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The Synthesis of D,L *p*-Vinylphenylglycine by Amidoalkylation, and its Reactions.

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Abstract: Amidoalkylation of (2-chloroethyl)benzene or (2-bromoethyl)benzene with α-hydroxyhippuric acid and *N*- methoxycarbonyl α-hydroxyglycine, followed by dehydrohalogenation, affords *N*-protected *p*-vinylphenylglycines. Transformation of the vinyl group leads to *N*-methoxycarbonyl-*p*-[1-(methoxycarbonylamino)ethyl]phenylglycine, *N*-methoxycarbonyl-*p*-(epoxyethyl) phenylglycine, *N*-methoxycarbonyl-*p*-formyl phenylglycine and *N*-methoxycarbonyl-*p*-carboxy phenylglycine. The deprotection of these compounds is described.

Aromatic α-amino acids of the phenylglycine type occur in nature[1,2]. They have found application in the synthesis of semisynthetic β-lactam antibiotics[3]. These amino acids are generally prepared from the corresponding aldehydes by the Strecker synthesis[4]. We have described a synthesis of aromatic α-amino acids based on the amidoalkylation of aromatic compounds with glyoxilic acid - primary amide adducts such as α-hydroxyhippuric acid and *N*-methoxycarbonyl α-hydroxyglycine[5]. Since the amidoalkylation of aromatic compounds is an electrophilic aromatic substitution, it conforms to the aromatic substitution rules, and therefore derivatives that have *meta* directing groups, such as the carbonyl group at the *para* position cannot be synthesized directly. Moreover, since the amidoalkylation reaction is carried out in strongly acidic conditions we cannot prepare in a direct way[5b] derivatives with a substituent that is sensitive to acidic conditions such as the vinyl group. But amidoalkylation of (2-haloethyl)benzene should afford a *p*-(2-haloethyl)phenylglycine (3), which appears as a useful intermediate in the synthesis of phenylglycines having a wide variety of substituents at the *para* position.

The amidoalkylation of 2-chloro or (2-bromoethyl)benzene with α-hydroxyhippuric acid (**2a**) in sulfuric acid as a solvent, afforded *N*-benzoyl-(2-haloethyl)phenylglycine as a mixture of *ortho para* isomers. The predominant *para* isomer (**3a, 3b**) was separated in pure form by chromatography. The reaction of *N*-methoxycarbonyl α-hydroxyglycine (**2b**), as an electrophile, was carried out in methanesulphonic acid as a solvent, and gave *N*-methoxycarbonyl-*p*-(2-haloethyl)phenylglycine (**3c, 3d**), only.

Elimination of HCl from *N*-methoxycarbonyl-*p*-(2-chloroethyl)phenylglycine (**3c**) and *N*-benzoyl-*p*-(2-chloroethyl)phenylglycine (**3a**) was carried out in KOH/MeOH under reflux to give *N*-protected-*p*-vinylphenylglycine (**5a, 5b**). The vinyl group on the aromatic ring opens possibilities to introduce new functions by addition or oxidation reactions.

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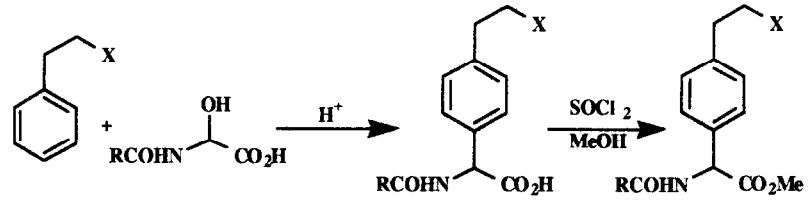
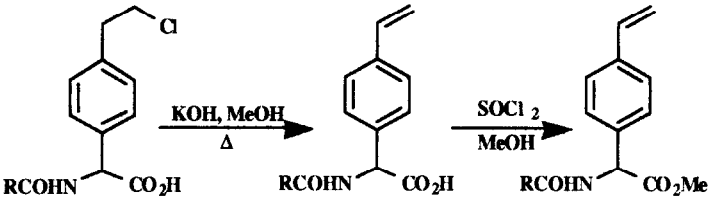


1a X = Cl
1b X = Br

2a R = Ph
2b R = MeO

3a R = Ph X = Cl
3b R = Ph X = Br
3c R = MeO X = Cl
3d R = MeO X = Br

4a R = Ph X = Cl
4b R = Ph X = Br
4c R = MeO X = Cl
4d R = MeO X = Br



4a R = Ph X = Cl
4c R = MeO X = Cl

5a R = Ph
5b R = MeO

6a R = Ph
6b R = MeO

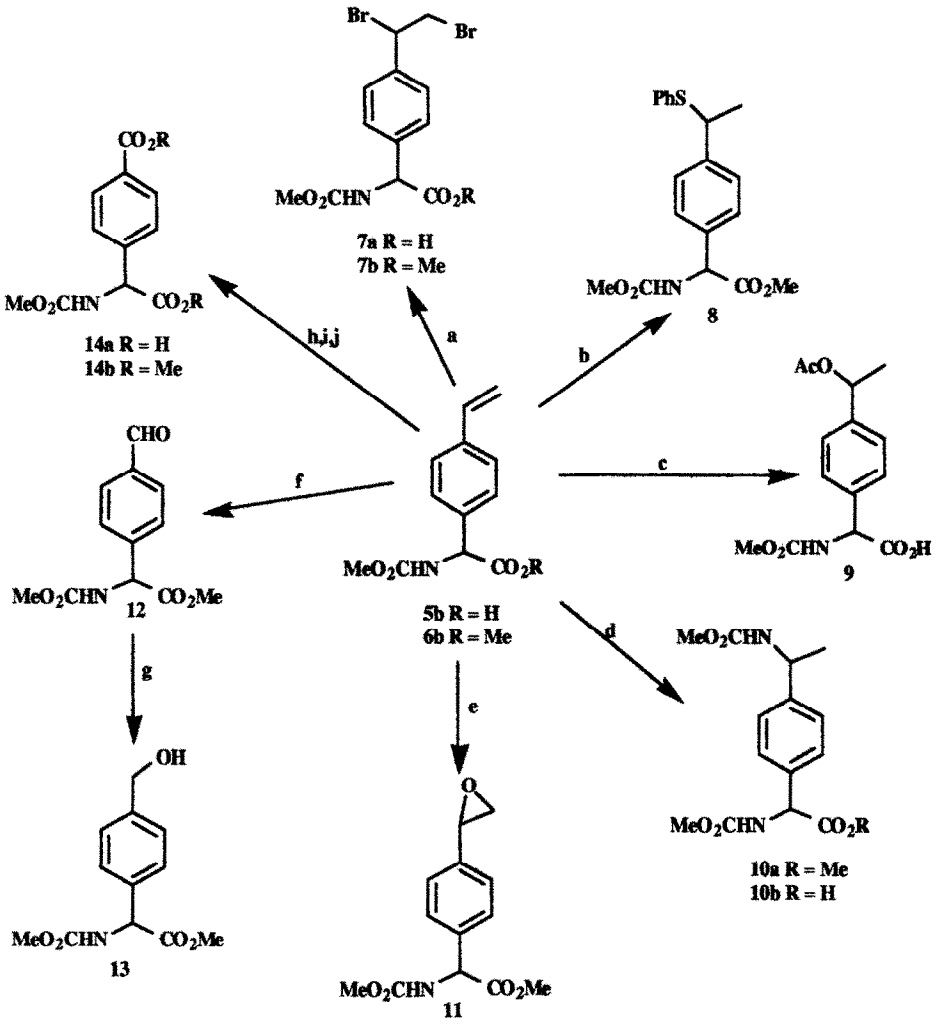
The addition of Br_2 to **5b** or **6b** gave the 1,2-dibromo compound (**7a, b**). Other nucleophiles, such as thiophenol, acetic acid and methyl carbamate were added to the double bond, according to the Markovnikov rule, under acidic catalysis, to give *N*-methoxycarbonyl-*p*-[1-(thiophenyl) ethyl]phenylglycine (**8**), *N*-methoxycarbonyl-*p*-(1-acetoxyethyl)phenylglycine (**9**), and *N*-methoxycarbonyl-*p*-[1-(methoxycarbonylamino)ethyl]phenylglycine (**10a, b**).

Oxidation of the vinyl group was carried out by different methods. Oxidation with *m*-CPBA in CH_2Cl_2 gave the epoxide (**11**). Ozonolysis in CH_2Cl_2 at -78°c gave the aldehyde (**12**) (identified as the DNP derivative). Reduction of the aldehyde (**12**) by $NaBH_4$ in MeOH , gave the benzylic alcohol (**13**)[5c]. Oxidation of the vinyl group under basic conditions (to dissolve the *N*-methoxycarbonyl-*p*-vinyl phenylglycine (**5b**) in water) in the presence of $KMnO_4$ and $NaIO_4$ gave *N*-methoxycarbonyl-*p*-carboxyphenylglycine (**14a**) which was hygroscopic, thus identified as dimethyl ester (**14b**).

Cleavage of Moc , with no harm to the substituent on the aromatic ring, was achieved by using 10% HBr/ AcOH at 60°C for 1 h The hygroscopic hydrobromide was neutralized by propylene oxide in MeOH, to precipitate the free amino acid in its zwitterionic form. For this reason Moc was superior to *N*-benzoyl, as protecting group, as the later requires more drastic conditions for its removal.

Using the above general method we have prepared *p*-(2-bromoethyl)phenylglycine (**16**), *p*-(1,2-dibromoethyl)phenylglycine hydrobromide (**17**), *p*-(1-aminoethyl)phenylglycine (**18**) and methyl-*p*-formyl phenylglycine hydrobromide (**19**). Neutralizations of the monohydrobromides undergo smoothly, but when

we had additional amine group (**18**), owing to the fast precipitation of the zwitterionic form, the neutralization is not completed, thus poor analysis was obtained, however ^{1}H and ^{13}C nmr (in D_2O+TFA) are supporting the structure. The chlorine analogue of **16** could not be obtained owing to exchange of the chlorine with bromine.

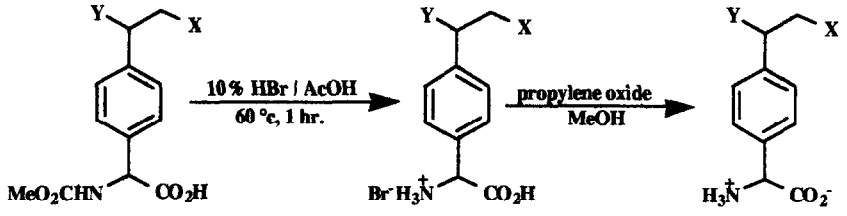


a) Br_2, CH_2Cl_2, b) PhSH, CH_2Cl_2, H_2SO_4(cat.), c) AcOH:H_2SO_4(10:1), d) MeO_2CNH_2, CH_2Cl_2, H_2SO_4cat.), e)m-CPBA, CH_2Cl_2 Δ, f) O_3, CH_2Cl_2, -78°c, g) $NaBH_4$, MeOH, h) K_2CO_3, H_2O, i) $NaIO_4$, $KMnO_4$, J) $SOCl_2$, MeOH

Cleavage of the *N*-methoxycarbonyl group from *N*-methoxycarbonyl-*p*-vinylphenylglycine (**5b**) was accompanied by addition of HBr to give *p*-(1-bromoethyl)phenylglycine (**20**). However the *p*-

vinylphenylglycine (**21**) was prepared by subjecting *p*-(2-bromoethyl)phenylglycine (**16**) to elimination conditions.

The previously reported Strecker[6] synthesis of *p*-vinylphenylglycine (**21**), using as a starting material a mixture of *ortho : para* isomers (1:4) of the desired aldehyde, gave in low yield a mixture of two isomers.

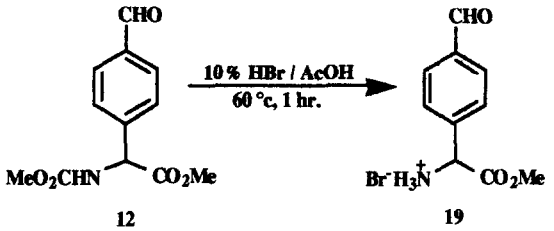


3d Y = H, X = Br **15** **16** Y = H, X = Br

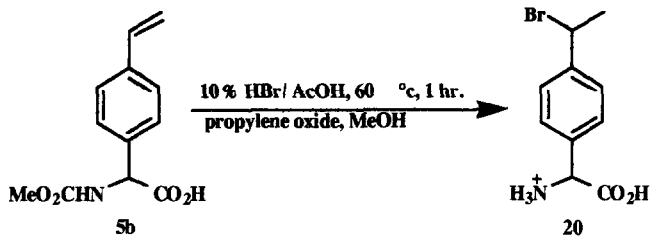
3c Y = H, X = Cl

7a Y = X = Br **17** Y = X = Br

10a Y = MeO_2CHN, X = H **18** Y = $Br^-H_3N^+$, X = H



12 **19**



5b **20**

Thus, we could prepare a list of new interesting *para* substituted phenylglycines in high purity and high yields. Identification of the free amino acid, described above, was made by I.R. and ^1H nmr spectra, every acid showed one spot on plate chromatography identified by ninhydrin.

Experimental:

Melting points are uncorrected. The Infrared spectra were recorded on a 298 Perkin Elmer spectrophotometer. ^1H nmr and ^{13}C nmr were measured on a Bruker EM-200 MHz. Mass specra were obtained on a Varian MAT 711 double focusing mass spectrometer. Elemental Analyses were performed by the Microanalytical Service of the Chemistry Department, the Hebrew University, Jerusalem. TLC was performed on Merck silica gel 60 F_{256} and flash chromatography on silica gel (Merck 70-230 mesh).

Amidoalkylation of (2-chloro or 2-bromoethyl)benzene (1a, 1b) :

Procedure A: **1a-b** (0.055 mol) was added to cold (0°C) suspension of α-hydroxyhippuric acid (**2a**) (0.05 mol) in con. H_2SO_4 (100 ml, Merck 96%) and stirred for 48 h at room temperature. The mixture was poured into ice water, extracted with EtOAc, dried over $MgSO_4$, filtered, concentrated and chromatographed on a silica column.

Procedure B: **1a-b** (0.055 mol) was added to cold (0°C) suspension of *N*-methoxycarbonyl α-hydroxyglycine (**2b**) (0.05 mol) in methane sulphonic acid (100 ml) and stirred for 24 h at room temperature. The mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered, concentrated and chromatographed on a silica column.

***N*-Benzoyl *p*-(2-chloroethyl)phenylglycine 3a:**

(2-Chloroethyl)benzene (**1a**) (0.05 mol, 7.73 g) was amidoalkylated as described in the **procedure A**. The crude product was chromatographed on a silica column. Elution with 5% acetone:chloroform afforded an oily product which was triturated with ether and filtered to give **3a**, 9.8 g (62%) as a white powder, m.p. 140°C. MS (HR): M^+ 317.0746 Calc. for $C_{17}H_{16}NO_3Cl$ 371.0819. ^1H nmr ($CDCl_3$): 9.84 (s, 1H, CO_2H), 7.79-7.16 (m, 10H, aromatic protons + NH), 5.75 (d, 1H, *J*=4.15, -CH-), 3.67 (t, 2H, *J*=7.11, CH_2Cl), 3.03 (t, 2H, *J*=9.3, $-CH_2-$). I.R ($CHCl_3$): 3400, 3000, 1730, 1660 and 1500 cm^{-1}.

***N*-Benzoyl *p*-(2-bromoethyl)phenylglycine 3b:**

(2-Bromoethyl)benzene (**1b**) (0.05 mol, 9.79 g) was amidoalkylated as described in **procedure A**. The crude product was chromatographed on a silica column. Elution with 5% acetone:chloroform afforded a yellow oil which was triturated with ether and filtered to give **3b**, 11.0 g (61%) as a white powder , m.p. 141°C. MS (HR): M^+ 361.0400, 361.0252 Calc. for $C_{17}H_{16}NO_3Br$ 361.0314, 361. 0252. ^1H nmr ($CDCl_3$): 9.82 (s, 1H, CO_2H), 7.80-7.20 (m, 10H, aromatic protons + NH), 5.75 (d, 1H, *J*=4.21, -CH-), 3.52 (t, 2H, *J*=7.0, CH_2Br), 3.12 (t, 2H, *J*=7.6, $-CH_2-$). I.R ($CHCl_3$): 3400, 3000, 1730, 1660 and 1500 cm^{-1}.

***N*-Methoxycarbonyl *p*-(2-chloroethyl)phenylglycine 3c:**

(2-Chloroethyl)benzene (**1a**) (0.05 mol, 7.5 g) was amidoalkylated as described in **procedure B.** The crude product was chromatographed on a silica column. Elution with 5% acetone:chloroform afforded a yellow oil which was triturated with ether and filtered to give **3c**, 10.0 g (74%) as a white powder, m.p. 124°C. MS (HR): M^+ 271.200, 273.200 Calc. for $C_{12}H_{14}NO_4Cl$ 271.2379, 273.2469. ^1H nmr (Acetond-d_6) :7.32 (d, 2H, *J*=8.3, aromatic protons), 7.22 (d, 2H, *J*=8.3, aromatic protons), 6.84 (d, 1H, *J*=5.8, NH), 5.27 (d, 1H, *J*=7.7, -CH-), 3.76 (t, 2H, *J*=6.9, CH_2Cl), 3.54 (s, 3H, CH_3O_2C-), 3.02 (t, 2H, *J*=7.3, $-CH_2-$). I.R ($CHCl_3$): 3420, 1720 and 1500 cm^{-1}.

***N*-Methoxycarbonyl *p*-(2-bromoethyl)phenylglycine 3d:**

(2-Bromoethyl)benzene (**1b**) (0.05 mol, 9.8 g) was amidoalkylated as described in **procedure B.** The crude product was chromatographed on a silica column. Elution with 5% acetone:chloroform afforded a yellow oil which was triturated with ether and filtered to give **3d**, 11.91 g (71%) as a white powder, m.p. 122°C. MS (HR): M^+ 315.100, 317.100 Calc. for $C_{12}H_{14}NO_4Br$ 315.2253, 317.2353. ^1H nmr (Acetond-d_6) :7.32 (d, 2H, *J*=7.3, aromatic protons), 7.22 (d, 2H, *J*=7.6, aromatic protons), 6.84 (d,

1H, *J*=7.3, NH), 5.27 (d, 1H, *J*=7.9, -CH-), 3.63 (t, 2H, *J*=7.5, CH_2Br), 3.25 (s, 3H, CH_3O_2C-), 3.12 (t, 2H, *J*=7.2, -CH_2-). I.R ($CHCl_3$): 3420, 1720 and 1500 cm^{-1}.

Esterification :

General Method: Thionyl chloride (0.025 mol, 2.0 ml) was added dropwise into a cold (0°C) solution of the *N*-protected acid (0.025 mmol) in MeOH (80 ml), under nitrogen atmosphere. The mixture was stirred at room temperature overnight, saturated with $NaHCO_3$ and the solvent evaporated. The ester was exracted with EtOAc washed with water, dried over $MgSO_4$, filtered and concentrated.

Methyl *N*-benzoyl *p*-(2-chloroethyl)phenylglycine 4a:

4a, 7.3 g (89%) was prepared using the above general method, m.p. 102°C. MS (HR): M^+ 331.100, 333.0997 Calc. for $C_{18}H_{18}NO_3Cl$ 331.0976, 333.0945. ^1H nmr ($CDCl_3$): 7.83-7.2 (m, 10H, aromatic protons + NH), 5.75 (d, 1H, *J*=4.2, -CH-), 3.75 (s, 3H, CO_2Me), 3.65 (t, 2H, *J*=7.16, CH_2Cl), 3.02 (t, 2H, *J*=7.6, -CH_2-). I.R ($CHCl_3$): 3400, 3000, 1730, 1660 and 1550 cm^{-1}.

Methyl *N*-benzoyl *p*-(2-bromoethyl)phenylglycine 4b:

4b, 7.5 g (80%), m.p. 105°C. MS (HR): M^+ 375.0452, 377.0474 Calc. for $C_{18}H_{18}NO_3Br$ 375.0469, 377.0450. ^1H nmr ($CDCl_3$): 7.80-7.2 (m, 10H, aromatic protons + NH), 5.74 (d, 1H, *J*=4.3, -CH-), 3.74 (s, 3H, CO_2Me), 3.52 (t, 2H, *J*=7.10 CH_2Br), 3.12 (t, 2H, *J*=7.6, -CH_2-). I.R ($CHCl_3$): 3400, 3000, 1730, 1660 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(2-chloroethyl)phenylglycine 4c:

4c, 6.3 g (90%), m.p. 67°C. MS (HR): M^+ 285.2, 287.2 Calc. for $C_{13}H_{16}NO_4Cl$ 285.2737, 287.3712. ^1H nmr ($CDCl_3$): 7.32 (d, 2H, *J*=8.3, aromatic protons), 7.22 (d, 2H, *J*=8.3, aromatic protons), 5.88 (d, 1H, *J*=6.6, NH), 5.31 (d, 1H, *J*=6.9, -CH-), 3.67 (t, 2H, *J*=6.8, CH_2Cl), 3.66 (s, 3H, CH_3O_2C-), 3.61 (s, 3H, CH_3O_2CHN-), 3.0 (t, 2H, *J*=7.2, -CH_2-). I.R ($CHCl_3$): 3420, 1720 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(2-bromoethyl)phenylglycine 4d:

4d, 8.91 g (90%), m.p. 75°C. MS (HR): M^+ 329.2, 331.2 Calc. for $C_{13}H_{16}NO_4Br$ 329.2737, 331.2731. ^1H nmr ($CDCl_3$): 7.32 (d, 2H, *J*=8.3, aromatic protons), 7.22 (d, 2H, *J*=8.3, aromatic protons), 5.81 (d, 1H, *J*=6.7,, NH), 5.34 (d, 1H, *J*=6.9, -CH-), 3.7 (s, 3H, CH_3O_2C-), 3.64 (s, 3H, CH_3O_2CHN-), 3.52 (t, 2H, *J*=7.9, CH_2Br), 3.12 (t, 2H, *J*=7.4, -CH_2-). I.R ($CHCl_3$): 3420, 2980, 1720 and 1500 cm^{-1}.

Elimination Reactions:

General Method: KOH (85%, 2.2 eq., 1.7 g) was added to the chloride (**3a** or **3b**) (0.0125 mol) in abs. MeOH (90 ml) under nitrogen atmosphere, and stirred under reflux for 5 h. At the end of the reaction, monitored by TLC, cooled to room temp. and catalytic amount of hydroquinon was added to avoid polymerization. The mixture was evaporated to dryness, redissolved in EtOAc to which crushed ice and HCl were added. The organic layer was washed with water dried over $MgSO_4$, filtered (hydroquinon was added) and concentrated.

***N*-Benzoyl *p*-vinylphenylglycine 5a:**

5a, 3.46 g (82%) , was prepared according to the above elimination method. m.p. 138°C. MS (HR): M^+ 281.1075 Calc. for $C_{17}H_{15}NO_3$ 281.1098. ^1H nmr ($CDCl_3$) : 8.84 (s, 1H, CO_2H), 7.9-7.8 (m, 10H, aromatic protons + NH), 6.64 (dd, 1H, J_1=17.6, J_2=10.8 -CH=), 5.74 (d, 1H, *J*=7.7, -CH-), 5.67 (d, 1H, *J*=17.7, =CH_2), 5.23 (d, 1H, *J*=10.9, =CH_2). I.R ($CHCl_3$): 3420, 1720, 1660 and 1500 cm^{-1}.

N-Methoxycarbonyl *p*-vinylphenylglycine 5b:

5b, 2.35 g (80%) of yellow oil. MS (HR): M^+ 235.2 Calc. for $C_{12}H_{13}NO_4$ 235.2391. ^1H nmr (acetone-d_6) : 7.32 (d, 2H, *J*=7.3, aromatic protons), 7.22 (d, 2H, *J*=7.6, aromatic protons), 6.87 (d, 1H, *J*=7.4, NH), 6.69 (dd, 1H, J_1=17.7, J_2=10.8 -CH=) 5.5 (d, 1H, *J*=17.5, $=CH_2$), 5.31 (d, 1H, *J*=7.7, -CH-), 5.18 (d, 1H, *J*=11.0, $=CH_2$), 3.54 (s, 3H, CH_3O_2C-). I.R ($CHCl_3$): 3420, 1720 and 1500 cm^{-1}.

Methyl *N*-benzoyl *p*-vinylphenylglycine 6a:

5a, 1.4 g (0.005 mol) was esterified using the above esterification general method yielding **6a**, 1.27 g (86%), m.p. 131°C. MS (HR): M^+ 295.1252 Calc. for $C_{18}H_{17}NO_3$ 295.1208. ^1H nmr ($CDCl_3$) : 7.9-7.8 (m, 10H, aromatic protons + NH), 6.63 (dd, 1H, J_1=17.6, J_2=10.8 -CH=), 5.74 (d, 1H, *J*=6.8, -CH-), 5.67 (d, 1H, *J*=17.5, $=CH_2$), 5.23 (d, 1H, *J*=10.6, $=CH_2$), 3.67 (s, 3H, CH_3O_2C-). I.R ($CHCl_3$): 3420, 2980, 1740, 1660 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-vinylphenylglycine 6b:

5b, 7.05 g (0.03 mol) was esterified as above yielding **6b**, 7.0 g (93%) as a yellow oil . MS (HR): M^+ 249.1 Calc. for $C_{13}H_{15}NO_4$ 249.2658. ^1H nmr ($CDCl_3$) : 7.32 (d, 2H, *J*=8.3, aromatic protons), 7.22 (d, 2H, *J*=7.6, aromatic protons), 6.70 (dd, 1H, J_1=17.7, J_2=10.9 -CH=), 5.96 (d, 1H, *J*=7.4, NH), 5.75 (d, 1H, *J*=17.5, $=CH_2$), 5.37 (d, 1H, *J*=7.3, -CH-), 5.26 (d, 1H, *J*=10.9, $=CH_2$), 3.72 (s, 3H, CH_3O_2C-), 3.54 (s, 3H, CH_3O_2CHN-). I.R ($CHCl_3$): 3420, 2980, 1725 and 1500 cm^{-1}.

N-Methoxycarbonyl *p*-(1,2-dibromoethyl)phenylglycine 7a:

Br_2 (3 ml, in excess) was added dropwise into the cold solution (0°C) of **5b**, 5.0 g (0.021 mol) in CH_2Cl_2 (50 ml) under nitrogen atmosphere, and stirred for 30 min. at r.t. The solvent was evaporated and the residue triturated in ether to give **7a**, 6.7 g (80%) as a white solid, m.p. 160°C. MS (HR): M^+ 392.9191, 394.9227, 396.9192 Calc. for $C_{12}H_{13}NO_4Br_2$ 392.9212, 394.9191, 396.9171. ^1H nmr (DMSO-d_3) : 8.04 (s, 1H, -NH-) 7.47 (d, 2H, *J*=2.5, aromatic protons), 7.39 (d, 2H, *J*=2.5, aromatic protons), 5.54 (dd, 1H, J_1=10.2, J_2=5.7, -CHBr-), 5.17 (d, 1H, *J*=8.3, -CH-), 4.38 (t, 1H, *J*=10.2, - CH_2Br), 4.25 (dd, 1H, J_1=10.1, J_2=5.6, - CH_2Br), 3.55 (s, 3H, CH_3O_2C-). I.R (KBr): 3400, 1740 and 1520 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(1,2-dibromoethyl)phenylglycine 7b:

7a, 9.89 g (0.025 mol) was esterified as described above yielding **7b**, 9.4 g (92%), m.p. 154°C. MS (HR): M^+ 406.9459, 408.9501, 410.9471 Calc. for $C_{13}H_{19}NO_4Br_2$ 406.9480, 408.9459, 410.9439. ^1H nmr (DMSO-d_3) : 8.19 (d, 1H, *J*=7.8, -NH-), 7.47 (d, 2H, *J*=2.5, aromatic protons), 7.39 (d, 2H, *J*=2.5, aromatic protons), 5.34 (dd, 1H, J_1=10.0, J_2=5.7, -CHBr-), 5.29 (d, 1H, *J*=8.0, -CH-), 4.38 (t, 1H, *J*=10.2, - CH_2Br), 4.26 (dd, 1H, J_1=10.1, J_2=5.8, $-CH_2Br$), 3.64 (s, 3H, $-CO_2CH_3$), 3.57 (s, 3H, CH_3O_2CHN-). I.R (KBr): 3400, 1740 and 1520 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(1-thiophenylethyl)phenylglycine 8:

BF_3·OEt_2 (2 ml) was added dropwise to the cold solution (0°C) of **6b**, 1.23 g (0.005 mol) and thiophenol (0.54 g, 0.005 mol) in 1,2-dichloroethane (40 ml), under nitrogen atmosphere. The mixture was stirred at r.t. for 48 h, EtOAc (200ml) was added, washed thrice with 10% $NaHCO_3$, dried over $MgSO_4$, concentrated and chromatographed on a silica column. Elution with 10% EtOAc:hexane afforded **8**, 1.39 g (79%) as an oil. MS (HR): M^+ 359.2 Calc. for $C_{19}H_{21}NO_4S$ 359.4392. ^1H nmr ($CDCl_3$) : 7.17 (m, 9H, aromatic protons), 6.03 (d, 1H, *J*=2.9, -NH-), 5.32 (d, 1H, *J*=2.9, -CH-), 4.6 (q, 1H, *J*=6.8, -C<u>H</u>CH_3), 3.60 (s, 3H, - CO_2CH_3), 3.58 (s, 3H, CH_3O_2CHN-), 1.53 (d, 3H, *J*=6.8, -CH<u>CH_3</u>). I.R ($CHCl_3$): 3420, 2920, 1720 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(1-acetoxyethyl)phenylglycine 9:

H_2SO_4 (1.5 ml, 96%) was added dropwise at 0°C into a solution of **6b**, 2.1 g (0.009 mol) in AcOH (30 ml), and stirred at r.t. for 48 h then poured on crushed ice and extracted with EtOAc. The organic layer washed thrice with water and then with 10% $NaHCO_3$,

dried over $MgSO_4$ and concentrated to give **9**, 1.86 g (71%) as an oil. ^1H nmr ($CDCl_3$) : 7.3 (m, 4H, aromatic protons), 5.97 (d, 1H, *J*=6.81, -NH-), 5.83 (q, 1H, *J*=6.44, -CHCH$_3$), 5.32 (d, 1H, *J*=6.46, -CH-), 3.76 (s, 3H, -CO_2CH_3), 3.61 (s, 3H, CH_3O_2CHN-), 2.04 (s, 3H, CH_3O_2C-), 148 (d, 3H, *J*=6.44, -CHCH$_3$). I.R ($CHCl_3$): 3420,, 1720 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-[1-(methoxycarbonyl)aminoethyl]phenylglycine 10a:

H_2SO_4 (1.5 ml, 96%) was added dropwise at 0°C into a solution of **6b**, 5.66g (0.023 mol) and methyl carbamate (1.73 g, 0.023 mol) in $CHCl_3$ (60 ml), under nitrogen atmosphere and stirred under reflux for 24 h, cooled extracted with $CHCl_3$, washed with water and then with 10% $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a crude product that was chromatographed on a silica column. Elution with 5% acetone: CH_2Cl_2 afforded **10a**, 5.8 g (69%) as a white powder, m.p. 113°C. MS (HR): (M^+-CO_2Me) 265.1285 Calc. for $C_{13}H_{17}N_2O_4$ 265.2883 .^1H nmr ($CDCl_3$) : 7.33 (m, 4H, aromatic protons), 5.72 (d, 1H, *J*=6.7, -NH-), 5.62 (bs, 1H, -NH-), 5.31 (d, 1H, *J*=6.9, -CH-), 4.79 (q, 1H, *J*=6.6, -CHCH$_3$), 3.70 (s, 3H, -CO_2CH_3), 3.64 (s, 3H, CH_3O_2CHN-), 3.62 (s, 3H, CH_3O_2CHN-),1.42 (d, 3H, *J*=6.7, -CHCH$_3$). I.R ($CHCl_3$): 3430, 2980, 1720 and 1500 cm^{-1}.

***N*-Methoxycarbonyl *p*-[1-(methoxycarbonyl)aminoethyl]phenylglycine 10b:**

10a, 1.38 g (0.0042 mol) was dissolved in MeOH (25 ml) containing KOH (0.28 g, 0.005 mol) and stirred at r.t. overnight. The solvent was evaporated. The residue dissolved in water and acidified with 37% HCl, extracted with EtOAc, dried over $MgSO_4$, and concentrated to give **10b**, 1.13 g (86%) as a white powder, m.p. 102°C. ^1H nmr (DMSO-d_3) : 12.94 (s, 1H, -CO_2H), 7.92 (d, 1H, *J*=8.0, -NH-), 7.70 (d, 1H, *J*=7.92, -NH-), 7.29 (m, 4H, aromatic protons), 5.09 (d, 1H, *J*=8.0, -CH-), 4.62 (q, 1H, *J*=7.22, -CHCH$_3$), 3.54 (s, 3H, -CO_2CH_3), 3.49 (s, 3H, CH_3O_2CHN-), 3.48 (s, 3H, CH_3O_2CHN-), 1.3 (d, 3H, *J*=6.9, -CHCH$_3$). I.R ($CHCl_3$): 3430, 2980, 1720 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-(epoxyethyl)phenylglycine 11:

6b, 3.22 g (0.013 mol) was dissolved in CH_2Cl_2 (60 ml) under nitrogen atmosphere, m-CPBA (2.93 g, 1.3 eq) was added and the mixture was stirred under reflux overnight, cooled to r.t.,washed thrice with 10% $NaHCO_3$, dried over $MgSO_4$, and concentrated to give **11**, 3.12 g (91%) as a yellow oil. MS (HR): M^+ 265.0993 Calc. for $C_{13}H_{15}NO_5$ 265.0951. ^1H nmr ($CDCl_3$) : 7.33 (m, 4H, aromatic protons), 5.8 (d, 1H, *J*=6.8, -NH-), 5.31 (d, 1H, *J*=6.9, -CH-), 3.84 (t, 1H, *J*=3, -CHO-), 3.70 (s, 3H, -CO_2CH_3), 3.65 (s, 3H, CH_3O_2CHN-), 3.13 (t, 1H, *J*=5.2, -CH_2O-), 2.76 (dd, 1H, J_1=5.3, J_2=2.9, -CH_2O-). I.R ($CHCl_3$): 3430, 1720 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-formylphenylglycine 12:

6b, 4.89g (0.02 mol) was dissolved in CH_2Cl_2 (90 ml), and cooled to -78°C. Ozone , produced by ozonatur 120v, 5.5-6 p.s.i. was bubbled through the reaction mixture until a blue color appeared. The excess of ozone was removed by oxygen. DMSO (1.5 ml, 1.4 eq.) was added and the mixture warmed to r.t., stirred for 3 h, washed with water, dried over $MgSO_4$, and concentrated. The crude oil was chromatographed on a silica column. Elution with 10% acetone: CH_2Cl_2 afforded **12**, 3.95 g (78%) as a white powder, m.p. 120°C. MS (HR): M^+ 251.2 Calc. for $C_{12}H_{13}NO_5$ 251.2384. ^1H nmr ($CDCl_3$) : 9.97 (s, 1H, CHO), 7.69 (d, 2H, *J*=6.8, aromatic protons), 7.43 (d, 2H, *J*=6.9, aromatic protons), 5.95 (d, 1H, *J*=6.2, -NH-), 5.42 (d, 1H, *J*=6.96 -CH-), 3.70 (s, 3H, -CO_2CH_3), 3.65 (s, 3H, CH_3O_2CHN-). I.R ($CHCl_3$): 3420, 1725 and 1500 cm^{-1}.

Methyl *N*-methoxycarbonyl *p*-hydroxymethylphenylglycine 13:

12, 0.29 g (0.0012 mol) was dissolved in MeOH (18 ml), $NaBH_4$ was added and the mixture was stirred at r.t. for 1 h. Water and CH_2Cl_2 were added The organic layer was washed with water dried over $MgSO_4$, and concentrated to give **13**, 0.24 g (79%) as a yellow oil. MS (HR): M^+ 253.0996 Calc. for $C_{12}H_{15}NO_5$ 253.0950. ^1H nmr ($CDCl_3$) : 7.24 (m, 4H, aromatic protons), 6.02 (d, 1H, *J*=7.3, -NH-), 5.27 (d, 1H, *J*=7.3 -CH-), 4.54 (s, 2H, -CH_2O-), 3.70 (s, 3H, -CO_2CH_3), 3.65 (s, 3H, CH_3O_2CHN-), 2.92 (bs, 1H -OH). I.R ($CHCl_3$): 3580, 3420, 2940, 1720 and 1500 cm^{-1}.

N-Methoxycarbonyl *p*-carboxyphenylglycine 14a and Methyl *N*-methoxycarbonyl *p*-methoxycarbonylphenylglycine 14b:

5b,4.7 g (0.02 mol) and K_2CO_3 (2.76 g, 0.02 mol) were dissolved in H_2O (60 ml) at 0°C, $NaIO_4$ (4.28 g, 0.02 mol) and $KMnO_4$ (1.58 g, 0.01 mol) in H_2O (60 ml) were added. The mixture was stirred at r.t. overnight. The brown participate, MnO_2 was removed by filtration. The water solution was acidified with 37% HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated to give **14a**, 3.05 g as a hygroscopic solid. ^1H nmr (DMSO-d_6) : 8.30 (d, 1H, *J*=7.6, -NH-), 7.74 (m, 4H, aromatic protons), 5.38 (d, 1H, *J*=7.7 -CH-), 3.55 (s, 3H, CH_3O_2C-). Esterification of **14a**, afforded **14b**, 5.0 g (54%) as an oil MS (HR): M^+ 281.2 Calc. for $C_{13}H_{15}NO_6$ 281.2646. ^1H nmr ($CDCl_3$) : 7.33 (m, 4H, aromatic protons), 5.78 (d, 1H, *J*=6.9, -NH-), 5.33 (d, 1H, *J*=7.3 -CH-), 3.71 (s, 3H, $-CO_2CH_3$), 3.66 (s, 3H, $-CO_2CH_3$), 3.61 (s, 3H, CH_3O_2CHN-). I.R ($CHCl_3$): 3440, 2960, 2820, 1720 and 1500 cm^{-1}.

Removal of *N*-methoxycarbonyl protecting group

General method: The *N*-protected derivative (0.025 mol) was dissolved in 10% HBr in acetic acid (45 ml.). The mixture was stirred at 60°C for 1-2 h. The acids were removed in vacuo. The hygroscopic residue was washed several times with anhydrous ether, and redissolved in MeOH (35 ml) at 0°C to which propylene oxide (2-3 ml) was added until the solution became turbide, and the mixture was stirred at room temp. for 2 h. The solid was filtered and dried in vacuo. TLC was performed using butanol: water: AcOH (10:1:3)[7], spraying with ninhydrin.

p-(2-Bromoethyl)phenylglycine 16:

3d, 7.9 g (0.025 mol) afforded **16**, 6.25 g (97%) as a white powder, m.p. (dec.) above 220°C. ^1H nmr (D_2O+TFA): 6.32 (d, 2H, *J*=7.95, aromatic protons), 6.29 (d, 2H, *J*=8.02, aromatic protons), 4.07 (s, 1H, -CH-), 2.54 (t, 2H, *J*=6.9, $-CH_2Br$), 2.06 (t, 2H, *J*=6.3, $-CH_2$-). ^{13}C nmr (D_2O+TFA): 171.4 (CO), 143.7, 132.0, 131.8, 130.0 (aromatic carbons), 58.32 (C-CO_2), 39.86 (CH_2), 34.95 (CH_2Br). Analysis calc. for $C_{10}H_{12}NO_2Br2H_2O$ C, 40.27; H, 4.11; N, 4.76% Found C, 40.27; H, 4.68; N 4.37%. Rf^7 = 0.36

p-(1,2-Dibromoethyl)phenylglycine hydrobromide 17:

7a, 3.84 g (0.01 mol) was dissolved in 10% HBr in acetic acid (45 ml.). The mixture was stirred at 60°C for 1-2 h. The acids were removed in vacuo, and the residue was washed several times with anhydrous ether, afforded **17**, 4.06 g (97%) as a white powder, m.p. (dec.) above 250°C. ^1H nmr (D_2O): 8.79 (s, 3H, $-NH_3$), 7.29 (d, 2H, *J*=7.97, aromatic protons), 7.12 (d, 2H, *J*=8.01, aromatic protons), 5.19 (s, 1H, -CH-), 4.42 (t, 1H, J_1=10.3, $-CH_2Br$), 4.26 (dd, 1H, J_1=10.3, J_2=5.6, $-CH_2Br$), 3.58 (dd, 1H, J_1=10.4, J_2=5.6, -CHBr-). ^{13}C nmr (D_2O): 171.9 (CO), 143.2, 133.6, 130.7, 130.4 (aromatic carbons), 58.1 (C-CO_2), 51.35 (CHBr), 36.35 (CH_2Br) . Analysis calc. for $C_{10}H_{11}NO_2Br_2.HBr$ C, 28.7; H, 2.87; N, 3.35% Found C, 27.64; H, 2.95; N 3.27%. Rf^7 = 0.29.

p-(1-Aminoethyl)phenylglycine monohydrobromide 18:

10b, 0.62 g (0.002 mol), using the deprotection general procedure, afforded **18**, 0.3 g (85%) as a white powder, m.p. (dec.) above 200°C. ^1H nmr (D_2O+TFA): 6.39 (d, 2H, *J*=7.03, aromatic protons), 6.31 (d, 2H, *J*=6.95, aromatic protons), 4.09 (s, 1H, -CH-), 3.75 (q, 1H, *J*=6.55, $-CHNH_3^+$-), 0.93 (d, 3H, *J*=6.35, $-CH_3$). ^{13}C nmr (D_2O+TFA): 172.5 (CO), 146.9, 132.6, 130.1, 125.5 (aromatic carbons), 81.3 ($CHNH_3^+Br^-$), 58.4 (C-CO_2), 23.9 (CH_3). Analysis calc. for $C_{10}H_{11}N_2O_2.HBr$ C, 43.65 H, 5.49% Found C, 42.67; H, 5.73%. Rf^7 = 0.43.

Methyl *p*-formylphenylglycine hydrobromide 19:

12, 0.5 g (0.002 mol), (using the same procedure as used for **17**) afforded **19**, 0.49 g (90%) as a white powder, m.p. (dec.) above 200°C. ^1H nmr (DMSO-d_6): 10.05 (s, 1H, CHO) 9.06 (bs, 3H, NH_3^+) 7.87 (d, 2H, *J*=5.4, aromatic protons), 7.29 (d, 2H, *J*=5.7, aromatic protons), 5.55 (s, 1H, -CH-), 3.73 (s, 3H ,$-CO_2CH_3$).

p-(1-Bromoethyl)phenylglycine 20:

5b, 2.35 g (0.01 mol), using the deprotection general procedure, afforded **20**, 2.26 g (88%) as a white powder, m.p. (dec.) above 250°C. ^{1}H nmr (D_2O+TFA): 6.31 (d, 2H, *J*=8.03, aromatic protons), 6.29 (d, 2H, *J*=8.02, aromatic protons), 4.09 (s, 1H, -CH-), 3.82 (q, 1H, J_1=6.42, -CHBr-), 0.33 (d, 3H, *J*=6.35, -CH_3). ^{13}C nmr (D_2O+TFA): 172.2 (CO), 147.2, 137.41, 130.0, 129.2 (aromatic carbons), 71.4 (CHBr), 57.3 (C-CO_2), 25.2 (CH_3). Analysis calc. for $C_{10}H_{11}NO_2Br$ C, 45.54; H, 4.69; N, 5.43% Found C, 45.6; H, 4.68; N, 5.27%. Rf^7 = 0.44

p-Vinylphenylglycine 21:

16, 5.16 g (0.02 mol), using the elimination general procedure, afforded **21**, 3.0 g (84%) as a white powder, m.p. (dec.) above 180°C. ^{1}H nmr (D_2O+TFA) : 6.11 (d, 2H, *J*=8.03, aromatic protons), 5.8 (d, 2H, *J*=8.02, aromatic protons), 5.05 (dd, 1H, J_1=16.6, J_2=10.9 -CH=) 4.18 (d, 1H, *J*=17.5, =CH_2), 3.67 (d, 1H, *J*=10.9, =CH_2), 3.50 (s, 1H, -CH-). ^{13}C nmr (D_2O+TFA): 172.52 (CO), 147.2 (aromatic carbon), 141.6 (C$\underline{H}$=CH_2), 137.8 (aromatic carbon), 132.4 (CH=C$\underline{H}_2$), 130.4, 129.3 (aromatic carbons), 58.4 (C-CO_2). Analysis calc. for $C_{10}H_{11}NO_2.2H_2O$ C, 56.32; H, 5.2; N, 6.56% Found C, 56.44; H, 5.32; N, 6.57%. Rf^7 = 0.48.

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7) D,L-Phenylglycine had a Rf value of 0.22 under the same conditions (butanol: water: acetic acid 10:1:3).

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