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# Chiral Non-racemic Bis(vicinal 1,2-Diamines): 4,5-Diamino-N-(3,4-diaminobutyl)pentanamide Tetrahydrochloride, N,N'-Bis[3,4-bis (t-butoxycarbonylamino)butyl]urea and N,N'-Bis[3,4-bis(t-butoxycarbonylamino)butyl]hexanamide<sup>†</sup>

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Abstract: The reaction of (R) or (S)- $N^4$ ,  $N^5$ -bis(*t*-butoxycarbonyl)-4,5-diaminopentanoic acid (6) with (R) or (S)- $N^3$ ,  $N^4$ -bis(*t*-butoxycarbonyl)-3,4-diaminobutylisocyanate (8) catalyzed by 4-dimethylamino pyridine (DMAP), leads to the synthesis of (R,R), (S,S), (R,S) and (S,R) isomeric amides (11 a - d). The addition of adipic acid monomethyl ester to (R) or (S) isocyanate, followed by saponification, acidification and subsequent reaction with the second molecule of (R) or (S) isocyanate allows isolation of the (R,R). (S,S) and the meso isomers of N, N-bis[3,4-bis(*t*-butoxycarbonylamino) butyl]hexanediamide (17). Removal of protecting groups with HC1/EtOH affords chiral non-racemic molecules having two free vicinal diamine units.

Vicinal diamines and triamines are important ligands for *cis*-platinum complexes<sup>1</sup>. Recently there has been a growing interest in platinum complexes capable of intra and interstrand-DNA binding and forming DNA-protein linkage<sup>2</sup>. We have reported the synthesis of chiral racemic dicarboxylic acid bis(1,2,4-triaminobutane- $N^4$ ) amides<sup>3</sup> in which two 1,2,4-triaminobutane units are bridged as  $\alpha,\omega$ -dicarboxylic acid amides with two vicinal diamines yielding bis[platinum(II)] complexes. These complexes in which two cis-PtCl<sub>2</sub> fragments are bridged by a spacer show a pronounced interstrand binding ability<sup>4</sup>. Independently we developed a stereospecific synthesis of selectively protected (S)-1,2,4-triaminobutanes using (S)-pyroglutamic acid methyl ester as a source of chirality<sup>5</sup>. The enantiomeric purity was confirmed by <sup>13</sup>C NMR spectra of their (-)-menthyl carbamate derivatives<sup>6</sup>.

Now we report the synthesis of the (R) isomer in order to obtain compounds containing two vicinal diamine units in all isomeric forms, to study the influence of configuration on DNA-interstrand binding. The selectively protected chiral 1,2,4 triamines may lead to three systems: one in which (R) or  $(S)-N^1N^2$ -di-Boc-1,2,4-triaminobutane (Boc = butoxycarbonyl) is bound to (R) or  $(S)-N^4,N^5$ -di-Boc-4,5-diaminopentanoic acid; the other in which two molecules of (R) or  $(S)-N^1N^2$ -di-Boc-1,2,4-triaminobutane are bridged as dicarboxylic acid bis(amides); a third one with urea type linked amines. Starting from (R)-pyroglutamic acid methyl ester, the  $(R)-N^3N^4$ -di-Boc-3,4-diaminobutylisocyanate (**8a**) has been prepared by the same procedure as for the previously reported (S) isomer<sup>5</sup> (Scheme 1). Thus, the ester was reduced by LiBH<sub>4</sub> to the known *R*-(hydroxymethyl)-2-pyrrolidone<sup>7</sup>; the alcohol was converted by the Mitsunobu reaction<sup>8</sup> with hydrazoic acid to (R)-azide (1) which was catalytically reduced to (R)-5-(aminomethyl)-2-pyrrolidone (2). The single set of signals in the <sup>13</sup>C NMR spectrum for the diastereotopic carbons of (1R, 3R, 4S)-menthyl carbamate (4) confirmed its optical purity. Amine 2 was converted to the di-Boc lactam derivative 5 in a two-step one-pot reaction (Rf = 0.30, EtOAc; NH absorption at 3440 cm<sup>-1</sup>, CHCl<sub>3</sub>). Nucleophilic ring opening of 5 by LiOH in THF/water and acidification led to (R)-N<sup>4</sup>,N<sup>5</sup>-di-Boc-4,5-diaminopentanoic acid 6. Using a mixed anhydride

method 6 was transformed to acyl azide 7 (IR absorption at 2155 cm<sup>-1</sup>), which underwent Curtius rearrangement to the isocyanate 8 (2260 cm<sup>-1</sup>). In small scales (0.1 mmol) 8 was converted with LiOH to (R)- $N^1$ . $N^2$ -di-Boc-1,2,4-triaminobutane (9) (see Scheme 1). In larger quantities the formation of the corresponding urea was also observed.

Previously we have shown that the preparation of the mixed urethane  $(S)-N^1.N^2$ -di-Boc- $N^4$ -Z-1,2,4-triaminobutane<sup>5</sup> does not require isolation of the amine 9 and the acyl function in position 4 is introduced by addition of benzyl alcohol to isocyanate 8b in the presence of catalytical amount of *p*-toluenesulfonic acid (*p*-TSA). Under the above conditions amidation with acids did not occur but 8b reacted with isobutyric acid using DMAP<sup>9</sup> as catalyst to give the amide 13b in 78% yield.



Scheme 1.

The reaction of the isocyanate **8a** with the acid **6a** afforded the amide **11a** with the configuration (*R*,*R*) (mp 178-9°,  $[\alpha]^{24}_D$  +34.6). The (S,S) enantiomer **11b** was obtained by reacting the isocyanate **8b** with the (S)-

acid 6b (mp 178-9°,  $[\alpha]^{24}_D$  -34.8). The second enantiomeric pair (R,S) 11c (mp 194°,  $[\alpha]^{24}_D$  +37.0) and (S,R) 11d (mp 195°,  $[\alpha]^{24}_D$  -37.8) was obtained by reacting the isocyanate 8a with the acid 6b and 8b with 6a, respectively (see Scheme 2).



#### Scheme 2.

The (R,S) and (S,R) isomers of 11 were purified by trituration and crystallisation whereas the less polar (R,R) and (S,S) isomers required silica gel column purification to remove unchanged acid. (Yields of 60-70% were obtained by chromatographic means of isolation whereas triturations and crystallization afforded 50% yields). Formation of urea as a side product was not observed. The diastereomers differ in their melting points and in their solubilities. No differences between them was observed in NMR spectra. In the <sup>13</sup>C NMR spectra the C-1 and the C-9 atoms have the same chemical shifts, the C-8 atom absorbs at a lower field than C-2. (The numbering of carbons in the NMR spectra, for sake of comparison with the previously reported data, refers to 1,2,4-triaminobutane). The assignment is based on comparison with 10 and 13 as model compounds. All proton NMR signals are very broad due to hindered rotation imposed by Boc protecting groups<sup>10</sup>. The isomers were characterized by their retention time on a ChiraDex<sup>R</sup> column. The retention times of the (R,R), (S,S), (R,S) and

(S,R) isomers 11 were 19.82, 23.45, 18.18 and 20.19 min respectively. The behaviour of each enantiomeric pair was investigated separately which allowed the verification of their enantiomeric purity. The removal of Boc-protecting groups with dry HCl in EtOH afforded hygroscopic tetraamines as hydrochlorides 12a-d.

The approach to the (R,R) and (S,S) isomers of N,N'-[3,4-bis(*t*-butoxycarbonylamino)butyl]hexanamide (17), by reacting S or R isocyanate 8 with adipic acid in the presence of DMAP in benzene, led to the formation of urea 14 instead of the expected bisamides. The formation of 14 was also observed in the absence of DMAP. The low solubility of adipic acid in benzene or in chloroform and its acidity are probably responsible for this reaction. The synthesis of the compounds 17 was achieved by a stepwise procedure. The isocyanate 8 reacted with the monomethyl ester of adipic acid which is highly soluble in benzene. The resulting ester 15 was saponified to the acid 16 which subsequently reacted with the second molecule of isocyanate 8. By this method all three (R,R), (S,S) and meso (R,S) isomers of bisamide 17 were prepared (see Scheme 3).

It should be noted that the by-product 14 contains two potential vicinal diamine units linked as urea. There has recently been a growing interest in urea linked amino acids, amines and diamines<sup>11</sup> due to the higher metabolic stability of the urea linkage compared to the amide linkage.



Scheme 3.

The retention times of the (R,S), (R,R) and (S,S) isomers 17 on a ChiraDexR column were 20.07, 21.79 and 23.53 min respectively whereas that of urea 14 was 16.92 min for the (R,R) isomer and 20.18 min for the (S,S) isomer.

Addition of the monomethyl ester of adipic acid to 8 rarely exceeded 50% yield and was accompanied by formation of the urea 14. The addition of 8 to 16, under the same conditions, was in the range of 60-70%. (Yields are reported on isolated compounds after trituration and chromatography. Trituration removed the unchanged acid 16 with a Rf very close to that of the bisamide 17, whereas a silica gel column was efficient in separation of the urea 14 from 17).

The addition of different acids to the isocyanate 8 to form the amides 11, 13, 15, 17 and urea 14, using DMAP as catalyst, calls for some comments. According to the mechanism proposed by Steglich<sup>9</sup>, DMAP and isocyanate form a dipolar complex 19 which undergoes protonation to the reactive *N*-carbamoylpyridinium ion 20. Apparently the nature of the acid present in the mixture also has an influence on the reaction pathway. Carboxylates of branched acids react with 20 to form probably a mixed carbamic acid anhydride 21 which loses  $CO_2$  to give the expected amides (pathway *a*). Non-branched acids react with the *N*-carbamoylpyridinium ion but, in addition, they also react with the mixed anhydride, releasing free carbamic acid 24 which subsequently gives rise to amine 25 (pathway *b*). The amine then reacts with 20, or with isocyanate, to give urea. In the presence of isobutyric acid and substituted 4,5-diaminopentanoic acid the pathway *a* is the predominant one.



#### Scheme 4.

The reactions of phenylacetic acid with phenylisocyanate or with 6-isocyanatopenicillanic acid also follow pathway  $a^{12}$ . In the case of adipic acid monomethyl ester both pathways, a and b, give a mixture of amide and urea. More acidic acids, like dicarboxylic acids, do not require the intermediacy of DMAP. Direct addition to isocyanate, release of carbamic acid and its decarboxylation to amine will lead to urea as a single reaction product.

In summary, by addition of acids to isocyanate 8 chiral non-racemic molecules containing two vicinal diamino units bound as amides, bisamides or urea were prepared in all isomeric forms. The removal of the Boc protecting groups and the reaction with  $K_2PtCl_4$  will lead to optically active bis[platinum(II)] complexes.

# **EXPERIMENTAL**

Melting points are uncorrected. Flash chromatography was carried out on silica gel (Merck, 70-230 mesh), TLC was performed on Merck Kieselgel 60 F<sub>254</sub> plates and ethanolic 0.2% ninhidrin was used for visualization. Data for the compounds **1a** - **9a**: Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR were measured on an AM Bruker 400 MHz WB spectrometer. Mass spectra were obtained on a TSQ-70 mass spectrometer and on a Varian Mat 711 double focusing mass spectrometer. Specific rotation was measured with a DIP JASCO polarimeter. Elemental analyses were performed by the Microanalytical Services of the Chemistry Department at the Hebrew University, Jerusalem. Data for the compounds **10** -**17**: IR spectra were measured on a Nicolet 520 FT-IR spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Jeol EX-400 instrument. Specific rotation was measured with a 241 Perkin Elmer polarimeter. HPLC: chromatography pomp 655-A12 (Merck -Hitachi), UV detector. 210 nm (Bischoff), integrator D-2000 (Merck-Hitachi), LiChroCart<sup>R</sup> 250-4 ChiraDex<sup>R</sup>, HPLC-cartridge (250 x 4 mm) and LiChroCart<sup>R</sup> RP18 precolumn (4 x 4). C. H, N analyses were performed with a Heraeus VT. (*R*) and (*S*)-Pyroglutamic acids were obtained from Merck-Schuchard.

### The compounds 1a - 9a were prepared according to the procedure reported for the S series<sup>5</sup>.

#### (R)-5-(Azidomethyl)-2-pyrrolidone (1a):

Mp 62-63°; [α]<sub>D</sub><sup>30</sup> - 72.0 (c 5. EtOH); IR (CHCl<sub>3</sub>): 2104 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.76 (m, 1H, AB part of ABCD CH<sub>2</sub>); 2.21 (m, 1 H, AB part of ABCD, CH<sub>2</sub>): 2.24 - 2.41 (m, 2 H, CH<sub>2</sub>CO); 3 12 (dd, 1 H, AB part of ABX, CH<sub>2</sub>N<sub>3</sub>); 3.36 (dd, 1 H, AB part of ABX, CH<sub>2</sub>N<sub>3</sub>); 3.77 (q, 1 H, CHN); 7.29 (br, 1 H, NH): <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 23.9 (C-4); 29.7 (C-3); 53.6 (C-6); 55.9 (C-5); 178.5 (C-2); CIMS: *m*/z 141 [MH]<sup>+</sup> (100%). C5H<sub>8</sub>N<sub>4</sub>O requires 140.

### (R)-5-(Aminomethyl)-2-pyrrolidone (2a):

Oil.  $[\alpha]_D^{30}$  - 37.0 (c 2, EtOH): <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.80 (m. 1 H. part of ABCD. CH<sub>2</sub>): 2.04 (s, 2H, NH<sub>2</sub>); 2.09 (m, part of ABCD. 1 H, CH<sub>2</sub>): 2 20 (m, 2 H. CH<sub>2</sub>CO); 2.54 (dd. 1 H. AB part of ABX. CH<sub>2</sub>N); 2.78 (dd. 1 H, AB part of ABX, CH<sub>2</sub>N); 3.56 (q, 1 H. CHN): 7.74 (br. 1 H. NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  23.9 (C-4); 30.1 (C-3); 47.1 (C-6); 56.7 (C-5); 178.5 (C-2); HRMS: *m/z* 114.0756 [MH]<sup>+</sup> (1.2%): 97.0551 [M - NH<sub>3</sub>]<sup>+</sup> (35.8%). 85 0492 [M - CH<sub>2</sub>NH<sub>2</sub>]<sup>+</sup> (78%); 84.0422 [M - CH<sub>2</sub>NH<sub>3</sub>]<sup>+</sup> (100%); C5H<sub>10</sub>N<sub>2</sub>O requires 114.0793.

# (R)-5-(t-Butoxycarbonylaminomethyl)-2-pyrrolidone (3a):

Oil;  $[\alpha]_D^{28} - 12.1$  (c 2, EtOH); IR (CHCl<sub>3</sub>): 3439, 1700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.39 (s, 9 H, Me); 1.74 (m, 1H, AB part of ABCD, 1H, CH<sub>2</sub>); 2 15 (m, part of ABCD, 1H, CH<sub>2</sub>): 2 30 (m, 2 H, CH<sub>2</sub>CO); 3 05 (m, 1 H, AB part of CH<sub>2</sub>N); 3.28 (m, 1H, AB part of CH<sub>2</sub>N); 3.74 (m, 1H, CHN); 5 34 (br, 1H, NH); 7.04 (br, 1 H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  24.1 (C-4); 28.3 (Me); 30.0 (C-3): 45.4 (C-6): 54.8 (C-5): 79.7 (CMe<sub>3</sub>); 156.2 (CO<sub>2</sub>): 178.5 (CO): CIMS: *m/z* 215 [MH]<sup>+</sup> (100%). C<sub>10</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub> requires 215.Anal. Found: C, 54.03; H, 8.10. C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> · 1/2H<sub>2</sub>O requires C, 53.81; H, 8.52%.

# (R)-5-[(1R, 3R, 4S)-Menthyloxycarbonylaminomethyl]-2-pyrrolidone (4a):

Mp 127-129°;  $[\alpha]_D{}^{30}$  = 58.9 (c 2, EtOH); IR (CHCl<sub>3</sub>): 3440, 1695 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.74 (d, 3H, Me); 0.98 (d, 3H, Me); 1.00 (d, 3H, Me): 0.9 - 1.97 (m, 9H, cyclohexyl): 1.7-1.8 2 05- 2.22 (m, 1H, part of AB, CH<sub>2</sub>-4); 3.32(t, 2H, CH<sub>2</sub>CO); 3.10-3.15 (q, 1H, part of AB, CH<sub>2</sub>CO): 3.31-3 35 (m, 1H, part of AB, CH<sub>2</sub>N); 3.76 (s br, 1H, CHN); 4.49 (q, 1H, CHO); 5.44 (s, 1H, NH); 7.06 (s, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  16.5 (Me): 20.7 (Me): 22.0 (Me): 23.6 (C-5'); 24.2 (C-8'); 26.3 (C-4); 30.0 (C-1'); 31.3 (C-1'

(C-3); 34.3 (C-6'); 41.4 (C-2'); 45.7 (C-6'); 47.4 (C-6); 54.7 (C-5); 74.8 (C-3'); 156.8 (CO<sub>2</sub>); 178.5 (CO); CIMS: m/z 297 [MH]<sup>+</sup> (100%). C<sub>16</sub>H<sub>29</sub>N<sub>2</sub>O<sub>5</sub> requires 297. Anal. Found: C. 64.86; H. 9.50; N. 9.41. C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> requires C. 65.05; H. 9.21; N. 9.48%

#### (R)-5-(t-Butoxycarbonylaminomethyl)-1-(t-butoxycarbonyl)-2-pyrrolidone (5a):

**5a** was prepared from **2a**. Mp 133°:  $[\alpha]_D^{30} + 60.5$  (c 2. EtOH): IR (CHCl<sub>3</sub>): 3440, 1780, 1730sh, 1710 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.33 (s, 9H. Me): 1.43 (s, 9H. Me); 1.85-2.03 (m, 2H. CH<sub>2</sub>-4); 2.28-2.56 (m, 2H, CH<sub>2</sub>CO); 3.26-3.34 (m, 2H, CH<sub>2</sub>N); 4.11(m, 1H, CHN); 4.98 (t, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  21.1 (C-4); 27.9, 28.2 (Me); 31.4 (C-3); 42.9 (C-6); 57.8 (C-5); 79.5, 83.1 (<u>C</u>(Me)<sub>3</sub>); 150.0, 156.0 ((CO<sub>2</sub>);): 174.2 (CO): CIMS: *m z* 315 [MH]<sup>+</sup> (15%). C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> requires 315. Anal. Found: C, 57.60; H. 8.36; N. 8.87. C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub> requires C, 57.32; H.8.33; N. 8.91%.

# (R)-N<sup>4</sup>, N<sup>5</sup>-Bis(t- butoxycarbonyl)-4, 5-diaminopentanoic acid (6a):

Mp 129-131°C:  $[\alpha]_D^{24}$  +12.2 (c 2. EtOH); IR (nujol): 3440, 1700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.44 (s, 18H, Me); 1.62-1.82 (m, 2H, CH<sub>2</sub>CO): 2.30-2.40 (m, 2H, CH<sub>2</sub>CO); 3.1-3.2 (m, 2H, CH<sub>2</sub>N); 3.64 (m, 1H, CHN); 4.91(d, 1H, NH); 5.00 (t, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  27.7 (C<sup>2</sup>3): 28.3 (Me); 44.6 (C-5); 51.0 (C-4); 79.5 (<u>C</u>(Me)<sub>3</sub>); 156.4, 156.7 (CO<sub>2</sub>); 177.2 (CO<sub>2</sub>H); Anal. Found: C, 54.31; H, 8.56; N, 8.85. C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub> requires C, 54.21; H, 8.49; N, 8.42%.

# (R)-N<sup>3</sup>,N<sup>4</sup>-Bis(t- butoxycarbonyl)-3,4-diaminobutylisocyanate (8a):

Isobutyl chloroformate (544 mg, 4 mmol) was added to a mixture of 6a (662 mg, 2mmol) and Et<sub>3</sub>N (505 mg, 5mmol) in dry THF (16mL) at 0°C. After 1 h, NaN<sub>3</sub> (2.4 g.) in 8 mL of water was added and the reaction mixture stirred for 30 min at 0°C. EtOAc (80 mL) was added. The organic layer was separated, washed once with water, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and dried in vacuo at room temperature for 5 h. The IR (nujol) of the crude acyl azide 7 had an absorption at 2155 cm<sup>-1</sup>. The residue was redissolved in benzene (70 mL) and heated at 60°C for 1 h. Benzene was evaporated yielding quantitatively the isocyanate 8a, (630 mg) mp 99-102°C,  $[\alpha]_D^{24}$  +68.0 (c 2.07, benzene); IR (nujol): 3377. 3355, 2271. 1697, 1682, 1528 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.41 (s, 18H, Me); 1.50-1.82 (m, 2H, CH<sub>2</sub>-2); 3.16 (m, 2H, CH<sub>2</sub>N-4); 3.40 (t. 2H, *J*=6.8, CH<sub>2</sub>N-1); 3.72 (m, 1H, CHN-2); 4.80 (br, 1H, NH); 4.90 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  28.3 (Me); 34.4 (C-2): 40.0 (C-4), 44.3 (C-1); 49.4 (C-3); 79.7 (C(Me)<sub>3</sub>); 79.5 (C(Me)<sub>3</sub>); 156.0, 156.1 (CO<sub>2</sub>); 156.6 (N=C=O): Anal. Found: C, 54.94; H. 8.23; N, 12.91. C<sub>15</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub> requires C, 54.69; H, 8.26; N, 12.45%.

#### (S)- $N^3$ , $N^4$ -Bis(t- butoxycarbonyl)-3,4-diaminobutylisocyanate (8b):

The full IR and NMR data of 8b are the same as of 8a, mp 98-101°,  $[\alpha]_D^{24}$  -67.9 (c 1.55, benzene); Anal. Found: C, 54.75; H, 8.35; N, 12.76. C<sub>15</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub> requires C, 54.69; H, 8.26; N, 12.45%.

### (R)-N<sup>1</sup>,N<sup>2</sup>-Bis(t- butoxycarbonyl)-1,2,4-triaminobutane (9a):

Mp 76-78°C;  $[\alpha]_{D}^{24}$  +26.8 (c 2. EtOH); IR (CHCl<sub>3</sub>): 1700, 1498 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.38 (s, 18H, Me); 1.53 (br, 2H, CH<sub>2</sub>); 1.93 (br. 2H, NH<sub>2</sub>): 2.74 (t, 2H. <u>CH<sub>2</sub>NH<sub>2</sub></u>): 3.14 (br. 2H. CH<sub>2</sub>N-1); 3.69 (br. 1H, CHN); 5.05 (br. 1H, NH); 5.11 (br. 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  28.3, 28.5 (Me); 36.2 (C-3); 38.4 (C-4); 44.7 C-1); 49.3 (C-2); 79.2 (<u>C</u>(Me)<sub>3</sub>); 156.0, 156.4 (CO<sub>2</sub>); CIMS: m/z 304 [MH]<sup>+</sup> (100%). C<sub>1</sub>4H<sub>30</sub>N<sub>3</sub>O<sub>4</sub> requires 304.

# (S)-4,5-Bis(t-butoxycarbonylamino)-N-(i-butyl)pentanamide (10b):

Dicyclohexylcarbodiimide (227 mg. 1.1 mmol) was added to the cold solution of the acid **6b** (331 mg, 1 mmol) and N-hydroxysuccinimide (127 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The mixture was left overnight at  $4^{\circ}$ C and filtered from DCU.

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Isobutylamine (352 mg. 2.8 mmol) was added to the active ester and the reaction mixture stirred 1 h at 0°C and overnight at ambient temperature. CH<sub>2</sub>Cl<sub>2</sub> was evaporated, the residue mixed with EtOAc (50 mL) and water. The organic layer was washed twice with water, dried, concentrated and chromatographed on silica gel column. Traces of DCU were eluted with a mixture of 30% EtOAc/hexane and the product was eluted with 70% EtOAc/hexane (356 mg, 92%), mp 138°C (from EtOAc/hexane),  $[\alpha]_D^{24}$  -57.5 (c 2, EtOH): IR (nujol): 3364, 1684, 1648, 1533 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  0.80 (d, 6H, Me), 1.36 (s, 18H, Me superimposed on m. IH, part of AB CH<sub>2</sub>-3); 1.61 (m. 2H, <u>CH</u>(Me)<sub>2</sub> and part of AB CH<sub>2</sub>-3); 2.02 (m. 2H, CH<sub>2</sub>CO); 2.82 (t, 2H, <u>CH<sub>2</sub>NH<sub>2</sub>); 2.88 (br, 2H, CH<sub>2</sub>N); 3.38 (br, 1H, CHN); 6.48 (d, 1H, NH); 6.69 (t, 1H, NH); 7.70 (t, 1H, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  20.1 (Me); 28.0, 28.2 (Me); 32.1 (C-3); 37.1 (CH): 43.8 (<u>CH<sub>2</sub>N); 45.9 (CH<sub>2</sub>N); 50.1 (CHN); 77.4, 77.7 (<u>C</u>(Me)<sub>3</sub>); 155.3, 155.7 (CO<sub>2</sub>); 171.7 (CO): Anal. Found: C. 58.71; H. 9.62; N. 10.83. C<sub>1</sub>9H<sub>3</sub>7N<sub>3</sub>O<sub>5</sub> requires C, 58.88; H, 9.62; N, 10.84%.</u></u>

#### 4,5-Bis(t-butoxycarbonylamino)-N-[3,4-bis(t-butoxycarbonylamino)butyl]pentanamide (11 a-d):

General Method: 6 (662 mg. 2 mmol). DMAP (80 mg) and isocyanate 8 (658 mg, 2 mmol) were stirred in benzene (80 mL) for 12 h. In the case of the reaction of 6a with 8a or 6b with 8b. EtOAc (100 mL) was added to dissolve the product. The solution was washed once with 5% citric acid to remove DMAP, once with water and once with 5% aq. NaHCO3. dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a volume of 50 mL to which 10 g of silica gel was added. The solvent was evaporated and the absorbed silica was introduced on the top of a silica gel column (40 g) prepared with a mixture EtOAc/hexane 1:2. Some impurities were eluted with the same mixture. 11a or 11b were eluted with EtOAc/hexane 3:1, (Rf = 0.43, EtOAc-5% MeOH, visualisation with ninhydrin). Traces of unreacted acid 6 were eluted with EtOAc (Rf = 0.24, EtOAc-5% MeOH). In the case of the reaction of 6a with 8b or 6b with 8a CHCl<sub>3</sub> (120 mL) was added to benzene the solution. After washing as above the more polar 11c or 11d were isolated by trituration with EtOAc (3 x 8 mL) and once with EtOH (10 mL).

11a: (936 mg, 76%) mp 178-179°C:  $[\alpha]_D^{24}$  +26.0 (c 2, EtOH): IR (nujol): 3355, 1685, 1645, 1531 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$ 1.37 (s. 18H, Me): 1.4-1.7 (br, 2H, CH<sub>2</sub>-3): 2.0 (m, 2H, CH<sub>2</sub>CO): 2.90 (m, 5H, part of AB of CH<sub>2</sub>-4, CH<sub>2</sub>-1, CH<sub>2</sub>-9, ); 3.04 (m, 1H, part of AB of CH<sub>2</sub>): 3.3-3.5 (m, 2H, CHN-2, CHN-8): 6.49 (d, 1H, NH): 6.55 (d, 1H, NH); 6.69 (t, 2H, NH-1 and NH-9); 7.64 (s, br, 1H, NH): <sup>13</sup>C NMR ((DMSO-d<sub>6</sub>):  $\delta$  27.8 (C-7): 28.1 (Me); 31.7 (C-3); 32.0 (C-6); 35.8 (C-4); 43.7 C-1 + C-9); 48.3 (C-2); 50.0 (C-8): 77.4. 77 5 (<u>C</u>(Me)<sub>3</sub>); 155.3. 155.5 (CO<sub>2</sub>) 171 6 (CO); HPLC (MeOH/H<sub>2</sub>O 55:45, flow rate 1.00 mL/min, 200 bar) 18.92 min. Anal. Found: C, 56.32; H, 9.04; N, 11.21. C<sub>2</sub>9H55N5O9 requires C, 56.38; H, 8.97; N, 11.33 %.

11b: (730 mg, 62%) mp 178-179°C:  $[\alpha]_D^{24}$  -25.5 (c 2. EtOH): IR (nujol): 3355, 1685, 1645, 1531 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.37 (s, 18H, Me); 1.4-1.7 (br. 2H. CH<sub>2</sub>-3): 2.0 (m, 2H. CH<sub>2</sub>CO); 2.90 (m, 5H. part of AB of CH<sub>2</sub>-4, CH<sub>2</sub>-1, CH<sub>2</sub>-9, ); 3.04 (m, 1H. part of AB of CH<sub>2</sub>-4); 3.3-3.5 (m, 2H, CHN-2, CHN-8); 6.49 (d, 1H, NH); 6.55 (d, 1H, NH): 6.69 (t, 2H, NH-1 and 9); 7.64 (s, br. 1H, NH); <sup>-13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  27.8 (C-7); 28.1 (Me): 31.7 (C-3); 32.0 (C-6); 35.8 (C-4): 43.7 C-1 + C-9); 48.3 (C-2); 50.0 (C-8): 77.4. 77.5 (<u>C</u>(Me)<sub>3</sub>): 155.3. 155.6 (CO<sub>2</sub>) <u>171</u> 6 (CO): HPLC (MeOH/H<sub>2</sub>O 55:45, flow rate 1.00 mL/min, 200 bar) 23.21 min: Anal. Found: C. 56.34; H. 8.94; N. 11.27. C<sub>2</sub>9H<sub>5</sub>5N<sub>5</sub>O9 requires C. 56.38; H. 8.97; N, 11.33 %.

11e: (707mg. 57%) mp 195°C:  $[\alpha]_D^{24}$  +14.8 (c 1. EtOH); IR (nujol): 3339, 1682, 1644, 1528 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.37 (s. 18H, Me): 1.4-1 7 (m,br, 2H, CH<sub>2</sub>-3): 2.0 (m, 2H, CH<sub>2</sub>CO): 2.90 (m, 5H, part of AB of CH<sub>2</sub>-4, CH<sub>2</sub>-1, CH<sub>2</sub>-9, ); 3.04 (m, 1H, part of AB of CH<sub>2</sub>): 3.3-3 5 (m, 2H, CHN-2, CHN-8). 6.49 (d. 1H, NH); 6.55 (d, 1H, NH); 6.69 (s. br. 2H, NH); 7.64 (s, br, 1H, NH): <sup>-13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  27.8 (C-7): 28.2 (Me): 31.8 (C-3); 32.0 (C-6); 35.8 (C-4); 43.8 (C-1 + C-9); 48.4 (C-2); 50.0 (C-8): 77.4, 77.5 (<u>C(Me)<sub>3</sub></u>). 155.3. 155.5 (CO<sub>2</sub>) 171.6 (CO): HPLC (MeOH/H<sub>2</sub>O 55:45, flow rate 1.00 mL/min, 200 bar) 18.18 min; Anal. Found: C, 56.32; H, 9.04; N, 11.21. C<sub>29</sub>H55N5O9 requires C, 56.38; H, 8.97; N, 11.33 %.

11d: (802 mg 65%) mp 195°C,  $[\alpha]_D^{24}$  -13.8 (c 1. EtOH); IR (nujol): 3339, 1682, 1644, 1528 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.37 (s, 18H. Me): 1.4-1.7 (br, 2H, CH<sub>2</sub>-3); 2.0 (m, 2H, CH<sub>2</sub>CO); 2.90 (m, 5H, part of AB of CH<sub>2</sub>-4, CH<sub>2</sub>-1, CH<sub>2</sub>-9); 3.04 (m, 1H, part of AB of CH<sub>2</sub>): 3.3-3.5 (m, 2H, CHN-2, CHN-8). 6.49 (d, 1H, NH); 6.55 (d, 1H, NH); 6.69 (t, 2H, NH); 7.64 (t, 1H, NH); <sup>13</sup>C

NMR (DMSO-d<sub>6</sub>): δ 27.8 (C-7); 28.0 (Me); 31.7 (C-3); 32.0 (C-6): 35.8 (C-4); 43.7 C-1 + C-9); 48.3 (C-2); 50.0 (C-8); 77.4, 77.5 (<u>C</u>(Me)<sub>3</sub>): 155.3, 155.6 (CO<sub>2</sub>) 171.5 (CO); HPLC (MeOH/H<sub>2</sub>O 55:45, flow rate 1.00 mL/min, 200 bar) 20.19 min; Anal. Found: C, 56.26: H, 9.17; N, 11.32. C<sub>29</sub>H<sub>55</sub>N<sub>5</sub>O<sub>9</sub> requires C, 56.38; H, 8.97; N, 11.33 %.

#### 4,5-Diamino-N-(3,4-diaminobutyl) pentanamide tetrahydrochloride (12 a-d):

**General Method:** 11 (617 mg, 1 mmol) was suspended in a solution of dry 2.5 M HCl in EtOH (10 mL) and the mixture was stirred at ambient temperature for 15 h and then heated at 50°C in water bath for 1 h, cooled and centrifugated. One trituration with EtOH (10 mL), three triturations with dry ether and drying in high vacuo at 50°C for 10 h yielded the hygroscopic tetrahydrochloride 12 in quantitative yields, containing with 0.5 - 1.0 mmol of EtOH.

12a:  $[\alpha]_D^{24}$  -0.8 (c 2, EtOH); <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  1.7-2.0 (m, 4H, CH<sub>2</sub>-3 and CH<sub>2</sub>-7); 2.37 (t, 2H, CH<sub>2</sub>CO); 3.1-3.3 (m, 6H, CH<sub>2</sub>-4, CH<sub>2</sub>-1, CH<sub>2</sub>-9, ); 3.50-3.55 (m, 2H, CHN-2, CHN-8); <sup>13</sup>C NMR (D<sub>2</sub>O):  $\delta$  26.6 (C-6); 31.0 (C-7); 31.7 (C-3); 35.9 (C4); 41.5 (C-1): 41.7 (C-9: 48.1 (C-2); 50.0 (C-8); 175.7 (CO): Anal. Found: C. 32.48; H. 8.13; N, 16,31. C9H<sub>2</sub>7Cl<sub>4</sub>N<sub>5</sub>O-CH<sub>3</sub>CH<sub>2</sub>OH requires C, 32.28; H, 8.12; N, 17.11 %

12b:  $[\alpha]_D^{24}$  +0.9 (c 2. EtOH); <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  1.7-2.1 (m, 4H, CH<sub>2</sub>-3 and 7); 2.58 (t, 2H, CH<sub>2</sub>CO); 3.20-3.35 (m, 6H, CH<sub>2</sub>-1, CH<sub>2</sub>-4, CH<sub>2</sub>-9, ); 3.48 (m, 1H, CHN); 3.72 (m, 1H, CHN): <sup>13</sup>C NMR (CD<sub>3</sub>OD):  $\delta$  27.4 (C-6); 31.3 (C-7); 32.3 (C-3); 35.9 (C4); 42.1 (C-9); 42.4 (C-1); 48.4 (C-2); 50.6 (C-8); 175.3 (CO); Anal. Found: C, 32.91; H, 8.22; N, 16.92. C9H<sub>2</sub>7Cl4N<sub>5</sub>O·CH<sub>3</sub>CH<sub>2</sub>OH requires C, 32.28; H, 8,12; N, 17.11%

**12c:**  $[\alpha]_D^{24}$  -2.9 (c 2, EtOH); IR (nujol): 3500-2900, 1643, 1608, 1558, 1498 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O): 1.7-2.1 (m, 4H, CH<sub>2</sub>-3 and 7); 2.38 (t, 2H, CH<sub>2</sub>CO): 3.2-3.3 (m, 6H, CH<sub>2</sub>-1, CH<sub>2</sub>-4, CH<sub>2</sub>-9, ): 3.50-3.55 (m, CHN-2, CHN-8, ); <sup>13</sup>C NMR (D<sub>2</sub>O):  $\delta$  26.7 (C-6); 31.0 (C-7); 31.7 (C-3); 35.9 (C4); 41.5 (C-9); 41.7 (C-1); 48.1 (C-2); 50.0 (C-8); 175.7 (CO); Anal. Found: C, 31.44; H, 7.99; N, 15.91. C9H<sub>2</sub>7Cl4N<sub>5</sub>O · 1/2CH<sub>3</sub>CH<sub>2</sub>OH·H<sub>2</sub>O requires C, 30.89; H, 8.26; N, 16.31 %

12d:  $[\alpha]_D^{24} + 2.4$  (c 2, EtOH); IR (nujol): 3500-2900, 1643, 1608, 1558, 1498 cm<sup>-1</sup>; <sup>1</sup>H NMR (D<sub>2</sub>O):  $\delta$  1.7-2.1 (m, 4H, CH<sub>2</sub>-3 and 7); 2.38 (t, 2H, CH<sub>2</sub>CO); 3.2-3.3 (m, 6H, CH<sub>2</sub>-1, CH<sub>2</sub>-4, CH<sub>2</sub>-9, ): 3.50-3.55 (m, CHN-2, CHN-8, ); <sup>13</sup>C NMR (D<sub>2</sub>O):  $\delta$  26.7 (C-6); 31.0 (C-7); 31.7 (C-3); 35.9 (C4); 41.5 (C-9); 41.7 (C-1); 48.1 (C-2); 50.0 (C-8); 175.7 (CO); Anal. Found: C, 31.39; H, 7.54; C9H<sub>2</sub>7C4N<sub>5</sub>O · 1/2CH<sub>3</sub>CH<sub>2</sub>OH requires C, 31.00; H, 7.87 %

# $(S)-N^{1},N^{2}$ -Bis(t- butoxycarbonyl)- $N^{4}$ -(isobutyryl)-1,2,4-triaminobutane (13b):

**8b** (329 mg, 1mmol), DMAP (50 mg) and isobutyric acid (1 mL) were stirred in benzene (40 mL) for 12 h. EtOAc (40 mL) was added and the mixture was washed with water, 5% citric acid, water, 10% aq NaHCO<sub>3</sub> dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was absorbed on silica gel (5 g) and put on a silica gel column (10 g). Elution with 40% EtOAc/hexane afforded 13 (291 mg 78%), mp 154°C;  $[\alpha]_D^{24}$  -35.1 (c 2, EtOH); IR (nujol): 3318, 1682, 1646, 1532cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  0.97 (d, 6H, CH(<u>Me</u>)<sub>2</sub>); 1.37 (s, 18H, CH(Me)<sub>3</sub>); 1.34; 1.48 (m, 2H, CH<sub>2</sub>-3); 2.28 (q, 1H, <u>CH(Me)<sub>2</sub></u>); 2.95 (m, 3H, CH-2 and part of AB CH<sub>2</sub>-4); 3.04 (m, 1H, CH<sub>2</sub>-4); 3.46 (m, 1H, CH-2 and part of AB CH<sub>2</sub>-4, ); 6.57 (d, 1H, NH-2); 6.73 (t, 1H, NH-1); 7.56 (t, 1H, NH-4); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  19.5, 19.6 (CH(<u>Me</u>)<sub>2</sub>); 28.2 (CH(<u>Me</u>)<sub>3</sub>); 32.8 (C-3), 33.9 (CH(<u>Me</u>)<sub>2</sub>); 35.4 (C-4); 43.8 (C-1); 48.3 (C-2); 79.5 (C-O); 155.3, 155.7 (CO<sub>2</sub>); 175.7 (CO); Anal. Found: C, 58.36; H, 9.36; N, 11.04. C1<sub>8</sub>H<sub>37</sub>N<sub>3O5</sub> requires C, 57.88; H, 9.44; N, 11.25 %.

#### (R)-Methyl 5-[3,4-bis(t- butoxycarbonylamino)butylaminocarbonyl]pentanoate (15a):

Isocyanate 8a (536 mg, 1.63 mmol), DMAP (60 mg, 0.5 mmol) and adipic acid monomethyl ester (288 mg, 1.8 mmol) were stirred in benzene (70 mL) for 12 h at ambient temperature. CHCl<sub>3</sub> (100 mL) was added to dissolve formed solids. The mixture was washed with 5% citric acid (to remove DMAP), water, 5% aq NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was

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triturated with EtOAc (20 mL). The sparingly soluble urea 14a (205 mg, 40%) was removed by filtration. The solution was concentrated and chromatographed on silica gel column (25 g) prepared in 30% EtOAc/hexane. 15a was eluted with 55% EtOAc-hexane: 342 mg, 47%. mp 66-67°C:  $[\alpha]_D^{24}$  +26.2 (c 1.86. EtOH); IR (nujol): 3340,3297, 1739, 1678, 1631, 1528 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.25-1.50 (s. 18H. Me and m. 2H. CH<sub>2</sub>-3): 1.66 (m, 4H, CH<sub>2</sub>-7 and 8); 2.25 (t, 2H. CH<sub>2</sub>CONH); 2.36 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>H). 2.88 (br. 1H. part of AB. CH<sub>2</sub>-4); 3.1 (br. 1H, part of AB. CH<sub>2</sub>-1); 3.24 (br, 1H, part of AB, CH<sub>2</sub>-1); 3.33 (m, 5H, CH-2, part of AB CH<sub>2</sub>-4 and OMe); 5.05 (br, 1H. NH); 5.19 (1H, NH); 7.01 (br, 1H, NH); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  24.4 (C-7); 25.1 (C-8): 28.3 (Me): 32.8 (C-3): 33.7 (C-9): 35.8 (C-4); 36.1 (C-6); 44.3 (C-1); 49.9 (C-2); 51.6 (OMe); 79.7, 79.8 (C(Me)\_3); 157.1 (CO<sub>2</sub>): 173.1 (CO): 174.1 (CO); Anal. Found: C, 56.71; H, 8.84; N, 9.29. C<sub>2</sub>1H<sub>3</sub>9N<sub>3</sub>O<sub>7</sub> requires C, 56.61; H, 8.82; N, 9.43.%.

# (S)-Methyl 5-[3,4-bis(t- butoxycarbonylamino)butylaminocarbonyl]pentanoate (15b):

15b was prepared as described for 15a from 709 mg of 8b: (554 mg, 58%), mp 66-67°C;  $[\alpha]_D^{24}$  -26.4 (c 1.52, EtOH); IR (nujol): <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3340,3297, 1739, 1678, 1631, 1528 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.25-1.50 (s, 18H, Me and m, 2H, CH<sub>2</sub>-3); 1.66 (m. 4H, CH<sub>2</sub>-7 and 8): 2.25 (t. 2H, CH<sub>2</sub>CONH): 2.36 (t. 2H, CH<sub>2</sub>CO<sub>2</sub>H); 2.88 (br, 1H, part of AB, CH<sub>2</sub>-4); 3.1 (br, 1H, part of AB, CH<sub>2</sub>-1): 3.24 (br. 1H. part of AB, CH<sub>2</sub>-1); 3.33 (m, 5H, CH-2, part of AB CH<sub>2</sub>-4 and OMe); 5.05 (br, 1H, NH); 5.19 (1H, NH); 7.01 (br. 1H, NH): <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  24.4 (C-7); 25.1 (C-8): 28.3 (Me); 32.9 (C-3); 33.7 (C-9); 35.8 (C-4); 36.2 (C-6); 44.4 (C-1): 49.9 (C-2): 51.5 (OMe). 79.6 (<u>C</u>(Me)<sub>3</sub>). 157.1 (CO<sub>2</sub>). 173.0 (CO): 174.0 (CO); Anal. Found: C. 56.74; H, 8.96; N, 9.31. C<sub>21</sub>H<sub>39</sub>N<sub>3</sub>O<sub>7</sub> requires C, 56.61; H. 8, 82: N, 9.43 %

# (R,R)-N,N'-Bis[3,4-bis(t- butoxycarbonylamino)butyl]urea (14a):

Isocyanate **8a** (595 mg, 1.8 mmol), DMAP (75 mg, 0.62 mmol, and adipic acid (123 mg, 0.85 mmol) were stirred in CHCl<sub>3</sub> (50 mL) for 12 h. The solution was washed with water, citric acid, water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, the residue was chromatographed on silica gel column (20 g). Elution with 2.5% MeOH/CHCl<sub>3</sub> afforded **14a**, 408 mg (71%), mp 190-192°C;  $[\alpha]_D^{24}$  +44.1 (c 1. EtOH): IR (nujol): 3349, 3367, 1682, 1648, 1640, 1565, 1532 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.28-1.49 (m, 4H, CH<sub>2</sub>-3, and s. 36H. Me ): 2.80 (m. 2H, part of B, CH<sub>2</sub>-4): 2.91 (m, 4H, CH<sub>2</sub>-1): 3.05 (m, 2H, part of AB CH<sub>2</sub>-4); 3.44 (br, 2H, CH-2): 5.79 (t. 2H, NH-4): 6.56 (d. 2H, NH-2): 6.72 (t. 2H, NH-1); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  28.1 (Me); 32.8 (C-3); 36.3 (C-4); 43.8 (C-1): 48.2 (C-2). 77.4 (<u>C</u>(Me)<sub>3</sub>): 155.4. 155.7 (CO<sub>2</sub>): 157.8 (CO): Anal. Found: C, 54.27; H, 8.92; N, 12.86. C<sub>29</sub>H<sub>56</sub>N<sub>6</sub>O9 requires C, 55.05; H, 8.92, N, 13.28 %.

14a was also isolated in 40% yield as a by-product of 15a by trituration with EtOAc in which 15a is soluble.

#### (S,S)-N,N'-Bis[3,4-bis(t- butoxycarbonylamino)butyl]urea (14b):

14b was prepared as described for 14a and also was isolated as the by-product of 15b, mp 190-192°C;  $[\alpha]_D^{24}$  -44.7 (c 1, EtOH); IR (nujol): 3370, 3340, 1680, 1648, 1637, 1552, 1531 cm<sup>-1</sup>: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.2-1.6 (m, 4H, CH<sub>2</sub>-3, and s, 36H, Me ); 2.8 (m, 2H, part of AB, CH<sub>2</sub>-4); 2.96 (m, 4H, CH<sub>2</sub>-1); 3.06 (m, 2H, part of AB CH<sub>2</sub>-4); 3.45 (br, 2H, CH-2); 5.79 (t, 2H, NH-4); 6.53 (d. 2H, NH-2); 6.73 (t. 2H, NH-1); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  28.1 (Me); 32.7 (C-3); 36.3 (C-4); 43.8 (C-1); 48.1 (C-2); 77.4 (<u>C</u>(Me)<sub>3</sub>): 155.3, 155.6 (CO<sub>2</sub>): 157.8 (CO); Anal. Found: C, 54.67; H, 9.13; N, 12.96. C<sub>29</sub>H<sub>56</sub>N<sub>6</sub>O<sub>9</sub> requires C, 55.05; H, 8,92; N, 13.28 % NMR

#### (R)-5-[3,4-Bis(t- butoxycarbonylamino)butylaminocarbonyl]pentanoic acid (16a):

Ester 15 (445 mg, 1 mmol) was dissolved in a solution of NaOH in 30 mL MeOH (prepared from 150 mg Na and 0.3 mL water) and left for 12 h at ambient temperature. MeOH was evaporated and water (30 mL) was added. The aqueous layer was acidified upon cooling in ice bath with 5% citric acid, then extracted with ethyl acetate. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and

concentrated yielding quantitatively the acid 16a. mp 43-45°C:  $[\alpha]_D^{24}$  +28.9 (c 2. EtOH); IR (nujol): 3350, 1741, 1711, 1695, 1648, 1527 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.2-1.5 (m, 2H, CH<sub>2</sub>-3, and s. 18H, Me): 1.65 (t, 4H, CH<sub>2</sub>-7 and 8); 2.22 (t, 2H, CH<sub>2</sub>CONH); 2 34 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>H): 2 91 (br. 1H, part of AB, CH<sub>2</sub>-4); 3.14 (br. 2H, CH<sub>2</sub>-1); 3.62 (br, 2H, CH-2 and part of AB, CH<sub>2</sub>-4); 5.11 (br. 1H, NH); 5.21 (1H, NH); 6.77 (br, 1H, NH); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  24.7 (C-7); 25.3 (C-8); 28.5 (Me); 33.1 (C-3); 33.9 (C-9); 36.1 (C-4), 36.5 (C-6); 44.8 (C-1); 50.1 (C-2); 79.9 (C(Me)<sub>3</sub>); 157.4, 157.5 (NHCO<sub>2</sub>); 173.5 (CO); 176.0 (CO); Anaf. Found: C. 56.08; H, 8.79; N, 9.30. C<sub>20</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub> requires C, 55.67; H, 8,64; N, 9.74 %.

# (S)-5-[3,4-Bis(t- butoxycarbonylamino)butylaminocarbonyl]pentanoic acid (16b):

16b was prepared as described for 16a, mp 44-46°C;  $[\alpha]_D^{24}$ -29.1 (c 1.49, EtOH); IR (nujol): 3350, 1741, 1711, 1695, 1648, 1527 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  1.2-1.5 (m, 2H, CH<sub>2</sub>-3, and s. 18H, Me); 1.65 (t, 4H, CH<sub>2</sub>-7 and 8); 2.22 (t, 2H, CH<sub>2</sub>CONH); 2.34 (t, 2H, CH<sub>2</sub>CO<sub>2</sub>H); 2.91 (br. 1H, part of AB, CH<sub>2</sub>-4); 3.14 (br. 2H, CH<sub>2</sub>-1); 3.62 (br. 2H, CH-2 and part of AB, CH<sub>2</sub>-4); 5.11 (br, 1H, NH); 5.21 (1H, NH); 6.77 (br. 1H, NH); <sup>13</sup>C NMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  24.7 (C-7); 25.3 (C-8); 28.5 (Me); 33.1 (C-3); 33.9 (C-9); 36.1 (C-4); 36.5 (C-6); 44.8 (C-1): 50.1 (C-2): 79.9 (<u>C</u>(Me)<sub>3</sub>): 157.4. 157.5 (NHCO<sub>2</sub>); 173.5 (CO); 176.0 (CO); Anal. Found: C, 55.86; H, 9.00: N.9.21. C<sub>2</sub>0H<sub>3</sub>7N<sub>3</sub>O<sub>7</sub> requires C, 55.67; H, 8.64; N, 9.74 %.

# N,N'-Bis-[3,4-bis(t- butoxycarbonylamino)butyl]hexanediamide (17):

General method: The acid 16 (454 mg, 1 mmol), the isocyanate 8 (289 mg, 0.95 mmol) and DMAP (50 mg) were stirred for 12 h in benzene (70 mL). CHCl<sub>3</sub> (150 mL) was added to dissolve the gelatinous precipitation of the product and of urea. The mixture was washed with 5% citric acid (to remove DMAP), water. 5% aq NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and triturated with EtOAc to remove the unreacted acid. The precipitated compounds were filtered, redissolved in 5% MeOH-CHCl<sub>3</sub> to which silica gel (5 g) was added and the solvent was evaporated. The absorbed silica gel was put onto the top of the column prepared from 10 g of silica gel in CHCl<sub>3</sub>. Elution with 1% MeOH/CHCl<sub>3</sub> removed the urea and the elution with 5% MeOH/CHCl<sub>3</sub> gave 17.

17a: (from 16a 348 mg, 0.80 mmol and 8a 267 mg, 0.81 mmol ) 355 mg, 61%; mp 189-190°C;  $[\alpha]_D^{24}$  +36.1 (c 1.5, EtOH); IR (nujol): 3348, 1681, 1643, 1530 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.2-1.50 (m, 44H. C(Me)3, CH<sub>2</sub>-3, CH<sub>2</sub>-7); 2.02 (t, 4H, CH<sub>2</sub>-6); 2.8-2.9 (m, 6H, CH<sub>2</sub>-1 part of AB, CH<sub>2</sub>-4); 3.06 (m, 2H, part of AB CH<sub>2</sub>-4): 3.45 (br, 2H, CH-2); 6.53 (d, 2H, NH-2); 6.73 (t, 2H, NH-1); 7.67 (t, 2H, NH-4); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  24.9 (C-7); 28.1 (Me); 31.7 (C-3); 35.1 (C-6); 35.7 (C-4); 43.8 (C-1); 48.3 (C-2); 77.4, 77.5 (<u>C</u>(Me)<sub>3</sub>): 155.3, 155.6 (CO<sub>2</sub>): 171.6 (C-5): Anal. Found: C. 56.77; H, 9.05; N, 11.33. C34H64N6O<sub>10</sub> requires C, 56.96; H, 9.00; N, 11.72 %.

17b: (from 16b and 8b) 429 mg, 68%; mp 189-190°C;  $[\alpha]_D^{24}$ -35.9 (c 1.5, EtOH); IR (nujol): 3355, 1680, 1645, 1529 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.2-1.50 (m, 44H, C(Me)<sub>3</sub>, CH<sub>2</sub>-3, CH<sub>2</sub>-7); 2.04 (t, 4H, CH<sub>2</sub>-6); 2.8-2.9 (m, 6H, CH<sub>2</sub>-1 part of AB, CH<sub>2</sub>-4); 3.06 (m, 2H, part of AB CH<sub>2</sub>-4); 3.45 (br, 2H, CH-2); 6.55 (d, 2H, NH-2); 6.70 (t, 2H, NH-1); 7.67 (t, 2H, NH-4); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  24.9 (C-7); 28.1 (Me); 31.8 (C-3); 35.2 (C-6): 35.8 (C-4); 43.7 (C-1); 48.3 (C-2); 77.4, 77.5 (<u>C</u>(Me)<sub>3</sub>); 155.3, 155.7 (CO<sub>2</sub>): 171.6 (C-5):  $\delta$  Anal. Found: C. 56 92; H, 9.21; N, 11.51. C34H64N6O<sub>10</sub> requires C, 56.96; H, 9.00; N, 11.72 %.

17c: (from 16b 511 mg, 1.18 mmol and 8a 397 mg, 1.3 mmol) 585 mg, 69%; mp 200-202°C;  $[\alpha]_D^{24}$  0.0 (c 1.5, EtOH); IR (nujol): 3355. 3334. 1681. 1646. 1530 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.2-1.50 (m, 44H, C(Me)<sub>3</sub>, CH<sub>2</sub>-3, CH<sub>2</sub>-7); 2.8-2.9 (m, 6H, CH<sub>2</sub>-1 part of AB, CH<sub>2</sub>-4); 3.06 (m, 2H, part of AB CH<sub>2</sub>-4); 3.45 (br, 2H, CH-2); 6.53 (d, 2H, NH-2); 6.73 (t, 2H, NH-1); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  25.0 (C-7); 28.3 (Me); 31.8 (C-3); 35.3 (C-6); 35.9 (C-4): 43.9 (C-1); 48.4 (C-2); 77.4, 77.5 (C(Me)<sub>3</sub>); 155.4, 155.8 (CO<sub>2</sub>): 171.6 (C-5): Anal. Found: C. 56.77; H. 8.84; N, 11.66. C<sub>34</sub>H<sub>64</sub>N<sub>6</sub>O<sub>10</sub> requires C, 56.96; H, 9.00; N, 11.72 %.

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