydrogenolysis of the imino group, a mixture of compounds **24** and **23** being isolated in 16% and 20% yields, respectively. Opening and hydrolysis of the pyroglutamate ester **24** was carried out *via* its *N*-*tert*-butoxycarbonyl derivative **25** (prepared in 95% yield from **24**) or directly, by heating **24** with 6M HCl at 70 °C. The corresponding amino acid hydrochloride, **26.HCl** was obtained in 75% and 48% yields, respectively, and it was converted to the free amino acid 2-(3-phenylpropyl)glutamic acid, **26**, in 30% yield by propylene oxide in methanol.

In Scheme 4 we present the synthetic routes leading to amino acid derivatives featuring isoxazolone and pyrazolone moieties. The double Michael addition of **1** to excess ethyl acrylate was performed in the presence of excess solid sodium ethoxide and a catalytic amount of tetrabutylammonium bromide in acetonitrile at 0°C. The resulting dialkylated derivative was not isolated but experimented a Dieckmann type cyclisation under the basic conditions to afford the ketimine **27**. This compound was accompanied by some ethyl 3-ethoxypropanoate and by a small amount of benzophenone. Whithout further purification the crude mixture was subjected to mild hydrolysis of the Schiff base to yield the amino ester **28** (38% from **1**). Tautomeric keto-enol equilibrium favoring the enolic tautomer was observed by ^{1}H-NMR. The reaction of the β-oxoester moiety of **28** with one equivalent of hydrazine hydrate gave the bicyclic pyrazolone **29** (83% yield), which was converted to 5-amino-2,3,4,5,6,7-hexahydro-3-oxo-1*H*-indazole-5-carboxylic acid hydrochloride, **30**, (95% yield) by the usual way. This amino acid hydrochloride was extremely insoluble in organic solvents.

On the other hand, the reaction of the β-oxoester moiety of the *N*-protected derivative **31** (obtained in 80% yield from **28**) with hydroxylamine (prepared *in situ* from its hydrochloride and sodium hydroxide) under the conditions indicated in Scheme 4 afforded the bicyclic isoxazolone **32** (80% yield). An attempted simultaneous hydrolysis of the carbamate and ester groups of **32** with 6M HCl at 70°C gave a complex mixture from which no defined products could be identified. Selective amino group deprotection was performed by treatment of an ethereal solution of **32** with gaseous hydrogen chloride at room temperature, but the resulting amino ester hydrochloride **33** was not stable und underwent spontaneous decomposition. The preparation of this amino ester hydrochloride **33** is also possible by reaction of **28** with hydroxylamine under the same conditions f) indicated in Scheme 4 but the extreme insolubility of **33** in organic solvents prevented its complete separation from the sodium chloride formed in the reaction. *N*-*tert*-butoxicarbonyl derivative **32** is less polar and much more soluble in organic solvents, being easily purified by recrystallization.

The reaction of β-oxoesters with hydroxylamine can give rise to 5-isoxazolone or 3-hydroxyisoxazole regioisomeric compounds. The regioselectivities of these reactions are dependent upon the pH conditions and the final acidification method.[22] This is not the case for β-ketoesters of cyclohexanone and piperidone series, where the ketone carbonyl group is more reactive and only 5-hydroxyisoxazoles or 5-isoxazolones are obtained.[22b,22e,23] Structural assignment in **32** is in agreement with these literature precedents. Confirmation of structure **32** could be obtained by catalytic hydrogenation (Pd/C) at atmospheric pressure that would lead to ethyl 1-*tert*-butoxycarbonylamino-4-oxocyclohexanecarboxylate. However, no defined products could be

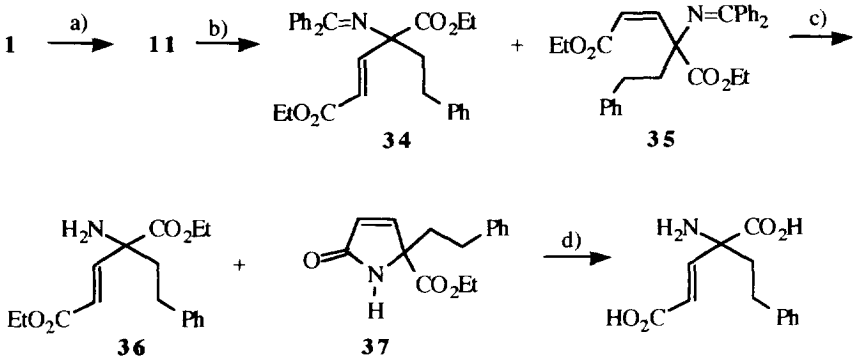
isolated from this hydrogenation experiment. Thus, we prepared the *N*-cinnamyl derivative of **32** (see experimental) under Pd(0) catalysis[23] and we performed on it an ^{1}H-^{13}C 2D HMBC[24] experiment which confirmed the proposed structure.



a) Ethyl acrylate (5 eq.), NaOEt (6 eq.), $BrNBu_4$ (0.1 eq.),CH_3CN, 0°C, stirring. b) 1M HCl, Et_2O, rt, stirring; then $KHCO_3$. c) NH_2-NH_2.H_2O (1 eq.), EtOH, 70°C. d) 6M HCl, 70°C. e) $(Boc)_2O$, refl. $CHCl_3$. f) NH_2OH.HCl (1 eq.), NaOH (1 eq.), H_2O-EtOH, 0°C; then conc HCl. g) HCl $_{(g)}$, Et_2O, rt, stirring.

SCHEME 4

Finally, an acetylenic Michael acceptor was tested (see Scheme 5). The monoalkylated ketimine **11** was reacted with ethyl propiolate under solid-liquid phase transfer conditions using sodium ethoxide as base. The resulting crude mixture, containing *E* and *Z* dialkylated ketimines **34** and **35** together with ethyl 3,3-diethoxypropanoate arising from double conjugate addition of ethoxide anion to ethyl propiolate, was hydrolyzed to give diethyl (*E*)-2-(2-phenylethyl)-3,4-dehydroglutamate, **36** (14% overall yield from **11**) and ethyl 2-(2-phenylethyl)-3,4-dehydropyroglutamate, **37** (19% overall yield from **11**). The preparation of **36** and **37** from **11** using potassium *tert*-butoxide in tetrahydrofuran at -75°C and the subsequent conversion of these compounds to (*E*)-2-(2-phenylethyl)-3,4-dehydroglutamic acid has been recently reported.[25]



a.- KO^{t}Bu, ICH_2CH_2Ph, THF, rt. b) Ethyl propiolate, NaOEt, $BrNBu_4$, CH_3CN, 0°C, stirring. c) 1M HCl, Et_2O, rt, stirring; then K_2CO_3, pH > 8. d) See ref. 25.

SCHEME 5

In summary, appropriate solid-liquid phase-transfer catalysis conditions have been found to carry out monoalkylations, dialkylations and Michael additions to ethylenic and acetylenic acceptors of ketimine **1**. Further modifications on the α-disubstituted ketimines have led to non-proteinogenic α-amino acids and derivatives with potential biological activities.

EXPERIMENTAL

Ethyl *N*-(diphenylmethylene)glycinate, **1**, is commercially available (97% purity). ^{1}H-NMR (^{13}C-NMR) spectra were recorded at 250 MHz (62.5 MHz) using TMS as internal standard. NMR values are given in δ units. Mass spectra were determined under electron impact (70 eV).

*Ethyl 3-phenylalaninate, **3a**.* A mixture of **1** (5.00 g, 18.7 mmole), potassium carbonate (12.90 g, 93.5 mmole), benzyl bromide (4.15 g, 24.3 mmole) and acetonitrile (80 mL) was refluxed during 48 h (GLC monitoring). The solid was filtered off, the organic solution was dried with anhydrous sodium sulfate and the solvent was evaporated, affording crude **2a** as an orange oil (7.04 g); ^{1}H-NMR ($CDCl_3$): 1.24 (t, J = 7.1 Hz, 3H), 3.10-3.40 (m, 2H), 4.10-4.30 (m, 3H), 6.50-7.90 (m, 15H). A portion of this crude **2a** (0.87 g) was dissolved in diethyl ether (30 mL), a solution of 1M hydrochloric acid was added (15 mL, 15.0 mmole) and the mixture vigorously stirred at room temperature for 20 h. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate (3x25 mL).The ethyl acetate extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to yield **3a** (yellow oil, 0.25 g, 52% overall yield from **1**); b.p. 150°C (oven temperature) / 3 mm Hg (lit.[26] b.p. 117-118°C / 4 mm Hg); IR (film): 3380, 3309, 1734 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.0 Hz, 3H), 1.50 (broad s, 2H), 2.82 (dd, J_1 = 13.5 Hz, J_2 = 7.6 Hz, 1H), 3.05 (dd, J_1 = 13.5 Hz, J_2 = 5.5 Hz, 1H), 3.67 (dd, J_1 = 7.6 Hz, J_2 = 5.5 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 7.10-7.40 (m, 5H).

*Ethyl 2-cinnamylglycinate, **3b**.* It was prepared from **1** and cinnamyl bromide in 59% overall yield as for **3a**. ^{1}H-NMR ($CDCl_3$) of intermediate ethyl 2-cinnamyl-*N*-(diphenylmethylene)glycinate, **2b**: 1.22 (t, J = 7.1 Hz, 3H), 2.65-2.90 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.08-4.22 (m, 1H), 6.00 (dt, J_1 = 15.6 Hz, J_2 = 7.5 Hz, 1H), 6.18 (d, J = 15.6 Hz, 1H), 7.10-7.85 (m, 15H). Compound **3b**: b.p. 200-210°C (oven temperature) / 0.6 mm Hg; IR (film): 3381, 3318, 1733 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.24 (t, J = 7.1 Hz, 3H), 1.68 (broad s, 2H), 2.44-2.70 (m, 2H), 3.56 (dd, J_1 = 6.9 Hz, J_2 = 5.5 Hz, 1H), 4.10-4.25 (m, 2H), 6.03-6.20 (m, 1H), 6.46 (d, J = 15.5 Hz, 1H), 7.10-7.45 (m, 5H).

Ethyl 2-allylglycinate, 3c. It was prepared from **1** and excess allyl bromide in 33% overall yield as for **3a**. ^{1}H-NMR ($CDCl_3$) of intermediate ethyl 2-allyl-*N*-(diphenylmethylene)glycinate, **2c**: 1.20 (t, J = 7.1 Hz, 3H), 2.50-2.70 (m, 2H), 4.00-4.20 (m, 3H), 4.90-5.10 (m, 2H), 5.55-5.75 (m, 1H), 7.00-7.80 (m, 10H). Compound **3c**: b.p. 110-115°C (oven temperature) / 16 mm Hg (lit.[27] b.p. 80-85°C / 10 mm Hg); IR (film): 3384 and 3319 (weak), 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.25 (t, J = 7.0 Hz, 3H), 1.65 (s, 2H), 2.25-2.55 (m, 2H), 3.49 (dd, J_1 = 6.9 Hz, J_2 = 5.1 Hz, 1H), 4.10-4.20 (m, 2H), 5.00-5.20 (m, 2H), 5.60-5.80 (m, 1H).

Ethyl 2-propargylglycinate, 3d. It was prepared from **1** and excess propargyl bromide in 46% overall yield as for **3a**. ^{1}H-NMR ($CDCl_3$) of intermediate ethyl *N*-(diphenylmethylene)-2-propargylglycinate, **2d**: 1.23 (t, J = 7.0 Hz, 3H), 1.90 (apparent t, J = 2.5 Hz, 1H), 2.74 (ddd, J_1 = 16.8 Hz, J_2 = 8.0 Hz, J_3 = 2.5 Hz, 1H), 2.83 (ddd, J_1 = 16.8 Hz, J_2 = 5.5 Hz, J_3 = 2.5 Hz, 1H), 4.07-4.22 (m, 2H), 4.25 (dd, J_1 = 8.0 Hz, J_2 = 5.5 Hz, 1H), 7.15-7.85 (m, 10H). Compound **3d**: b.p. 125-130°C (oven temperature) / 16 mm Hg (lit.[28] b.p. 90-100°C (oven temperature) / 13 mm Hg); IR (film): 3383, 3293, 2122 (weak), 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.25 (t, J = 7.0 Hz, 3H), 1.73 (broad s, 2H), 2.04 (dd, J_1 = 2.9 Hz, J_2 = 2.5 Hz, 1H), 2.57 (ddd, J_1 = 16.8 Hz, J_2 = 6.2 Hz, J_3 = 2.9 Hz, 1H), 2.65 (ddd, J_1 = 16.8 Hz, J_2 = 5.1 Hz, J_3 = 2.5 Hz, 1H), 3.60 (dd, J_1 = 6.2 Hz, J_2 = 5.1 Hz, 1H), 4.12-4.26 (m, 2H).

Ethyl 3-(4-nitrophenyl)alaninate, 3e. It was prepared from **1** and 4-nitrobenzyl bromide in 92% overall yield as for **3a**. Intermediate ethyl 3-(4-nitrophenyl)-*N*-(diphenylmethylene)alaninate, **2e** (orange crystals): m.p. 111-112°C (hexane); ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.0 Hz, 3H), 3.18 (dd, J_1 = 13.5 Hz, J_2 = 8.8 Hz, 1H), 3.25 (dd, J_1 = 13.5 Hz, J_2 = 5.1 Hz, 1H), 4.00-4.15 (m, 2H), 4.18 (dd, J_1 = 8.8 Hz, J_2 = 5.1 Hz, 1H), 6.60-8.10 (m, 14H). Compound **3e**: b.p. 225-230°C (oven temperature) / 1.5 mm Hg (lit.[29] b.p. 185-187°C / 2.5 mm Hg); IR (film): 3385, 3318, 1733, 1519, 1347 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.0 Hz, 3H), 1.55 (broad s, 2H), 2.93 (dd, J_1 = 13.5 Hz, J_2 = 7.7 Hz, 1H), 3.15 (dd, J_1 = 13.5 Hz, J_2 = 5.5 Hz, 1H), 3.70 (dd, J_1 = 7.7 Hz, J_2 = 5.5 Hz, 1H), 4.15 (q, J =7.0 Hz, 2H), 7.34-7.38 (AA'BB' system, 2H), 8.12-8.15 (AA'BB' system, 2H).

Ethyl 2-(2-bromoallyl)glycinate, 3f. It was prepared from **1** and 2,3-dibromopropene in 51% overall yield as for **3a**. ^{1}H-NMR ($CDCl_3$) of intermediate ethyl 2-(2-bromoallyl)-*N*-(diphenylmethylene)glycinate, **2f**: 1.23 (t, J = 7.0 Hz, 3H), 3.00-3.08 (m, 2H), 4.05-4.25 (m, 2H), 4.35 (dd, J_1 = 6.9 Hz, J_2 = 5.8 Hz, 1H), 5.40 (d, J = 1.4 Hz, 1H), 5.64-5.68 (m, 1H), 7.00-7.80 (m, 10H). Compound **3f**: b.p. 155-160°C (oven temperature) / 13 mm Hg; IR (film): 3382, 3318, 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.27 (t, J = 7.0 Hz, 3H), 1.55 (broad s, 2H), 2.58 (dd, J_1 = 14.5 Hz, J_2 = 8.8 Hz, 1H), 2.88 (dd, J_1 = 14.5 Hz, J_2 = 4.7 Hz, 1H), 3.77 (dd, J_1 = 8.8 Hz, J_2 = 4.7 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 5.53 (d, J = 1.5 Hz, 1H), 5.69 (broad s, 1H); ^{13}C-NMR ($CDCl_3$): 14.6, 47.0, 53.0, 61.7, 120.8, 130.0, 174.7. Anal.: Calcd. for $C_7H_{12}NO_2Br$: C, 37.86; H, 5.45; N, 6.31. Found: C, 37.40; H, 5.40; N, 6.11.

Ethyl 2-benzylphenylalaninate, 5a. A solution of **1** (4.00 g, 14.4 mmole) in excess benzyl bromide (12.27 g, 71.8 mmole) was added dropwise to a stirred mixture of anhydrous powdered potassium hydroxide (8.08 g, 144.0 mmole) and tetra-*n*-butylammonium bromide (0.46 g, 1.4 mmole) kept at 0°C. Then the mixture was stirred at room temperature for 16 h (GLC monitoring). The solid was filtered off and excess benzyl bromide was evaporated. The residue was dissolved in diethyl ether (30 mL) and washed with distilled water (4x25 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to give crude **4a** (thick oil, 10.57 g). Whithout further purification it was dissolved in diethyl ether (150 mL), 1M hydrochloric acid (100 mL, 100.0 mmole) was added to the ethereal solution and the mixture vigorously stirred at room temperature for 48 h. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate (4x80 mL). The combined ethyl acetate extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to afford a yellow oil which was identified by ^{1}H-NMR as a mixture of **5a** (0.99 g, 24% yield from **1**) and benzyl 2-benzylphenylalaninate (0.45 g, 9% yield from **1**). Both esters were separated by recristallyzation of the mixture in hexane. Compound **5a**: colourless oil; b.p. 220-230°C (oven temperature) / 0.5 mm Hg; IR (film): 3381 and 3318 (weak), 1734 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.3 Hz, 3H), 1.45 (broad s, 2H), 2.80 (d, J = 13.6 Hz, 2H), 3.35 (d, J = 13.6 Hz, 2H), 4.00 (q, J = 7.3 Hz, 2H), 7.10-7.35 (m, 10H); ^{13}C-NMR ($CDCl_3$): 14.0, 46.2, 60.9, 62.9, 126.9, 128.3, 129.8, 136.1, 175.6; MS (m/e): 284 (M+1, 1), 210 (24), 192 (81), 118 (52), 91 (100); HRMS: Calcd. for ($C_{18}H_{21}NO_2$ + 1): M^+

284.165578. Found: M+ 284.165054. Benzyl 2-benzylphenylalaninate: white crystals; m.p. 93-94°C; IR (KBr): 3369, 3029, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.50 (broad s, 2H), 2.80 (d, J = 13.0 Hz, 2H), 3.35 (d, J = 13.0 Hz, 2H), 5.00 (s, 2H), 7.00-7.50 (m, 15H); ^{13}C-NMR ($CDCl_3$): 46.3, 63.2, 66.8, 126.9, 128.4, 128.5, 128 7, 129.7, 129.8, 129.9, 130.0, 135.2, 136.0, 175.6; MS (m/e): 254 (25), 210(11), 91 (100). Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.80; H, 6.69; N, 4.09.

*Ethyl 2,2-dicinnamylglycinate, **5b**.* A solution of **1** (3.00 g, 10.8 mmole) and cinnamyl bromide (4.66 g, 22.7 mmole) in anhydrous acetonitrile (30 mL) was added dropwise (30 min) to a stirred mixture of powdered potassium hydroxide (6.06 g, 108.0 mmole) and tetra-*n*-butylammonium bromide (0.35 g, 1.1 mmole) in anhydrous acetonitrile (30 mL) kept at 0°C. Then the stirred mixture was left at this temperature for 5 h (TLC monitoring). The solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (50 mL) and the ethereal solution washed with distilled water (4x40 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to afford crude **4b** (orange oil, 4.00 g). Whithout further purification it was dissolved in diethyl ether (75 mL), 1M hydrochloric acid (120 mL, 120.0 mmole) was added to the ethereal solution and the mixture vigorously stirred at room temperature for 48 h. The aqueous layer was basified with potassium carbonate and extracted with ethyl acetate (4x80 mL). The combined ethyl acetate extracts were dried with anhydrous sodium sulfate, the solvent was evaporated and the residue (orange oil) was chromatographed on silica gel under pressure. Elution with dichloromethane afforded **5b** (thick and colourless oil, 1.23 g, 34% overall yield from **1**); IR (film): 3378, 3319, 1727 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.26 (t, J = 7.1 Hz, 3H), 1.60 (broad s, 2H), 2.43 (dd, J_1 = 13.5 Hz, J_2 = 8.8 Hz, 2H), 2.74 (ddd, J_1 = 13.5 Hz, J_2 = 6.6 Hz, J_3 = 1.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.08 (ddd, J_1 = 15.5 Hz, J_2 = 8.8 Hz, J_3 = 6.6 Hz, 2H), 6.47 (d, J = 15.5 Hz, 2H), 7.10-7.15 (m, 10H); ^{13}C-NMR ($CDCl_3$): 14.3, 43.2, 60.9, 61.0, 123.7, 126.0, 127.3, 128.3, 128.4, 128.5, 134.3, 136.8, 175.9; MS (m/e): 335 (M+1, 0.3), 262 (9), 218 (100), 144 (58), 129 (52), 117 (60), 115 (49), 91 (38). Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.17. Found: C, 79.04; H, 7.44; N, 4.11.

*Ethyl 2,2-diallylglycinate, **5c**.* It was prepared from **1** and excess allyl bromide as for **5b** except that the dialkylation reaction was monitored by GLC. A mixture (^{1}H-NMR) of **5c** (37% overall yield from **1**) and allyl 2,2-diallylglycinate (5% overall yield from **1**) was obtained after acid hydrolysis. This mixture decomposed spontaneously after several days in the refrigerator, their components could not be separated and were identified by GLC/MS. Physical and spectroscopic data correspond to the mixture. B.p. 75-77°C (oven temperature) / 14 mm Hg; IR (film): 3381 and 3325 (weak), 1733 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.26 (t, J = 7.0 Hz, 3H), 1.64 (broad s, 2H + 2H), 2.24 (dd, J_1 = 13.5 Hz, J_2 = 8.4 Hz, 2H + 2H), 2.54 (dd, J_1 = 13.5 Hz, J_2 = 6.6 Hz, 2H + 2H), 4.15 (q, J = 7.0 Hz, 2H), 4.58 (apparent t, J = 1.3 Hz, 1H), 4.60 (apparent t, J = 1.3 Hz, 1H), 5.00-5.20 (m, 4H + 4H), 5.20-5.35 (m, 2H), 5.60-5.80 (m, 2H + 2H), 5.80-6.00 (m, 1H); MS (m/e) of **5c**: 184 (M+1, 0.1), 142 (39), 110 (62), 96 (19), 68 (100) . 13); MS (m/e) of allyl ester: 196 (M+1, 1), 154 (100), 110 (97), 68 (57), 41 (88).

*Ethyl 2,2-bis(4-nitrobenzyl)glycinate, **5e**.* It was prepared from **1** and 4 nitr enzyl bromide in 19% overall yield as for **5b** except that no chromatography was needed; orange crystals; m 154-155°C; IR (KBr): 3395, 3367, 3310, 1730, 1516, 1345 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.0 Hz, l), 1.45 (broad s, 2H), 2.95 (d, J = 13.1 Hz, 2H), 3.40 (d, J = 13.1 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H, 7.34-7.37 (AA'BB' system, 4H), 8.13-8.16 (AA'BB' system, 4H); ^{13}C-NMR ($CDCl_3$): 14.0, 45.7, 61.5, 62.7, 123.3, 130.8, 143.4, 146.9, 174.4; MS (m/e): 374 (M+1, 1), 300 (42), 254 (4), 237 (100), 163 (52). Anal. Calcd. for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.13; N, 11.25. Found: C, 57.89; H, 5.14; N, 11.28.

*Ethyl 2,2-bis(2-bromoallyl)glycinate, **5f**.* See reference 10.

*Ethyl 2-allyl-2-propargylglycinate, **7a**.* A solution of propargyl bromide (16.52 g, 111.0 mmole) in anhydrous acetonitrile (100 mL) was added under argon atmosphere to a stirred mixture of **1** (15.03 g, 54.5 mmole), potassium carbonate (23.02 g, 166.0 mmole), tetra-*n*-butylammonium bromide (1.81 g, 5.61 mmole) and anhydrous acetonitrile (150 mL). The mixture was refluxed under argon for 24 h (GLC monitoring). The solid was filtered off, the filtrate was dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x100 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to yield crude

ethyl *N*-(diphenylmethylene)-2-propargylglycinate, **2d** (17.06 g) as a brown oil. A solution of a portion of this crude **2d** (8.20 g, 26.8 mmole) and allyl bromide (6.58 g, 54.4 mmole) in anhydrous acetonitrile (50 mL) was added dropwise, under argon atmosphere, to a stirred mixture of powdered and dried potassium hydroxide (5.36 g, 81.2 mmole), tetra-*n*-butylammonium bromide (0.886 g, 2.75 mmole) and anhydrous acetonitrile (100 mL) kept at 0°C. Then the stirred mixture was left overnight under argon at this temperature (GLC monitoring). The solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (150 mL) and the ethereal solution washed with distilled water (4x100 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford a brown oil (8.54 g) identified (^{1}H-NMR) as ethyl 2-allyl-*N*-(diphenylmethylene)-2-propargylglycinate, **6a**, impurified (4%) with allyl 2-allyl-*N*-(diphenylmethylene)-2-propargylglycinate; ^{1}H-NMR ($CDCl_3$) of the mixture: 1.09 (t, J = 7.3 Hz, 3H), 1.93 (t, J = 2.6 Hz, 1H+1H), 2.76 (d, J = 2.6 Hz, 2H+2H), 2.80-2.85 (m, 2H+2H), 3.71 (q, J = 7.3 Hz, 2H), 4.13 (apparent t, J = 1.5 Hz, 1H), 4.15 (apparent t, J = 1.5 Hz, 1H), 5.08-5.24 (m, 2H+4H), 5.74-5.90 (m, 1H+2H), 7.10-7.80 (m, 10H+10H). This crude mixture (8.42 g) was dissolved in diethyl ether, a 15% aqueous solution of citric acid was added (400 g of solution, 312 mmole of citric acid) and the vigorously stirred mixture was left at room temperature for 3 d. The ethereal phase was discarded, the aqueous phase was basified with potassium carbonate and extracted with chloroform (3x150 mL). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a colourless oil identified (^{1}H-NMR) as **7a** (3.06 g, 65% overall yield from **1**) contaminated with allyl 2-allyl-2-propargylglycinate (0.13 g, 3% overall yield from **1**). See reference 10 for data of the mixture.

*Ethyl 2-benzyl-2-(2-bromoallyl)glycinate, **7b**.* It was prepared in 33% overall yield from **1** via **2f** and **6b** (see Scheme 1). B.p. 150-170°C (oven temperature)/0.4 mm Hg ; IR (film): 3381 (weak), 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.25 (t, J = 7.1 Hz, 3H), 1.64 (broad s, 2H), 2.73 (d, J = 13.5 Hz, 2H), 3.14-3.24 (m, 2H), 4.05-4.19 (m, 2H), 5.56 (d, J = 1.4 Hz, 1H), 5.70 (s, 1H), 7.00-7.50 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.0, 46.4, 50.9, 61.2, 61.3, 121.9, 127.1, 127.2, 128.4, 130.0, 135.4, 175.2; MS (m/e): 314 (M+1, 0.3), 312 (M+1, 0.3), 240 (30), 238 (32), 222 (80), 220 (86), 194 (10), 192 (39), 148 (27), 146 (27), 118 (50), 91 (100), 65 (21). Anal. Calcd. for $C_{14}H_{18}NO_2Br$: C, 53.86; H, 5.81; N, 4.49. Found: C, 53.77; H, 5.80; N, 4.39.

*Ethyl 2-(2-bromoallyl)-2-cinnamylglycinate, **7c**.* It was prepared in 25% overall yield from **1** via **2f** and **6c** as indicated in Scheme 1. Ketimine **6c**: ^{1}H-NMR ($CDCl_3$): 1.10 (t, J = 7.3 Hz, 3H), 2.98 (m, 2H), 3.15 (broad s, 2H), 3.65-3.77 (m, 2H), 5.60 (d, J = 1.5 Hz, 1H), 5.79 (d, J = 1.5 Hz, 1H), 6.05-6.20 (m, 1H), 6.45 (d, J = 15.7 Hz, 1H), 7.00-7.90 (m, 15H). **7c**: b.p. 210-220°C (oven temperature) / 0.5 mm Hg; IR (film): 3435, 3381, 3309, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.28 (t, J = 7.0 Hz, 3H), 1.73 (broad s, 2H), 2.39 (dd, J_1 = 13.5 Hz, J_2 = 8.7 Hz, 1H), 2.65-2.80 (m, 2H), 3.10 (d, J = 14.6 Hz, 1H), 4.00-4.30 (m, 2H), 5.56 (d, J = 1.5 Hz, 1H), 5.70 (broad s, 1H), 6.02 (ddd, J_1 = 15.7 Hz, J_2 = 8.7 Hz, J_3 = 6.6 Hz, 1H), 6.50 (d, J = 15.7 Hz, 1H), 7.10-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.7, 44.6, 51.0, 60.8, 61.9, 122.3, 123.6, 126.7, 127.7, 128.0, 129.0, 135.4, 137.3, 176.0; MS (m/e): 340 (M+1, 0.3), 338 (M+1, 0.3), 266 (11), 264 (12), 222 (100), 220 (99), 194 (12), 192 (13), 148 (27), 146 (28), 117 (21), 115 (25), 91 (16). Anal. Calcd. for $C_{16}H_{20}NO_2Br$: C, 56.81; H, 5.96; N, 4.14. Found: C, 56.80; H, 6.02; N, 4.18.

*Ethyl 2-allyl-2-(2-bromoallyl)glycinate, **7d**.* It was prepared in 23% overall yield from **1** via **2f** and **6d** as indicated in Scheme 1. B.p. 100°C (oven temperature) / 0.3 mm Hg; IR (film): 3382 and 3318 (weak), 1734 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.25 (t, J = 7.0 Hz, 3H), 1.65 (broad s, 2H), 2.22 (dd, J_1 = 13.5 Hz, J_2 = 8.4 Hz, 1H), 2.55 (dd, J_1 = 13.5 Hz, J_2 = 5.1 Hz, 1H), 2.65 (d, J = 14.2 Hz, 1H), 3.00 (dd, J_1 = 14.2 Hz, J_2 = 1.1 Hz, 1H), 4.00-4.25 (m, 2H), 5.00-5.20 (m, 2H), 5.40-5.70 (m, 3H); ^{13}C-NMR ($CDCl_3$): 14.2, 44.8, 50.4, 59.8, 61.4, 120.1, 121.8, 127.3, 131.8, 175.5; MS (m/e): 264 (M+1, 0.5), 262 (M+1, 0.4), 222 (38), 220 (36), 190 (63), 188 (62), 148 (23), 146 (24), 142 (52), 68 (100), 41 (61). Anal. Calcd. for $C_{10}H_{16}NO_2Br$: C, 45.82; H, 6.15; N, 5.34. Found: C, 45.68; H, 6.09; N, 5.32.

*Ethyl 2-(2-bromoallyl)-2-propargylglycinate, **7e**.* It was prepared in 40% overall yield from **1** via **2f** and **6e** (see Scheme 1). Ketimine **6e**: ^{1}H-NMR ($CDCl_3$): 1.13 (t, J = 7.3 Hz, 3H), 1.95 (apparent t, J = 2.5 Hz, 1H), 2.90 (dd, J_1 = 17.2 Hz, J_2 = 2.5 Hz, 1H), 3.00 (dd, J_1 = 17.2 Hz, J_2 = 2.5 Hz, 1H), 3.24 (d, J = 14.9 Hz, 1H), 3.40 (d, J = 14.9 Hz, 1H), 3.70-3.85 (m, 2H), 5.65 (d, J = 1.5 Hz, 1H), 5.90 (m, 1H), 7.10-8.00 (m, 10H). **7e**: b.p. 95-105°C (oven temperature)/0.5 mm Hg; IR (film): 3381, 3299, 2123 (weak), 1737 cm^{-1};

^{1}H-NMR ($CDCl_3$): 1.28 (t, J = 6.9 Hz, 3H), 1.84 (broad s, 2H), 2.05 (apparent t, J = 2.6 Hz, 1H), 2.48 (dd, J_1 = 16.2 Hz, J_2 = 2.6 Hz, 1H), 2.68 (dd, J_1 = 16.2 Hz, J_2 = 2.6 Hz, 1H), 2.76 (d, J = 14.2 Hz, 1H), 2.97 (d, J = 14.2 Hz, 1H), 4.05-4.25 (m, 2H), 5.56 (J = 1.4 Hz, 1H), 5.70 (m, 1H); ^{13}C-NMR ($CDCl_3$): 14.0, 30.1, 49.7, 59.7, 61.7, 71.9, 78.7, 122.0, 126.5, 174.0; MS (m/e): 262 (M+1, 1), 260 (M+1, 1), 222 (14), 220 (14), 188 (74), 186 (70), 148 (17), 146 (16), 140 (100), 112 (15), 66 (61). Anal. Calcd. for $C_{10}H_{14}NO_2Br$: C, 46.17; H, 5.42; N, 5.38; Nr, 30.72. Found: C, 46.13; H, 5.46; N, 5.28; Br, 30.53.

Diethyl N-(diphenylmethylene)aspartate, 2 g. A solution of ethyl bromoacetate (20.62 g, 123 mmole) in anhydrous acetonitrile (50 mL) was added to a stirred mixture of **1** (15.36 g, 55.7 mmole), potassium carbonate (23.30 g, 168 mmole), tetra-*n*-butylammonium bromide (1.89 g, 5.86 mmole) and anhydrous acetonitrile (200 mL). The mixture was refluxed for 12 h (GLC monitoring). The solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x150 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to give **2 g** as a thick oil which crystallized when was dried *in vacuum* and was purified by recrystallization in hexane (white crystals, 14.76 g, 75% yield); m.p. 64-67°C; IR (KBr): 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.17 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 2.82 (dd, J_1 = 16.1 Hz, J_2 = 7.7 Hz, 1H), 3.02 (dd, J_1 = 16.1 Hz, J_2 = 5.5 Hz, 1H), 4.05 (apparent q, J = 7.1 Hz, 1H), 4.06 (apparent q, J = 7.1 Hz, 1H), 4.12 (apparent q, J = 7.1 Hz, 1H), 4.15 (dq, J_1 = 10.6 Hz, J_2 = 7.1 Hz, 1H), 4.49 (dd, J_1 = 7.7 Hz, J_2 = 5.5 Hz, 1H), 7.2-7.7 (m, 10H); ^{13}C-NMR ($CDCl_3$): 13.9, 14.0, 38.1, 60.3, 61.1, 61.7, 127.7, 127.8, 128.2, 128.6, 128.7, 130.2, 135.9, 139.3, 170.7, 171.6.

Diethyl 2-cinnamyl-N-(diphenylmethylene)aspartate, 6 f. A solution of **2 g** (13.37 g, 37.8 mmole) and cinnamyl bromide (8.99 g, 45.6 mmole) in anhydrous acetonitrile (75 mL) was added dropwise to a stirred mixture, kept at 0°C, of tetra-*n*-butylammonium bromide (1.26 g, 3.90 mmole), sodium ethoxide (10.38 g, 152.0 mmole) (previously prepared from 3.5 g of sodium and 150 ml of absolute ethanol and evaporation of the solvent to dryness) and anhydrous acetonitrile (125 mL). The stirred mixture was left overnight at this temperature (GLC monitoring). The solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x150 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford **6 f** as a thick oil which crystallized when was dried *in vacuum* and was purified by recrystallization in hexane (white crystals, 10.48 g, 59% yield); m.p. 71-73°C; IR (KBr): 1729 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.05 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 2.89 (d, J = 14.5 Hz, 1H), 2.97 (d, J = 14.5 Hz, 1H), 3.03 (ddd, J_1 = 14.0 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, 1H), 3.08 (ddd, J_1 = 14.0 Hz, J_2 = 7.7 Hz, J_3 = 0.7 Hz, 1H), 3.64 (dq, J_1 = 11.0 Hz, J_2 = 7.1 Hz, 1H), 3.66 (dq, J_1 = 11.0 Hz, J_2 = 7.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 6.21 (dt, J_1 = 15.7 Hz, J_2 = 7.3 Hz, 1H), 6.50 (d, J = 15.7 Hz, 1H), 7.10-7.60 (m, 15H); ^{13}C-NMR ($CDCl_3$): 12.9, 13.2, 40.9, 41.6, 59.5, 59.9, 67.1, 124.1, 125.4, 126.4, 127.0, 127.1, 127.5, 127.6, 127.7, 127.8, 129.4, 133.3, 135.9, 136.7, 139.8, 166.6, 169.7, 171.7.

Diethyl 2-cinnamylaspartate, 7 f. 1M Hydrochloric acid (85 mL, 85 mmole) was added to a solution of **6 f** (3.06 g, 6.53 mmole) in diethyl ether (100 mL) and the vigorously stirred mixture left overnight at room temperature. The ethereal phase was discarded and the aqueous layer was washed with diethyl ether (3x75 mL) to eliminate residual benzophenone. The aqueous phase was basified with potassium carbonate and extracted with ethyl acetate (4x75 mL). The combined ethyl acetate extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to yield **7 f** as an oil (1.59 g, 80%); b.p. 170-175°C (oven temperature) / 0.3 mm Hg; IR (film): 3383, 3319, 1733 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.20 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 7.3 Hz, 3H), 1.90-2.15 (broad s, 2H), 2.41 (ddd, J_1 = 13.7 Hz, J_2 = 8.4 Hz, J_3 = 1.1 Hz, 1H), 2.52 (ddd, J_1 = 13.7 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz, 1H), 2.53 (d, J = 16.6 Hz, 1H), 2.98 (d, J = 16.6 Hz, 1H), 4.09 (q, J = 7.3 Hz, 2H), 4.16 (apparent q, J = 7.3 Hz, 1H), 4.17 (apparent q, J = 7.3 Hz, 1H), 6.05 (ddd, J_1 = 15.7 Hz, J_2 = 8.4 Hz, J_3 = 6.8 Hz, 1H), 6.44 (d, J = 15.7 Hz, 1H), 7.15-7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.0, 14.1, 43.1, 43.6, 59.0, 60.5, 61.2, 122.9, 126.1, 127.4, 128.4, 134.6, 136.7, 171.2. Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.85; H, 7.60; N, 4.59. Found: C, 66.81; H, 7.66; N, 4.61.

2-Cinnamylaspartic acid hydrochloride, 8. 6M Hydrochloric acid (40 mL, 240 mmole) was added to **7 f** (1.00 g, 3.27 mmole) and the stirred mixture left at room temperature until dissolution, then it was heated at 70°C for

2 d (^{1}H-NMR monitoring). The solvent was evaporated to give a crude which was purified by digestion in chloroform. Compound **8** (0.57 g, 61% yield) was obtained as a white powdery solid; m.p. 146-149°C; IR (KBr): 3700-2200 (broad), 1732 (broad) cm^{-1}; ^{1}H-NMR (CD_3OD): 2.73 (apparent d, J = 7.7 Hz, 1H), 2.78 (apparent d, J = 7.7 Hz, 1H), 2.86 (d, J = 17.9 Hz, 1H), 3.17 (d, J = 17.9 Hz, 1H), 6.15 (dt, J_1 = 15.7 Hz, J_2 = 7.7 Hz, 1H), 6.61 (d, J = 15.7 Hz, 1H), 7.12-7.43 (m, 5H); ^{13}C-NMR (CD_3OD): 38.7, 40.0, 60.9, 120.0, 126.9, 128.3, 128.9, 137.0, 137.2, 171.4, 172.3. Anal. Calcd. for $C_{13}H_{15}NO_4$.HCl: C, 54.72; H, 5.66; N, 4.91; Cl, 12.45. Calcd. for $C_{13}H_{15}NO_4$.HCl.1/2H_2O: C, 53.05; H, 5.83; N, 4.76; Cl, 11.83. Found: C, 53.65; H, 5.65; N, 4.84; Cl, 11.25.

Diethyl 2-(3-phenylpropyl)aspartate, ***9***. A stirred mixture of **7f** (1.75 g, 5.73 mmole), 10% palladium on charcoal (0.17 g) and absolute ethanol (50 mL) was hydrogenated at atmospheric pressure and room temperature. After 2 h (TLC monitoring) the mixture was filtered through Celite and the solvent from the filtrate was evaporated, yielding **9** (1.62 g, 92%) as an oil; b.p. 155°C (oven temperature) / 0.3 mm Hg; IR (film): 3388, 3200-2400 (broad), 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.19 (t, J = 7.1 Hz, 3H), 2.00 (t, J = 7.1 Hz, 3H), 1.45-1.70 (m, 4H), 1.94-2.12 (broad s, 2H), 2.44 (d, J = 16.8 Hz, 1H), 2.70 (d, J = 16.8 Hz, 1H), 2.55 (apparent t, J = 5.5 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 4.11 (apparent q, J = 7.1 Hz, 1H), 4.12 (apparent q, J = 7.1 Hz, 1H), 7.1-7.3 (m, 5H); ^{13}C-NMR ($CDCl_3$): 13.8, 24.8, 35.3, 38.3, 41.9, 59.3, 60.7, 61.4, 125.7, 128.0, 128.1, 141.2, 170.9, 174.0. Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.20; N, 4.51.

2-(3-Phenylpropyl)aspartic acid hydrochloride, ***10***. It was prepared from **9** in 69% yield as for **8**; white powdery solid; m.p. 138-143°C; IR (KBr): 3700-2400 (broad), 1755, 1727 cm^{-1}; ^{1}H-NMR (CD_3OD): 1.50-1.95 (m, 4H), 2.55-2.67 (apparent t, J = 6.9 Hz, 2H), 2.77 (d, J = 17.9 Hz, 1H), 3.07 (d, J = 17.9 Hz, 1H), 7.09-7.27 (m, 5H); ^{13}C-NMR (CD_3OD): 25.2, 35.4, 36.0, 38.9, 51.1, 126.3, 128.6, 128.7, 141.5, 172.2, 172.4; MS (m/e): 251 (M, 1), 206 (15), 104 (26), 91 (38), 57 (100). Anal. Calcd. for $C_{13}H_{17}NO_4$.HCl: C, 54.34; H, 6.32; N, 4.88; Cl, 12.18. Calcd. for $C_{13}H_{17}NO_4$.HCl.1/2H_2O: C, 52.69; H, 6.47; N, 4.73; Cl, 11.81. Found: C, 53.06; H, 6.44; N, 4.76; Cl, 11.68.

Ethyl 2-(2-phenylethyl)-N-(diphenylmethylene)glycinate, ***11***. A mixture of **1** (10.00 g, 37.4 mmole), potassium *tert* -butoxide (5.08 g, 45.4 mmole) and anhydrous tetrahydrofuran (50 mL) was stirred at room temperature, under nitrogen atmosphere, for 20 min; then a solution of 1-iodo-2-phenylethane (11.17 g, 48.2 mmole) in tetrahydrofuran (50 mL) was added and the stirred mixture left at room temperature for 45 min (TLC monitoring). A saturated solution of ammonium chloride was added (200 mL) and the solution extracted with diethyl ether (3x150 mL). The organic layer was washed with distilled water (2x200 mL) and dried with anhydrous sodium sulfate. After evaporation of the solvent, crude **11** (thick oil, 10.68 g, 80% yield) was obtained; IR (film): 1737 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.22 (t, J = 7.1 Hz, 3H), 2.15-2.30 (m, 2H), 2.44-2.70 (m, 2H), 4.06 (dd, J_1 = 5.5 Hz, J_2 = 7.7 Hz, 1H), 4.13 (m, 2H), 7.05-7.80 (m, 15H); GLC-MS (m/e): 372 (M+1, 1), 298 (45), 267 (76), 238 (58), 193 (82), 165 (32), 91 (100).

Diethyl 2-(2-phenylethyl)aspartate, ***13***. A solution of crude **11** (0.99 g, 2.7 mmole) and ethyl iodoacetate (1.14 g, 5.3 mmole) in anhydrous acetonitrile (10 mL) was added dropwise (20 min) to a stirred mixture of sodium ethoxide (0.73 g, 10.7 mmole), tetra-*n*-butylammonium fluoride (0.77 g, 2.9 mmole) and anhydrous acetonitrile (15 mL) kept at room temperature under nitrogen atmosphere. The stirred mixture was left at this temperature for 24 h (TLC monitoring showed no further evolution of the reaction). The solvent was evaporated and the residue was dissolved in diethyl ether (50 mL). The ethereal solution was washed with distilled water (6x100 mL), the organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to give an orange oil (0.92 g), containing **12**, which was not further purified. This crude mixture was dissolved in diethyl ether (50 mL) and 1M hydrochloric acid (50 mL, 50.0 mmole) was added. The vigorously stirred mixture was left at room temperature for 2 d. The ethereal phase was discarded. The aqueous phase was basified with potassium carbonate and extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with distilled water (2x200 mL) and dried with anhydrous sodium sulfate. The solvent was evaporated to afford a yellow oil (0.50 g) identified as a 53:47 mixture (^{1}H-NMR) of **13** (0.26 g, 34% yield from **11**) and ethyl 2-(2-phenylethyl)glycinate, **14** (0.23 g, 42% recovery from **11**). Pure samples of both products were obtained by column chromatography through silica gel under pressure.

Compound **13** was eluted with hexanes-ethyl acetate 85:15; oil; b.p. 250°C (oven temperature) / 17 mm Hg; IR (film): 3387, 3323, 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.22 (t, J = 6.9 Hz, 3H), 1.24 (t, J = 6.9 Hz, 3H), 1.80-2.00 (m, 4H), 2.45-2.70 (m, 2H), 2.55 (d, J = 16.4 Hz, 1H), 2.95 (d, J = 16.4 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 4.16 (q, J = 6.9 Hz, 2H), 7.08-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.1, 14.2, 29.9, 42.0, 43.3, 58.9, 60.6, 61.3, 126.0, 128.3, 128.4, 141.1, 171.3, 176.0; MS (m/e): 293 (M, 1), 220 (100), 174 (15), 132 (37), 91 (80). Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 64.91; H, 7.83; N, 4.50. Compound **14** was eluted with hexanes-ethyl acetate 75:25; oil; b.p. 200°C (oven temperature) / 17 mm Hg (lit.[30] b.p. 161-62°C / 16 mm Hg); IR (film): 3383, 3320, 1732 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.15 (t, J = 7.1 Hz, 3H), 1.61 (broad s, 2H), 1.60-1.82 (m, 1H), 1.88-2.07 (m, 1H), 2.50-2.70 (m, 2H), 3.32 (dd, J_1 = 8.0 Hz, J_2 = 5.5 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 7.00-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.1, 31.8, 36.3, 53.8, 60.7, 125.8, 128.2, 128.3, 141.2, 175.8; MS (m/e): 207 (M, 4), 134 (77), 117 (27), 91 (100).

*2-(2-Phenylethyl)aspartic acid hydrochloride, **15**.* 6M Hydrochloric acid (10 mL) was added to **13** (0.060 g, 0.2 mmole) and the mixture refluxed for 2 d (^{1}H-NMR monitoring). The aqueous solution was washed with chloroform (3x20 mL). After water evaporation compound **15** was obtained (0.55 g, 92% yield) as a white crystalline solid; m.p. 192-194°C; IR (KBr): 3423 (broad), 3300-2400, 1759, 1734 cm^{-1}; ^{1}H-NMR (D_2O): 1.92-2.10 (m, 2H), 2.38-2.68 (m, 2H), 2.78 (d, J = 18.1 Hz, 1H), 3.04 (d, J = 18.1 Hz, 1H), 7.06-7.23 (m, 5H); ^{13}C-NMR (d_6-DMSO): 29.4, 37.4, 42.3, 59.4, 126.3, 128.2, 128.8, 140.9, 170.2, 172.4; MS (m/e): 237 (M, 1), 219 (4), 202 (16), 192 (9), 174 (7), 147 (24), 146 (19), 129 (46), 91 (100).

*Diethyl 2-(2-phenylethyl)-N-(diphenylmethylene)glutamate, **16**.* A solution of crude **11** (12.55 g, 33.8 mmole) and ethyl acrylate (6.76 g, 67.6 mmole) in anhydrous acetonitrile (150 mL) was added dropwise (30 min) to a stirred mixture of sodium ethoxide (4.59 g, 67.6 mmole), tetra-*n*-butylammonium bromide (1.09 g, 3.4 mmole) and anhydrous acetonitrile (100 mL), kept under nitrogen atmosphere at 0°C. Then the stirred mixture was left for 16 h at this temperature (TLC monitoring). The sodium ethoxide was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x150 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated to afford crude **16** (thick oil, 12.17 g, 76%); IR (film): 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.08 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 2.13-2.35 (m, 4H), 2.45-2.70 (m, 4H), 3.55-3.71 (m, 2H), 3.93-4.07 (m, 2H), 7.10-7.55 (m, 15H); ^{13}C-NMR ($CDCl_3$): 13.8, 14.1, 29.3, 30.2, 32.4, 39.9, 60.3, 60.4, 67.8, 125.8, 127.7, 127.8, 128.3, 128.5, 130.0, 137.0, 140.8, 142.0, 166.7, 173.6, 173.7.

*Ethyl 2-(2-phenylethyl)pyroglutamate, **17**.* A 15% aqueous solution of citric acid (350 mL) was added to a solution of **16** (11.91 g, 25.3 mmole) in tetrahydrofuran (200 mL) and the stirred solution left at room temperature for 3 d. Tetrahydrofuran was evaporated and the aqueous solution was basified with potassium carbonate and extracted with ethyl acetate (3x200 mL). The organic layer was washed with distilled water (2x300 mL), dried with anhydrous sodium sulfate and the solvent was evaporated. The resulting crude was purified by distillation *in vacuum* yielding **17** (3.57 g, 54%) as a thick colourless oil; b.p. 240-250°C (oven temperature) / 0.4 mm Hg; IR (film): 3353, 3228, 1733, 1703 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.28 (t, J = 7.1 Hz, 3H), 1.90-2.24 (m, 3H), 2.34-2.65 (m, 5H), 4.19 (q, J = 7.1 Hz, 2H), 6.48 (broad s, 1H), 7.11-7.31 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.1, 29.5, 30.5, 30.8, 41.0, 61.7, 65.3, 126.2, 128.2, 128.5, 140.2, 173.2, 176.9; MS (m/e): 262 (M + 1, 1), 234 (24), 188 (38), 160 (5), 128 (7), 91 (100). Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 69.06; H, 7.11; N, 5.21. Found: C, 68.94; H, 7.33; N, 5.36.

*Ethyl N-tert-butoxycarbonyl-2-(2-phenylethyl)pyroglutamate, **18**.* A solution of **17** (3.00 g, 11.5 mmole), triethylamine (1.16 g, 11.5 mmole), 4-dimethylaminopyridine (1.40 g, 11.5 mmole) and di-*tert*-butyldicarbonate (5.01 g, 23.0 mmole) in dichloromethane (50 mL) was stirred at room temperature, under nitrogen atmosphere, for 16 h (TLC monitoring). The solution was washed with 1M hydrochloric acid (4x100 mL), then with distilled water until neutrality. The organic layer was dried with anhydrous sodium sulfate and evaporated to afford **18** (thick oil, 3.48 g, 84% yield); IR (film): 1791, 1721 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.23 (t, J = 7.1 Hz, 3H), 1.43 and 1.47 (two s, 9H), 2.05-2.31 (m, 3H), 2.42-2.71 (m, 5H), 4.17 (q, J = 7.1 Hz, 2H), 7.10-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.1, 27.2, 27.9, 29.7, 30.7, 36.8, 61.7, 67.8, 83.7, 126.2, 128.3, 128.6, 140.8, 149.4, 172.8, 174.3; MS (m/e): 288 (M-CO_2Et, 1), 261 (4), 188 (71), 157 (27), 91

(100), 56 (24), 41 (45). Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.87. Found: C, 65.43; H, 7.31; N, 3.87.

*2-(2-Phenylethyl)glutamic acid, **19***. Its hydrochloride, **19.HCl**, was obtained in 70 % yield from **18** as for **15**. White and very hygroscopic solid (1.67 g, 70% yield); IR (KBr): 3400 (broad), 3300-2400, 1722 cm^{-1}; ^{1}H-NMR (CD_3OD): 2.00-2.85 (m, 8H), 7.15-7.33 (m, 5H); ^{13}C-NMR (CD_3OD): 29.1, 30.6, 32.1, 39.2, 63.8, 127.5, 129.2, 129.7, 141.2, 172.5, 175.3. Propylene oxide (1.66 g, 28.5 mmole) was added to a solution of **19.HCl** (1.20 g, 4.2 mmole) in anhydrous methanol (20 mL). The stirred solution was left at room temperature for 20 min, a white solid being formed after this time. This solid was collected by filtration and washed with methanol to yield **19** (0.94 g, 90%); m.p. 158-160°C; IR (KBr): 3423 (broad), 3300-2400, 1710 cm^{-1}; ^{1}H-NMR (D_6-DMSO): 1.70-2.10 (m, 4H), 2.13-2.35 (m, 1H), 2.36-2.55 (m, 2H), 2.56-2.85 (m, 1H), 7.05-7.35 (m, 5H); ^{13}C-NMR (D_6-DMSO): 29.6, 29.8, 31.8, 38.7, 62.7, 125.9, 128.3, 128.5, 141.9, 171.7, 174.6; MS (m/e): 234 (M-NH_3, 1), 188 (54), 128 (14), 91 (100). Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.59; H, 6.56; N, 5.50.

The dialkylated ketimine **20** was prepared from **1** via **2b** or via **21** as indicated in Scheme 3. Compound **20** was not purified, but the crude reaction mixture containing **20** was used for the preparation of **22**.

*Preparation of **20** from **2b** using sodium ethoxide as base*. A solution of crude **2b** (2.30 g, 6.00 mmole) and ethyl acrylate (3.20 g, 32.0 mmole) in anhydrous acetonitrile (50 mL) was added dropwise to a stirred mixture of sodium ethoxide (3.03 g, 44.5 mmole), tetra-*n*-butylammonium bromide (0.470 g, 1.46 mmole) and anhydrous acetonitrile (50 mL) kept at 0°C under nitrogen atmosphere. The stirred mixture was left overnight at this temperature (GLC monitoring). The solid was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (100 mL) and the ethereal solution washed with distilled water (4x75 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford crude **20** (orange oil, 2.12 g) contaminated with benzophenone and ethyl 3-ethoxypropanoate.

*Preparation of **20** from **2b** using potassium hydroxide as base*. A solution of crude **2b** (4.44 g, 11.6 mmole) and ethyl acrylate (1.67 g, 16.7 mmole) in anhydrous acetonitrile (25 mL) was added dropwise to a stirred mixture of powdered potassium hydroxide (1.48 g, 22.4 mmole), tetra-n-butylammonium bromide (0.240 g, 0.74 mmole) and anhydrous acetonitrile (25 mL) kept at 0°C under nitrogen atmosphere. The stirred mixture was left overnight at this temperature (GLC monitoring). The potassium hydroxide was filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether (100 mL) and the ethereal solution washed with distilled water. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford crude **20** (orange oil, 5.13 g) contaminated with benzophenone. IR (film): 1738, 1626 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.05 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H), 2.20-2.31 (m, 2H), 2.52 (apparent d, J = 8.0 Hz, 1H), 2.58 (apparent d, J = 8.0 Hz, 1H), 2.78-2.92 (m, 2H), 3.61 (q, J = 7.1 Hz, 2H), 3.97 (apparent q, J = 7.1 Hz, 1H), 3.98 (apparent q, J = 7.1 Hz, 1H), 6.14 (dt, J_1 = 16.1 Hz, J_2 = 8.0 Hz, 1H), 6.58 (d, J = 16.1 Hz, 1H), 7.05-7.90 (m, 15H).

*Diethyl N-(diphenylmethylene)glutamate, **21***. A solution of ethyl acrylate (14.50 g, 145.0 mmole) in anhydrous acetonitrile (50 mL) was added at room temperature to a stirred mixture of **1** (19.90 g, 72.2 mmole), potassium carbonate (29.92 g, 217.0 mmole), tetra-*n*-butylammonium bromide (2.33 g, 7.22 mmole) and anhydrous acetonitrile (250 mL). The mixture was left at room temperature for 5 h (GLC monitoring). The solid was filtered off and the solvent from the filtrate was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x150 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated, affording crude **21** (24.69 g, 93%) as a yellow oil, which was used in the next reaction without further purification; IR (film): 1736 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.14 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.17-2.37 (m, 4H), 3.95 (q, J = 7.1 Hz, 2H), 4.07 (t, J = 6.2 Hz, 1H), 4.11 (apparent q, J = 7.1 Hz, 1H), 4.13 (apparent q, J = 7.1 Hz, 1H), 7.15-7.85 (m, 10H).

*Preparation of **20** from **21** using sodium ethoxide as base*. A solution of crude **21** (23.14 g, 63.0 mmole) and cinnamyl bromide (14.93 g, 75.8 mmole) in anhydrous acetonitrile (100 mL) was added dropwise to a stirred mixture of sodium ethoxide (12.90 g, 189 mmole), tetra-*n*-butylammonium bromide (2.13 g, 6.61 mmole) and anhydrous acetonitrile (200 mL) kept at 0°C under nitrogen atmosphere. The stirred mixture was left at this temperature for 12 h (GLC monitoring). The solid was filtered off and the solvent from the filtrate was

evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution washed with distilled water (4x150 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to give crude **20** (orange oil, 27.39 g) contaminated with benzophenone and cinnamyl ethyl ether.

Preparation of ***20*** *from* ***21*** *using potassium hydroxide as base.* A solution of **21** (4.71 g, 12.8 mmole) and cinnamyl bromide (3.13 g, 15.9 mmole) in anhydrous acetonitrile (50 mL) was added dropwise to a stirred mixture of powdered potassium hydroxide (2,56 g, 38.8 mmole), tetra-*n*-butylammonium bromide (0.430 g, 1.33 mmole) and anhydrous acetonitrile (50 mL) kept at 0°C under nitrogen atmosphere. The stirred reaction mixture was left for 16 h at this temperature (GLC monitoring). The solid was filtered off and the solvent from the filtrate was evaporated. The residue was dissolved in diethyl ether (100 mL) and the ethereal solution was washed with distilled water (4x50 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated, yielding crude **20** (orange oil, 5.40 g) contaminated with benzophenone.

Ethyl 2-cinnamylpyroglutamate, ***22***. Crude ketimine **20** (27.37 g) (obtained from **21** using sodium ethoxide as base) was dissolved in tetrahydrofuran (250 mL) and a 15% aqueous solution of citric acid (450 g of solution, 351 mmole of citric acid) was added. The stirred solution was left at room temperature for 48 h. Tetrahydrofuran was evaporated and the aqueous solution was washed with diethyl ether (2x200 mL) to eliminate neutral products. Then it was basified with potassium carbonate and extracted with chloroform (3x200 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford **22** (6.28 g, 34% overall yield from **1**) as an oil, which was purified by *vacuum* distillation and crystallized spontaneously upon standing in the refrigerator ; b.p. 200-205°C (oven temperature) / 0.3 mm Hg; m.p. 62-64°C; IR (KBr): 3205, 3107, 1739, 1701 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.28 (t, J = 7.1 Hz, 3H), 2.11-2.21 (m, 2H), 2.36-2.55 (m, 2H), 2.36-2.55 (m, 2H), 2.56 (dd, J_1 = 13.9 Hz, J_2 = 8.4 Hz, 1H), 2.81 (ddd, J_1 = 13.9 Hz, J_2 = 6.6 Hz, J_3 = 1.5 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 6.04 (ddd, J_1 = 15.7 Hz, J_2 = 8.4 Hz, J_3 = 6.6 Hz, 1H), 6.18 (broad s, 1H), 6.50 (d, J = 15.7 Hz, 1H), 7.20-7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.1, 29.7, 30.0, 42.6, 61.7, 65.4, 122.1, 126.2, 127.6, 128.4, 135.1, 136.4, 173.0, 176.9; MS (m/e): 273 (M, 3), 200 (11), 156 (100), 128 (34), 115 (19), 100 (17). Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.32; H, 7.11; N, 4.96.

Compound **22** was also obtained, following an analogous procedure, by hydrolysis of crude **20** prepared from **21** using potassium hydroxide as base (33% overall yield from **1**) and by hydrolysis of crude **20** prepared from **2b** using sodium ethoxide and potassium hydroxide as bases (31% and 28% overall yields from **1**, respectively).

Reaction of ketimine ***20*** *with hydrogen (2 and 3 atm of pressure) and 10% Pd-C in ethanol.* A mechanically stirred mixture of **20** (12.38 g, 25.6 mmole), 10% palladium on charcoal (1.05 g) and absolute ethanol (100 mL) was hydrogenated at 2 atm of hydrogen pressure and room temperature. After 36 h (TLC monitoring) the reaction mixture was filtered through Celite and the solvent from the filtrate was evaporated. The residue was chromatographed on silica gel under pressure, with increasing polarity mixtures as eluents, from hexanes-ethyl acetate 95:5 to ethyl acetate. The following fractions were obtained: diethyl *N*-(diphenylmethyl)-2-(3-phenylpropyl)glutamate, **23**, (2.53 g, 20% yield); IR (film): 3269 (broad), 3090-2870, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.11 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.35-1.70 (m, 4H), 1.75-1.98 (m, 2H), 2.08-2.20 (m, 2H), 2.21 (broad s, 1H), 2.30-2.40 (m, 2H), 3.95 (q, J = 7.1 Hz, 2H), 3.98 (q, J = 7.1 Hz, 2H), 4.54 (s, 1H), 7.00-7.45 (m, 15H); ethyl 2-(3-phenylpropyl)pyroglutamate, **24** (1.12 g, 16% yield). When an analogous reaction was performed at 3 atm of pressure, **24** was the only isolated compound (22% yield).

Preparation of ethyl 2-(3-phenylpropyl)pyroglutamate, ***24****, by catalytic hydrogenation of* ***22***. A stirred mixture of **22** (1.20 g, 4.39 mmole), 10% palladium on charcoal (0.12 g) and absolute ethanol (25 mL) was hydrogenated at atmospheric pressure and room temperature. After 1 h (GLC monitoring), the reaction mixture was filtered through Celite and the solvent from the filtrate was evaporated to afford **24** (1.17 g, 98% yield); colourless oil; b.p. 195-200°C (oven temperature) / 0.3 mm Hg; IR (film): 3220 (broad), 2938 (broad), 1736, 1701 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.13 (t, J = 7.1 Hz, 3H), 1.35-1.97 (m, 5H), 2.17-2.38 (m, 3H), 2.50 (apparent t, J = 7.2 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 7.00-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$): 13.9, 25.4, 29.6, 30.4, 35.4, 38.5, 61.4, 65.5, 125.8, 128.1, 128.2, 141.1, 173.3, 177.2. Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.75; H, 7.69; N, 5.04.

Ethyl N-tert-butoxycarbonyl-2-(3-phenylpropyl)pyroglutamate, 25. It was obtained in 95% yield from **24** as for **18**. Oil; mixture 75:25 of geometric isomers; IR (film): 1789, 1747 (broad) cm^{-1}; ^1H-NMR ($CDCl_3$): 1.21 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.37 (s, 9H), 1.43 (s, 9H), 1.40-1.72 (m, 3H+3H), 1.80-2.08 (m, 3H+3H), 2.20-2.60 (m, 4H+4H), 4.15 (q, J = 7.1 Hz, 2H), 4.16 (m, 2H).

2-(3-Phenylpropyl)glutamic acid, 26. Its hydrochloride, **26.HCl**, was prepared from **25** in 75% yield as for **15**, and from **24** in 48% yield as for **8**. M.p. 151-156°C (digestion with chloroform); IR (KBr): 3500-2500, 1750, 1722 cm^{-1}; ^1H-NMR (D_6-DMSO): 1.30-1.50 (m, 1H), 1.60-1.90 (m, 3H), 1.90-2.25 (m, 3H), 2.30-2.50 (m, 3H), 7.05-7.25 (m, 5H); ^{13}C-NMR (D_6-DMSO): 24.9, 28.3, 30.7, 35.0, 35.1, 61.7, 126.0, 128.3, 128.4, 141.4, 172.0, 173.2. Anal. Calcd. for $C_{14}H_{20}NO_4Cl$: C, 55.79; H, 6.69; N, 4.65; Cl, 11.61. Found: C, 55.67; H, 6.68; N, 4.59; Cl, 11.58. Free amino acid **26** was obtained from its hydrochloride in 30% yield as for **19**. M.p. 178-181°C; IR (KBr): 3200-2500, 1709 cm^{-1}; ^1H-NMR (D_6-DMSO): 1.40-1.90 (m, 6H), 2.10-2.60 (m, 4H), 7.00-7.30 (m, 5H); ^{13}C-NMR (D_6-DMSO): 25.3, 29.5, 30.8, 35.5, 36.4, 62.6, 125.8, 128.3, 128.4, 142.0, 171.6, 174.4; MS (m/e): 247 ($M-NH_4$, 20), 202 (100), 128 (31), 91 (54), 84 (33).

Diethyl 4-oxo-1-(diphenylmethylenamino)cyclohexane-1,3-dicarboxylate, 27. A solution of **1** (12.73 g, 45.8 mmole) and ethyl acrylate (23.14 g, 231 mmole) in anhydrous acetonitrile (100 mL) was added to a stirred mixture, kept at 0°C under argon atmosphere, of sodium ethoxide (18.87 g, 277.0 mmole), tetra-*n*-butylammonium bromide (1.50 g, 4.65 mmole) and anhydrous acetonitrile (100 mL). The stirred reaction mixture was left at 0°C, under argon atmosphere, for 16 h (GLC monitoring). The solid was filtered off and the solvent from the filtrate was evaporated. The residue was dissolved in diethyl ether (200 mL) and the ethereal solution was washed with diluted hydrochloric acid (3x150 mL) and with distilled water. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to give crude **27** (orange oil, 9.23 g) contaminated with benzophenone and ethyl 3-ethoxypropanoate; ^1H-NMR ($CDCl_3$): 1.08 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.00-2.65 (m, 6H), 3.71 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 7.05-7.90 (m, 10H), 9.6 (s, 1H). This compound was not further purified.

Diethyl 1-amino-4-oxocyclohexane-1,3-dicarboxylate, 28. Crude **27** (9.23 g) obtained as indicated above was dissolved in diethyl ether (275 mL), 1M hydrochloric acid (275 mL, 275 mmole) was added to the vigorously stirred ethereal solution and the reaction mixture left at room temperature for 24 h (TLC monitoring). The ethereal phase was discarded and the aqueous phase was washed with diethyl ether (3x150 mL) to eliminate residual benzophenone. Then the aqueous layer was neutralized with potassium hydrogeno carbonate and extracted with ethyl acetate (3x150 mL). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to afford **28** (4.44 g, 38% overall yield from **1**) as a yellow oil. It was purified by column chromatography on silica gel under pressure with hexanes-ethyl acetate 6:4 as eluent; b.p. 130°C (oven temperature) / 0.3 mm Hg; IR (film): 3381 and 3318 (weak), 1729, 1659 cm^{-1}; ^1H-NMR ($CDCl_3$): 1.25 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.60 (broad s, 2H), 1.65-1.80 (m, 1H), 1.95-2.10 (m, 1H), 2.25 (d, J = 16.0 Hz, 1H), 2.15-2.37 (m, 1H), 2.50 (d, J = 16.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 9.70 (s, 1H).

Ethyl 5-amino-2,3,4,5,6,7-hexahydro-3-oxo-1H-indazole-5-carboxylate, 29. A solution of hydrazine hydrate (0.41 g, 8.06 mmole) in ethanol (2 mL) was added to a stirred solution of **28** (2.04 g, 7.93 mmole) in ethanol (5 mL). The reaction mixture was heated overnight at 70°C (TLC monitoring), then it was cooled at room temperature and a white solid precipitated. This solid was collected by filtration and washed with cold ethanol, yielding **29** (white hygroscopic crystals, 1.48 g, 83%); m.p. 90-92°C; IR (KBr): 3625-2010, 1746, 1654, 1583 cm^{-1}; ^1H-NMR (CD_3OD): 1.23 (t, J = 7.2 Hz, 3H), 1.90 (apparent dt, J_1 = 13.4 Hz, J_2 = 6.2 Hz, 1H), 2.12 (ddd, J_1 = 13.4 Hz, J_2 = 7.7 Hz, J_3 = 6.3 Hz, 1H), 2.33 (d, J = 15.5 Hz, 1H), 2.55-2.66 (m, 2H), 2.83 (d, J = 15.5 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H); ^{13}C-NMR (CD_3OD): 14.4, 19.3, 30.5, 32.1, 57.8, 62.4, 99.1, 144.9, 163.4, 177.1; MS (m/e): 225 (M, 11), 208 (16), 152 (100), 135 (18), 110 (42). Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Calcd. for $C_{10}H_{15}N_3O_3 \cdot 1/2\ H_2O$: C, 51.26; H, 6.89; N, 17.94. Found: C, 51.70; H, 6.96; N, 17.88.

5-Amino-2,3,4,5,6,7-hexahydro-3-oxo-1H-indazole-5-carboxylic acid hydrochloride, 30. It was prepared from **29** in 95% yield as for **8**. Recrystallized from 6M hydrochloric acid; white crystals; m.p. 269-274°C (dec); IR (KBr): 3600-3300, 3300-2200, 1637, 1581 cm^{-1}; ^1H-NMR (CD_3OD): 2.22-2.37 (apparent dt, J_1 =

14.8 Hz, J_2 = 6.7 Hz, 1H), 2.37-2.52 (m, 1H), 2.71-2.87 (m, 1H), 2.82 (d, J = 16.1 Hz, 1H), 2.99 (apparent dt, J_1 = 17.9 Hz, J_2 = 6.3 Hz, 1H), 3.19 (d, J = 16.1 Hz, 1H); ^{13}C-NMR (CD_3OD): 18.5, 26.7, 28.8, 58.6, 97.4, 145.8, 156.0, 172.3; MS (m/e): 198 (M, 3), 180 (18), 152 (31), 110 (100), 88 (17), 44 (82), 42 (18). Anal. Calcd. for $C_8H_{11}N_3O_3$.HCl: C, 41.12; H, 5.18; N, 17.98. Calcd. for $C_8H_{11}N_3O_3$.1.5HCl: C, 38.15; H, 5.00; N, 16.68. Found: C, 40.13; H, 5.19; N, 17.24.

Diethyl 1-tert-butoxycarbonylamino-4-oxocyclohexane-1,3-dicarboxylate, 31. A solution of di-*tert*-butyl dicarbonate (3.26 g, 14.5 mmole) in chloroform (10 mL) was added to a stirred solution of **28** (3.34 g, 13.0 mmole) in chloroform (20 mL). The reaction mixture was refluxed overnight (TLC monitoring). The solvent was evaporated to dryness and the solid residue recrystallized in hexane to give **31** (white crystals, 3.69 g, 80% yield); m.p. 90-92°C; IR (KBr): 3360, 1708, 1666, 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.21 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.35 (broad s, 9H), 1.87-2.05 (m, 1H), 2.21-2.35 (m, 3H), 2.43 (d, J = 16.1 Hz, 1H), 2.55 (d, J = 16.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 4H), 4.81 (broad s, 1H), 9.7 (s, 1H); ^{13}C-NMR ($CDCl_3$): 13.9, 14.0, 25.3, 25.9, 28.0, 31.9, 56.6, 60.3, 61.1, 79.5, 93.0, 154.6, 171.5, 171.7, 173.3. Anal. Calcd. for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61; N, 3.90. Found: C, 57.30; H, 7.46; N, 3.80.

Ethyl 5-tert-butoxycarbonylamino-1,3,4,5,6,7-hexahydro-3-oxo-2,1-benzisoxazole-5-carboxylate, 32. A solution of hydroxylamine hydrochloride (0.433 g, 6.23 mmole) in water (1 mL) was added to a stirred solution of sodium hydroxide (0.43 g, 10.5 mmole) in water (5 mL) kept at 0°C. Then a solution of **31** (1.55 g, 4.34 mmole) in ethanol (5 mL) was added dropwise and the stirred reaction mixture left at 0°C for one hour (TLC monitoring). Concentrated hydrochloric acid was added dropwise to the solution until pH 3-4. Ethanol was eliminated *in vacuum* and the aqueous solution was extracted with chloroform (3x5 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was recrystallized in diethyl ether-hexane 3:1 to afford **32** (1.14 g, 80% yield); m.p. 139-141°C; IR (KBr): 3700-2600, 1722 (broad), 1637 cm^{-1}; ^{1}H-NMR (CD_3OD): 1.22 (t, J = 7.1 Hz, 3H), 1.38 (s, 9H), 1.95-2.15 (m, 1H), 2.35-2.60 (m, 3H), 2.52 (d, J = 16.4 Hz, 1H), 2.62 (d, J = 16.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 7.8 (broad s, 1H); ^{13}C-NMR (CD_3OD): 13.7, 18.4, 27.6, 27.9, 57.9, 61.7, 79.9, 94.2, 156.6, 164.1, 173.5, 174.3. Anal. Calcd. for $C_{15}H_{22}N_2O_6$: C, 55.19; H, 6.80; N, 8.59. Found: C, 55.20; H, 6.89; N, 8.52.

Ethyl 5-tert-butoxycarbonylamino-1-cinnamyl-1,3,4,5,6,7-hexahydro-3-oxo-2,1-benzisoxazole-5-carboxylate. A solution of cinnamyl ethyl carbonate (0.074 g, 0.37 mmole) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.03 mmole) in anhydrous tetrahydrofuran (5 mL) was added under nitrogen atmosphere to a stirred solution of **32** (0.100 g, 0.31 mmole) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was refluxed under nitrogen atmosphere for 8 h (TLC monitoring). The solvent was evaporated and the residue was chromatographed through silica-gel under pressure eluting with hexanes-ethyl acetate 9:1. The title compound was obtained as an oil (0.085 g, 63 % yield); ^{1}H-NMR ($CDCl_3$): 1.17 (t, J = 7.2 Hz, 3H), 1.32 (s, 9H), 2.03-2.18 (m, 1H), 2.13-2.68 (m, 3H), 2.43 (d, J = 16.1 Hz, 1H), 2.59 (d, J = 16.1 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.20 (d, J = 6.6 Hz, 2H), 4.85 (s, 1H), 6.05 (dt, J_1 = 15.7 Hz, J_2 = 6.6 Hz, 1H), 6.55 (d, J = 15.7 Hz, 1H), 7.15-7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$): 14.0, 19.2, 26.9, 28.1, 29.0, 53.6, 57.1, 61.4, 80.2, 98.2, 119.9, 126.5, 128.3, 128.5, 135.5, 135.7, 154.9, 163.5, 170.0, 172.8.

Ethyl 5-amino-1,3,4,5,6,7-hexahydro-3-oxo-2,1-benzisoxazole-5-carboxylate hydrochloride, 33. Dry hydrogen chloride was bubbled into a stirred solution of **32** (0.146 g, 0.447 mmole) in anhydrous diethyl ether (15 mL). After 2 h a white solid precipitated from the solution, which was filtered and washed with cold diethyl ether to give **33** (0.080 g, 68% yield); IR (film): 3670-2300, 1742, 1710, 1624 cm^{-1}; ^{1}H-NMR (CD_3OD): 1.32 (t, J = 7.3 Hz, 3H), 2.23 (dt, J_1 = 14.2 Hz, J_2 = 6.9 Hz, 1H), 2.44 (dt, J_1 = 14.2 Hz, J_2 = 6.9 Hz, 1H), 2.61 (d, J = 16.4 Hz, 1H), 2.52 (dt, J_1 = 19.0 Hz, J_2 = 6.9 Hz, 1H), 2.84 (dt, J_1 = 19.0 Hz, J_2 = 6.9 Hz, 1H), 2.97 (d, J = 16.4 Hz, 1H), 4.34 (q, J = 7.3 Hz, 2H); ^{13}C-NMR (CD_3OD): 13.5, 18.1, 25.8, 27.9, 58.1, 63.7, 92.0, 162.5, 170.2, 172.4. This compound was unstable, even under inert atmosphere.

Diethyl (E)-2-(2-phenylethyl)-3,4-dehydroglutamate, 36, and ethyl 2-(2-phenylethyl)-3,4-dehydro-pyroglutamate, 37. A solution of **11** (3.48 g, 9.38 mmole) and ethyl propiolate (2.02 g, 20.6 mmole) in anhydrous acetonitrile (25 mL) was added dropwise to a stirred mixture, kept at 0°C, of sodium ethoxide (1.92

g, 28.2 mmole), tetra-*n*-butylammonium bromide (0.320 g, 0.993 mmole) and anhydrous acetonitrile (50 mL). The stirred mixture was left overnight at 0°C. The solid was filtered off and the solvent from filtrate was evaporated. The residue was dissolved in diethyl ether (75 mL) and the ethereal solution washed with distilled water (4x50 mL). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to afford a brown oil (2.75 g) containing the ketimines **34** and **35**. This crude mixture was not further purified. It was dissolved in diethyl ether (75 mL) and 1M hydrochloric acid (75 mL, 75.0 mmole) was added to the vigorously stirred ethereal solution. The stirred mixture was left at room temperature for 2 d (TLC monitoring). The two phases were separated. The aqueous phase was washed with diethyl ether (3x50 mL). Then it was basified with potassium carbonate and extracted with ethyl acetate. The ethyl acetate extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a residue which was purified by *vacuum* distillation, yielding **36** (0.39 g, 14% overall yield from **11**) as a colourless oil. B.p. 125°C (oven temperature) / 0.3 mm Hg; IR (film): 3388, 3325, 1722, 1652 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.29 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.65 (broad s, 2H), 1.80-2.21 (m, 2H), 2.50-2.75 (m, 2H), 4.19 (q, J = 7.1 Hz, 4H), 6.15 (d, J = 15.2 Hz, 1H), 7.12 (d, J = 15.2 Hz, 1H), 7.12-7.37 (m, 5H). The combined ethereal extracts were dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was digested with hexane to eliminate benzophenone and then it was distilled *in vacuum* to afford **37** (0.45 g, 19% overall yield from **11**) as a colourless oil. B.p. 150°C (oven temperature) / 0.3 mm Hg; IR (film): 3500-3150, 3150-2850, 1743, 1701, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.24 (t, J = 7.1 Hz, 3H), 1.95-2.18 (m, 1H), 2.19-2.35 (m, 1H), 2.45-2.60 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 6.07 (dt, J_1 = 5.8 Hz, J_2 = 1.5 Hz, 1H), 6.60 (broad s, 1H), 7.03 (dt, J_1 = 5.8 Hz, J_2 = 1.5 Hz, 1H), 7.04-7.53 (m, 5H); when the signal at 6.60 was selectively irradiated, absorptions at 6.07 and 7.03 were converted into doublets with J = 5.8 Hz.

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