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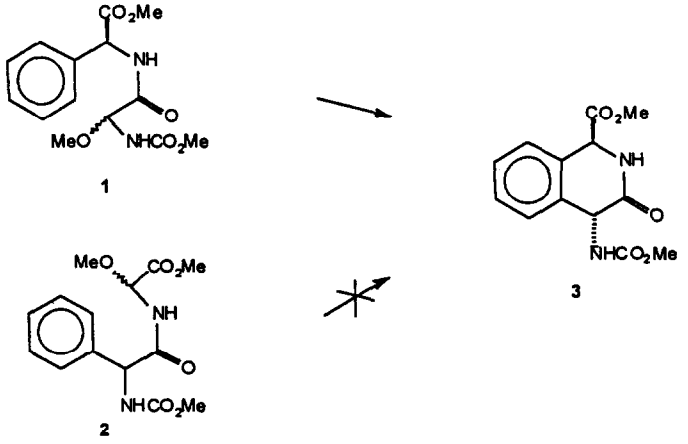
Intramolecular Amidoalkylation of Aromatics III. Synthesis of Conformationally Restricted Bridged Peptide Analogues of Phe-Gly

Amal Rabi-Barakay* and Dov Ben-Ishai✡

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

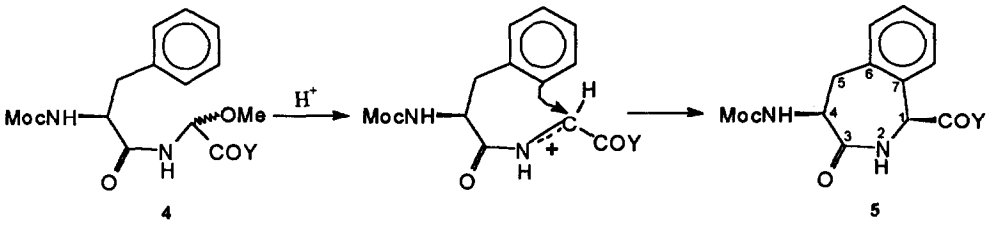
Abstract: Derivatives of the Phe-α-methoxyglycine (4) were prepared and found to undergo stereospecific intramolecular amidoalkylation to give derivatives of 4-amino-2-benzazepin-3-one-1-carboxylic acid 5 (ABZC). The cyclic compounds **5a-g** are conformationally restricted peptides containing a bridged Phe-Gly moiety.

Bridging between two neighbouring amino acids in peptides leads to conformationally restricted modified peptides which can imitate or block at the receptor level biological function of natural peptides and are stable towards proteolysis[1]. For this reason there has been a growing trend to use modified peptides as a new type of drug[2]. In the course of a study on the intramolecular amidoalkylation of aromatic compounds with glyoxylic acid-primary amide adducts[3] we have prepared dipeptides containing α-methoxyglycine attached to phenylglycine (Phg) at either the amino (1) or the carboxy (2) end and studied their intramolecular amidoalkylation of the aromatic side chain as an entry to bridged dipeptide analogues. It was found that only the dipeptide 1 cyclized, in methanesulfonic acid solution at room temperature, to the isoquinolone derivative 3. The isomeric dipeptide 2, which reacted smoothly with toluene intermolecularly, did not cyclize to give any of the isoquinolone derivative 3[3a]:



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

We have now extended the intramolecular amidoalkylation of aromatics to synthesize a cyclic dipeptide analogue of Phe-Gly in which the side chain phenyl group is connected to the α-carbon of glycine and have tried to incorporate it into longer peptides. The ultimate goal was to prepare analogues of biologically active peptides (e.g. substance P and related peptides)[4], substituting the normal Phe-Gly moiety for the cyclic analogue (**5**). We first synthesized a number of open-chain dipeptide derivatives of S-phenylalanine and α-methoxy-R,S-glycine (**4**) by reaction between S-phenylalanine amide and glyoxylic acid .



4 **5**

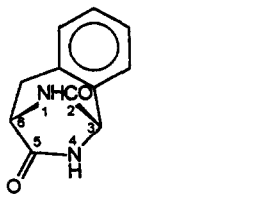
Moc = MeOCO

a Y = OH
b Y = OMe
c Y = NH_2
d Y = $NHCH_2CH(CH_3)_2$

e Y = Leu-OH
f Y = Leu-OMe
g Y = Leu-NH_2
h Y = Leu-Met-NH_2

N-Moc-S-Phe-α-MeO-Gly-OMe (**4b**) was submitted to intramolecular amidoalkylation in concentrated sulfuric acid (96%) at room temperature. This process involves a seven-membered cyclic transition state of *N*-acyliminium ion induced aromatic substitution. The site of approach of the aromatic ring appears to be sensitive to steric factors. The S configuration of the *N*-carbomethoxy group and the conformational behaviour of the *N*-acyliminium ion determine the chirality of the new stereocenter leading to formation of a single isomer of methyl *N*-Moc-4-amino-2-benzazepin-3-one-1-carboxylate (**5**) in 67% yield. This isomer is, according to its H-1 H-4 NOE correlation, the *cis* 1S, 4S isomer with the preference for the equatorial orientation of two substituents in the seven-membered ring product[5]. The S configuration of *N*-carbomethoxy group of the lower homologue, *N*-Moc-S-Phg-α-MeO-Gly-OMe (**1**), in the less puckered six-membered transition state, gave exclusively the *trans* isomer **3**[3a].

The attempts to remove the Moc protecting group from the nitrogen, under non-hydrolytic acidic conditions, converted compound **5b** to a 3,6-bridged piperazine-2,5-dione **6**. The same bridged piperazinedione **6** was also obtained on attempts to equilibrate the methyl ester **5b** in refluxing methanol in the presence of triethylamine. Cyclizing *N*-Moc-Phe-α-MeO-Gly (**4a**) in concentrated sulfuric acid at room temperature gave a mixture of the acid **5a** together with the *N*-Moc derivative of the bridged piperazine-2,5-dione **7**, which is most probably the intermediate in the formation of **6** from **5b**. The easy formation of the bridged piperazinedione **6** from **5a**, **5b** and **5c** in acid media, in addition to spectral data, supports the *cis* configuration of the products. The structure of the two bridged piperazinediones **6** and **7** is confirmed by X-ray crystal analysis.



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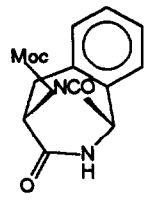

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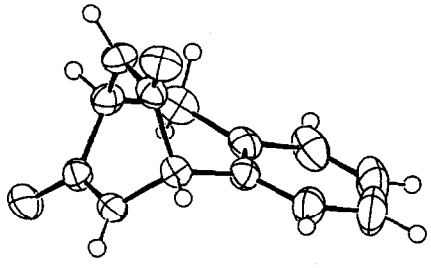

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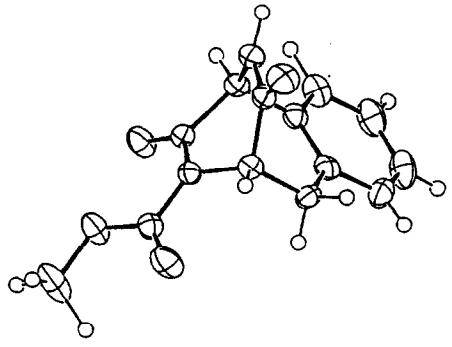


7

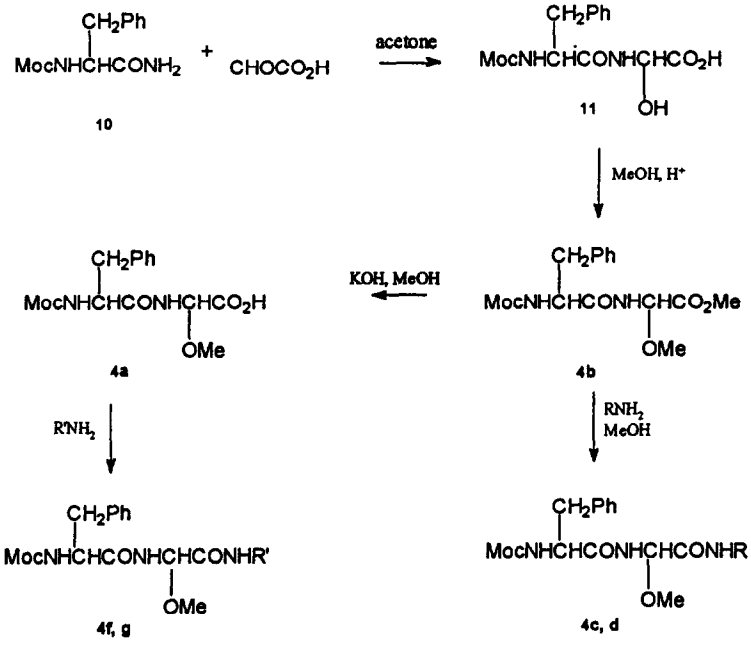
ORTEP Drawing of **6** and **7**

Cyclization of the amide **4c** and the isobutylamide **4d** afforded the cyclic benzazepinone derivatives **5c** and **5d** in 43% and 89% yield respectively as crystalline compounds. Only one isomer was obtained in each case. The most characteristic absorptions in the ^{1}H NMR of the cyclic derivatives is that of the benzylic hydrogen at position 1 of the azepinone ring at 5.2-5.6 ppm. It appears as a sharp doublet. Its neighbouring NH appears as a doublet at 8.2-8.7 ppm in $DMSOd_6$ solutions. The *cis* relation of the amino and carboxyl groups on the azepinone ring system is supported by a 1,4 NOE correlation of the hydrogens on the two chiral centers. The α-benzylic position of amides is sensitive to epimerization under basic conditions. Equilibration of the isobutylamide **5d** in refluxing methanol and in the presence of triethylamine gave a mixture of two isomers, the *cis* (1S, 4S) and the *trans* (1R, 4S) in a 1:1 ratio, as detected in NMR spectrum from two distinct doublets of two different benzylic hydrogens. Amidation of the bicyclic ester **5b** in a methanolic ammonia solution gave the amide **5c** as a mixture of two isomers, in a 2:1 ratio (*trans:cis*), which were separated on a silica column. The ammonia is probably basic enough to equilibrate the pure isomers. The *cis-trans* assignment of the two isomers is based on the H-1 H-4 NOE correlation. The isobutylamide derivative of the benzazepinone **5d** is more stable than the methyl ester **5b** or the primary amide **4c** towards piperazinedione formation. The Moc protecting group can, in this case, be removed and exchanged for other acyl groups. The Moc protecting group was removed according to the Yajima procedure[6] (dimethyl sulfide in methanesulfonic acid) and the free amine was further acylated with either benzyl chloroformate or protected

amino acids. Thus the isobutylamide of *N*-Z-4-amino-2-benzazepin-3-one-1-carboxylic acid (**8**) was obtained in 75% yield from the corresponding *N*-Moc derivative **5d**.

The smooth cyclizations of the open chain amide **4d** to the corresponding benzazepinone **5d** and the relative stability of the isobutylamide towards the formation of the bridged piperazinedione **6**, encouraged us to use this sequence of reactions for the synthesis of higher bridged peptide analogues. Instead of the isobutylamide we have synthesized open chain tripeptide derivatives by adding Leu, Leu-OMe and $LeuNH_2$ to the carboxy end of the dipeptide **4a**[7]. The tripeptide intermediates **4e-g** were then cyclized in concentrated sulfuric acid at room temperature to the corresponding benzazepinone derivatives **5e-g** in 51%, 40% and 56% yield. In the last case we have further replaced the Moc protecting group by the Cbz group using the procedure described above for the synthesis of the *N*-Cbz derivative **8**. We have also synthesized one tetrapeptide analogue **5h** (Y=Leu-Met-NH_2). This compound was synthesized either from the acid **5a**, by the addition of Met-NH_2 to its carboxy end, or by cyclizing the corresponding open chain tetrapeptide **4h** in concentrated sulfuric acid. The acid catalyzed cyclizations afforded only one isomer in each case.

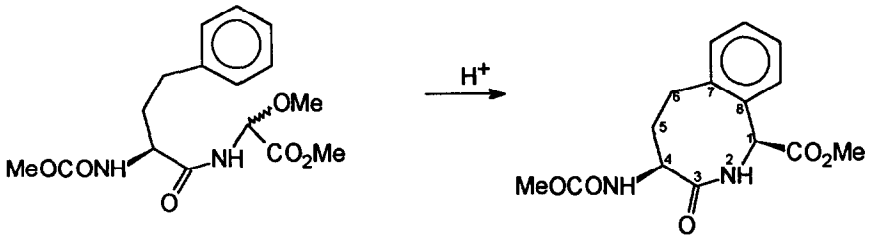
The intermediates, open chain peptides **4**, were prepared by the general scheme:



The glyoxylic acid primary amide adduct **11** was prepared by refluxing a mixture of *N*-Moc-Phe-NH_2 and glyoxylic acid monohydrate in acetone, containing a catalytic amount of trifluoroacetic acid, for 24h. The adduct *N*-Moc-Phe-α-OH-Gly (**11**) was further converted to *N*-Moc-Phe-α-OMe-Gly-OMe (**4b**) on treatment with methanolic hydrogen chloride at room temperature overnight. The methyl ester **4b** was hydrolyzed, with one equivalent of methanolic potassium hydroxide, to the acid *N*-Moc-Phe-α-MeO-Gly (**4a**). Amidation of the methyl ester **4b** with methanolic ammonia at room temperature or with isobutylamine

in refluxing methanol afforded the amides *N*-Moc-Phe-α-MeO-Gly-NHR **4c** and **4d**. At the other end coupling of the acid **4a** with Leu-OMe or Leu-NH_2 by the mixed anhydride procedure afforded the open chain tripeptide analogues **4f** and **4g**. The tripeptide derivative, *N*-Moc-Phe-α-MeO-Gly-Leu (**4e**) was prepared by hydrolyzing the methyl ester **4f** in methanolic potassium hydroxide (1 eq.).

The intramolecular amidoalkylation of the open chain dipeptide *N*-Moc-R,S-Homophe-α-MeO-Gly-OMe (**12**) in concentrated sulfuric acid leads to the cyclic analogue of Homophe-Gly. The benzazinone derivative **13** was obtained in 52% yield. The yield of the eight-membered compound **13** was lower than the seven-membered **5b** with no evidence for any linear intermolecular amidoalkylation side product. According to the 1,4 H NOE correlation the benzazinone **13** is also the *cis* isomer.



12 **13**

Thus, the intramolecular amidoalkylation of *N*-Moc-S-Phe-α-MeO-Gly-OMe and *N*-Moc-R,S-Homophe-α-MeO-Gly-OMe leads to a short and stereoselective synthesis of conformationally restricted analogues of Phe-Gly peptides containing an aromatic ring fused with a seven membered ring and an eight membered cyclic analogue of Homophe-Gly.

Experimental

M.P.'s are uncorrected. The I.R. spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian-T-60, a Bruker 200 and a Bruker 400 MHz instruments. Mass spectra were obtained on a Varian Matt-711 double focusing instrument. TLC was performed 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. Crystal structure analyses of the compounds 6 and 7 were carried out at the Technion using the Philips PW 1100/20 four circle diffractometer. Programs used for structure solution and refinement were Shelx-86 and Shelx-76.

N-Moc-S-Phenylalanine-α-hydroxyglycine (11):

A mixture of Moc-S-Phe-NH_2 (35.0 g, 157.5 mmol), glyoxylic acid monohydrate (21.75 g 50% excess) and TFA (0.5 ml) in acetone (200 ml) was refluxed overnight. The acetone was evaporated and the residue was dissolved in EtOAc (250 ml), washed with water (75 ml) and dried with anhydrous $MgSO_4$. The oil product obtained after the removal of the EtOAc was triturated with anhydrous ether (100 ml) to give a white crystalline material (32.0 g 68.8%, m.p. 122-126°C) $[\alpha]_D^{23}$ +7.1 (*c* 1, MeOH) IR (KBr) 3550-2800 (b, OH, NH), 1755, 1700 and 1670 (CO) and 1550 cm^{-1} (NH); ^{1}H-NMR (DMSO-d_6) δ: 8.80 (d, *J*=11, 1H NH), 7.25 (m, 6H, ar + NH), 5.42 (d, *J*= 11, 1H, CH), 4.24 (t, 1H, CH), 3.41 (s, 3H, OMe), 3.1 - 2.54 (m, 2H, CH_2); MS (HR): *m/z* = 246.1042 (M^+ - H_2O - MeOH), $C_{12}H_{10}N_2O_4$ requires 246.0640.

Methyl-*N*-Moc-S-phenylalanine-α-methoxyglycinate (4b):

N-Moc-S-Phe-α-hydroxygly-OH (10.0 g, 33.7 mmol) was suspended in MeOH (200 ml) and $SOCl_2$ (4.3 g, 37.1 mmol) was slowly added with cooling (ice + H_2O) and stirring. After stirring overnight at room temperature the MeOHl solution was neutralized with solid $NaHCO_3$ and the methanol evaporated. The residue was divided between EtOAc (120 ml) and H_2O (100 ml). The organic layer was washed with water (50 ml) and dried. The EtOAc was evaporated and the oily residue was triturated with anhydrous ether to give a white solid (9.0 g 82%), m.p. 101-104°C, IR ($CHCl_3$): 3425 (NH), 1760, 1730 and 1700 (CO) and 1510 cm^{-1} (NH), ^{1}H-NMR ($CDCl_3$) δ: 7.25 (bs, 6H, ar + NH), 5.83-5.43 (d,d + bs; 2H, CH + NH), 4.85 - 4.30 (m, 1H, CH), 3.83 (s, 3H, CO_2Me), 3.60 (s, 3H, $NHCO_2$ Me), 3.50, 3.37 (2s, 3H, OMe 2-isomers). MS (HR) *m/z* = 324.1328 (M^+) $C_{15}H_{20}N_2O_6$ requires 324.1321.

N-Moc-S-phenylalanine-α-methoxyglycine (4a):

The methoxy methyl ester 4b (10 g, 32 mmol) was dissolved in MeOH-KOH (2.0 g in 150 ml) and left at room temperature overnight. The MeOH was evaporated and the residue was dissolved in H_2O (100 ml) and extracted with ether (2 x 50 ml). The aqueous solution was then acidified with H_3PO_4 (5% in H_2O) and extracted with EtOAc (2 x 100 ml), dried over anhydrous $MgSO_4$, filtered and evaporated to give a yellowish oily product (7.0 g, 73%). IR ($CHCl_3$); 3600-3150 (b, OH), 3410 (NH), 1725 and 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) δ: 8.97 (t, 1H, NH) 7.25 (m, 6H, ar. + NH), 5.30 (d, *J*=7.5, 1H, CH) 4.30 (m, 1H, CH), 3.25 (s, 3H, $NHCO_2$ Me), 3.24, 3.17 (2s, 3H, OMe 1:1 isomers), 3.00-2.74 (m, 2H, CH_2). MS (HR) *m/z* = 292.1089 (M^+-H_2O); $C_{14}H_{16}N_2O_5$ requires 292.1060.

N-Moc-S-phenylalanine-α-methoxyglycinamide (4c):

The methoxy methyl ester 4b mentioned above, (12.0 g, 37 mmol) was dissolved in NH_3-MeOH (15.0 g in 100 ml) and left in a pressure bottle overnight. The NH_3 and MeOH was evaporated and the residue triturated with anhydrous ether to give a solid (10.5 g 92%) m.p. 178-182°C, $[\alpha]_D^{23}$ -13.8 (*c* 1, MeOH) IR (KBr): 3550-3510 (b, NH_2), 1700, 1650 (CO) and 1560 cm^{-1} (NH_2). ^{1}H-NMR (DMSO-d6) δ: 8.68 (d, *J*=11, 1H, NH), 7.56-7.12 (m, 8H, ar + NH_2 + NH) 5.21 (d,d, 1H, CH, 2-isomers), 4.30 (m, 1H, CH), 3.43, 3.42 (2s, 3H, $NHCO_2$ Me, 2-isomers), 3.23, 3.21 (2s, 3H, OMe - 2- isomers). 3.05-2.70 (m, 2H, CH_2). MS HR) *m/z* = 309.1337, $C_{14}H_{19}N_3O_5$ requires 309.1324.

N-Moc-S-phenylalanine-α-methoxyglycyl-isobutylamide (4d):

A mixture of Moc-S-Phe-α-OMe-Gly-OMe (4b, 2g, 6 mmol), isobutylamide (1.0 g, 13 mmol) in methanol (30 ml) was left at room temperature overnight. The MeOH was evaporated and the residue triturated with ether to give the *N*-isobutylamide (4d) (2.03 g, 91%), m.p. 134-135°C). $[\alpha]_D^{23}$ +13.3 (*c* 1, MeOH), IR ($CHCl_3$): 3410 (NH), 1720, 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) : 8.27 (d, *J*=10, 1H, NH), 8.15 (bs, 1H, NH), 7.425 (d, *J*=9, 1H, NH), 7.35-7.11 (m, 5H, ar), 5.32 (d, *J*=10, 1H, CH), 4.32 (m, 1H, CH), 3.42 (s, 3H, OMe), 2.95 (m, 3H, CH_2+½CH_2), 2.71 (t, *J*=6.0, 1H, ½CH_2), 1.71 (m, 1H, CH), 0.85 (d, *J*=7.6, 6H, HCMe2). MS (HR) *m/z* = 365.1995; $C_{18}H_{27}N_3O_5$ requires 365.1950. The NMR spectra of the crude product shows peaks of a second isomer.

Methyl-*N*-Moc-S-phenylalanine-α-methoxyglycine-S-leucinate (4f):

A mixture of *N*-Moc-S-Phe-α-OMe-Gly-OH (19.0 g, 60 mmol), morpholine (6.2 g, 60 mmol) and isobutyl chloroformate (8.37 g, 60 mmol) in cooled THF (70 ml, ice-salt bath) was stirred for 1 minute. To the cold stirred solution a mixture of LeuOMe.HCl (11.12 g, 60 mmol) and Et_3N (6.02 g, 60 mmol) was added. After stirring for 30 minutes the salts were filtered off, the THF evaporated and the residue chromatographed over silica (Merck 70-340 mesh, 200 g) to give 19.5 g (73%) of product m.p. 119-122°C, $[\alpha]_D^{23}$ +82.7 (*c* 1, MeOH) IR ($CHCl_3$): 3410 (NH), 1730, 1715, 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (400 MHz, DMSO-d6) δ: 8.82 and 8.71 (2d, *J*=10, 1H, NH 2-isomers), 8.5, 8.51 (2d, *J*=9.3, 1H, NH, 2-isomers), 7.451 and 7.37 (2d, *J*=9.3, 1H, NH), 7.33-7.08 (m, 5H, ar), 5.38 (2d, *J*=11, 1H, CH) 4.32 (m, 2H, CH), 3.62 and 3.43 (2s, 3H, CO_2

Me), 3.24 and 3.16 (2s, 3H, OMe 2-isomers), 2.87 (m, 1H, CH), 2.72 (m, 1H, CH), 1.61 (m, 3H, CH_2+CH), 0.86 (2d, J=16.5, 6H, 2Me), MS (HR) *m/z* = 437.2174; $C_{21}H_{31}N_3O_7$ requires 437.2162.

N-Moc-S-phenylalanine-α-methoxyglycyl-S-leucineamide (4g):

To a cooled solution (ice and salt) of *N*-Moc-S-Phe-α-OMe-Gly-OH (11.0 g, 35 mmol) in dry THF (70 ml) were added Et_3N (3.60 g, 35 mmol) and isobutyl chloroformate (4.85 g, 35 mmol). After stirring for 1 minute, a mixture of $LeuNH_2$-HBr (7.4 g) in DMF (20 ml) was added followed by Et_3N (3.6 g). After stirring at room temperature for an additional 30 minutes, the salts were filtered, the THF was evaporated and the residue was triturated with ether to give 8.0 g (53%) of a crystalline product (m.p. 152°C from EtOAc-Hexane). $[\alpha]_D^{23}$-13.7° (*c* 1, MeOH), IR (KBr) 3500-3300 (NH_2+NH), 1720, 1670, 1650 (CO) and 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) δ: 8.29 (t, *J*=8.0, 1H, NH, 2-isomers) 8.06 (t, *J*=8.8, 1H, NH, 2-isomers) 7.44-6.98 (m, 8H, ar. + NH + NH_2), 5.39-5.28 (2d, *J*=8.8, *J*=8.0, 1H, CH, 2-isomers), 4.24 (m, 2H, CH), 3.43 (s, 3H, NCO_2Me), 3.43 and 3.15 (2s, 3H, OMe, 2-isomers), 3.07-2.62 (m, 2H, CH_2), 1.46 (m, 2H, CH_2+CH), 0.85 (d, 6H, $CHMe_2$).

N-Moc-S-phenylalanine-α-methoxyglycyl-S-leucine (4e):

The methyl ester 4f (17 g, 38 mmol) was hydrolyzed with KOH-MeOH (2.40 g in 200 ml) at room temperature overnight. The MeOH was evaporated and the salt was dissolved in H_2O (120 ml) extracted with ether to remove neutral materials. The H_2O solution was then acidified with H_3PO_4 (10% in H_2O) and extracted with EtOAc. The oily product was chromatographed over silica (250 g) to give 14.8 g (89%) of product. IR ($CHCl_3$): 3600-2400 (b. CO_2H), 3405 (NH), 1730, 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$)δ: 7.65 (d, *J*=8, 1H, NH), 7.10 (bs, S, 5H), 5.85 (bs, 1H, NH), 5.40 (d, *J*=8, 1H, CH), 5.20 (d, *J*=8, 1H, CH), 4.50 (m, 2H, CH), 3.55 (s, 3H, NCO_2Me), 3.35 (s, 3H, OMe), 3.00 (m, 2H, CH_2), 1.75 (m, 3H, CH_2+CH), 0.98 (d, 6H, $HCMe_2$). MS (HR) *m/z* = 392.1787 (M^+-OMe) $C_{19}H_{26}N_3O_6$ requires: 392.1812.

N-Moc-S-phenylalanine-α-methoxyglycyl-S-leucyl-S-methionylamide (4h):

4a (10.8 g, 0.0348 mol) and *N*-hydroxysuccinimide 4.3 g, 34.8 mmol) were dissolved in DMF (50 ml) and cooled in ice-salt bath. DCC (7.7 g, 34.8 mmol) was added followed by a mixture of leucyl-methionine amide hydrobromide (12.2 g, 34.8 mmol) and Et_3N (5.2 ml) in DMF (20 ml). The reaction mixture was stirred overnight at room temperature and concentrated in high vacuum. The residue was stirred with EtOAc and filtered from urea and salts. The organic layer was washed with water, dil. HCl, water, aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated giving 4h (9.2 g, 48%), m.p. 118-126°C. IR (KBr): 3300 (NH), 1720, 1670 (CO), 1530 (NH). ^{1}H NMR (DMSO-d_6) δ: 0.85 (d, *J*=4.0, 6H, $CH(CH_3)_2$), 1.04-1.97 (m, 5H, $CH_2CH(CH_3)_2$ + $CH_2CH_2SCH_3$), 2.01 (2, 3H, SCH_3), 2.40 (m, 2H, CH_2SCH_3), 2.57-2.94 (m, 2H, CH_2Ph), 3.15-3.23 (2s, 3H, OCH_3 two isomers), 3.42 (s, 3H, CO_2CH_3), 4.27 (m, 3H, CH), 5.21, 5.33 (2d, *J*=7.5, 1H, NHCH, two isomers), 7.04 (bs, 2H, NH_2), 7.25 (m, 6H, arom + NH), 8.03 (m, NH, two isomers), 8.17 (d, *J*=7.1, NH), 8.78 (m, NH, two isomers). MS (HR) *m/z* = 504.4821; [M^+-CH_3OH-NH_3)] $C_{24}H_{32}N_4O_6S$ requires 504.2310.

Methyl (1S, 4S) *N*-Moc-4-amino-2-benzazepin-3-one-1-carboxylate (5b):

N-Moc-S-Phe-α-MeO-Gly-OMe (4b) (10 g, 32 mmol) in cooled (ice + water) concentrated sulfuric acid (100 ml) was stirred overnight (24 h). The reaction mixture was poured onto crushed ice (150 g) and extracted with CH_2Cl_2 (2 x 150 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The oily residue was purified on a silica column (Merck 70-230 mesh, 100 gr) and eluted with CH_2Cl_2: EtOAc affording 6 g (67%). $[\alpha]_D^{23}$ +97.8 (*c* 1, MeOH), IR ($CHCl_3$): 3410 (NH), 1760 ester, 1730 carbamate, 1695 amide (CO) and 1505 cm^{-1} (NH), 1H-NMR (DMSO-d_6) δ: 8.08 (d, *J*=6.96, 1H, NH

(amide), 7.46 (d, *J*=7.70, 1H, NH (carbamate), 7.32-7.25 (m, 4H, ar), 5.21 (d, *J*=7.7, 1H, CH), 4.07 (m, 1H, CH), 3.66 (s, 3H, CO_2 Me), 3.54 (s, 3H, $NHCO_2$ Me), 3.06 (t, *J*=12.9, 1H, CH), 2.90 (d.d, *J*=3.2, CH). M.S. (HR) *m/z* = 292.1057 (M^+, 5.8%), 233.0926 (M^+-CO_2Me, 100%), $C_{14}H_{16}N_2O_5$ requires 292.1059.

Piperazin-2,5-dione (6):

The methyl ester **5b** (0.5 g, 1.5 mmol) in dry MeOH (20 ml) containing NaOMe (50 mg) was left at room temperature overnight. The MeOH was evaporated, the residue dissolved in H_2O (10 ml) and continuously extracted overnight with $CHCl_3$ to give a high melting product (>270°C dec, 0.24 g, 69%), $[\alpha]_D^{23}$ -171.8 (*c* 1, MeOH), IR (KBr) 3200 (NH), 1690 (CO). ^{1}H-NMR (400 MHz, DMSO-d6): 8.95 (d, *J*=4.2, 1H, NH), 8.50 (d, *J*=4.10, 1H, NH), 7.32-7.17 (m, 4H, ar) 4.36 (d, *J*=4.2, 1H, CH), 3.86 (m, 1H, CH), 3.21, (d, *J*=17.4, 1H, CH)., 3.1 (m, 1H, CH). MS (HR) = 202.0723 (M^+), $C_{11}H_{10}N_2O_2$ requires 202.0742. X-ray crystal structure analysis agrees with the suggested formula of **6**. Anal. Found: C, 65.17; H, 5.07; N, 13.76. $C_{11}H_{10}N_2O_2$ requires C, 65.38; H, 4.98; N, 13.86%.

(1S,4S)-*N*-Moc-*cis*-4-amino-2-benzazepin-3-one-1-carboxylic acid (5a):

Moc-S-Phe-α-OH-GlyOH (0.60 g, 2.02 mmole) was suspended in cold water 96% H_2SO_4 (ice + water, 12.0 ml) and the mixture was stirred in the cold (0.5 h) and then at room temperature for 4h. The reaction mixture was poured onto crushed ice and extracted with EtOAc (2 x 50 ml). The EtOAc was dried over $MgSO_4$, filtered and evaporated to give 0.36 g (64%) of a product which melted at 208-210°C after trituration with dry ether. IR (KBr): 3320 (NH), 3600-2250 (vb CO_2H), 1735; 1705 and 1630 (CO) and 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) : 7.60 (d, 1H, *J*=6.7, NH), 7.40 (d, 1H, *J*=7.5, NH) 7.23 (m, 4H, ar), 5.11 (d, 1H, *J*=6.7, CH), 3.55 (s, 3H, OMe), 4.18 (m, 1H, CH), 3.15-2.85 (m, 2H, CH_2). MS (HR) = 278.0927 (M^+); $C_{13}H_{14}N_2O_5$ requires 278.0902. Anal.: Found:$C_{13}H_{14}N_2O_5$.C, 55.88; H, 5.24; N, 10.00. $C_{13}H_{14}N_2O_5$ requires C,56.14; H, 5.07; N, 10.07%.C, 55.88; H, 5.24; N, 10.00.

5a was also obtained by hydrolysis of **5b** (1.0 g, 34 mmol) with KOH-MeOH-H_2O (0.2 g in 10 ml MeOH + 20 ml H_2O). After stirring at room temperature overnight the MeOH was evaporated, the solution acidified and extracted with EtOAc. Concentration and crystallization afforded **5a** in 67% yield.

1,4-Bridged-2,5-piperazinedione (7):

If the above cyclization is carried out at room temperature for 24 h. a mixture of **5a** and the neutral compound **7** is obtained in a 3:1 ratio. The two compounds can be separated using an aq $NaHCO_3$ extraction. The neutral **7** melts at 316-217°C. $[\alpha]_D^{23}$ +162.4 (*c* 1, MeOH), IR (KBr): 3490 (NH), 1740, 1720 and 1700 cm^{-1} (CO). 1H-NMR (DMSO-d6) δ: 9.30 (d, 1H, *J*=5.0, NH), 7.40-7.18 (m, 4H, ar), 4.7 (d, 1H, *J*=5.30), 4.89 (m, 1H, CH), 3.77 (s, 3H, OMe), 3.40 (m, 2H, CH_2). MS (HR) *m/z* = 260.0823 (M^+), $C_{13}H_{12}N_2O_4$ requires 260.0797. The structure of **7** was proved also by an X-ray crystal structure analysis (see attached X-ray structure).

***N*-Moc-4-amino-2-benzazepin-3-one-1-carboxamide (5c):**

The open chain amide (**4c**, 1g, 3.2 mmol) was dissolved with cooling (ice + water) in concentrated sulfuric acid (20 ml 96% Merck). The mixture was stirred at room temperature overnight (24 h.). The mixture was poured onto crushed ice and solid $NaHCO_3$ and the product extracted with EtOAc (3 x 50 ml). The EtOAc solution was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The residue was triturated with ether and filtered to give 0.3 g (43%) of a solid m.p. 91°C from EtOAc), [$\alpha]_D^{23}$ +110.3 (*c* 1, MeOH), IR (KBr) 3600-3150 (b, NH + NH_2), 1695 (CO) and 1535 cm-1 (NH). ^{1}H-NMR (DMSO-d6) δ:

7.66 (d, *J*=5, 2H, NH_2), 7.52 (d, *J*=6.5, 1H, NH), 7.40 (d, *J*=8.0, 1H, NH), 7.22 (bs, 4H, ar), 5.21 (d, *J*=6.5, 1H, CH), 4.40 (bq, 1H, CH), 3.55 (s, 3H, CO_2Me), 3.40-3.10 (m, 2H, CH_2), MS (HR) = 277.1060, (M^+). $C_{13}H_{15}N_3O_4$ requires 277.1060. Amidation of the bicyclic **5b** (1g) methyl ester (1 g) with NH_3-MeOH (15 g in 100 ml) for 24h and evaporation of the NH_3 and MeOH gave 0.84 g (89%) of a product which according to the NMR is a mixture of two isomeric amides (*cis* + *trans* 1:2). ^{1}H-NMR (DMSO-d_6) δ: 8.0-7.6 (NH_2 + NH), 7.20 (bs, 4H, ar), 5.21 and 5.05 (2d, J_1=6.5, J_2=6.6, 1H, CH), 4.65 and 4.40 (2m, 1H, CH), 3.55, 3.54 (2s, 3H, CO_2 Me), 3.35-2.90 (m, 2H, CH_2). Anal. Founf: C, 56.08; H, 5.71; N, 14.85. $C_{13}H_{14}N_3O_4$ requires C,56.32; H, 5.45; N, 15.16%.

N-Moc-4-amino-2-benezazepin-3-one-1-carboxyisobutylamide (5d):

The open chain isobutylamide **4d** (2.0 g 5.5 mmol) was added to cooled concentrated sulfuric acid (20 ml, 96% Merck). The solution was stirred at room temperature overnight, poured onto crushed ice (100 g) and extracted with CH_2Cl_2 (2 x 100 ml). The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and evaporated. The residue was triturated with hexane to give 1.62 g (89%) of a crystalline (5d) (m.p. 98°C from EtOAc-hexane). $[\alpha]_D^{23}$ +106.7 (*c* 1, MeOH), IR ($CHCl_3$); 3400 (NH), 1720, 1680 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ: 8.31 (b, 1H, NH), 7.55 (d, *J*=7, 1H, NH), 7.45 (d, *J*=7, 1H, NH), 7.31-7.11 (m, 4H, ar.), 5.31 (d, *J*=7, 1H, CH), 4.45 (m, 1H, CH), 3.55 (s, 3H, CO_2 Me), 3.21-2.90 (m, 4H, $2CH_2$), 0.85 (dd, *J*=6.0, 6H, HC(Me)2). MS (HR) *m/z* = 333.1721 (M^+), $C_{17}H_{23}N_3O_4$ requires 333.1689. Anal. Found: C, 60.93, H,7.05; N, 12.31. $C_{17}H_{23}N_3O_4$ requires C, 61,21; H, 6.95; N, 12.61.

Equilibration of compound 5d:

A solution of the isobutylamide **5d** (0.5 g, 1.5 mmol) in MeOH (30 ml) containing Et_3N (0.5 ml) was refluxed overnight. The MeOH was evaporated and the residue was triturated with hexane, filtered and dried ^{1}H-NMR (DMSO-d_6) δ: 8.30 (b, 1H, NH), 8.15 and 7.92 (2d, *J*=6, *J*=8, 1H, NH), 7.67 and 7.22 (2d, *J*=8, *J*=9, 1H, NH), 7.20-7.10 (m, 4H, ar), 5.37 and 5.10 (2d, *J*=9, *J*=8, 1H, CH), 4.75 and 4.50 (2m, CH, 1H), 3.56 and 3.54 (2s, 3H, HNCOMe), 3.35-2.75 (m, 4H, $2CH_2$), 1.75 (m, 1H, CH), 0.83 (d, *J*=6.0, 6H, $CHMe_2$). According to the NMR it is a mixture of two isomers (*cis, trans*) in a ratio of about 1:1.

N-Z-4-amino-2-benzazepin-3-one-1-carboxyisobutylamide (8):

The *N*-Moc-derivative **5d** (0.6 g, 1.8 mmol) was suspended in cooled (ice + H_2O) methanesulfonic acid and dimethyl sulfide (1 ml) was added. The mixture was stirred for 6 h. and the product was precipitated with anhydrous ether. The oily precipitate was dissolved in cold water and carbobenzoxylated with benzyl chloroformate at pH 9 (Na_2CO_3). The product was extracted with CH_2CH_2, dried over $MgSO_4$, filtered and evaporated. The residue was triturated with ether-hexane (1:3) and crystallized from EtOAc-hexane (m.p. 81°C, 0.5 g 75%). IR ($CHCl_3$), 3420, 3345 (NH), 1715, 1680 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) δ: 8.23 (bs, 1H, NH), 7.58 (d, *J*=7.7, 1H, NH), 7.52-7.15 (m, 11H, NH, ar), 5.33 (d, *J*=7.7, 1H, CH), 5.06 (s, 2H, CH_2), 4.49 (m, 1H, CH), 3.22-2.95 (m, 4H, $2CH_2$), 1.75 (m, 1H, CH), 0.86 (d, *J*=7.5, 6H). M.S. (HR) *m/z* = 409.2069 (M^+), $C_{23}H_{27}N_3O_4$ requires 409.2001. Anal. Found: C, 67.31; H, 6.84; N, 10.28. $C_{23}H_{27}N_3O_4$ requires C, 61.51; H, 6.64; N, 10.27.

N-Moc-4-amino-2-benzaepin-2-one-1-carboxamidoleucinate (5e):

The open chain tripeptide **4e** (14.0 g, 33 mmol) was suspended in cooled (ice + H_2O) concentrated sulfuric acid and the mixture was stirred overnight at room temperature. The solution was poured onto crushed ice, extracted with EtOAc (2 x 200

ml) and the organic layer was washed with water (2 x 75 ml) and dried over anhydrous $MgSO_4$. The crude product was triturated with acetone and crystallized from EtOAc-EtOH, m.p. 148-150°C, $[\alpha]_D^{23}$ +54.9 (*c* 1, MeOH), (6.0 g, 51%). IR ($CHCl_3$): ^{1}H-NMR (400 MH_Z : DMSO-d6) δ: 8.67 (d, *J*=6.8, 1H, NH), 7.48 (d, *J*=6.5, 1H, NH), 7.41 (d, *J*=7.7, 1H, NH), 7.37-7.14 (m, 4H, ar), 5.50 (d, *J*=6.8, 1H, CH), 4.62 (m, 1H, CH), 4.37 (m, 1H, CH), 3.56 (s, 3H, NCO_2Me), 3.17 (m, 1H, CH), 3.08 (m, 1H, CH), 1.62 (m, 3H, CH_2 + CH), 0.88 (q or 2d, 6H,-CHMe2) MS (HR), *m/z* = 391.1755 (M^+), $C_{19}H_{25}N_3O_6$ requires 391.1743. Anal. Found: C, 57.99; H, 6.58, N, 10.41. $C_{19}H_{25}N_3O_6$ requires C, 58.34; H, 6.43; N, 10.74%.

Methyl-4-*N*-Moc-2-benzazepin-3-one-1-carboxamide leucinate (5f):

The tripeptide **4f** (1.5 g, 3.4 mmol) was dissolved in the cooled (ice +H_2O) conc. sulfuric acid (30 ml 96%) and stirred overnight. The reaction mixture was poured onto crushed ice and extracted with CH_2Cl_2 (100 ml). The organic solution was washed with H_2O, aq. $NaHCO_3$ and H_2O and dried over $MgSO_4$. Evaporation of the solvent gave a product which was chromatographed over silica (Merck 70-230 mesh, 50 g) and eluted with CH_2Cl_2 : 0.93 g, (67%); m.p. 65-70°C, $[\alpha]_D^{23}$ +42.4 (*c* 1, MeOH), IR ($CHCl_3$): 3405, 3385 (NH) 1740, 1720, 1680 (CO) and 1510 cm -1 (NH). ^{1}H-NMR (400 MHz, DMSO-d-d6) δ = 8.80 (d, J=7.0, 1H, NH), 7.49 (d, *J*=6.3, 1H, NH), 7.40 (d, *J*=7.5, 1H, NH) 7.33, 72.25 (2d, *J*=7.5, 2H, ar) 7.20 (d, *J*=6.7, 2H, ar), 5.47 (d, *J*=7, 1H, CH), 4.57 (m, 1H, CH), 4.38 (m, 1H, CH), 3.67 (s, 3H, CO_2 Me), 3.56 (s, 3H, N-CO_2 Me), 3.10 (m, 2H, CH_2), 1.12 (m, 3H, CH_2+CH), 0.89 (2d, *J*=10.9, J_2=6.4, 6H, 2Me). MS (HR) *m/z* = 405.1885 (M^+), $C_{20}H_{27}N_3O_6$ requires 405.1899. Anal. Found: C, 56.74; H. 65; N, 9.80. $C_{20}H_{27}N_3O_6$ requires C, 56.76; H, 6.91; N, 13.72%.

N-Moc-4-amino-2-benzazepin-3-one-1-carboxamidoleucinamide (5g):

The open chain tripeptide amide (**4g**, 3.0 g, 7.1 mmol) was suspended in concentrated sulfuric acid (100 ml, 96%) and stirred overnight at room temp. The solution was then poured onto crushed ice and extracted with EtOAc (2 x 75 ml). The EtOAc solution was dried over $MgSO_4$, filtered and evaporated. The residue was triturated with ether to give 1.55 of a crystalline product 1.55 g, (56%) m.p. 137°C. $[\alpha]_D^{23}$ +72.5 (*c* 1, MeOH). IR (KBr): 3600-3190 (b, NH, NH_2), 1740-1660 (CO) and 1530 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) : 8.42 (d, *J*=6.8, 1H, NH), 7.55-7.06 (m, 8H, ar + NH + NH_2), 5.50 (d, *J*=6.8, 1H, CH), 4.58 (m, 1H, CH), 4.38 (m, 1H, CH), 3.55 (s, 3H, N-CO_2 Me) 3.12 (m, 1H, CH), 1.497 (m, 3H, CH_2 + CH), 0.87 (2d, 6H, CHMe2). MS (HR) *m/z* = 390.1941 (M^+), $C_{19}H_{26}N_4O_5$ requires: 390.1903. Anal. Found: C, 56.35; H, 6.79; N, 13.82. $C_{19}H_{26}N_4O_5$ requires C, 55.90; H, 6.91; N, 13.72%.

N-Z-4-amino-2-benzazepin-3-one-1-carboxamido-S-leucineamide (14):

The benzazepinone amide **5g**, (0.5 g, 1.3 mmol) was suspended in cold MSA (5 ml, ice + H_2O) and dimethyl sulfide (1 ml, excess) was added. The reaction mixture was stirred at 5°C for 5h and then ether (150 ml) was slowly added to precipitate the product. The ether was removed by decantation. The crude product was then dissolved in aqueous $NaHCO_3$ solution and acylated with benzyl chloroformate by the Schotten-Baumann procedure. The product was extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent evaporated. Trituration with ether gave a white solid (0.47 g, 79%, m.p. 118-120°C). $[\alpha]_D^{23}$ - 51.5° (*c* 1, MeOH). IR (KBr) 3600-3150 (b, NH + NH_2), 1750-1650 (b, CO) 1580 and 1530 (NH_2 + NH). ^{1}H-NMR (DMSO-d6) δ: 8.48 (d, *J*=7.7, 1H, NH), 7.57 - 7.06 (m, 13H, ar + NH_2 + NH), 5.54 (d, *J*=7.5, 1H, CH), 5.06 (s, 2H, CH_2), 4.63 (m, 1H, CH), 4.43 (m, 1H, CH), 3.15 (m, 2H, CH_2), 1.52 (m, 3H, CH_2+ CH), 0.90 (d, *J*=6, 6H, CHMe2), MS (HR) *m/z* = 467.2323 (M^{++}1), $C_{25}H_{31}N_4O_5$ requires 467.2294. Anal. Found: C, 63.98; H, 6.74; N, 11.92. $C_{25}H_{31}N_4O_5$ requires C, 64.26; H, 6.68; N, 11.99%.

Methyl-*N*-Z-4-amino-2-benzazepin-3-one-carboxamido-S-leucinate (9):

The *N*-Moc derivative **5f** (0.8 g, 1.97 mmol) was dissolved in cooled methanesulfonic acid (8.0 ml) and dimethyl sulfide (1.0 ml excess) added. The mixture was stirred for 6h and the product was precipitated with anhydrous ether. The ether was removed by decantation and the residue dissolved in aqueous cold $NaHCO_3$ and carbobenzoxylated with benzyl chloroformate. The product was extracted into EtOAc and chromatographed on silica (50 g). Elution with $CHCl_3$ gave an oil (0.38 g, 40%). IR ($CHCl_3$): 3420 (NH), 1750, 1715, 1680 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.50 (d, *J*=9.0, 1H, NH) 7.32-7.02 (m, 9H ar.), 6.90 (d, *J*=4.0, 1H, NH), 6.19 (d, *J*=8.2, 1H, NH), 5.49 (d, *J*=9.0, 1H, CH), 5.10 (q, 2H, CH_2), 4.68 (m, 1H, CH), 4.45 (m, 1H, CH), 3.69 (s, 3H, CO_2 Me), 3.25 (q, 1H, CH), 2.30 (q, 1H, CH), 1.66-1.45 (m, 3H, CH_2 + CH), 0.90 (d, *J*=11.2, 6H, 2Me). MS (HR) *m/z* = 481.2260 (M^+), $C_{26}H_{31}N_3O_6$ requires: 481.2213.

***N*-Moc-4-amino-2-benzazepin-3-one-1-carboxamidoleucyl-methionylamide (5h):**

The tetrapeptide **4h** (2g, 3.6 mmol) was dissolved in cooled (ice-water) conc. H_2SO_4 (20 ml) and stirred overnight at room temperature. The reaction mixture was poured onto crushed ice, extracted with EtOAc, dried ($MgSO_4$) and concentrated. The residue was triturated with ether giving **5h** 0.38 g, (20%), mp 120-123°C, $[\alpha]_D^{23}$ +34.2 (*c* 1, MeOH). IR (KBr): 3310 (NH), 1725,1670 (CO), 1530 (NH), ^{1}H NMR (DMSO-d_6) δ: 0.86 (2d, J=6.0, 6H, $CH(CH_3)_2$), 1.40 (m, 2H, CH_2CH), 1.59 (m, 1H, $CHCH_2$), 1.67 (m, 2H, CH_2CH_2S), 2.01 (s, 3H, SCH_3), 2.42 (m, 2H, CH_2S), 3.04-3.25 (m, 2H, CH_2Ph), 3.55 (s, 3H, CH_3OCO); 4.31 (m, 1H, CH), 4.51 (m, 1H, CH), 4.66 (m, 1H, CH), 5.54 (d, *J*=6.8, 1H, NHCH), 7.05 (bs, NH_2), 7.12-7.36 (m, 7H, arom+NH), 8,22 (d, *J*=8.0, 1H, NH), 8.52 (d, *J*=7.6,1H, NH), MS (HR) *m/z* = 521.5102 (M^+). $C_{24}H_{35}N_5O_6S$ requires 521.5251. Anal. Found: C, 54.96; H, 6.74; N, 13.69. $C_{24}H_{35}N_5O_6S$ requires C, 55.27; H, 6.48; N, 13.43%.

***N*-Moc-R,S-homophenylalanine-α-hydroxyglycine (15):**

A mixture of *N*-Moc-dl-Homophe-NH_2 (2.0 g, 8.5 mmol), glyoxylic acid monohydrate (1.15 g, 50% excess), 0.1 ml TFA in acetone (75 ml) was refluxed overnight. The solvent was evaporated to give a yellowish oil 2.09 g, 80%. IR ($CHCl_3$): 3600-2400 (b, OH), 3410 (NH) 1720, 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d6) δ: 8.52 (d, *J*=9, 1H, NH), 7.36 (d, *J*=10,1H, NH), 7.20 (m, 5H, ar), 5.41 (d, *J*=9, 1H, CH), 4.09 (m, 1H, CH), 2.50 (m, 2H), 1.75 (m, 2H).

Methyl-*N*-Moc-R,S-homophenylalanine-α-methoxyglycinate (12):

The crude hydroxy acid (1.5 g, 4.8 mmol) described above was dissolved in MeOH and 1.5 ml of $SOCl_2$ was added dropwise. The solution was left at room temperature overnight, neutralized with solid $NaHCO_3$ and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (120 ml), washed with H_2O (2 x 50 ml) and the organic layer was dried over $MgSO_4$. The crude oily product was chromatographed over silica (Merck 70-230 mesh, 50 g) and eluted with CH_2Cl_2 - EtOAc (9:1) to give 1.5 g (68%) of product. IR ($CHCl_3$): 3410 (NH), 1720, 1690 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$) δ: 7.55 (d, *J*=9, 1H, NH), 7.19 (b, s, 5H, ar), 5.87 (d, *J*=9, 1H, NH), 5.62 (d, *J*=9, 1H, CH), 4.46 (m, 1H, CH), 3.85 (s, 3H, CO_2 Me), 3.76 (s, 3H, NCO_2Me), 3.52 (s, 3H, OMe), 2.85 (m, 2H, CH_2), 2.22 (m, 2H, CH_2). MS (HR) *m/z* = 300, 1272 (M^+-MeOH), $C_{15}H_{18}N_5O_2$ requires 300.1460.

Methyl-*N*-Moc-4-amino-2-benzazin-3-one-1-carboxylate (13):

The methoxy ester **12** (1.5 g, 4.43 mmol) was dissolved in cooled (ice + H_2O) concentrated sulfuric acid (30 ml, 96%). The solution was stirred overnight at room temperature and then poured onto crushed ice and extracted with CH_2Cl_2 (2 x 100

ml). The CH_2Cl_2 solution was washed with H_2O (50 ml) dried over $MgSO_4$ and evaporated. The oily residue was chromatographed over silica and eluted with EtOAc to give an oily product (0.7 g, 52%). IR ($CHCl_3$): 3360 (NH), 1750, 1715, 1675 (CO) and 1510 cm^{-1} (NH). ^{1}H-NMR (DMSO-d_6) : 8.05 (d, *J*=10, 1H, NH), 7.72-6.90 (m, 5H, ar + NH), 5.94 (d, *J*=10, 1H, CH), 4.65 (m, 1H, CH), 3.73 (s, 3H, CO_2 Me), 3.51 (s, 3H, NCO_2 Me), 3.34 (m, 1H, CH), 2.95 (m, 1H, CH), 2.1 (m, 1H, CH), 1.36 (m, 1H, CH). MS (HR) *m/z* = 306.1230 (M^+), $C_{15}H_{18}N_2O_5$ requires: 306.1216.

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