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Palladium Catalysis in Bridge-Forming Reactions Between Stereoselectively Substituted Glycine Auxiliaries.

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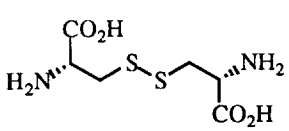
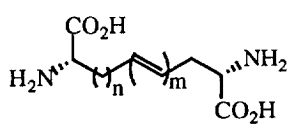
Abstract: The disulfide bridge in cystine has formally been replaced by substitution of two α-alanines at the β-carbon into the 2,3-positions in 1,3-butadiene. The key reactions are stereoselective alkylation of lithiated (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with 2,3-dibromopropene. The alkene-alkene bond formation was effected by Pd-catalysis either with the 2′-bromoallyl products from the alkylation as substrate or with the corresponding amino acid appropriately protected.

The disulfide bond in disulfide (oligo)peptides and proteins derived from cystine confers conformational constraint on the peptide or protein structure. The constraint may be essential for the spacing of the pharmacophoric region in physiologically essential (oligo)peptides and proteins in their interaction with the bioreceptor. Isosteric structures may be envisaged to replace cystine when cystine (**A**) (Scheme 1) exerts mainly a structural function, *i.e.* the disulfide linkage in cystine may be replaced by an ethylene unit, and this may be variously substituted for subtle tuning of conformational constraint. Because of the medical implications which may arise from such interactions, we have initiated a program on the preparation of bridged amino acids as cystine substitutes (**B**).[1,2,3] In its simplest case, when the -CH_2S-SCH_2-bridge between the two glycine carbons in *L*-cystine is replaced by the all carbon -$(CH_2)_4$-bridge, the new bridge



(**A**)



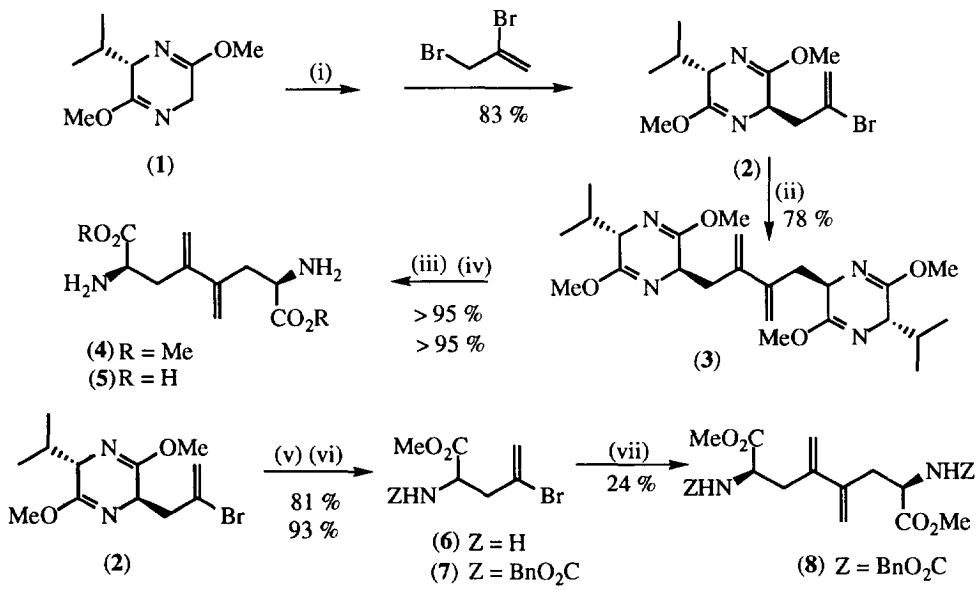
m = 0,1; n = 0-5
(**B**)

Scheme 1

amino acid is (*S,S*)-α,α-diaminosuberic acid (**B**; m = 0, n = 3). In the work herein reported for the (*R*)-series we have retained the four atoms in the backbone bridge. C2 and C3 in the bridge, which replace the sulfur atoms in cystine, carry a double bond to provide for electronic properties with some resemblance to that of the lone pairs of the sulfur atoms in a disulfide bridge (**5**) (Scheme 2). In our program we have prepared conformationally flexible bridged bis(amino acids) with one to six carbons in the bridge (**B**; m = 0, 1; n = 0-5), and we have introduced substantial configurational constraint into the cystine substitutes and their peptides by interrupting the bridge by unsaturation as in the *cis*- and *trans*- 4C-bridged structure (**B**; m = n = 1); an even more rigid arrangement is available in the 4C-analogue where the double bond has been substituted by a tripple bond.[1] An additional number of stereoselective syntheses of C-bridged amino acids have recently been described. These diacids may also be regarded as structural analogues of cystine *e.g.* the

1C-analogue (B, m = n = 0), [1,4] the 2C-analogue (B; m = 0, n = 1),[1,5] the 3C- and bridge-substituted 3C-analogues,[1,6a] the 4C-analogue (m = 0, n = 3),[6, 7] besides diacids from our own work (*vide supra*),[1] the 5C- and bridge substituted 5C-analogues,[1,8] and the 6C-bridge.[1]

Several chiral auxiliaries are available for stereoselective amino acid constructions.[9] In the most widely used methods for the bridging of two glycines, embodied in chiral auxiliaries, the metallated chiral auxiliary is reacted with electrophilic carbons at both termini in the chain which is to become the bridge. In this project we have chosen an alternative pathway. Two appropriately substituted amino acid "monomers" are initially prepared by chiral auxiliary mediated stereoselective synthesis as discussed above. Subsequently, two amino acid monomers are joined by a coupling operation to furnish C_2-symmetric bis(amino acids). In particular, for our target molecules with C_2-symmetry, unsaturation would allow for metal-catalyzed homocoupling as shown in Scheme 2.



(i) nBuLi, THF, -78 °C
(ii) $Pd(OAc)_2/PPh_3$, K_2CO_3, MeCN, 50 °C
(iii) 0.25 M HCl, dioxane-H_2O, 20 °C
(iv) 6 M HCl, 20 °C
(v) 0.1 M TFA, MeCN, 20 °C, 14 h
(vi) Z-Cl, DMAP, CH_2Cl_2, 0 °C
(vii) $Pd(OAc)_2/PPh_3$, Na_2CO_3, MeCN, 50 °C

Scheme 2

The substrate for the coupling reaction was to be the 2′-bromoallyl derivative (**2**) which was readily available by the Schöllkopf technology by alkylation of lithiated (2*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with 2,3-dibromopropene in THF at -78 °C. The reaction proceeds in high yield with d.e. in excess of 95 % to yield the (*R*)-isomer (**2**). Our results correlated well with the findings by essentially the

same reaction conditions as used by another group of workers who reported their results for the (*S*)-isomer after the completion of our own work.[10,11]

Several methods are available for the construction of symmetrical 1,3-butadienes from alkenes.[12] Reactions involving metallation of the bromoalkenyl derivative (**2**) were expected to be complicated by metal-hydrogen exchange in the 5-position in the dihydropyrazine ring. Direct dimerization of the alkenyl bromide (**2**) was therefore attempted. Initial work with nickel-catalysis was unsatisfactory; low yields of the desired product and substantial amounts of biproducts were formed. Excellent reaction conditions, however, were found by adoption of the conditions described by Grigg for palladium-catalyzed inter- and intramolecular coupling of vinyl bromides.[13] As recommended, excess triphenylphosphine and potassium carbonate were used to regenerate the active Pd(0) species. In this case, the potassium carbonate also serves to prevent acid promoted break-down of the acid sensitive dihydropyrazine ring system.

The homocoupling proceeded well in acetonitrile with formation of (**3**) without interference with the stereogenic centers. When mild acid hydrolytic conditions are used, as recommended for hydrolysis of the bis-lactim dihydropyrazine systems by Schöllkopf,[14] essentially quantitative yields of the amino acid methyl ester (**4**) were obtained. Subsequently, the methyl ester was hydrolyzed to the corresponding amino acid (**5**) with 6 M HCl; the formation of the acid (**5**) is essentially quantitative at ambient temperature.

Very recently, the acid (**5**) has been obtained as a racemate from the stereoisomers formed by alkylation of the lithiated enolate of benzophenone imine of glycine ethyl ester with 2,3-bis(bromomethyl)-1,3-butadiene.[15]

Homocoupling has also been effected at the amino acid level with the protected amino acid (**7**) as substrate. The alkylated product (**2**) is highly sensitive to acidic conditions. Occasionally it may be partially lost on silica gel chromatography. In this case removal of the dihydropyrazinyl system with selective formation of the desired amino acid ester (**6**) was best effected by running the cleavage with 0.1 M TFA in acetonitrile.[14] Z-protection of the amino group in the latter proceeds well using benzyloxycarbonyl chloride in the presence of 4-dimethylaminopyridine (DMAP) as base in acetonitrile. The Pd-promoted homocoupling reaction was effected under the same conditions as before to form (**8**) using $Pd(OAc)_2$ in the presence of triphenylphosphine and potassium carbonate. This route for the synthesis of (**4**) seems inferior to the previous route, however, since the Pd-mediated reaction gave a low yield (24 %) of the coupling product (**8**).

EXPERIMENTAL

The mass spectra under electron impact conditions were recorded at 70 eV (EI). CH_4 was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.). The ^1H NMR spectra were recorded at 200 MHz or 300 MHz and the ^{13}C NMR spectra at 50 MHz or 75 MHz.

(2*R*,5*S*)-2-(2-Bromoallyl)-2,5 dihydro-3,6-dimethoxy-5-isopropylpyrazine (**2**). n-Butyllithium (4.28 ml, 5.57 mmol, 1.3 M in hexane) was added to a solution of (*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.03 g, 5.57 mmol) in dry THF (20 ml) under argon at -78 °C. The mixture was stirred for 30 min before dropwise addition of neat 2,3-dibromopropene (1.22 g, 6.10 mmol). The mixture was stirred at -78 °C for 1.5 h. The cooling-bath was removed, the solvent evaporated at reduced pressure, and the residue dissolved in diethyl ether (50 ml). The ether solution was washed with water (20 ml), dried ($MgSO_4$), evaporated and the residual product purified by bulb-to-bulb distillation; yield 1.55 g (92 %); b.p. 69 °C/0.04 mmHg. GLC analysis gave

diastereoisomer ratio (*R,S*):*S,S*) 97:3. The minor isomer was removed by flash chromatography on silica gel using 1 % of hexane/ethyl acetate 3:7 in dichloromethane for elution; the product is the (*RS*) isomer (1.40 g). Found: C, 47.01; H, 6.19 %. Calc. for $C_{12}H_{19}BrN_2O_2$: C, 47.54; H, 6.32 %. $[\alpha]_D$ -14.6° (c = 0.486, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.67, 1.02 [2d, *J* 7 Hz, 6H, $CH(\underline{CH_3})_2$], 2.24 [d.sept, *J* 3.3 Hz and *J* 7 Hz, 1H, $\underline{CH}(CH_3)_2$], 2.70 (dd, *J* 7.3 Hz and *J* 14.5 Hz, 1H, $\underline{CH_2}$-CBr), 2.96 (dd, *J* 4.3 Hz and *J* 14.5 Hz, 1H, $\underline{CH_2}$-CBr), 3.65 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.94 [dd, *J* 3.3 Hz and *J* 3.6 Hz, 1H, $\underline{CH}$-$CH(CH_3)_2$], 4.21 (ddd, *J* 3.6 Hz, *J* 4.3 Hz and *J* 7.3 Hz, 1H, $\underline{CH}$-CH_2), 5.46 (d, *J* 1.5 Hz, 1H, $=\underline{CH_2}$), 5.57 (d, *J* 1.5 Hz, 1H, $\underline{CH_2}$). ^{13}C NMR ($CDCl_3$): δ 16.56, 19.01 [$CH(\underline{CH_3})_2$], 31.64 [$\underline{CH}(CH_3)_2$], 45.52 ($\underline{CH_2}$-CBr), 52.29, 52.40 (OCH_3), 54.16 (C-3), 60.74 (C-6), 119.35 ($=CH_2$), 129.60 (CH_2-$\underline{C}$Br), 162.27, 163.81 (C-2, C-5). MS(EI): 304/302(6/7, M^+), 261/259(7/8), 223(8), 183(43), 141(100).

1,4-Bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-5-isopropyl-2-pyrazinyl]-2,3-bis(methylene)butane (3). A solution of (2*R*,5*S*)-2-(2-bromoallyl)-2,5 dihydro-3,6-dimethoxy-5-isopropylpyrazine (2.12 g, 7.00 mmol) in dry acetonitrile (10 ml) was added with stirring to a suspension of potassium carbonate (2.42 g, 17.50 mmol), triphenylphosphine (1.38 g, 5.25 mmol) and $Pd(OAc)_2$ (0.31 g, 1.40 mmol) in dry acetonitrile (80 ml) under argon. The mixture was heated at 50 °C for 5 h before the acetonitrile was removed at reduced pressure. Diethyl ether (150 ml) was added, and the solution was washed with 10 % aqueous ammonium chloride (2 x 50 ml). The dried ($MgSO_4$) solution was evaporated, and the product was purified by flash chromatography on silica gel using hexane/ethyl acetate 7:1; yield: 1.22 g (78 %). Found: C, 64.26; H, 8.52 %. Calc. for $C_{24}H_{38}N_4O_4$: C, 64.54; H, 8.57 %. ^1H NMR ($CDCl_3$): δ 0.62, 1.00 [2d, *J* 6.8 Hz, 12H, $(CH(\underline{CH_3})_2)$ x 2], 2.21 [d sept, *J* 3.3 Hz and *J* 6.8 Hz, 2H, $(\underline{CH}(CH_3)_2)$ x 2], 2.44 [dd, *J* 6.9 Hz and *J* 13.8 Hz, 2H, $(\underline{CH_2}$-C=) x 2], 2.91 [dd, *J* 4.0 Hz and *J* 13.8 Hz, 2H, $(\underline{CH_2}$-C=) x 2], 3.60 [s, 6H, (OCH_3) x2], 3.64 [s, 6H, (OCH_3) x2], 3.80 [dd, *J* 3.3 Hz and *J* 3.5 Hz, 2H, $(\underline{CH}$-$CH(CH_3)_2)$ x 2], 4.13 [ddd, *J* 3.5 Hz, *J* 4.0 Hz and *J* 6.9 Hz, 2H, $(\underline{CH}$-$CH_2)$ x 2], 4.82 [d, *J* 2 Hz, 2H, $(=CH_2)$ x 2], 5.11 [d, *J* 2 Hz, 2H, $(=CH_2)$ x 2]. ^{13}C NMR ($CDCl_3$): δ 16.49, 19.06 [$(CH(\underline{CH_3})_2)$ x 2], 31.35 [$(\underline{CH}(CH_3)_2)$ x 2], 38.95 [$(\underline{CH_2}$-C=) x 2], 52.06, 52.29 [(OCH_3) x 2], 55.30 [(C-3) x 2], 60.53 [(C-6) x 2], 115.17 [$(=CH_2)$ x 2], 144.99 [$(\underline{C}=CH_2)$ x 2], 163.10, 163.21 [(C-2, C-5) x 2]. MS(EI): 446(1, M^+), 431 (3), 403 (36), 263 (100), 249 (3), 221 (21), 183(9), 141(57).

(*R, R*)-2,7-Diamino-4,5-bis(methylene)octanedioic acid dimethyl ester (4). 0.5 M HCl (10.4 ml, 5.21 mmol) was added dropwise to a stirred solution of 1,4-bis[(2*R*,5*S*)-2,5-dihydro-3,6-dimethoxy-5-isopropyl-2-pyrazinyl]-2,3-bis(methylene)butane (0.55 g, 1.24 mmol) in dioxane (10.4 ml). The mixture was stirred at ambient temperature for 5 h before the pH was adjusted to 10 by the addition of conc. aqueous ammonia. The aqueous solution was extracted with dicloromethane (3 x 10 ml), the organic layer dried ($MgSO_4$) and evaporated. The valine methyl ester in the residue was removed by slow bulb-to-bulb distillation at 45-50 °C/0.05-0.1 mmHg. The residual title compound was used in the subsequent reaction without further purification; yield: 0.32 g (> 95 %), yellow oil. Found: C, 56.09; H, 7.80 %. Calc. for $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.86 %. $[\alpha]_D$ -40° (c = 0.548, MeOH). ^1H NMR ($CDCl_3$) : δ 1.76 [s, 4H, (NH_2) x 2], 2.30 [dd, *J* 9.2 Hz and *J* 14.0 Hz, 2H, $(\underline{CH_2}$-C=) x 2], 2.85 [dd, *J* 4.6 Hz and *J* 14.0 Hz, 2H, $(\underline{CH_2}$-C=) x 2], 3.60 [dd, *J* 4.6 Hz and *J* 9.2 Hz, 2H, $(\underline{CH}$-$CH_2)$ x 2], 3.66 [s, 6H, (OCH_3) x2], 5.05 [s, 2H, $(=CH_2)$ x 2], 5.20 [s, 2H, $(=\underline{CH_2})$ x 2]. ^{13}C NMR ($CDCl_3$): δ 40.14 [$(\underline{CH_2}$-C=) x 2], 52.01 [(OCH_3) x 2], 53.05 [(CH) x 2], 115.42 [$(=CH_2)$ x 2],

141.39 [(C=CH_2) x 2], 174.21 [(C=O) x2]. MS(EI): 256 (1, M^+), 239 (2), 224 (1), 197 (14), 180 (6), 169 (21), 168 (52), 154 (7), 88 (100).

(*R,R*)-2,7-Diamino-4,5-bis(methylene)octanedioic acid dihydrochloride (**5**). (*R*, *R*)-2,7-Diamino-4,5-bis-(methylene)octanedioic acid dimethyl ester (0.05 g, 0.02 mmol) in 6 M HCl (2 ml) was stirred at ambient temperature for 12 h. The solvent was removed at reduced pressure. The residue was the title compound; yield: 0.06 g (> 95 %). ^{1}H NMR (D_2O): δ 1.58 (s, 4H, NH_2), 2.72 [dd, *J* 8.2 Hz and *J* 14.8 Hz, 2H, (CH_2-C=) x 2], 3.05 [dd, *J* 6.0 Hz and *J* 14.8 Hz, 2H, (CH_2-C=) x 2], 3.96 [dd, *J* 6.0 Hz and *J* 8.2 Hz, 2H, (CH-CH_2) x 2], 5.25 [s, 2H, (=CH_2) x 2], 5.41 [s, 2H, (=CH_2) x 2], 8.10 (s, 2H, OH). ^{13}C NMR (D_2O) : δ 34.66 [(CH_2-C=) x 2], 52.13 [(CH-CH_2) x 2], 119.46 [(=CH_2) x 2], 139.02 [(C=CH_2) x 2], 171.74 [(C=O) x2].

Methyl (*R*)-2-amino-4-bromopent-4-enoate (**6**). 0.1 M TFA (48.34 ml, 4.83 mmol) was added dropwise to a stirred solution of (2*R*,5*S*)-2-(2-bromoallyl)-2,5 dihydro-3,6-dimethoxy-5-isopropylpyrazine (0.52 g, 1.61 mmol) in acetonitrile (8.06 ml). The mixture was stirred at ambient temperature for 10 h before the pH was adjusted to 10 with conc. aqueous ammonia. The aqueous solution was extracted with dicloromethane (3 x 50 ml), the organic solution dried ($MgSO_4$), evaporated and the residual product purified by flash chromatography on silica gel using CH_2Cl_2:MeOH:conc. aq. ammonia 20:1:0.1; yield: 0.27 g (81 %).^{1}H NMR ($CDCl_3$): δ 1.55 (s, 2H, NH_2), 2.59 (dd, *J* 8.8 Hz and *J* 14.3 Hz, 1H, CHCH_2), 2.88 (dd, *J* 4.0 Hz and *J* 14.3 Hz, 1H, CHCH_2), 3.73 (s, 3H, OCH_3), 3.80 (dd, *J* 4.0 Hz and *J* 8.8 Hz, 1H, CHCH_2), 5.54 (d, *J* 1.3 Hz, 1H, =CH_2), 5.69 (d, *J* 1.3 Hz, 1H, =CH_2). ^{13}C NMR ($CDCl_3$): δ 46.88 (CHCH_2), 52.51 (OCH_3), 52.85 (CHCH_2), 119.87 (=CH_2), 128.79 (CBr), 173.54 (C=O). MS(CI): 210/208 (3/4, M^+), 178/176 (1/1), 150/148 (10/13), 128 (3), 88 (100).

Methyl (*R*)-2-benzyloxycarbonylamino-4-bromopent-4-enoate (**7**). Benzyl chloroformate (0.24 g, 1.43 mmol) was added dropwise with stirring to a solution of methyl 2-(*R*)-amino-4-bromopent-4-enoate (0.27 g, 1.31 mmol) and 4-(*N,N*-dimethylamino)pyridine (0.18 g, 1.44 mmol) in dry dichloromethane (20 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 3 h, at ambient temperature for 6 h, diluted with dichlorometane and washed with 10 % aqueous ammonium chloride. The dried ($MgSO_4$) solution was evaporated, and the product was purified by flash chromatography on silica gel using 1 % hexane:ethyl acetate 3 : 7 in dicloromethane; yield 0.42 g (93 %). MS(HR): *m/z* calcd. for $C_{14}H_{16}BrNO_4$, 341.0263, 343.0242. Found: 341.0303, 343.0247. ^{1}H NMR ($CDCl_3$): δ 2.86 (dd, *J* 7 Hz and *J* 15 Hz, 1 H, CHCH_2CBr), 2.98 (dd, *J* 5.4 Hz and *J* 15 Hz, 1 H, CHCH_2CBr), 3.71 (s, 3H, OCH_3), 4.59 (ddd, *J* 5.4 Hz and *J* 7 Hz and *J* 8 Hz, 1 H, NHCHCH_2), 5.10 (s, 2 H, OCH_2Ph), 5.45 (d, *J* 8 Hz, 1 H, NH), 5.49 (d, *J* 1.7 Hz, 1H, =CH_2), 5.60 (d, *J* 1.7 Hz, 1H, =CH_2), 7.32 (s, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 43.78 (CHCH_2), 52.69 (CHCH_2), 52.82 (OCH_3), 67.14 (OCH_2Ph), 120.40 (=CH_2), 126.79 (CBr), 127.42 (C-2, C-6), 127.54 (C-4), 127.84 (C-3, C-5), 135.36 (C-1), 154.64 (O-CO-N), 170.28 (O-CO-CH). MS(EI): 343/341 (1/1, M^+), 284/282 (4/3), 262 (33), 240/238 (10/8), 234 (15), 222 (5), 178 (15), 154 (43), 107 (19), 91 (100).

(*R, R*)-2,7-Bis(benzyloxycarbonylamino)-4,5-bis(methylene)octanedioic acid dimethyl ester (**8**). A solution of methyl (*R*)-2-benzyloxycarbonylamino-4-bromopent-4-enoate (0.15 g, 0.45 mmol) in dry acetonitrile (3 ml) was added with stirring to a suspension of potassium carbonate (0.16 g, 1.14 mmol), triphenylphosphine

(0.09 g, 0.34 mmol) and $Pd(OAc)_2$ (0.02 g, 0.09 mmol) in dry acetonitrile (15 ml) under argon. The mixture was heated at 50 °C for 5 h before the acetonitrile was removed at reduced pressure. Diethyl ether (50 ml) was added, and the solution was washed with 10 % aqueous ammonium chloride (2 x 15 ml). The dried ($MgSO_4$) solution was evaporated, and the product was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH 50:1; yield: 0.06 g (24 %). ^1H NMR ($CDCl_3$): δ 2.37 [dd, *J* 8.2 Hz and *J* 14.2 Hz, 2H, ($\underline{CH_2}$-C=) x 2], 2.96 [dd, *J* 4.5 Hz and *J* 14.2 Hz, 2H, ($\underline{CH_2}$-C=) x 2], 3.62 [s, 6H, (OCH_3) x 2], 4.29 [ddd, *J* 4.5 Hz and *J* 8.2 Hz and *J* 8.3 Hz, 2H, ($\underline{CH}CH_2$) x 2], 4.89 [s, 2H, (=CH_2) x 2], 4.98 (s, 4H, $O\underline{CH_2}Ph$), 5.11 [s, 2H, (=CH_2) x 2], 5.63 [d, *J* 8.3 Hz, 2H, (NH) x 2], 7.2-7.3 [m, 10H, (Ph) x 2]. ^{13}C NMR ($CDCl_3$) : δ 36.57 [($\underline{CH_2}$-C=) x 2], 52.19 (OCH_3) x 2], 52.80 [($\underline{CH}CH_2$) x 2], 66.69 ($O\underline{CH_2}Ph$), 116.55 [(=CH_2) x 2], 127.90 [(C-2, C-6) x 2], 128.32 [(C-3, C-4, C-5) x 2], 136.33 (C-1), 141.00 [($\underline{C}$=CH_2) x 2], 155.67 [(O-CO-N) x 2], 172.17 [(O-$\underline{C}$O-CH) x 2]. MS(EI): 524(1, M^+), 446 (1), 389 (5), 313 (5), 302 (2), 281 (15), 221 (7), 178 (6), 166 (54), 108(45), 107 (35), 91 (100). MS(HR): *m/z* calcd. for $C_{28}H_{32}N_2O_8$: 524.2159. Found: 524.2124.

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