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Amidoalkylation of Aromatics with Glyoxylic Acid-γ-Lactam Adducts: 2-Pyrrolidinone, Pyroglutamic Acid Amide and Ester

Ecaterina Roth*, Janina Altman, Moshe Kapon and Dov Ben-Ishai✡

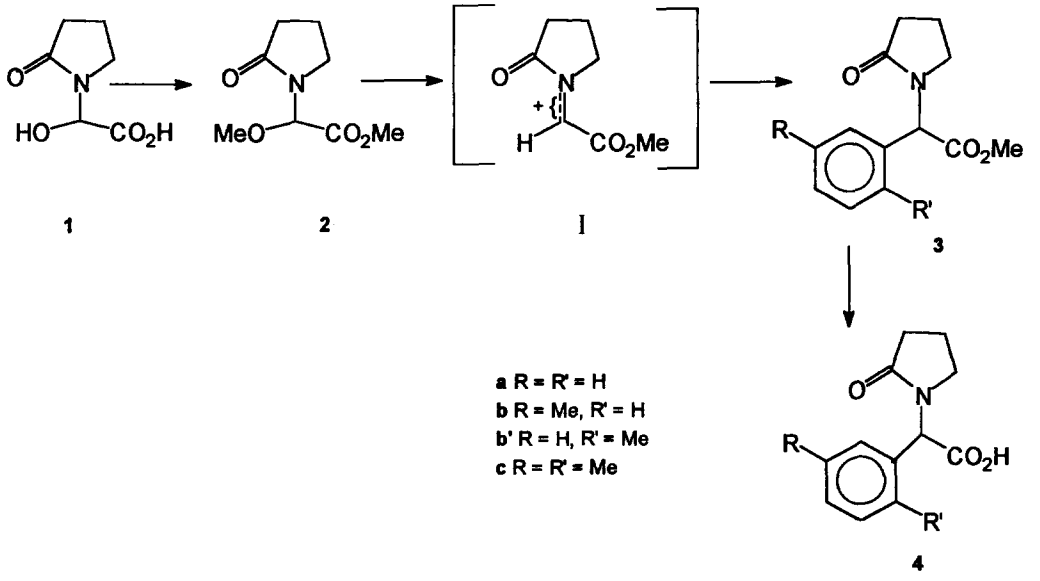
Department of Chemistry, Technion - Israel Institute of Technology, Technion City, Haifa 32000, Israel

A glyoxylic acid-2-pyrrolidinone adduct leads to *N*-acyliminium-ion induced intermolecular electrophilic aromatic substitution yielding nitrogen-substituted phenylglycine derivatives, whereas the benzylamide of glyoxylic acid-2-pyrrolidinone adduct undergoes intramolecular amidoalkylation to give an isoquinolone type compound. High stereospecifity and enantioselectivity was observed in intermolecular amidoalkylation of benzene using glyoxylic acid-*S*-pyroglutamic acid ester or amide adducts.

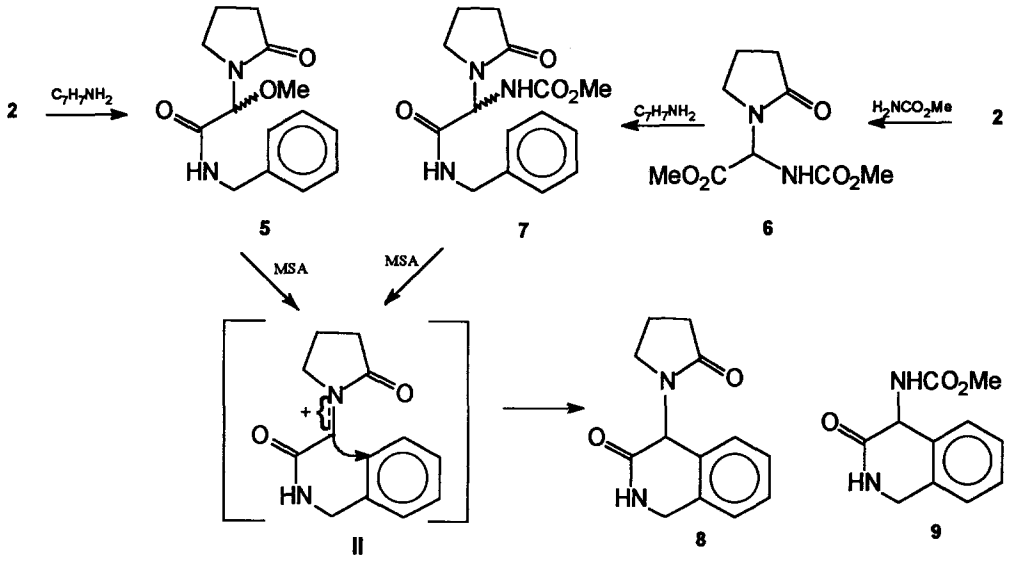
Synthetic peptides, retro-inverso analogues and pseudopeptides containing γ-lactams are known to adopt stable conformations in the solid state or in solutions and to imitate or block at the receptor level biological function of natural peptides[1]. Pyroglutamic acid (pyroGlu) - amino acid having γ-lactam moiety - appears as the end group in biologically active peptides (gonadotrophin-releasing hormone[2]), in depsipeptides (didemnins[3]) and in naturally occurring pseudopeptides[4]. For these reasons we were interested in the synthesis of phenylglycine (Phg) pseudopeptides substituted on nitrogen by γ-lactam moiety. We have previously described the synthesis of aromatic α-amino acids based on the amidoalkylation of aromatic compounds with glyoxylic acid-primary amide adducts such as α-hydroxyhippuric acid and *N*-methoxycarbonyl-α-hydroxyglycine[5], under strong acidic conditions, generating the *N*-acyliminium cation[6]. We applied this method to synthesize the conformationally restricted cyclic peptide analogues of Phg-Gly, Phe-Gly and Homophe-Gly by incorporating the electrophilic glycine analogue into peptides[7]. We now extend the amidoalkylation of aromatics to glyoxylic acid-secondary amide adducts such as 2-pyrrolidinone and pyroGlu to obtain Phg-γ-lactam pseudopeptides.

2-Pyrrolidinone and glyoxylic acid were condensed in 1:1.1 ratio to give the hydroxy acid **1** upon reflux in acetone. Treating of **1** with methanol, in the presence of acid catalysis, gave α-(R,S)-methoxy-methyl ester **2** which served as an "electrophilic glycine equivalent" for Friedel-Crafts type amidoalkylation of benzene, toluene and xylene. The amidoalkylation of benzene was performed in sulfuric acid as a solvent, at room temperature, and afforded the crude ester **3a** in 81% yield. Toluene and xylene, as better nucleophiles, were amidoalkylated in MSA. According to the ^{1}H NMR spectrum **3b** was a mixture of *ortho-para* isomers in 1:2.5 ratio. The esters **3a** and **3b** were obtained as oils. They were saponified to the corresponding acids **4a** and **4b** and purified by trituration. Several triturations of the toluene reaction products gave the pure *para* isomer **4b** in 31% yield (see scheme 1).

* Present address: c/o Prof. Ruth Ben-Ishai, Department of Biology, Technion, Haifa 32000, Israel
✡Deceased November 2, 1993



Scheme 1

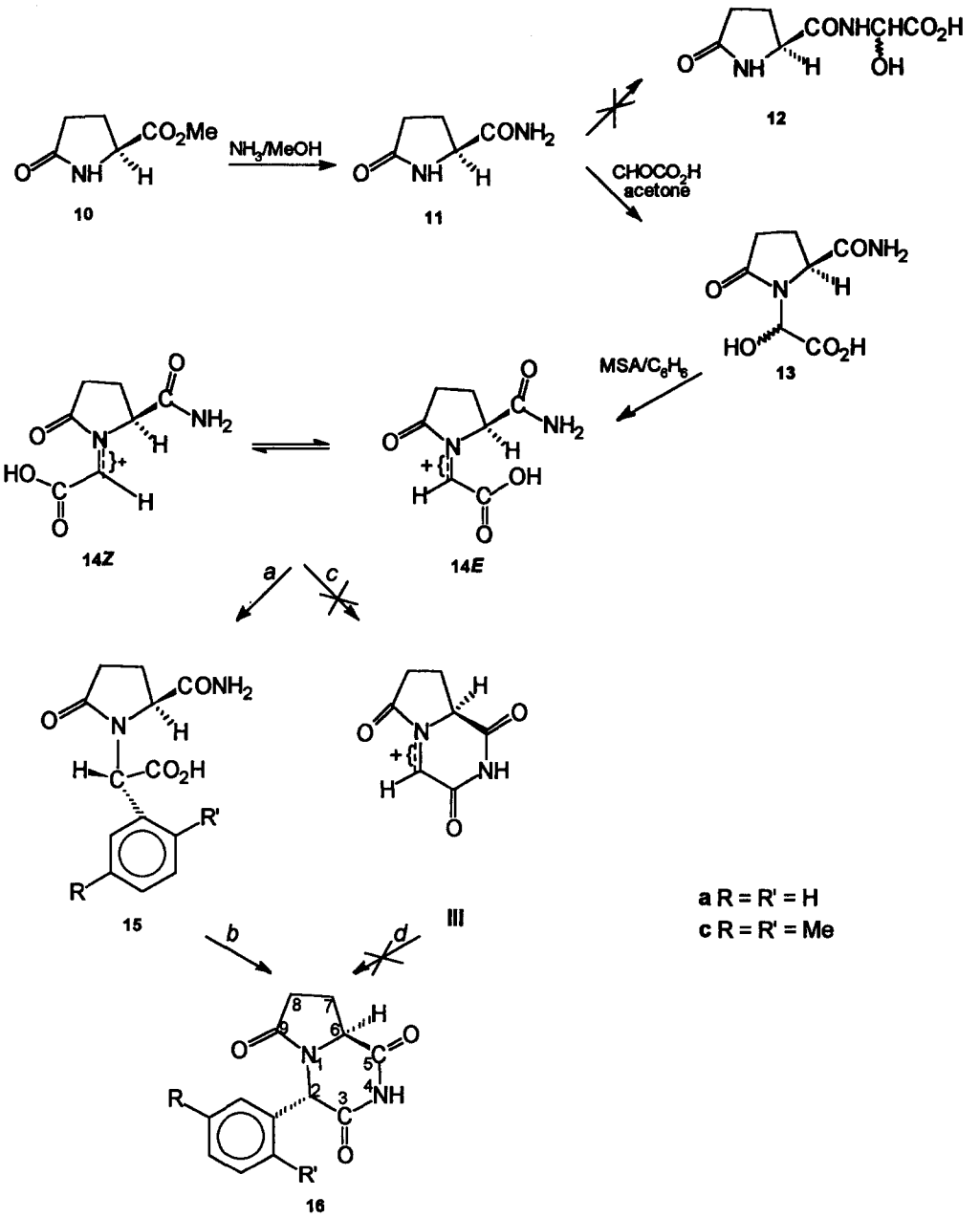


Scheme 2

Intramolecular amidoalkylation of benzylamide **5** in MSA, during 6 days, led to the isoquinolone derivative **8** in 84% yield (see scheme 2). Alternatively, **8** was formed as the main product when the

derivative **7** was subjected to the same reaction conditions. The urethane group is a much better leaving group than the amide[8], but less efficient than the hydroxy or methoxy group. Only 1.4% of **9**[5b] was formed as evaluated by MS-GC of the crude mixture. The methoxy-amide **6** shows in its ^1H and ^{13}C NMR spectra a single absorption pattern. In the spectra of the amide **7** a pattern of two distinct rotational isomers is present owing to rotational barriers of a hindered amide [9].

The chiral precursor (S)-pyrrolidinone-5-carboxamide **11** reacted with glyoxylic acid in 1:1.1 ratio in boiling acetone yielding α-(2-oxo-5-carboxamide-1-pyrrolidinone)hydroxyacetic acid **13** which, according to the ^1H NMR spectrum, was a mixture of two diastereomers in an approximate ratio of 9:1. Only the nitrogen of the lactam ring was involved in the reaction, with no evidence for the formation of glyoxylic acid-primary amide adduct **12** (see scheme 3). No attempt was made to separate the diastereomers. Upon formation of *N*-acyliminiun ion **14,** during the amidoalkylation process in MSA at 70°C, one stereocenter was lost in favour of a new one formed as a result of the electrophilic aromatic substitution. A single product was obtained. There are two reasons for the observed stereoselectivity: 1. Steric hindrance of the S-carboxamide group on the lactam ring directs the approach of the benzene ring as a nucleophile to the *N*-acyliminium ion from its opposite side; 2. Conformational requirements of *N*-acyliminium ion in the transition state: the *N*-acyliminium ion may adopt two forms, **14*E*** and **14*Z*,** in relation to the orientation of the carboxylic group towards the lactam carbonyl. Both forms, **14*E*** and **14*Z*,** have the *s-cis* configuration due to the *N*-acyl being part of the lactam ring. The planarity requirements of the CO and $C=N^+$ units would encounter more severe steric hindrance in **14*Z*** than in **14*E***. The distance, according to models, between the carboxamide carbonyl and the carboxyl group in **14*E*** appears to be larger than the distance between the lactam carbonyl and the carboxyl in **14*Z***. Hydrogen bonding interactions between the amide and the carboxylic group probably contribute as well to the higher population of **14*E***. The resulting sterically hindered acid **15**, as a primary amidoalkylation product, undergoes cyclization upon heating to the single tricyclic compound **16a** in 87% yield. A similar system of 5-membered ring fused with piperazinedione is a part of brevianamides[10]. It would seem that the acid catalyzed cyclization could take place before the amidoalkylation to give **16a** as well, but such a pathway may be ruled out because, when **13** is heated in MSA for 48 h prior to addition of benzene, only traces of **16a** are detected in TLC among tars. When xylene was amidoalkylated in MSA at room temperature for 48 h, the open amidoalkylation product **15c** was isolated in 33% yield. A 7-day reaction time increased the yield of **15c** to 68 %. **15c** shows in its ^1H NMR spectrum in DMSO-d_6 two distinct NH_2 groups and two singlets of benzylic hydrogen pointing to the presence of two rotational isomers due to hindered rotation of the aromatic ring bearing methyl substituents. Also in the ^{13}C NMR two signals for each carbon are observed. The spectra of **15c** could lead to a misleading conclusion about the formation of two diastereomers. However, when amidoalkylation of xylene was carried out at 70° for 48 h the simultaneous cyclization to the tricyclic product took place and **16c** was isolated in 80% yield as a single reaction product. According to ^1H and ^{13}C NMR spectra, and according to GC-MS, the reaction is diastereoselective and enantioselective. The X-ray crystal structure analysis of **16a** proves its absolute configuration to be (2S,6S)-2-phenyl-3,5,9-trioxo-1,4-diazobicyclo-[0,3,4]-nonane. We also prepared the racemic (2R,6R + 2S,6S) compound **16a'** starting from (R,S)-pyroglutamic acid amide. Two ORTEP drawings of the 2S,6S enantiomer **16a** are shown in figure I. The important torsion angles ψ, ϕ and ω in the optically active two crystallographically independent molecules A and B in **16a** and in the racemic molecule **16a'** are given in table I[11].



Scheme 3

(S)-PyroGlu methyl ester (**10**) yielded, in the presence of an excess of methyl methoxyglyoxalate hemiacetal, in boiling acetone, the hydroxy adduct **17** (see scheme 4). According to the ^1H NMR **17** was a 1:1 mixture of two diastereomers. The chiral center near the hydroxy group was lost in H_2SO_4 upon formation

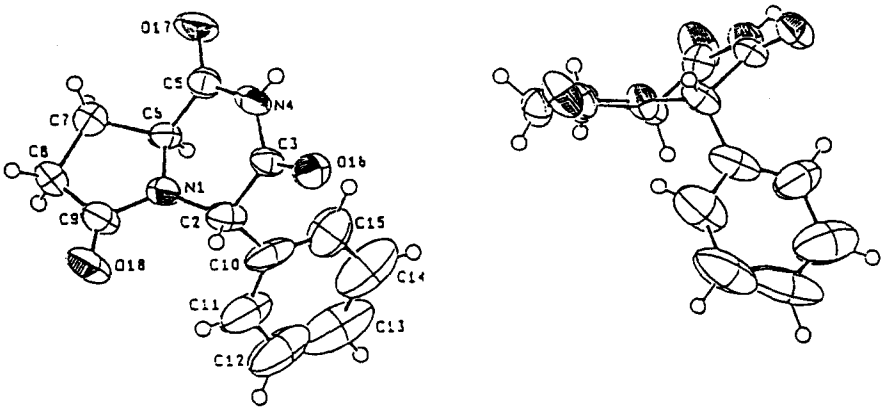
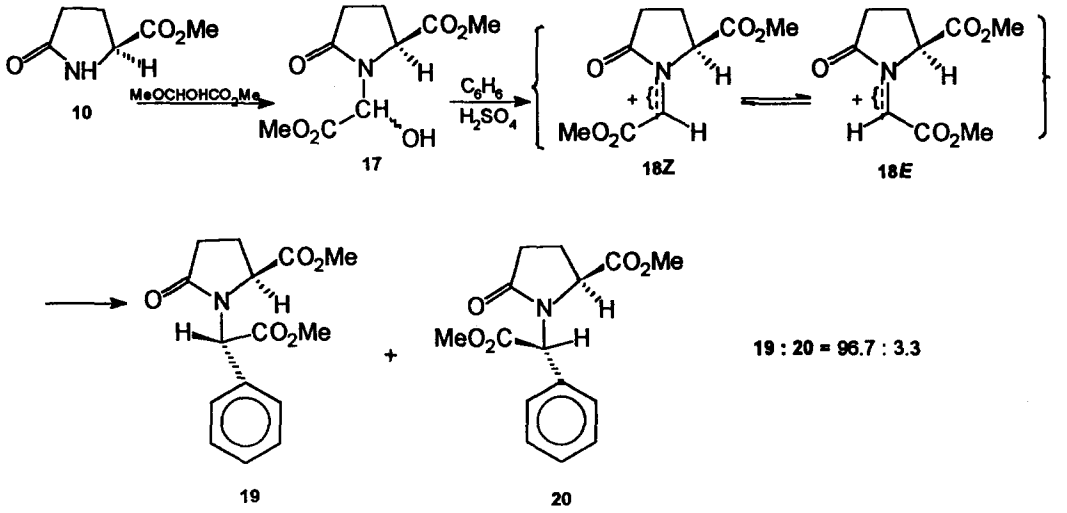


Figure I. Two ORTEP drawings of **16a**

Table I. Important angles in the two crystallographycally independent molecules A and B in the 2S,6S **16a** sructure and in the 2R,6R + 2S,6S srtucture **16a'**.

	Angle[11]		**16a**	
			A	B
ψ	N4-C3-C2-N1	- 21.3	- 18.7	- 16.8
ϕ	C3-C2-N1-C9	- 136.7	- 141.7	- 139.2
ω	C2-N1-C9-C8	- 177.0	- 179.9	- 182.9



Scheme 4

of *N*-acyliminium cation **18.** Again two rotamers **18*E*** and **18*Z*** are possible, each with different steric requirements in the transition state. Probably, as in the previous case, the planarity requirement of the *N*-acyliminium cation, with less steric repulsion, is better fulfilled by the form **18*E***. However, no hydrogen bonding interactions may contribute to its stabilization. As a result of the amidoalkylation process two diastereomers were detected in the reaction mixture. In the ^{1}H NMR spectrum a sharp singlet of the benzylic proton at 5.97 ppm was accompanied by a small satellite at 5.95 ppm, but its quantitative evaluation failed due

to the limited sensitivity range of the instrument. The diastereomers were not separated but the ratio of **19:20** was determined by GC-MS and found to be 96.7:3.3 (d.e. = e.e = 93.4%) The absolute configuration was not proved. We assume that by analogy with **16** the configuration of the major component **19** is S,S.

In intramolecular amidoalkylations, when a reactive *N*-acyliminium ion undergoes cyclization either with a proximal aromatic ring[12] or with a double bond[6b,13], high stereoselectivity is observed, e.g. in intramolecular amidoalkylation of benzene ring in *N*-Moc-(S)-Phe-a-(R,S)-OMe-Gly-OMe[7b] a single diastereomer is obtained as the cyclization product. The S configuration of the *N*-Moc group in a cyclic transition state of *N*-acyliminium ion efficiently induces high stereoselectivity of the new diastereogenic center. In intermolecular amidoalkylations the electronic, steric and conformational requirements appear to be much more stringent. In intermolecular amidoalkylation of aromatics, in a series of dipeptides of *N*-Z or *N*-Moc protected S-amino acid-α-(R,S)-hydroxyglycine (e.g. *N*-Z-Leu-α-(R,S)-OH-Gly) the S configuration of the *N*-Moc or *N*-Z group does not contribute at all to stereodifferentiation and mixtures of two diastereomeric dipeptides in 1:1 ratio are obtained[14]. Other methods have been reported to achieve high stereospecificity in the intermolecular amidoalkylations for the synthesis of peptides[15], *N*-protected amino acids[16, 17, 18], 2-substituted piperidines and pyrrolidines[19], as well as tetrahydroisoquinolines[20].

In the light of the above work, the intermolecular amidoalkylation of aromatics with adducts derived from pyroglutamic acid amide or ester are worth special attention. These adducts give rise to an *N*-acyliminium ion having an acyl function incorporated into the ring. The α-(S)-carboxamide or (S)-carbomethoxy group as substituents on the ring, become efficient inducers and contribute to high stereoselectivity.

Experimental

M.P.'s are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker 200 and a Bruker 400 MHz instruments. High resolution mass spectra were obtained on a Varian Matt-711 double focusing instrument and on TSQ-70 mass spectrometer. Low resolution mass spectra were obtained on a Finnigan Mat-Its-40 mass spectrometer, ion trap, GC with a DB-5 column (30 m x 0.25 mm). TLC was run on Merck silica gel 60 F_{256} and column chromatography on silica gel (Merck, 70-230 mesh). Specific rotation was measured with DIP JASCO polarimeter. Microanalyses were performed by the Microanalytical Laboratory at the Hebrew University of Jerusalem.

Methyl α-(2-oxo-1-pyrrolidinyl)methoxy acetate (2):
2-Pyrrolidinone (2.55 g, 0.03 mol) was added to a suspension of glyoxylic acid monohydrate (3.04 g, 0.033 mol) in acetone (50 ml). The mixture was refluxed for 48 h, cooled and concentrated yielding 5.69 g of **1** as a yellowish crude oil which was dissolved in MeOH (50 ml). Thionyl chloride (5.47 ml, 0.068 mol) was added dropwise upon cooling (0°C). The mixture was stirred at room temperature overnight, neutralized with solid $NaHCO_3$ and concentrated. The residue was divided between EtOAc and water. The organic layer was washed with water and dried over $MgSO_4$, filtered and concentrated. The crude product was chromatographed on a silica gel column and eluted with EtOAc, yielding **2** 4.3 g (76.6%) as a colorless oil. IR ($CHCl_3$): 1750, 1690 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.95-2.15 (m, 2H, CH_2), 2.40-2.48 (m, 2H, CH_2), 3.22-3.45 (m, 5H, OCH_3, CH_2), 3.75 (s, 3H, CO_2CH_3), 5.61 (s, 1H, $CHOCH_3$) ; ^{13}C NMR ($CDCl_3$): δ 17.49 (CH_2), 30.22 (CH_2CO), 41.88 (CH_2N), 52.04 (CH), 55.59 (OMe), 79.46 (OMe), 166.75 (CO), 175.86 (CO) ; MS (HR) : *m/z* =128.0718 (100%) M^+ - CO_2Me ; $C_6H_{10}NO_2$ requires 128.0712 ; GC-MS (LR): m/z = 188 (M^{+1}), 187 (M^+). $C_8H_{13}NO_4$ requires 187 ; Anal. found: C, 51.10% ; H, 7.14% ; N, 7.72%. $C_8H_{13}NO_4$ requires C, 51.36% ; H, 7.00% ; N, 7.52%.

Amidoalkylation - general procedure:
Procedure A: **2** (0.01 mol) was added to a cold (0°C) suspension of benzene (0.04 mol) in 20 ml of conc. H_2SO_4 (Merck 96%) and stirred for 24 h at room temperature. The mixture was poured into ice water, extracted with EtOAc, neutralized with $NaHCO_3$ 5%, dried over $MgSO_4$, filtered and concentrated. The crude product was either chromatographed on a silica column (**19, 20**), or isolated as acid after saponification (**4a**).
Procedure B: **2** (0.01 mol) was added to a cold (10°C) suspension of toluene or *p*-xylene (0.04 mol) in methane sulfonic acid (20 ml) and stirred for 48 h at room temperature. The mixture was poured into ice water, extracted with EtOAc, neutralized with $NaHCO_3$ 5%, dried over $MgSO_4$, filtered and concentrated. The crude product was either triturated with hexane (**3c**), or isolated as acid after saponification (**4b, 4c**).

α-(2-Oxo-1-pyrrolidinyl)phenylacetic acid (4a):
Benzene (3.55 ml, 0.04 mol) was amidoalkylated with **2** (1.87 g, 0.01 mol) as described in **procedure A** giving the crude ester **3a**. IR ($CHCl_3$): 1425, 1660, 1730 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.99 (m, 2H, CH_2), 2.34- 2.45 (m, 2H, CH_2), 2.89-2.93 (m, 1H, CH_2), 3.63-3.72 (m, 4H, CO_2CH_3, CH_2), 5.98 (s, 1H, $CHAr$), 7.18-7.37 (m, 5H, Ar) ; ^{13}C NMR ($CDCl_3$): δ 17.83 (CH_2), 30.59 (CH_2CO), 44.14 (CH_2N), 52.01 (CH), 57.85 (OMe), 128.34, 128.47, 128.67, 133,85 (Ar), 170.28 (CO), 175.08 (CO) ; MS (HR): *m/z* = 233.1043 $C_{13}H_{15}NO_3$ requires: 233.1051. The ester **3a** was saponified overnight with KOH (0.49 g, 0.0088 mol) in MeOH (16.7 ml) and water (4.2 ml). The MeOH was evaporated and the residue acidified with HCl conc. (3.85 ml) in ice, acid extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The crude oily product was triturated with ether yielding **4a** 1.03 g (64%) as a white powder. Mp 124-5° ; IR ($CHCl_3$): 1405, 1665, 1720 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.94 (m, 2H, CH_2), 2.4-2.51 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.64 (m, 1H, CH_2), 4.85 (s, 1H, OH), 5.96 (s, 1H, $CHAr$), 7.28-7.37 (m, 5H, Ar) ; ^{13}C NMR ($CDCl_3$): δ 17.97 (CH_2), 30.94 (CH_2CO), 44.88 (CH_2N), 58.48 (CH), 128.69, 128.92, 128.99, 133.54 (Ar), 172.58 (CO), 176.45 (CO) ; MS (HR): *m/z* = 219.0880 (6.97%) M^+. $C_{12}H_{13}NO_3$ requires 219.0896 ; Anal. found: C, 65.55% ; H, 6.11% ; N, 6.54%. $C_{12}H_{13}NO_3$ requires C, 65.78% ; H, 5.98% ; N, 6.42%.

α-(2-Oxo-1-pyrrolidinyl)-*p*-tolylacetic acid (4b):
Toluene (4.3 ml, 0.04 mol) was amidoalkylated with **2** (1.78 g, 0.01 mol) as described in **procedure B** giving the oily ester **3b**. IR ($CHCl_3$): 1410, 1665, 1735 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.93 (m, 2H, CH_2), 2.32-2.45 (m, 5H, CH_2, CH_3Ar), 2.90-2.97 (m, 1H, CH_2), 3.61-3.73 (m, 4H, CO_2CH_3, CH_2), 5.94 (s, 1H, $CHAr$), 7.08-7.18 (m, 4H, Ar) ; MS (HR): *m/z* = 247.1237 (13.62%) M+. $C_{14}H_{17}NO_3$ requires: 247.1209. The crude **3b** was saponified as above yielding 2.1 g, (83.6%) of a mixture of *ortho* : *para* isomers **4b** + **4b'** 1:2.55 according to the spectrum of ^1H NMR. The crude mixture was triturated with absolute ether affording 0.66 g (30.8%) of the pure *para* isomer **4b**. Mp 165° ; IR ($CHCl_3$): 1665, 1715, 2880 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.74-2.10 (m, 2H, CH_2), 2.33-2.50 (m+s, 5H, CH_3Ar, CH_2), 2.88-3.0 (m, 1H, CH_2), 3.55-3.70 (m, 1H, CH_2), 5.93 (s, 1H, $CHAr$), 7.13-7.24 (m, 4H, Ar) ; MS (HR): *m/z* = 233.1040 (24.71%) M^+. $C_{13}H_{15}NO_3$ requires 233.1052 ; Anal. found: C, 67.20; H, 6.66; N, 6.22. $C_{13}H_{15}NO_3$ requires C, 66.98; H, 6.48; N, 6.04%. The pure *ortho* isomer was not isolated.

Methyl α-(2-oxo-1-pyrrolidinyl)xylylacetate (3c):
p-Xylene (4.94 ml, 0.04 mol) was amidoalkylated with **2** (1.87 g, 0.01 mol) as described in **procedure B** yielding after trituration with hexane **3c** 0.99 g (52.7%) as a white powder. Mp 80° ; IR ($CHCl_3$): 1450, 1665, 1730 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.95 (m, 2H, CH_2), 2.23 (s, 3H, $ArCH_3$), 2.28 (s, 3H, $ArCH_3$), 2.38-2.48 (m, 2H, CH_2), 2.72-2.83 (m, 1H, CH_2), 3.54-3.66 (m, 1H, CH_2), 3.85 (s, 3H, CO_2CH_3), 6.06 (s, 1H, $CHAr$), 6.84 (s, 1H, Ar), 7.07-7.12 (m, 2H, Ar) ; MS (HR): *m/z* = 261.1367 (12.87%) M^+. $C_{15}H_{19}NO$ requires 261.1365 ; Anal. found: C, 68.68% ; H, 7.20% ; N, 5.64%. $C_{15}H_{19}NO$ requires: C, 68.99% ; H, 7.33% ; N, 5.39%.

α-(2-Oxo-1-pyrrolidinyl)xylylacetic acid (4c):
The ester **3c** (2.44 g, 0.009 mol) was saponified as above. The crude acid **4c** was filtered, dispersed in $CHCl_3$ (75 ml) and the moisture was removed by azeotropic distillation. The solubility of the dry **4c** increased upon drying. The solution was concentrated and triturated with ether yielding 1.64 g (60.9%). Mp 186-7° ; IR ($CHCl_3$): 1400-1450, 1660, 1715, 3300 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.78-2.53 (m, 10H, $2CH_3Ar$, $2CH_2$), 2.71-2.82 (m, 1H, CH_2), 3.45-3.62 (m, 1H, CH_2), 6.06 (s, 1H, $CHAr$), 7.01-7.07 (m, 3H, Ar) ; MS (HR): *m/z* = 247.1226 (7.89%) M^+. $C_{14}H_{17}NO_3$ requires 247.1208.

α-(2-Oxo-1-pyrrolidinyl)methoxyacetyl-benzylamide (5):
2 (7.48 g, 0.04 mol) was added to a solution of benzylamine (7.29 g, 0.068 mol) in MeOH (100 ml). The mixture was refluxed for 24 h, cooled and concentrated. The residue was dissolved in EtOAc, neutralized with H_3PO_4 10%, washed with water, dried over $MgSO_4$, filtered and concentrated. The crude oily product was triturated with ether : hexane (1:7.5) yielding **5** 5.93 g (56.6%) as a white powder. Mp 103° ; IR ($CHCl_3$): 1500, 1600, 1690, 3410 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.98-2.10 (m, 2H, CH_2), 2.43-2.52 (m, 2H, CH_2), 3.24-3.37 (s, m, 5H, OCH_3, CH_2), 4.43-4.46 (d, *J*=5.9, 2H, CH_2Ar), 5.57 (s, 1H, $CHOCH_3$), 7.01 (s, 1H, NH), 7.24-7.33 (m, 5H, Ar) ; ^{13}C NMR ($CDCl_3$): δ 17.91 (CH_2), 30.80 (CH_2CO), 42.02 (CH_2N), 43.32 (CH_2N), 56.10 (CH), 80.97 (OMe), 127.63, 127.77, 128.74, 137.78 (Ar), 166.10 (CO), 176.90 (CO) ; MS (HR): *m/z* = 231.1097 (0.10%) M^+-CH_3O, 128.0696 (100%) M^+-$CONHCH_2Ph$. $C_6H_{10}NO_2$ requires: 128.0711; Anal. found: C, 63.98% ; H, 7.05% ; N, 10.79%. $C_{14}H_{18}N_2O_3$ requires: C, 64.15% ; H, 6.92% ; N, 10.74%.

Methyl *N*-Moc-α-(2-oxo-1-pyrrolidinyl)glycinate (6):
2 (9.35 g, 0.05 mol) was added to a cold (10°C) suspension of methyl carbamate (4.5 g, 0.06 mol) in methane sulfonic acid (50 ml) and stirred 48 h at room temperature. The mixture was poured into ice water, extracted with $CHCl_3$, neutralized with $NaHCO_3$ 5%, dried over $MgSO_4$, filtered and concentrated. The crude oily product was triturated with ether yielding **6** 5.49 g (47.7%) ; Mp 102-4° ; IR ($CHCl_3$): 1500, 1675, 1715, 1740, 3400 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 2.02-2.13 (m, 2H, CH_2), 2.37 (m, 2H, CH_2), 3.53 (m, 2H, CH_2), 3.77 (s, 3H, $CHCO_2CH_3$), 5.64-5.67 (d, *J*=6.8, 1H, $CHCO_2CH_3$), 6.13 (br, 1H, NH) ; ^{13}C NMR ($CDCl_3$): δ 18.38 (CH_2), 30.47 (CH_2CO), 46.42 (CH_2N), 52.64 (CHN), 53.28 (OMe), 60.79 (OMe), 156.15 (CO), 167.84 (CO), 175.62 (CO) ; MS

(HR): *m/z* = 230.0904 (0.1%) M^+. $C_9H_{14}N_2O_5$ requires: 230.0903 ; Anal. found: C, 47.02% ; H, 6.35% ; N, 12.23%. $C_9H_{14}N_2O_5$ requires: C, 46.98% ; H, 6.13% ; N, 12.23%.

N-Moc-α-(2-oxo-1-pyrrolidinyl)-glycyl- benzylamide (7):

6 (2 g, 0.0087 mol) was added to a solution of benzylamine (1.12 g, 0.0104 mol) in MeOH (22 ml). The mixture was refluxed for 24 h, cooled and concentrated. The residue was dissolved in EtOAc, neutralized with H_3PO_4 10%, washed with water, dried over $MgSO_4$, filtered and concentrated. The crude oily product was triturated with ether yielding **7** 1.08 g (40.8%) as a white powder. Mp 133-4° ; IR ($CHCl_3$): 1490, 1680, 1730, 3390 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.93-2.08 (m, 2H, CH_2), 2.31-2.47 (m, 2H, CH_2), 3.17-3.24 (m, 1H, CH_2), 3.35-3.47 (m, 1H, CH_2), 3.68 (s, 3H, $NHCO_2CH_3$), 4.39-4.42 (d, *J*=5.99, 2H, CH_2Ar), 5.94-5.97 (d, *J*=6.6, 1H, $CHNHCO_2CH_3$), 6.21 (s, 1H, $NHCO_2CH_3$), 7.10-7.34 (m, 6H, Ar, $NHCH_2Ph$) ; ^{13}C NMR ($CDCl_3$): δ 17.58, 17.95 (CH_2, 2 rotamers), 30.38, 31.05 (CH_2CO, 2 rot.), 41.74, 42.45 (CH_2N, 2 rot.), 43.20, 43.64 (CH_2N, 2 rot.), 52.65 (CH), 60.31, 61.92 (OMe, 2 rot.), 127.46, 127.55, 128.05, 128.47, 128.66, 135.58, 137.51 (Ar, 2 rot.), 155.68, 156.07 (CO, 2 rot.), 166.58, 168.72 (CO, 2 rot.) 176.13, 176.42 (CO, 2 rot.) ; MS (HR): *m/z* = 274.1237 (0.94%) M^+-CH_3O, 171.0787 (100.00%) M^+-$CONHCH_2Ph$; $C_7H_{11}N_2O_3$ requires: 171.0797 ; Anal. found: C, 59.18% ; H, 6.36% ; N, 14.10%. $C_{15}H_{19}N_3O_4$ requires: C, 59.04% ; H, 6.27% ; N, 13.84%.

4-(2-Oxo-1-pyrrolidinyl)-1, 2-dihydro-3-isoquinolone (8):

Method A: **5** (5.77 g, 0.022 mol) was added to cold (10°C) methane sulfonic acid (44 ml) and stirred for 6 days at room temperature. Work up was performed as described in **procedure B** including trituration in ether yielding 4.25 g (84%) of **8**; Mp 213° dec. (from EtOH) ; IR ($CHCl_3$): 1670-1690, 3410 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 2.13 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 3.21 (m, 1H, CH_2), 3.47 (m, 1H, CH_2), 4.50 (qq, 2H, CH_2(isoq)), 5.88 (s, 1H, CH_2), 7.06-7.32 (m, 5H, NH, Ar) ; ^{13}C NMR ($CDCl_3$): δ 18.11 (CH_2), 30.50 (CH_2CO), 43.60 (CH_2N), 44.57 (CH_2N), 52.56 (CH), 125.46, 125.64, 127.63, 127.84, 130.95, 131.23 (Ar), 168.35 (CO), 176.83 (CO) ; MS (HR): *m/z* = 230.1086 (3.03%) M^+. $C_{13}H_{14}N_2O_2$ requires: 230.1055 ; Anal. found: C, 67.57% ; H, 6.05% ; N, 12.44%. $C_{13}H_{14}N_2O_2$ requires: C, 67.76% ; H, 6.12% ; N 12.22%.

Method B: **7** (3.05 g,0.01 mol) was amidoalkylated intramolecularly in methane sulfonic acid (20 ml) and worked up as above yielding a yelow-orange powder 1.78 g of a mixture of **8** and **9** in a ratio of 70:1 according to GC-MS. ^1H NMR ($CDCl_3$): δ 2.03-2.16 (m, 2H, CH_2), 2.52-2.62 (m, 2H, CH_2), 3.14-3.25 (m, 1H, CH_2), 3.44-3.64 (m, 1H, CH_2), 3.76 (s, 3H,CO_2CH_3), 4.43-4.65 (m, 4H, CH_2N(isoq), 2 comp.), 5.26 (d, *J* = 6.78, 1H, CHN **9**), 5.86-5.87 (m, 2H, CHN **8** (isoq), $NHCO_2CH_3$), 6.85 (s, 1H, NH **9**) 7.05-7.34 (m, 5H, NH **8**, Ar) ; MS (LR): *m/z* = 221 M+1$^+$ (retention time 12.20 min 1.4%) $C_{11}H_{12}N_2O_3$ requires: 220; 231 M+1$^+$ (retention time 12.43 min., 98.6%) $C_{13}H_{14}N_2O_2$ requires: 230.

(S) 2-Pyrrolidone-5-carboxamide (11):

10 (1.6 g, 0.011 mol) was dissolved in NH_3/MeOH 17% (20 ml). The solution was left overnight at room temperature, concentrated and triturated with ether yielding **11** 9.67 g (83.9%) as a white powder. Mp 202- 205° (from EtOH); lit.[21] 217.5°; $[\alpha]_D^{28}$ -19.1 (*c* 1, MeOH), lit.[21] $[\alpha]_D^{22}$ 0 (*c* 1), lit.[22] $[\alpha]_D^{24}$ -18.4 (*c* 1, MeOH). ^1H NMR (DMSO-d_6): δ 1.89 (m, 1H, CH), 2.08 (m, 2H, CH_2CO), 2.15 (m, 2H, CH), 3.92 (q, 1H, CHN), 7.06 (s, 1H, NH_2), 7.38 (s, 1H, NH_2), 7.75 (s, 1H, NH) ; ^{13}C NMR (DMSO-d_6): 25.34 (C-4), 29.34 (C-3), 55.66 (C-5), 174.47 (CO), 177.36 (CO).

α-(2-Oxo-5S-carboxamide-1-pyrrolidinyl)hydroxyacetic acid (13):

11 (7.69 g, 0.06 mol) was added to a suspension of glyoxylic acid monohydrate (6.08 g, 0.066 mol) in acetone (600 ml) and refluxed for 72 h . After cooling the precipitation was filtered and dried in vacuo over P_2O_5, yielding crude **13** 9.37 g (77.3%). Mp 145-6° ; IR (KBr): 1680, 1690, 1720, 3190, 3330-3360 cm^{-1} ; ^1H NMR (DMSO): δ 1.86-2.40 (m, 4H, $2CH_2$), 4.14 (d, *J*=7.10, 0.1H, $CHCONH_2$), 4.27-4.29 (d, *J*=7.64, 0.9H, $CHCONH_2$), 5.38 , 5.42 (2s, 1H, CHOH 2 isom.), 7.1, 7.22, 7.50, 7.60 (4s, 2H, NH_2, 2 isom.). According to ^1H NMR **13** was contaminated by small amounts of the starting compounds ; Anal. found: C, 42.56%; H, 5.10%; N, 13.84%. $C_7H_{10}N_2O_5$ requires: C, 41.61%; H, 4.98%; N, 13.93%.

α-(2-Oxo-5S-carboxamide-1-pyrrolidinyl)xylylacetic acid (15c):

p-Xylene (1 ml, 8 mmol) was amidoalkylated with crude **13** (404 mg, 2 mmol) for 48 h as described in **procedure B**. The crude **15c** was triturated with ether affording 180 mg (33 %) . The 7 days reaction time increased the yield to 394 mg (68%). Mp 220° (dec.) ; $[\alpha]_D^{30}$ + 83.6 (*c* 1, EtOH). ^1H NMR (DMSO-d_6): δ 1.87-2.46 (m, 10H, $2CH_2$, $2CH_3$), 3.38-3.43 (m, 1H, $CHCONH_2$), 5.44, 5.46 (2s, 1H, CHAr, 2 rotamers), 6.82-7.19 (m, 3H, Ar, 2 rot.), 7.53, 7.56 (2s, 1H, NH_2, 2 rot.), 7.96, 7.99 (2s, 1H, NH_2, 2 rot.) ; ^{13}C NMR (DMSO-d_6): δ 19.72, 20.57 (CH_3, 2 rotamers), 25.19, 25.27 (CH_2 2 rot.), 28.99, 29.09 (CH_2CO, 2 rot.), 58.06, 58.27 (CH, 2 rot.), 59.12 (CH), 126.91, 127.73, 128.25, 128.31, 129.10, 129.46, 129.70, 130.49, 130.49, 131.13, 131.28, 134.13, 135.29, 137.17, 138.26 (Ar, 2 rot.), 171.68, 171.89 (CO, 2 rot.), 175.48, 175.57 (CO, 2 rot.), 175.69, 175.80 (CO, 2 rot.) ; Anal. found: C, 62.35; H, 6.28; N, 9.31. $C_{15}H_{18}N_2O_3$ requires C, 62.05; H, 6.25; N, 9.25%.

(2S, 6S) 2-Phenyl-3,5,9-trioxo-1,4-diazabicyclo[4. 3. 0]nonane (16a):

Benzene (0.72 ml, 8 mmol) was amidoalkylated with crude **13** (404 mg, 2 mmol) at 70°C for 48 h as described in **procedure B**. The crude product was filtered through a silica-gel column with EtOAc yielding **16a** 395 mg (83.5%). Mp 182°C dec. (from EtOH) ; $[\alpha]_D^{30}$ + 81 (*c* 2, EtOH) ; IR ($CHCl_3$): 1735-1740, 3380 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.30-2.56 (m, 4H, $2CH_2$), 4.16-4.20

(t, *J*=7.6, 1H, CH), 6.02 (s, 1H, C*H*Ar), 7.24-7.32 (m, 5H, Ar), 9.50 (s, 1H, NH) ; ^{13}C NMR ($CDCl_3$): δ 20.37 (CH_2), 29.46 (CH_2CO), 53.89 (CH), 55.86 (CH), 126.62, 128.81, 129.11,132.60 (Ar), 168.51 (CO), 171.06 (CO), 173.64 (CO) ; MS (HR): *m/z* = 244.0852 (100%) M^+ $C_{13}H_{12}N_2O_3$ requires: 244.0848 MS (LR): *m/z* = 244 M^+ (retention time: 12.32 min.) ; Anal. found: C, 63.69% ; H, 4.92% ; N, 11.55% ; $C_{13}H_{12}N_2O_3$ requires: C, 63.97% ; H, 4.95% ; N, 11.53%.

(2R,6R + 2S, 6S) 2-Phenyl-3,5,9-trioxo-1,4-diazabicyclo[4, 3, 0]nonane (16a'):

Benzene (0.72 ml, 8 mmol) was amidoalkylated with crude **13'** (404 mg, 2 mmol, prepared from R,S-2-pyroGlu-NH_2 and glyoxylic acid hemiacetal as above) yielding 328 mg (67%) of enantiomeric pair **16a'**, mp 170-171°C, $[a]_D^{30}$ 0 (*c* 2, EtOH); IR and NMR data the same as of **16a.**

X-ray crystallography of derivatives 16a and 16a':

Crystal structure analysis was carried out using the Philips PW 1100/20 four circle diffractometer. The structures were solved by SHELXS 86 and refined by SHELX 76 program package.

(2S,6S)-2-Phenyl-1,5,9-trioxo-1,4-diazabicyclo[4,3,0]nonane **16a** (F. W. 244.2) crystallizes from EtOH in the monoclinic space group $P2_1$, a: 12.401(6), b: 12.917(6), c: 7.484(4) A, β: 98.69(5)°, V: 1185.1 A^3, Z: 4, ρcalc.: 1.369 g cm^{-3}, F(000): 512, x radiation: Mo Kα (λ : 0.71069 A), 2θ range: 4-48°, reflections measured: 2114, 1642 with Fo>3σ(Fo), refined by block diagonal least squares method. Non-hydrogen atoms were refined anisotropically and hydrogens isotropically, parameters refined: 397, R: 0.060, R_w: 0.058.

Structure (2R,6R + 2S,6S) **16a'** (F. W. 244.2) crystallizes from EtOAc in the monoclinic space group $P2_1/n$, a: 11.663(5), b: 13.358(6), c: 7.340(4) A, β: 96.11(5)°, V: 1137.0 A^3, Z: 4, ρcalc.: 1.427 g cm^{-3}, F(000) = 512, radiation Mo Kα (λ: 0.71069 A), 2θ range 4-50°, reflections measured: 2259, 1525 with Fo > 3σ(Fo), refined by full matrix method, parameters refined: 211, R: 0.046, R_w: 0.046. Full details, including positional parameters, bond lengths, angles and torsion angles are available as supplemental material.

(2S, 6S) 2-*p*-Xylyl 3,5,9-trioxo-1,4-diazabicyclo[4, 3, 0]nonane (16c):

p-Xylene (1ml, 8 mmol) was amidoalkylated with crude **13** (404 mg, 2 mmol) as described above, yielding **16c** 414 mg (76%). Mp 242°; $[a]_D^{30}$ + 57.3 (*c* 1, DMF) ; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 2.36-2.49 (m, 7H, CH_3, $2CH_2$), 4.21-4.24 (m, 1H, CH), 6.16 (s, 1H, CH), 6.83 (s, 1H, Ar), 7.06, 7.12 (q, AB, 2H, Ar), 8.89 (s, 1H, NH) ; 13C NMR ($CDCl_3$): δ 19.14 (CH_3), 19.99 (CH_3), 20.97 (CH_2), 29.38 (CH_2), 54.25 (CH), 54.49 (CH), 127.04, 130.05, 131.71, 134.99, 135.93, (Ar), 169.80 (CO), 171.21 (CO), 173.06 (CO) ; MS (LR): *m/z* = 272 M^+ (retention time: 13.30 min.) ; $C_{15}H_{16}N_2O_3$ requires: 272 ; Anal. found: C, 66.04, H, 5.92; N. 10.34. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.28%.

Methyl α-(2-oxo-5S-carbomethoxy-1-pyrrolidinyl)hydroxyacetate (17):

Methyl (S)-pyroglutamate **10** (8.58 g, 0.06 mol) was added to a solution of methyl methoxyglyoxalate hemiacetal (14.4 g, 0.12 mol) in acetone (300 ml). The mixture was refluxed for 48 h, cooled and concentrated. The crude oily product was redissolved in $CHCl_3$, and washed with water (100 ml). The aqueos phase was extracted with $CHCl_3$ (4x50 ml) and the overall organic phases were washed with water (2x50 ml) to remove most of the hemiacetal, dried over $MgSO_4$, filtered and concentrated yielding crude **17** 11.32 g (81.6%) of a yellowish oil still contaminated with hemiacetal. IR ($CHCl_3$): 1710, 1745, 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90-2.46 (m, 4H, $2CH_2$), 3.55-3.63 (4s, 6H, $2CO_2CH_3$), 4.16-4.20, 4.36-4.40 (2m, 1H, $CHCO_2CH_3$, 2 isomers), 5.61-5.65 (2s, 1H, C*H*OH) ; MS (HR): *m/z* = 172.0618 (100%) M^+-CO_2CH_3. $C_7H_{10}NO_4$ requires: 172.0610.

Methyl α-(2-oxo-5S-carbomethoxy-1-pyrrolidinyl)phenylacetate (19 and 20):

Benzene (3.55 ml, 0.04 mol) was amidoalkylated with the crude **17** (2.45 g, 0.01 mol) as described in **procedure A**. The product was chromatographed on a silica-gel column. Small amounts of methyl ester of mandelic acid and diphenylacetic acid, formed by the reaction of benzene with methyl methoxyglyoxalate hemiacetal which contaminated **17**, were eluted with CH_2Cl_2. Elution with CH_2Cl_2 : EtOAc 2:1 afforded a mixture of **19** and **20** 0.85 g (40%). $[\alpha]_D^{28}$ +52.6 (*c* 2, EtOH) ; IR ($CHCl_3$): 1593, 1685, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00-2.06 (m, 2H, CH_2), 2.31 (m, 1H, AB part of ABX, CH_2CO), 2.65 (m,1H, AB part of ABX, CH_2CO), 3.66, 3.68, 3.70, 3.72 (4s, 6H, $2CO_2CH_3$, 2 isom.), 4.02-4.04 (m, 1H, CH), 5.95, 5.97 (s, 1H, C*H*Ar, 2 isomers), 7.22-7.31 (m, 5H, Ar) ;^{13}C NMR ($CDCl_3$): δ 24.49 (CH_2), 29.23 (CH_2CO), 51.99 (CH), 52.19 (CH), 128.14, 128.29, 128.39, 134.05 (Ar), 169.51 (CO), 172.14 (CO), 175.39 (CO) ; GC-MS (LR): *m/z* = 292 M+1 (retention time 11.48 min., 3.3%, minor diastereomer); 292 M+1 (retention time 11.56 min, 96.7%, major diastereomer), $C_{15}H_{17}NO_5$ requires 292. Anal. found: C, 62.03%; H, 6.20%; N, 4.90%. $C_{15}H_{17}NO_5$ requires: C, 61.67%; H 5.86%; N, 4.82%.

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