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Synthesis of Chiral 1,2,4-Triaminobutanes

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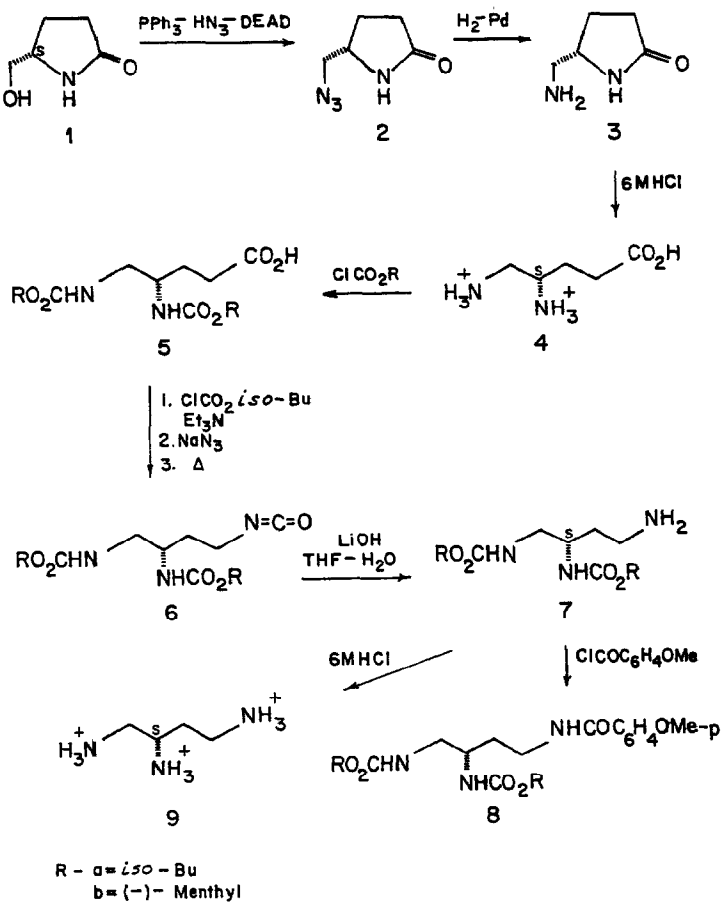
Abstract: (*S*)-5-(Azidomethyl)-2-pyrrolidone, obtained by the Mitsunobu reaction, was reduced to (*S*)-5-(aminomethyl)-2-pyrrolidone which was hydrolysed to (*S*)-4,5-diaminovaleric acid. The acid, after acylation with *t*-butyl or with (1*R*, 3*R*, 4*S*)-menthyl chloroformate, underwent a Curtius reaction yielding the corresponding (*S*)-1,2-dialkoxycarbonyl-1,2,4-triaminobutane. Alternatively, (*S*)-5-(aminomethyl)-2-pyrrolidone was subjected to exhaustive *t*-butoxycarbonylation followed by ring-cleavage with ammonia to give (*S*)-N^4,N^5,N^5-triboc-4,5-diaminovaleramide and was converted by a Hofmann rearrangement to (*S*)-N^1,N^2-di-*t*-butoxy carbonyl-4-methoxycarbonyl-1,2,4-triaminobutane.

Vicinal diamines and triamines are important in chelation chemistry as cis-platinum chelates[1]; they serve as intermediates in the synthesis of ligands used for radiolabelling and imaging[2], and in the synthesis of heteromacrocycles[3]. There are many approaches to the preparation of racemic compounds, but only a few for the enantiomerically pure forms[4]. We have previously described a method for racemic 1,2,4-triaminobutanes, bearing easily and preferentially removable protecting groups[5]. The method was based on Bamberger ring-cleavage[6] of N^w-acyl histamines to substituted (Z)-ene-1,2-dicarbamates, followed by hydrogenation and hydrolysis. When Rh(I) complexes, containing chiral phosphine ligands such as (2*S*, 3*S*) or (2*R*, 3*R*)-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), were used for homo-geneous hydrogenation of substituted 1,2-(1*R*, 3*R*, 4*S*)-dimenthyl carbamates, products with a moderate diastereomeric excess (de) of 40 and 48% respectively were obtained[7]. The need to assign an absolute configuration to the products motivated us to look for a stereospecific synthesis starting from commercially available (*S*)-pyroglutamic acid (5-oxo-L-proline). Amino acids have proven to be a convenient starting material for the synthesis of many chiral compounds[8]. Since Rudinger's synthesis of L-diaminopropionic acid (DAP) in 1960 from aspartic acid[9], boran reduction of amino acid amides was published by Meares in 1979[10], and Otsuka synthesised DAP from serine[11] in 1985. Only recently amino acids have found application in the synthesis of chiral vicinal diamines: Parker performed a borane reduction of lysine amide[3]; Misiti and coworkers, starting from aspartic acid, have prepared (*R*) and (*S*)-3,4-diaminobutyric acid[12]; Reetz reduced benzylaldimines derived from *N,N*-dibenzyl amino acids[4]. Whilst our work was in progress, Frydman at al. reported the synthesis of (*R*) and (*S*)-diaminovaleric acids[13]. Their synthesis involved $NaBH_4$ reduction of (*R*) or (*S*)-5-carbethoxy-2-pyrrolidone to the (*S*)-5-hydroxymethyl derivative, which was transformed *via* the chloride and phthalimide to (4*S*) or (4*R*)- 4,5-diaminovaleric acid.

We have used two different routes to synthesise the chiral 1,2,4-triaminobutane derivatives starting

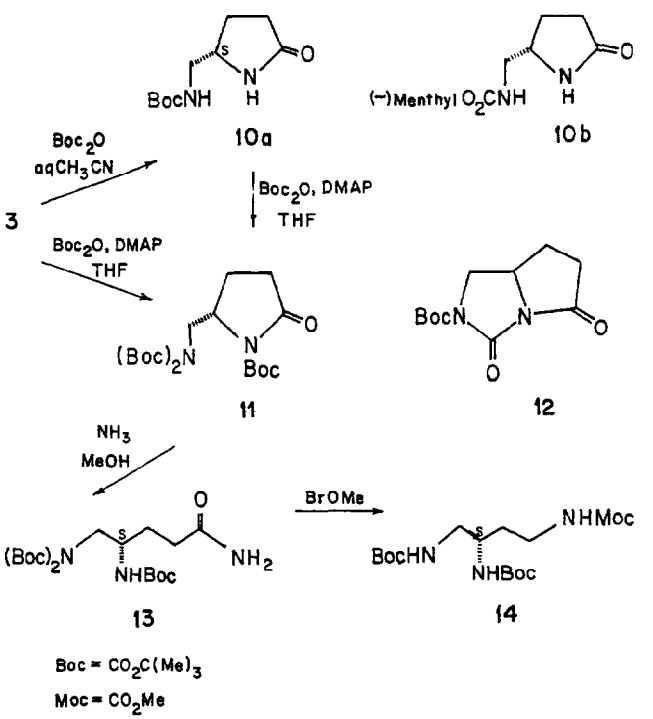
from (*S*)-pyroglutamic acid methyl ester. The ester was reduced to (*S*)-5-(hydroxymethyl)-pyrrolidone[14] (**1**), which was converted, by the Mitsunobu reaction[15] with hydrazoic acid to (*S*)-5-(azidomethyl)-2-pyrrolidone (**2**). The azido group showed the characteristic absorption in the IR at 2104 cm^{-1}. Catalytical hydrogenation converted the azide **2** to (*S*)-5-(aminomethyl)-2-pyrrolidone (**3**), which was further hydrolyzed with 6M HCl to the (*S*)-4,5-diaminovaleric acid (**4**)[13]. The oily amine **3** was characterized as the Boc derivative, **10a**, and as (1*R*, 3*R*, 4*S*)-menthyl carbamate, **10b**. The ^{13}C NMR spectrum of the latter exhibited a single set of signals for the diastereotopic carbons, confirming its optical purity.

The diaminovaleric acid (**4**) was acylated with *iso*-butyl chloroformate, and the *N*4,*N*5-protected amino acid **5**, thus obtained, was converted to the azide by the mixed anhydride procedure and sodium azide. The azide was not isolated; it underwent on heating a Curtius rearrangement which was followed by IR spectra. The acyl azide absorption is at 2155 cm^{-1} while the isocyanate absorbed at 2280 cm^{-1}. The isocyanate was hydrolysed with LiOH (THF + H_2O) to give (*S*)-*N*1,*N*2-di-*iso*-butoxycarbonyl-



1,2,4-triaminobutane (**7a**) which was further acylated with anisoyl chloride to give (*S*)-*N*1,*N*2-di-*iso*-butoxy carbonyl-4-anisoyl-1,2,4-triaminobutane (**8a**). We have also prepared by the same route *N*1,*N*2-di-(-)-menthyloxycarbonyl-*N*4-anisoyl-1,2,4-triaminobutane (**8b**). The ^{13}C NMR spectrum of the latter showed a single signal for each carbon of the butane skeleton, consistent with the optical purity of the compound. We required the two triaminobutane derivatives **8a** and **8b** for comparison, using NMR and optical rotation, with the compounds obtained before by homogeneous hydrogenation of substituted ene-1,2-dicarbamates[7]. If instead of acylating the di-*iso*-butoxycarbonyl derivative **7** with anisoyl chloride, we hydrolysed it with 6M HCl, (*S*)-1,2,4-triaminobutane trihydrochloride (**9**) was obtained. The racemic **9** has been previously prepared by Windaus[16].

The alternative procedure to synthesise derivatives of the chiral triaminobutane, which does not involve the intermediacy of the free (S)-4,5-diaminovaleric acid (**4**), was to exhaustively acylate[17,18] (S)-(5-aminomethyl)-2-pyrrolidone (**3**) with Boc_2O. A one step exhaustive acylation of (**3**) in the presence of a catalytic amount of dimethylaminopyridine (DMAP), gave a 51% yield of the (S)-5-(di-Boc-aminomethyl)-*N*1-Boc-2-pyrrolidone **11**, accompanied by the bicyclic compound **12** (25%). The formation of **12** could be avoided when *t*-butoxycarbonylation was carried out in two steps. We first prepared the 5-(Bocaminomethyl)-2-pyrrolidone **10a**, applying the standard Schotten-Baumann reaction procedure, and then further acylated it under anhydrous conditions using Boc_2O in the presence of DMAP. The tri-Boc derivative **11** reacted with NH_3 in methanol at room temperature, undergoing selective cleavage[17,19] to *N*4,*N*5,*N*5- tri-Boc-4,5-diamidovaleramide **13**, which was converted by the Hofmann rearrangement (Br_2 + NaOMe in MeOH), at low temperature, to the crystalline *N*1,*N*2-di-Boc-*N*4-Moc-1,2,4-triaminobutane (**14**), with a 68% yield.



The IR spectrum **14** showed one carbonyl absorption of the carbamate group at 1705 cm^{-1}. **8a** and **8b** exhibited, in addition to the carbamate, an amide CONH band at 1640 cm^{-1}. The CO stretching bands of the cyclic tri-Boc **11** appeared at 1780 (s), 1740 (s) and 1690 cm^{-1} and those of the open-chain tri-Boc-amide, at 1785 (w), 1720 (sh), and at 1690 (br, s) cm^{-1}. The highest carbonyl absorptions, at 1810 and 1800 cm^{-1}, were observed in the spectrum of the bicyclic compound **12** in addition to the bands at 1735 (sh) and 1707 cm^{-1} .

The ^{1}H NMR spectra of the cyclic compounds **1** and **3** (D_2O), **2**, **10a** and **10b** ($CDCl_3$) showed a distinct pattern of the proton at the stereogenic center at C-2 and of the enantiotopic methylene protons at C-1, C-3 and C-4 as multiplets of sharp signals. The assigment of the chemical shifts was possible on the basis of ^{1}H - ^{13}C correlated spectra. In the spectra of the open-chain *N*^{1},*N*^{2},*N*^{4}-1,2,4-triacylated compounds **8a**, **8b** and **14** a broadening was observed, caused by bulky carbamates which imposed a steric hindrance ; the broadening was much more pronounced for **8b** (R' = (-)-menthyl). According to the ^{1}H- ^{13}C correlated spectra, the methylene protons at C-4 exhibited the most pronounced diastereotopicity. In the spectra of *N*^{1},*N*^{2}-diacylated compounds **5a**, **5b** and **7**, broadening was observed as well while the diastereotopicity of the geminal protons at C-4 was diminished. After removal of the acyl groups sharp signals emerged again in the spectrum of (S)-4,5-diaminovaleric acid dihydrochloride (**4**) and (S)-1,2,3-triaminobutane (**9**) (D_2O).

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a 257 Perkin Elmer spectrophotometer. ^{1}H and ^{13}C NMR were measured on a ACF Bruker 200 MHz and a AM 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, the Hebrew University, Jerusalem. TLC was performed on Merck silica gel 60 F_{256}, and flash chromatography on silica gel (Merck, 70 - 230 mesh). (S).-Pyroglutamic acid (L-5-oxo-proline) was obtained from Merck - Schuchardt.

(*S*)-5-(Hydroxymethyl)-2-pyrrolidone (1):

1 was prepared by the modification of Silverman and Levy's procedure[14]. $LiBH_4$ (1g 0.047mol) was added in small portions into a solution of (S)-pyroglutamic acid methyl ester (6.16 g 0.043 mmol) im MeOH (75 mL) at -10°C under N_2. The reaction was left overnight at room temperature, quenched with 20% AcOH (40 mL) and evaporated to dryness The residue was crushed and stirred overnight with $CHCl_3$ (200 mL). The extract was concentrated to a small volume, put on a silica gel column (40 g) and eluted with $CHCl_3$-MeOH (9·1) yielding 7.6g (80%) of **1**, mp 68-69°C, lit.[14] 68°; lit.[13] oil.; $[\alpha]_D^{25}$ +28 (c 5, EtOH), lit.[14] +29 (EtOH); lit.[13] +24 (MeOH); ^{1}H NMR ($CDCl_3$): δ 1 6 - 1 8 (m, 1H, AB part of ABCD, CH_2), 2 0 - 2 2 (m, 1H, AB part of ABCD, CH_2); 2.25 - 2.35 (m, 2H CH_2CO); 3 35 (dd, 1H, AB part of ABX, CH_2O), 3.63 (dd, 1H, AB part of ABX, CH_2O); 3 7 - 3.8 (m, 1H, CH); 4 35 (br, 1H, OH); 7 45

(s, 1H, NH); CIMS: *m/z* 231 $[2MH]^+$ (100%), 116 $[MH]^+$ (58%). $C_5H_9N_2O_2$ requires 115.

(S)-5-(Azidomethyl)-2-pyrrolidone (2):

1 (3.28 g, 0.028 mol) and triphenylphosphine (9 g, 34 mmol) were dissolved in dry THF (20 mL) and cooled in an ice bath. 1.2M Benzene solution of HN_3 (34 mmol, 30 mL) and diethyl azodicarboxylate (5.3 g, 30 mmol) were added and the mixture stirred for 30 min at - 10°C, for 2 h at 0°C and overnight at room temperature. The solvents were evaporated, the residue redissolved in $CHCl_3$ (30 mL) and put on a silica gel column (200 g). Triphenylphosphine oxide and diethyl hydrazodicarboxylate were eluted with $CHCl_3$, the azide 2 with $CHCl_3$-MeOH (19:5), 3.0 g (75%): mp 63-64°C; $[\alpha]_D^{25}$ + 73.7 (c 5, EtOH); IR ($CHCl_3$): 2104 cm-1; ^1H NMR ($CDCl_3$): δ 1.72 (m, 1H, AB part of ABCD); 2.21(m, 1H, AB part of ABCD); 2.1 - 2.4 (m, 2H, CH_2CO); 3.12 (dd, 1H, AB part of ABX, CH_2N_3); 3.36 (dd, 1H, AB part of ABX, CH_2N_3); 3.70 (q, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 23.6 (C-2); 29.6 (C-3); 53.4 (C-5); 55.5 (C-6); 178.5 (C-2); CIMS: *m/z* 281 $[2M+H]^+$ (3%), 141 $[MH]^+$ (100%). $C_5H_8N_4O$ requires 140.

(*S*)-5-(Aminomethyl)-2-pyrrolidone (3):

2 (700 mg) was hydrogenated with 10% Pd on charoal (100 mg) in EtOH (50 mL), in a Parr apparatus at 40 psi for 6 h., yielding quantitatively 3 as an oil, $[\alpha]_D^{25}$ + 37.2 (c 2, EtOH); ^1H NMR (D_2O): δ 1.2 and 1.5 (m, 2H, CH_2-4); 1.3-1.7 (m, 2H, CH_2CO); 1.9 (dd, 1H, AB part of ABX) and 2.1(dd, 1H, AB part of ABX, CH_2N); 2.93 (q, 1H, CHN); ^{13}C NMR (D2O): δ 29.2 (C-4); 35.0 (C-3); 52.1 (C-6); 61.8 (C-5); 183.4 (CO); HRMS: *m/z* 114.0792 $[M]^+$ (2.8%); 97.0537 $[M - NH_3]^+$ (39.3%); 85.0492 $[M - CH_2NH_2]^+$ (86.6%); 84.0422 $[M - CH_3NH_2]^+$ (100%). $C_5H_{10}N_2O$ requires 114.07931.

(4S)-4,5-Diaminovaleric acid dihydrochloride (4):

3 (310 mg) was dissolved in 15 mL of 6M HCl and heated under reflux for 15 h, evaporated to dryness in vacuo and crystallized from MeOH-ether, to yield 4 (550 mg, 83%); mp 200-201°C, lit.[13] 180-181°C; $[\alpha]_D^{25}$ - 8.4 (c 2, water), lit.[13] $[\alpha]_D^{20}$ - 4.6 (water); ^1H NMR (D_2O): δ 1.80-2.00 (m, 2H, CH_2-3); 2.43 (t, 2H, CH_2-2); 3.16 (d, 2H, CH_2-5); 3.52 (q, 1H, CH-4). 13C NMR (D2O): δ 27.6 (C-3); 31.7 (C-2); 43.2 (C-5); 51.4 (C-5); 178.8 (C-1). Anal. Found: C, 30.27; H, 6.79; N, 13.34. C5H14N2Cl2 requires: C, 29.29; H, 6.88; N, 13.66%.

(*S*)-*N*^{4},*N*^{5}-Di-*i*-butoxycarbonyl-4,5-diaminovaleric acid (5a):

4 (186 mg, 0.9 mmol) was dissolved in 1 mL of water, neutralized with 1M KOH (2.7 mL) and cooled in an ice-bath. Simultanously, from two separate funnels, *iso*butyryl chloroformate (361 mg, 2,7 nmol) in THF (4mL) and 1M KOH (2.7 mL) were slowly added. The mixture was stirred for 1 h at 0°C and overnight at room temperature. THF was removed in vacuo and the water layer extracted with EtOAc to remove neutral impurities. The water layer was acidified with 2M HCl and extracted with EtOAc. The extract was dried (Na_2SO_4) and concentrated, giving 267 mg (88%) of 5a mp 98-100°C (recrystallized from EtOAc-hexane); $[\alpha]_D^{25}$ - 10.2 (c 2, EtOH); IR ($CHCl_3$): 1720 cm-1; ^1H NMR ($CDCl_3$): δ 0.88 (d, 12 H, Me); 1.60-1.69 (m, 4 H, CH_2 and CH); 2.42 (m, 2H, CH_2CO); 3.25 (m, 2H, CH_2N); 3.6-3.8 (m, 5H, CH_2O and CHN); 5.16 (br, 2H, NH); Anal. Found: C, 54.40; H, 8.53; N, 8.79. $C_{15}H_{28}N_2O_6$ requires: C, 54.20; H, 8.49; N, 8.40%.

(*S*)-*N*^{1},*N*^{2}-Di-*i*-butoxycarbonyl-1,2,4-triaminobutane (7a):

Iso-butyl chloroformate (94mg) was added into a mixture of **5a** (200 mg, 0.6 mmol) and Et_3N (72 mg) in dry THF (4 mL) at 0°C. After 1 h, NaN_3 (650 mg) in 1.6 mL of water was added and the reaction mixture stirred for 30 min at 0°C. EtOAc (20 mL) was added. The organic layer was separated, washed once with water, dried (Na_2SO_4), concentrated and dried in vacuo at room temperature for 3 h. The IR ($CHCl_3$) of the crude acyl azide had an absorption at 2155 cm^{-1}. The residue was redissolved in benzene (20 mL) and heated at 60°C for 1h showing in IR ($CHCl_3$) absorption at 2280 cm^{-1} of the rearranged isocyanate. The benzene was evaporated and the residue redissoved in THF (6 mL) to which $LiOH{\cdot}H_2O$ (100 mg) in water (6 mL) was added and the mixture stirred overnight at room temperature. EtOAc (25 mL) was added, the organic layer was separated, washed twice with water, dried (Na_2SO_4) and concentrated, yielding 114 mg (62%) of **7a**; mp 149-150°C, $[\alpha]_D^{25}$ - 4.2 (c 1, EtOH); IR ($CHCl_3$): 1700, 1680sh, 1500-1540 br cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (d, 12H, Me); 1.62 (m, 2H, CH_2-3); 1.90 (m, 2H, CH); 1.97 (br, 2H, NH_2); 2.76 (t, 2H, $C\underline{H}_2NH_2$); 3.22 (br, 2H, CH_2N-1); 3.76 (d, 4H, CH_2O + br m, 1H, CHN-2); 5.42 (br, 1H, NH-1); 5.54 (br, 1H, NH-2); CIMS: *m/z* 304 $[MH]^+$ (100%); HRMS: *m/z* 304.2260 $[MH]^+$ (0.7%); 186.1369 $[M - NH_2CO_2C_4H_9]^+$ (16%); 173.1283 $[M - CH_2NHCO_2C_4H_9]^+$ (31.7%); 144.1040 $[M - C_7H_{11}N_2O_2]^+$ (100%). $C_{14}H_{29}N_3O_4$ requires 303.2158.

(S)-*N*^{1},*N*^{2}-Di-*i*-butoxycarbonyl-*N*^{4}-anisoyl-1,2,4-triaminobutane (8a):

6 (69 mg, 0.22 mmol), Et_3N (40.4 mg 0.4 mmol) and anisoyl chloride (60 mg, 0.35 mmol) were stirred in dry THF (3mL) at 0°C for 3 h. THF was evaporated, the residue was redissolved in EtOAc and stirred with 10% Na_2CO_3 (5mL) overnight to remove anisic acid. The organic layer was separated, washed with water, dried and purified on preparative silica gel TLC. Elution was performed with 70% EtOAc-hexane. **8a** was extracted from silica with 5% MeOH-EtOAc (70 mL) giving 79 mg (78%) , mp 105-107°C (from EtOAc-hexane); $[\alpha]_D^{25}$ - 37.2 (c 3.6, EtOH); IR ($CHCl_3$): 1700, 1640, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$); δ 0.83 (d, 6H, Me); 0.87 (d, 6H, Me); 1.5 (m, 1H, part of AB, CH_2-3); 1.7 - 1.9 (m, 3H, part of AB, CH_2-3 and $CH(Me)_2$); 3.04 (m, 1H, part of AB, CH_2-4); 3.23 (br s, 2H, CH_2N-1); 3.75 (m, 1H, CHN); 3.79 (s, 3H, Me); 5.34 (br, 1H, NH-1); 5.53 (d, 1H, NH-2); 6.86 (d, 2H, arom); 7.84 (s, 1H NH-4); 7.78 (dd, 2H, arom); ^{13}C NMR (CDCl3): δ 18.9 (Me), 27.9 (CH); 32.7 (C-3); 36.0 (C-4); 44.8 (C-1); 50.2 (C-2); 71.3 (CH_2O); 113.4 (C-arom), 126 7 (C-arom); 128.7 (C-arom); 157.9 (CO_2); 162.0 (C-arom); 166.8 (CO); CIMS: *m/z* 438 $[MH]^+$ (100%). Anal. Found: C, 60.54; H, 7.98; N, 9.38. $C_{22}H_{35}N_3O_6$ requires: C, 60.39, H, 8.06; N, 9.60%.

(*S*)-*N*^{4},*N*^{5}-Di-(1*R*,3*R*,4*S*-)-menthyloxycarbonyl-4,5-diaminovaleric acid (5b):

4 (307mg,1.5mmol) was dissolved in a mixture of water (7mL) and THF (10 mL), neutralized with 1M KOH (4.5 mL) and cooled in an ice bath. (-)Menthyl chloroformate (1.3g, 6 mmol) in THF (10 mL) and 1M KOH (6 mL) were slowly added from two separate funnels. The mixture was stirred for 2 h at 0°C and overnight at room temperature. THF was evaporated .To thesparingly soluble potassium salt of **5b** EtOAc (50 mL) and 2M HCl (10 mL) were added and the mixture stirred for 12 h. The organic layer was separated, washed 3 times with water, dried and concentrated. The residue was triturated with 20% EtOAc-hexane (10 mL) to remove menthol and dimenthyl carbonate, and recrystallized from EtOAc-hexane, giving 380mg (51%) of **5b**, mp 171°C; $[\alpha]_D^{25}$ - 90.0 (c 1, EtOH); IR 1700 cm^{-1}; ^{1}H NMR

($CDCl_3$): δ 0.76 (d, 6H, Me); 0.86 (d,12H, Me); 0.98-2.02 (m, 20H, CH_2 and CH); 2.34 (m, 2H, CH_2CO); 3.1-3.4 (m, 2H, CH_2N); 3.75 (m, 1H, CHN); 4.51 (m, 2H, CHO); 5.05 (m, 2H, NH); CIMS: *m/z* 497 $[MH]^+$ (100%); 315 $[M - CO_2C_{10}H_{19}]^+$ (25%); 296 $[M - NH_2CO_2C_{10}H_{19}]^+$ (18%). $C_{27}H_{48}N_2O_6$ requires 496.

(*S*)-N^1,N^2-Di-(1*R*, 3*R*, 4*S*-)-menthyloxycarbonyl-N^4-anisoyl-1,2,4-triaminobutane (8b):

iso-Butyl chloroformate (110 mg, 0.81 mmol) was added into the mixture of **5b** (333 mg, 0.67 mmol) and Et_3N (81 mg, 0.81 mmol) in dry THF (10 mL) at 0°C and the reaction mixture was stirred for 30 min. NaN_3 (859 mg) in 2 mL of water was added to the mixed anhydride and the stirring continued for 1 h. THF was evaporated in vacuo, EtOAc (20 mL) was added, the organic layer was washed twice with water, dried (Na_2SO_4) and concentrated, showing the presence of acyl azide (IR ($CHCl_3$): 2140, 1704 cm-1). The azide was rearranged to the isocyanate by heating in benzene (10mL) for 1 h at 60°C (IR ($CHCl_3$): 2280, 1705 cm-1). The benzene was evaporated and the isocyanate was hydrolyzed with $LiOH{\cdot}H_2O$ (980 mg) in a mixture of THF (6 mL) and water (6mL), by stirring at room temperature for 12 h. EtOAc (50 mL) was added and the organic layer was washed twice with water, dried and concentrated. **5b** (131 mg, 39%) was recovered from the water layer, after acidification. The crude amine **8b** (211mg,) and Et_3N (94 mg) were dissolved in dry THF (5mL) and cooled in an ice bath. At this point anisoyl chloride (88 mg) was added and the reaction mixture was left overnight at room temperature. The THF was evaporated and the residue redissolved in a mixture of EtOAc (50 mL) and 5% Na_2CO_3 (20 mL) and stirred for 6 h to remove most of the anisic acid. The organic layer was separated, washed twice with water, dried, concentrated and the crude product was put on two preparative silica gel TLC plates and eluted with 70% EtOAc-hexane. It was extracted from the plates with 5% MeOH-EtOAc yielding 165 mg (41%) of **8b**, mp 199-201°C (recrystallized from benzene). IR ($CHCl_3$): 1700, 1640, 1605 cm-1; ^1H NMR ($CDCl_3$): δ 0.73 (d, 6H, Me), 0.86 (d, 12H, Me); 0.9-2.1 (m, 20H, CH_2 and CH of the cyclohexane ring and at 1.5 and 1.7 CH_2-3); 3.2-3.3 (m, 2H, CH_2N-1), 3.0 and 3.8 (m, 2H, CH_2N-4); 3.7 (m, 1H, CHN-2); 3.81(s, 3H, MeO); 4.48-4.58 (m, 2H, CHO); 4.99 (br, 1H, NH-1); 5.43 (d, 1H, NH-2); 6.89 (d, 2H, arom); 7.45 (br, 1H, NH-4); 7.81 (d, 2H, arom); ^{13}C NMR ($CDCl_3$): δ 16.4 (C-10'), 20.7 and 20.8 (C-9'); 22.0 (C-7'); 23.4 and 23.5 (C-5'); 26.1 and 26.2 (C-8'); 31.4 (C-1'); 32.9 (C-3); 34.2 (C-6'); 36.1 (C-4); 41.2 and 41.3 (C-2'); 45.0 (C-1); 47.2 (C-4'); 49.6 (C-2); 55.1 (OMe); 75.0 and 75.2 (C-3'); 113.6 (C arom); 126.7 (C arom); 128.8 (C arom); 157.4 (CO_2); 162.0; (C arom); 166.8 (CO). CIMS: *m/z* 602 $[MH]^+$ (100%); $C_{34}H_{55}N_3O_6$ requires 601. Anal. Found: C, 67.57; H, 9.00; N, 6.92; $C_{34}H_{55}N_3O_6$ requires C, 67.85; H, 9.21; N, 6.98.

(*S*)-1,2,4-Triaminobutane trihydrochloride (9):

6 (60.6 mg, 0.2 mmol) was refluxed for 10h in 6M HCl (4 mL). The acid was evaporated in vacuo and the hydrochloride **9** recrystallized from EtOH yielding 35mg (83%); mp 222-224°C; $[\alpha]_D^{25}$ - 2.3 (c 2, water); ^1H NMR (D_2O): δ 1.9–2.1 (m, 2H, CH_2-3); 2.9-3.0 (m, 2H, CH_2N-4); 3.16 (d, 2H, CH2-1);13C NMR (D2O): δ 30.7 (C–2); 38.0 (C–4); 43.2 (C–1); 49.7 (C–2). Anal. Found: C, 22.84; H, 7.40; N, 19.41; $C_4H_{16}Cl_3N_3$ requires: C, 22.58; H, 7.58; N, 19.76%. The picrate had a mp of 235°C (dec).

(*S*)-5-(*t*-Butoxycarbonylaminomethyl)-2-pyrrolidone (10a):

Di-*tert*-butyl dicarbonate (305 mg, 1.4 mmol) was added to a soluton of the amine **3** (50mg, 0.7mmol) in a mixture of water (5mL) and CH_3CN (5mL) in an ice bath. The reaction was stirred at 0°C for 1 h and overnight at room temperature. The CH_3CN was evaporated, the residue redissolved in EtOAc (20mL), washed once with water, dried, concentrated and put on a silica gel column (5g). Impurities were eluted with a mixture of EtOAc-hexane 2:3. **10a** was eluted with EtOAc and obtained as an oil, 70mg (75%); $[\alpha]_D^{25}$ + 13.6 (c 3.8, EtOH); IR ($CHCl_3$): 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H, Me); 1.74 (m, 1H, AB part of ABCDX); 2.15 (m, 1H, AB part of ABCDX); 2.30 (m, 2H, CH2CO); 3.05 (m, 1H, AB part of CH_2N); 3.28 (m, 1H, AB part of CH_2N); 3.74 (m, 1H, CHN); 5.36 (br, 1H, NH); 7.05 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 24.1 (C-4); 28.3 (Me); 30.0 (C-3); 45.3 (C-6); 54.7 (C-5); 79.7 ($\underline{C}Me_3$)); 156.2 (CO_2); 178.5 (CO); HRMS: *m/z* 214.1262 $[M]^+$ (0.2%) ; 141.0645 $[M - OCMe_3]^+$ (71.5%); 97.0504 $[M - NH_2CO_2CMe_3]^+$ (100%). $C_{10}H_{18}N_2O_3$ requires 214.1317. Anal. Found: C, 54.19; H, 8.47; N, 12.49. $C_{10}H_{18}N_2O_3 \cdot 1/2H_2O$ requires: C, 53.81; H, 8.52; N, 12.55%.

(*S*)-5-[(1*R*, 3*R*, 4*S*)-Menthyloxycarbonylaminomethyl)]-2-pyrrolidone (10b):

(1R, 3R, 4S)-Menthyl chloroformate (1.09g, 5 mmol) in CH_3CN (10 mL) and $NaHCO_3$ (250 mg) in water (5 mL) were slowly added from separate funnels into a solution of the amine **3** (390 mg, 3.42mmol) in CH_3CN (20 mL) at 0°C. The mixture was stirred for 1 h at 0°C and overnight at room temperature. The CH_3CN was removed in vacuo and EtOAc (20 mL) was added. The organic layer was washed with water, dried and concentrated. The residue was triturated with hexane, yielding 970 mg (96%) of **10b**; mp 135°C; $[\alpha]_D^{25}$ - 59.3 (c 2, EtOH); ^1H NMR ($CDCl_3$); δ 0.73 (d, 3H, Me), 0.85 (d, 3H, Me), 0.87 (d, 3H, Me); 0.9 - 2.2 (m, 9H, cyclohexyl H); 1.7-1.8 (m, 1H, part of AB, CH_2-4); 2.1-2.2 (m, 1H, part of AB, CH_2-4); 2.20(t, 2H, CH_2CO); 3.07 (q,1H, part of AB, CH_2N); 3.5-3.6 (br, 1H, part of AB, CH_2N); 3.76 (m, 1H, CHN); 4.49 (m, 1H, CHO); 5.58 (br, 1H, NH); 7.19 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.4 (C-10'); 20.7 (C-9'); 22.0 (C-7'); 23.4 (C-5'); 24.0 (C-8'); 26.2 (C-4); 30.0 (C-1'); 31.3 (C-3); 34.2 (C-6'); 41.4 (C-2'); 45.7 (C-4'); 47.3 (C-6); 54.8 (C-5); 74.7 (C-3'); 156.2 (CO_2); 178.6 (CO); CIMS: 297 $[MH]^+$ (100%); 159 $[M - C_{10}H_{18}]^+$ (15%); Anal. Found: C, 65.35; H, 9.48; N, 9.38. $C_{16}H_{27}N_2O_3$ requires C, 65.05; H, 9.21; N, 9.48%.

(S)-5-[(Di-*t*-butoxycarbonyl)aminomethyl]-1-*t*-butoxycarbonyl-2-pyrrolidone (11):

A. **10a** (302 mg, 1.4 mmol), di-*tert*-butyl dicarbonate (732 mg, 3.36 mmol) and DMAP ((34 mg, 0.28 mmol) were dissolved in dry CH_3CN and stirred for 1h at 0°C. The reaction was left at room temperature for 48 h. CH_3CN was evaporated, the residue redissolved in minimum volume of EtOAc and put on a silica gel column (15g), prepared in hexane. The unreacted dicarbonate was eluted with hexane; **11** (413 mg, 70%) was eluted with 20% EtOAc-hexane, mp 98-99°C; $[\alpha]_D^{25}$ - 47.5 (c 2.5, EtOAc); IR ($CDCl_3$) 1780, 1740, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4-1.8 (27H, Me); 1.9-2.2 (m, 2H, CH_2-4); 2.3-2.7 (m, 2H, CH_2CO); 3.85 (d, 2H, CH2N); 4.43 (m, 1H, CHN); Anal. Found: C, 58.20; H, 8.22; N, 6.56. $C_{20}H_{34}N_2O_7$ requires: C,57.95; H, 8.26; N, 6.75%.

B. **3** (570 mg, 5 mmol) and di-*tert*-butyl dicarbonate (3.85 g, 17.7 mmol) were dissolved in CH_3CN (35 mL) at 0°C and stirred for 1h until the vigorous evolution of CO_2 ceased. DMAP (122 mg, 1mmol) was added and the reaction mixture left for 48h. The CH_3CN was evaporated, the residue redissolved in EtOAc

(50 mL), washed once with 5% $NaHSO_4$ and once with water. It was dried, concentrated and put on a silica gel column (25 g) prepared in hexane. The unreacted dicarbonate was eluted with hexane, **11** (1.06 g, 51%) was eluted with 20% EtOAc-hexane. EtOAc eluted the condensed bicyclic **2-pyrrolidinoimidazolidone 12** (320 mg, 25%) ; mp 132°C (recrystalized from EtOAc-hexane); IR ($CHCl_3$) 1815, 1800, 1735sh, 1707 cm^{-1}. $[\alpha]_D^{25}$ + 41.6 (c 1, EtOH) (no change in IR was observed after the sample was allowed to stand for 5 h at room temperature in EtOH); $[\alpha]_D^{25}$ + 61.4 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H, Me); 0.91 (m, 1H, AB part of ABXY, CH_2-4); 2.40 (m,q, 1H, AB part of ABXY, CH_2-4); 2.5-2.8 (m, 2H, CH_2CO); 3.50 (t, 1H, AB part of ABX, CH_2N); 4.03 (dd, 1H, AB part of ABX, CH_2N); 4.36 (m, 1H, CHN); ^{13}C NMR ($CDCl_3$): δ 27.9 (Me); 28.1 (C-4); 35.2 (C-3); 49.6 (CH_2N); 52.4 (CHN); 83.6 (C-O); 146.4 (NCON); 150.0 (CO_2); 180.0 (CON). Anal. Found: C, 55.21; H, 6.63; N, 11.52. $C_{11}H_{16}N_2O_4$ requires C, 54.19; H, 6.71; N, 11.65%. CIMS: *m/z* 241 $[MH]^+$ (0.3%); negative-ion spectrum: *m/z* 239 $[M-H]^-$ (100%).

(*S*)-*N*5,*N*5,*N*4–Tri-*t*-butoxycarbonyl-4,5-diaminovaleramide (13):

10 (400 mg, 0.96 mmol) was dissolved in a solution of 11% NH_3 in MeOH (25 mL) and left at room temperature for 5 days. The solvent was evaporated and the residue redissolved in EtOAc, washed twice with water, dried, concetrated and put onto a silica gel column (12 g) prepared in hexane. Impurities were removed with hexane. Elution with 70% EtOAc-hexane gave **13** as an oil (320 mg, 77%). IR ($CHCl_3$): 1785, 1725, 1690 cm^{-1}; ^1H NMR ($CHCl_3$): δ 1.38 (s, 9H, Me); 1.46 (s, 18H, Me); 1.4-1.6 (m, 2H, CH_2); 2.2-2.4 (m, 2H, CH_2CO); 3.5-3.7 (m, 2H, CH_2N); 3.85 (m, 1H, CHN); 4.95 (d, 1H, NH); 5.52 (s, 1H, NH); 6.63 (s, 1H, NH); CIMS: *m/z* 432 $[MH]^+$ (10%); 332.2 $[MH - CO_2C(Me)_3]^+$ (100%). $C_{20}H_{37}N_3O_7$ requires 431.52.

(*S*)-*N*1,*N*2-Di-*t*-butoxycarbonyl-*N*4-methoxycarbonyl-1,2,4-triaminobutane (14):

The amide **13** (298 mg, 0.67 mmol) in dry THF (3 mL) was slowly added into a BrOMe solution prepared from Na (47.4 mg, 2.03 mmol) and Br_2 (35.5 μL, 0.69 mmol) in absolute MeOH (3 mL) at - 78°C, under Ar. The mixture was stirred at - 78°C for 15 min, warmed to room temperature and heated for 30 min at 60°C. The MeOH was removed in vacuo, ether (30 mL) and water (30 mL) were added, the ether layer was washed twice with water, dried and concentrated. The residue was dissolved in 2.5 mL of EtOAc put onto a silica gel column (8 g) prepared in hexane. Elution with 30% EtOAc-hexane gave **14** (198 mg, 68%); mp 136°C; $[\alpha]_D^{25}$ - 30.3 (c 2, EtOH); IR ($CHCl_3$): 1705 cm^{-1}; ^1H NMR (CDCl3) δ 1.35 (s, 18H, Me); 1.37-1.63 (m, 2H, CH_2-3); 2.9 (m, 1H, part of AB, CH_2N-4); 3.0-3.2 (m, 2H, CH_2N-1); 3.38 (m, 1H, part of AB, CH_2N-4);3.57 (s, 3H, OMe); 3.61 (m, 1H, CHN-2); 5.05 (br, 1H, NH-1); 5.13 (d, 1H, NH-2); 5.68 (br, 1H, NH-4); ^{13}C NMR ($CDCl_3$): δ 28.2 (Me); 33.2 (C-3); 37.4 (C-4); 44.4 (C-1); 49.4 (C-2); 51.8 (OMe); 79.4 (CMe_3); 156.7 (CO_2); 157.1 (CO_2); CIMS: *m/z* 362 $[MH]^+$ (60%); Anal. Found: C,52.90; H,8.41; N, 11.78. $C_{16}H_{31}N_3O_6$ requires: C, 53.17; H, 8.64; N, 11.62%.

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References

1. Lippard, S. J. *Pure Appl. Chem.* **1987**, *59*, 731
   Pasini, A., Zunino, F. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 615.
   Reedijk, J. *Pure Appl. Chem.* **1987**, *39*, 181.
2. Sundberg, M. W., Meares, C. F., Goodwin, D. A., Diamanti, C. I. *J. Med. Chem.* **1974**, *17*, 1304.
   Kung, H. F., Guo, Y. Z., Yu, C. C., Billigs, J., Subramanyam, W., Calabrese, J. C. *J. Med. Chem.* **1989**, *32*, 433.
   Gustavson, L. M., Rao, T. N., Jones, D. S., Fritzberg, A. R. *Tetrahedron Lett.* **1991**, *32*, 5485.
3. Cox, J. P. L., Craig, A. S., Helps, I. M., Jankowski, K. J., Parker, D., Eaton, M. A. W., Millickan, A. T., Millar, K., Beeley, N. R. A., Boyce, B. A. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2567.
4. Zhu, J., Quirion, J. C., Husson, H. P. *Tetrahedron Lett.* **1989**, *30*, 5137.
   Bruni, E., Cardillo, G., Orena, M., Sandri, S., Tomasini, C. *Tetrahedron Lett.* **1989**, *30*, 1679.
   Reetz, M. T., Jaeger, R., Drewlies, R., Hubel, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103.
5. Altman, J., Schuhmann, E., Karaghiosoff, K., Eichin-Karaghiosoff, E., Beck, W. *Z. Naturforsch.* **1991**, *46b*, 1473.
6. Bamberger, E. *Liebigs Ann. Chem.* **1893**, *273*, 267.
7. Altman, J., Ben-Ishai, D., Berkovich, E. submitted for publication.
8. Coppola, G. M., Schuster. *H. F.* Asymmetric Synthesis, John Wiley & Sons, New York, 1987.
9. Rudinger, J., Poduska, K., Zaoral, M. *Collect. Czech. Chem. Commun.* ***1960***, *25*, 2022.
10. Yeh, S. M., Sherman, D. G., Meares, C. F. *Anal. Biochem.* **1979**, *100*, 152.
11. Otsuka, M., Kittaki, A., Iimori, T., Yamashita., Kobayashi, S., Ohmo, M. Chem. Pharm. Bull. **1985**, *33, 509.*
12. Misiti, D., Santaniello, M., Zappia, G. *Synth. Commun.* **1992**, 883.
13. Valasinas, A., Frydman, B., Friedmann, H. C. *J. Org. Chem.* **1992**, *57*, 2158.
14. Silverman, R., B., Levy, M., A. *J. Org. Chem.* **1980**, *45*, 815.
15. Mitsunobu, O. *Synthesis*, **1981**, 17.
16. Windaus, A., Doerries, H., Jensen, H. *Chem. Ber.* **1921**, *54*, 2745.
17. Flynn, D. L., Zelle, R. E., Grieco, P., A. J. *Org. Chem.* **1983**, *48*, 2424.
18. Grehn, L., Gunnarson, K., Ragnarsson, U. *Acta Chem. Scand., Ser. B*, **1986**. *40*, 745.
19. Grehn, L., Gunnarson, K., Ragnarsson, U. *Acta Chem. Scand., Ser. B*, **1987**,*41*, 18.