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Selectively Protected Chiral 1,2,4-Triaminobutanes and Chiral Vicinal 1,2-Diamines

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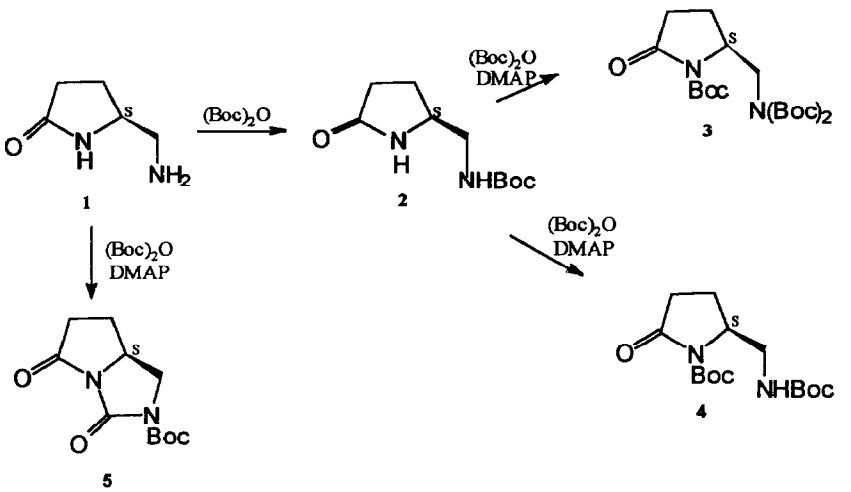
Abstract: Stepwise *t*-butoxycarbonylation of (S)-5-aminomethyl-2-pyrrolidone to mono-, di- and tri-acylated compounds has been elaborated. Ring opening of (S)-5-(Boc-aminomethyl)-N^1-Boc-2-pyrrolidone with LiOH afforded the Boc-protected 4,5-diaminovaleric acid, whereas with $NaBH_4$ the Boc-protected (S)-4,5-diamino-pentanol was obtained. The acid underwent Curtius rearrangement to the corresponding isocyanate which was transformed to (S)-N^1,N^2-di-Boc-1,2,4-triaminobutane and to N^1,N^2-di-Boc-N^4-Z-triaminobutane. Curtius rearrangement of (S)-N^4,N^5-di-Z-valeric acid and *p*TSA catalyzed addition of *t*-BuOH to the isocyanate, yielded N^1,N^2-di-Z-N^4-Boc-1,2,4-triaminobutane.

We previously reported the synthesis of substituted chiral 1,2,4-triaminobutanes as N^1,N^2-di-(-)-menthyl and di-*i*-butyl dicarbamates[1]. The (-)-menthyl carbamate groups were useful along the synthetic pathway as a tool for the evaluation of optical purity [1,2]. The drastic conditions needed for their removal[3] rended these compounds inapplicable in the fields where free amino groups are required: chelation for the preparation of *cis*-Platinum analogues[4], intermediates in the synthesis of compounds for radiolabelling and imaging[5] and in the synthesis of heteromacrocycles[6]. Now we wish to extend the method based on transformation of (S)-pyroglutamic acid as a source of chirality to chiral 1,2,4-triaminobutanes bearing easily and preferentially removable *t*-butoxy-carbonyl (Boc) and benzyloxycarbonyl (Z) groups.

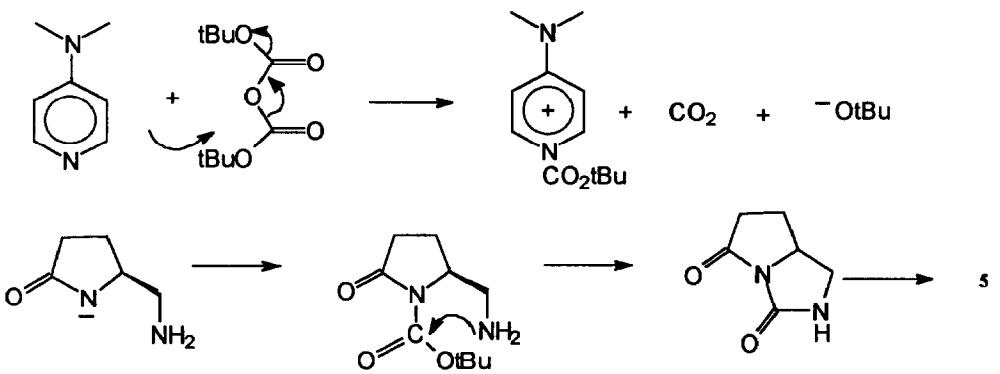
We reinvestigated the acylation of (S)-5-(aminomethyl)-2-pyrrolidone (**1**)[1] with *tert*-butyl dicarbonate (Boc_2O) in MeCN. Even in the presence of a large excess of $(Boc)_2O$ (3.15 equivalents) only the amine group reacted as a single nucleophile yielding (S)-5-(Boc-aminomethyl)-2-pyrrolidone (**2**) (Rf = 0.20, EtOAc) (see Scheme I). After the free amine disappeared and dimethylaminopyridine (DMAP) was added to the reaction mixture, *t*-butoxycarbonylation proceeded both at the lactam and at the carbamate nitrogens yielding tri-Boc derivative **3** (Rf = 0.62, EtOAc; no NH absorption in IR). When **2** reacted with one equivalent of Boc_2O in the presence of DMAP the di-Boc derivative **4** (Rf = 0.30, EtOAc; NH absorption at 3461 cm^{-1}) was obtained. Acylation of the lactam nitrogen occurred prior to that of the urethane nitrogen. Addition of DMAP to the reaction mixture of **1** and of an excess of $(Boc)_2O$ gave the ureide **5**[1] (Rf = 0.39, EtOAc; no NH absorption in IR) together with **3**. The formation of **5** points to the competition for the first equivalent of $(Boc)_2O$ between the lactam nitrogen and the free amine.

*Deceased November 2, 1993.



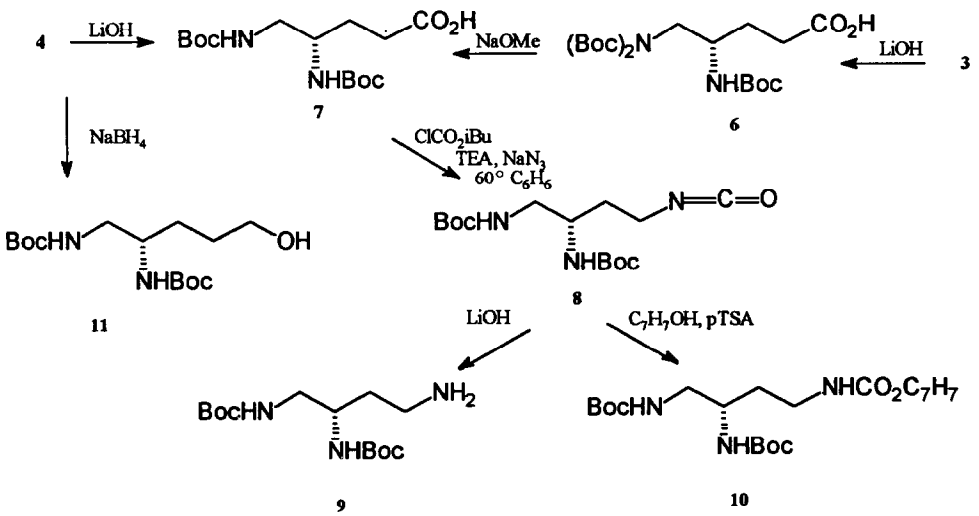
Scheme I

In the presence of DMAP the 1-*t*-Boc-dimethylaminopyridinium cation acts as an acylating reagent[7-10]. Guipe-Jampel and Wakselman have isolated it as the highly reactive chloride and as a more stable tetrafluoroborate[11]. Using $(Boc)_2O$, TEA and DMAP Flynn at al.[12] have prepared a series of *N*-*t*-Boc lactams and amides which were subsequently regioselectively hydrolyzed with LiOH to acyclic amides. Grehn et al. have observed that $(Boc)_2O$ cannot be replaced by Boc-N_3 and Boc-OPh in the acylation of amides and urethanes[10]. This observation leads to the conclusion that the counter anion of the *t*-Boc-dimethylpyridinium cation also plays a role in the exhaustive acylation of amides and urethanes. The highly basic *t*-butoxide generated from DMAP and $(Boc)_2O$ is involved in proton abstraction from the lactam ring of **1**, and the anionic species so formed competes even with the amine in the acylation process. Once *t*-Boc-lactam is formed, the aminomethyl group is involved in intramolecular cyclisation prior to further acylation to **5** (see Scheme II).



Scheme II

N-Boc protected pyroglutamates are known to undergo regioselective ring opening with various nucleophiles under mild conditions[12-17]. When **3** and **4** were exposed to LiOH corresponding acids **6** and **7** were isolated after acidification (see Scheme III). The sodium salt of **7** was also obtained by refluxing **6** with NaOMe in MeOH. LiOH in a mixture of THF-H_2O at 60°C was inefficient in transforming $N(Boc)_2$ to NHBoc. Both acids were converted by a mixed anhydride method to acyl azides (absorption at 2155 cm^{-1} in IR), which underwent Curtius rearrangement to isocyanates (2260 cm^{-1}). The isocyanate derived from the acid **6**, with aqueous LiOH in THF, gave a sparingly soluble urea as a result of amine addition. This complication was not encountered upon hydrolysis of the less lipophilic isocyanate **8**, which gave (S)-N^1,N^2-di-Boc-1,2,4-triaminobutane (**9**) in 72% yield. Treating **8** with benzyl alcohol in the presence of a catalytical amount of *p*TSA, according to the procedure of Canonne et al.[18], afforded N^1,N^2-di-Boc-N^4-Z-triaminobutane (**10**).

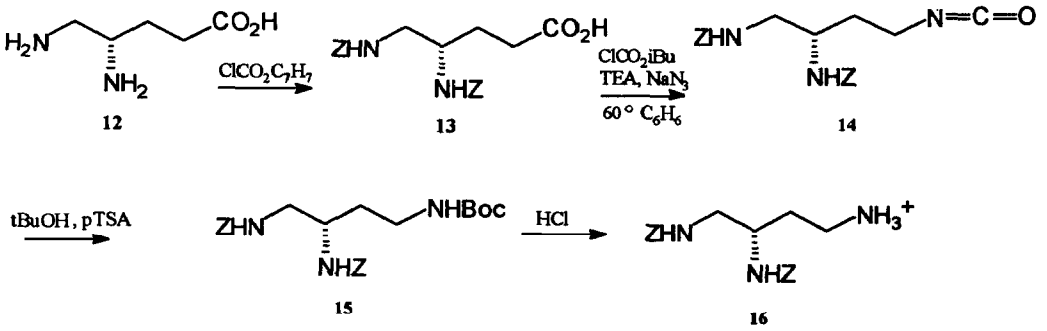


Scheme III

$NaBH_4$ at 0° in methanol led to nucleophilic ring opening of **4** and reduction to (4S)-N^4,N^5-di-Boc-4,5-diaminopentanol (**11**). (DIBAL-H at -78° reduces carbonyl amide to hydroxy compound without ring cleavage[19]). **11** is a higher analogue of 2,3-diaminopropanol known as a racemic mixture of its derivatives[20,21]. A chiral 2,3-diaminopropanol could be obtained by Cardillo et al.[22] from the substituted chiral imidazolidin-2-one systems.

(4S)-N^4,N^5-di-Z-4,5-diaminovaleric acid (**13**), prepared by acylation of **12** with benzyl chloroformate, was submitted to Curtius rearrangement conditions (see Scheme IV). Hydrolytic treatment of the isocyanate **14** yielded the undesired urea whereas the addition of *t*-BuOH, in the presence of *p*TSA, gave the Boc derivative **15** in 79% yield. Treatment of **15** with dry HCl in EtOH generated the free amine **16**.

The optically active 1,2,4-triaminobutanes **9**, **10**, **15** and **16** might be useful as ligands. The preferential removal of protecting groups has previously been demonstrated with enantiomeric mixtures[23].



Scheme IV

Experimental

Melting points are uncorrected. Data for the compounds **4** - **11**: Infrared spectra were recorded on a 257 Perkin Elmer spectrophotometer. ^1H and ^{13}C NMR were measured on 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. Elemental analyses were performed by the Microanalytical Services of the Chemistry Department at 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. Data for the compounds **13** - **16**: IR spectra were measured on a Nicolet 520 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol EX-400 instrument at 400 MHz. C, H, N analyses were performed by the Microanalytical Laboratory of the Institute of Inorganic Chemistry, University of Munich. Specific rotation of all compounds was measured with a DIP JASCO polarimeter.

(S)-5-(Aminomethyl)--pyrrolidone (1):

1 was prepared according to the previously reported procedure[1].

(S)-5-[(Di-*t*-butoxycarbonyl)aminomethyl]-1-*t*-butoxycarbonyl-2-pyrrolidone (3):

1 (2.8g, 0.0245 mol) was dissolved in dry CH_3CN (25 mL) and cooled in an ice bath. Di-*tert*-butyl dicarbonate (9.35 g, 0.075 mol) was added and the mixture stirred 2 h at 0° and overnight at room temperature. TLC on silica gel revealed a single spot of the **(S)-5-(t-butoxycarbonylaminomethyl)-2-pyrrolidone (2)** (Rf = 0.20, elution with EtOAc, visualization with ninhydrin) identical with the spot of **2** prepared previously[1]. The mixture was cooled again and DMAP (305 mg, 2.5 mmol) was added. Strong evolution of CO_2 was observed during 2 h. The stirring continued for 6 h at room temperature. CH_3CN was evaporated and the residue redissolved in EtOAc (100 mL). The organic layer was washed with cold aqueous 10% citric acid, water, 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue was introduced in a minimum volume of EtOAc onto silica column (80 g) treated with hexane. Some impurities were eluted with hexane. Elution with 20% EtOAc-hexane mixture afforded **3** (8.1 g, 80%), mp 98-99°C, identical in all respects to the sample reported previously[1].

(S)-5-[(t-Butoxycarbonyl)aminomethyl]-1-t-butoxycarbonyl-2-pyrrolidone (4):

1 (1.24 g, 0.011 mol) was dissolved in CH_3CN (20mL) and cooled in ice bath. Di-*t*-butyl dicarbonate (5.0 g, 0.023 mol) was added. After 12 h stirring at room temperature DMAP (112 mg, 1 mmol) was added. The reaction mixture was left overnight, concentrated, redissolved in EtOAc, washed with water, 10% citric acid, dried (Na_2SO_4) and concentrated. The residue was triturated with hexane yielding 4, 2.74g, (75%), mp 133-4°C (from EtOAc); $[\alpha]_D^{23}$ - 64.0 (c 2, EtOH); IR ($CHCl_3$) 3461, 1779s, 1738sh, 1709s cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H, Me); 1.50 (s, 9H, Me); 1.93 - 2.09 (m, 2H, CH_2); 2.35 - 2.60 (m, 2H, CH_2CO); 3.30 - 3.35 (q, 2H, CH_2N); 4.16 - 4.18 (m, 1H, CHN); 4.81 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.1 (C-4); 27.9 (Me); 28.2 (Me); 31.4 (C-3); 43.0 (C-6); 57.7 (C-5); 79.6 ($\underline{C}Me_3$); 83.1 ($\underline{C}Me_3$); 150.0; 156.0 (CO_2); 174.0 (CO); CIMS: m/z 315 $[MH]^+$ (10%), 215 [MH - $CO_2(Me)_3$] (90%); Anal. Found: C, 57.14; H, 8.17; N, 9.05. $C_{15}H_{26}N_2O_5$ requires C, 57.31; H, 8.33; N, 8.91%

(S) -N^4-N^5,N^5-Tri-t-butoxycarbonyl-4,5-diaminovaleric acid (6):

Lactam 3 (3g, 7.2 mmol) was stirred overnight in a mixture of $LiOH{\cdot}H_2O$ (1g), water (35 mL) and THF (35 mL). THF was evaporated. The aqueous layer was acidified with cold 10% aqueous citric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and concentrated affording 3g (96 %) of the acid 6 as an oil; $[\alpha]_D^{23}$ + 8.0 (c 2, EtOH); IR ($CHCl_3$): 1782, 1750sh, 1710s cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 (s, 9H, Me); 1.48 (s, 18H, Me); 1.80 (br, 2H, CH_2); 2.41 (t, 2H, CH_2CO); 3.60 (br, 2H, CH_2N); 3.92 (br, 1H, CHN); 4.90 (d, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 27.8 (C-3); 28.0, 28.3, 28.5 (Me); 30.6 (C-2); 49.0 (C-5); 49.8 (C-4); 79.2, 82.8 ($\underline{C}Me_3$); 152.8, 156.0 (CO_2); 177.8 ($\underline{C}O_2H$); CIMS: negative-ion spectrum: m/z 431 $[M-H]^-$ (100 %), 331 [M - $HCO_2C(Me)_3$]; Anal. Found: C, 55.48; H, 8.45; N, 6.42. $C_{20}H_{35}N_2O_8$ requires C, 55.58; H, 8.17; N, 6.49%.

(S)-N^4,N^5-Di-t-butoxycarbonyl-4,5-diaminovaleric acid (7):

A. The lactam 4 (1.59 g, 5 mmol), $LiOH{\cdot}H_2O$) (400 mg), THF (25 mL) and water (10 mL) were stirred for 17 h. THF was evaporated, the aqueous layer was acidified with citric acid, extracted with EtOAc and dried (Na_2SO_4). The organic layer was concentrated and the residue crystallized from EtOAc-hexane yielding 7, 1.62 g, (97 %), mp 126-8°C; $[\alpha]_D^{23}$ - 12.0 (c 2, EtOH); IR ($CHCl_3$): 3440, 1706 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 18H, Me); 1.62 - 1.82 (m, 2H, CH_2), 2.30 - 2.40 (m, 2H, CH_2CO); 3.1 - 3.2 (m, 2H, CH_2N); 3.64 (br, 1H, CHN); 4.93 (d, 1H, NH); 5.00 (t, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 27.7 (C-3); 28.3 (Me); 44.6 (C-5); 51.0 (C-4); 79.5 ($\underline{C}Me_3$); 156.4, 156.7 (CO_2); 177.3 (CO_2H); CIMS: negative-ion spectrum: *m/z* 331 $[M-H]^-$ (100%); Anal. Found: C, 54.02; H, 8.25; N, 8.57. $C_{15}H_{28}N_2O_6$ requires C, 54.21; H ,8.49; N, 8.42%.

B. The acid 6 (2.68 g, 6.2 mmol) was dissolved in methanol (50 mL) containing NaOMe prepared from Na (720 mg, 31 mmol). The solution was refluxed for 6 h. Then MeOH was evaporated, the residue redissolved in water (50 mL), acidified with citric acid, extracted with EtOAc, dried (Na_2SO_4) and concentrated yielding 7, 1.65 g (80%).

(S)-N^1,N^2-Di-t-butoxycarbonyl-1,2,4-triaminobutane (9):

Iso-butyl chloroformate (546 mg, 4mmol) was added to the cold mixture of the acid 7 (662 mg, 2mmol) and TEA (505 mg, 5 mmol) in dry THF (10 mL). After 30 min NaN_3 (2.4 g) in water (8 mL) was added and the reaction mixture stirred for 30 min at 0°C. EtOAc (50 mL) was added. The organic layer was separated, washed 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 2140 and 1710 cm^{-1}. The residue was redissolved in benzene (30 mL) and heated at 70°C for 1h showing an IR absorption of isocyanate 8 at 2260 cm^{-1}. The benzene was evaporated and the residue redissolved in THF (20 mL) to which $LiOH.H_2O$ (200 mg) in water (10 mL) was added. The mixture was stirred overnight at room temperature. EtOAc (50 mL) was added, the organic layer separated, washed twice

with water, dried (Na_2SO_4) and concentrated, yielding 440 mg (72 %) of **9**; mp 78-80°C.; $[\alpha]_D^{20}$ - 28.4 (c 2, EtOH); IR ($CHCl_3$): 1700, 1498 cm-1; ^1H NMR ($CDCl_3$): δ 1.38 (s, 18H, Me); 1.53 (br, 2H, CH_2); 1.93 (br, 2H , NH_2); 2.74 (t, 2H, $C\underline{H}_2NH_2$); 3.14 (br, 2H, CH_2N-1), 3.69 (br, 1H, CHN); 5.05 (br, 1H, NH); 5.10 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 28.3, 28.5 (Me); 36.2 (C-3); 38.4 (C-4); 44.7 (C-1); 49.3 (C-2); 79.2 ($\underline{C}(Me)_3$); 156.3, 156.5 (CO_2); CIMS: *m/z* 304 $[MH]^+$ (100%); Anal. Found: C, 55.43; H, 9.38: N, 13.48. $C_{14}H_{29}N_3O_4$ requires C, 55.42; H, 9.63; N, 13.85%.

(S)-N^1,N^2-Di-*t*-butoxycarbonyl-N^4-benzyloxycarbonyl-1,2,4-triaminobutane (10):

Isocyanate **8** was prepared as described above from 331 mg of **7**. To the still hot benzene solution, benzyl alcohol (1mL) and *p*TSA (20 mg) were added and the mixture was left overnight at room temperature, washed with 10% aqueous Na_2CO_3, water , dried and concentrated. The residue was introduced on a silica column (25g) treated with hexane. Benzyl alcohol was eluted with a mixture EtOAc-hexane (1/6) and **10** was eluted with EtOAc-hexane (1/1), 80 mg (62%), mp 122-3°C; $[\alpha]_D^{23}$ - 23.8 (c 2, EtOH); IR ($CHCl_3$): 3450, 1700, 1498 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30 - 1.50 (superposition of m, part of AB of CH_2-3 with two s of Me, 19H); 1.70 (m, 1H, part of AB, CH_2-3); 2.95 (m, part of AB, 1H, CH_2-4); 3.10-3.15 (m, 2H, CH_2-1); 3.42 (m, 1H, part of AB, CH_2-4); 3.64 (m, 1H, CH-1); 4.82 (br, 1H, NH); 5.01 - 5.09 (br, 3H, NH and CH2O); 5.65 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 28.3 (Me); 33.3 (C-3); 37.4 (C-4); 44.4 (C-1); 49.5 (C-2); 66.5 ($\underline{C}H_2O$); 79.5 ($\underline{C}(Me)_3$); 127.9, 128.0, 128.4, 136.7 (arom); 156.4, 156.7 (CO_2); HRMS: m/z 437.2552 [M]+ (0.93%). $C_{22}H_{35}N_3O_6$ requires 437.2526. Anal. Found: C, 60,12; H, 7.97; N, 9.79. $C_{22}H_{35}N_3O_6$ requires C, 60,40; H, 8.06; N, 9.60%.

(S)-N^4,N^5-Di-*t*-butoxycarbonyl-4,5-diaminopentane-1-ol (11):

$NaBH_4$ (1.52 g, 0.04 mol) was added in small portion to a cold solution of lactam **4** (3.13 g, 0.01 mol) in MeOH (100 mL). The reaction mixture was left overnight and quenched with NH_4Cl . MeOH was evaporated and the residue redissolved in a mixture of EtOAc (100 mL) and water (100 mL). The organic layer was washed once with water, dried and concentrated. The residue was crystallized fron EtOAc-hexane yielding 2.77 g of **11** (87%), mp 86-8°C; $[a]_D^{23}$ - 13.4 (c 2, EtOH); IR ($CHCl_3$): 3445, 1690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 - 1.7 (m of CH_2-2, CH_2-3 and s Me, 22H); 2.41 (s br, 1H, OH); 3.13 (br, 2H, CH_2N); 3.61 (br, 3H, CHN and CH_2O); 4.84 (br, 1H, NH); 4.96 (br, 1H, NH); ^{13}C NMR (CDCl3): δ 28.1, 28.3 (Me); 28.6 (C-2); 29.3 (C-3); 44.6 (C-5); 51.2 (C-4); 62.1 (C-1); 79.2 ($\underline{C}(Me)_3$); 156.3, 156.5 (CO_2); Anal. Found: C, 56.81; H, 9.33; N, 8.95. $C_{15}H_{30}N_2O_5$ requires C, 56.58; H, 9.61; N, 8.91%.

(S)-N^4,N^5-Dibenzyloxycarbonyl-4,5-diaminovaleric acid (13):

(S)-N^4,N^5-Diaminovaleric acid (**12**)[1] (460 mg, 2 mmol) was dissolved in 5 mL of water, neutralized with 1 M NaOH (6 mL) and cooled in an ice bath. Benzyl chloroformate (750 mg, 5 mmol) in THT (5 mL) and 1 M NaOH (5 mL) were slowly added from two separate funnels. The mixture was stirred for 1 h at 0°C and overnight at room temperature, keeping pH in the range 9-10. THF was evaporated and the water layer extracted with ether to remove neutral impurities. The water layer was acidified with 2 M HCl and extracted with EtOAc. The extract was dried (Na_2SO_4)and concentrated and the residue recrystallized from EtOAC-hexane giving **12**, 602 mg (75%), mp 136-8°C; $[\alpha]_D^{21}$ - 7.8 (c 1, EtOH); IR (Nujol): 3333, 1694, 1608, 1541 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.60 - 1.90 (m, 2H, CH_2); 2.72 (m, 2H, CH_2CO); 3.24 - 3.29 (q, 2H, CH_2N); 3.72 (br, 1H, CHN); 5.04 (s, 4H, CH_2O); 5.27 (d, 1H, NH); 5.34 (br, 1H, NH); 7.29 (s, 5H, arom); 7.30 (s, 5H, arom); ^{13}C NMR ($CDCl_3$) : δ 27.3 (C-3); 30.3 (C-2); 44.9 (C-5); 51.5 (C-4); 66.9 ($\underline{C}H_2O$); 127.9, 128.0, 128.1, 128.5, 136.3 (C-arom), 156.8, 157.2 (CO_2); 177.2 (CO); Anal. Found: C, 63.11; H, 6.11; N, 7.11. $C_{21}H_{24}N_2O_6$ requires C,62.99; H,6.04; N,6.99%.

(S)-N^1,N^2-Dibenzyloxycarbonyl-N^4-*t*-butoxycarbonyl-1,2,4-triaminobutane (15):

The acid **12** (1.54 g, 3.87 mmol) and Et_3N (808 mg, 8 mmol) were dissolved in dry THF (30 mL) and cooled to -5°C. Isobutyl chloroformate (790 mg, 5.81 mmol) was added and the reaction mixture stirred for 1 h. NaN_3 (4.3 g in 13 mL of water) was added and the reaction mixture stirred for 30 min at -5°C and for 1 h at room temperatere, then mixed with EtOAc (150 mL). The organic layer was washed once with water, dried (Na_2SO_4) and concentrated. The crude azide had an absorption at 2137 cm^{-1}. The residue was redissolved in benzene (100 mL) and heated for 1 h at 70°C showing absorption of isocyanate **14** at 2262 cm^{-1}. *t*-BuOH (15 mL) and *p*TSA (50 mg) were added to the hot solution which was left for overnight at room temperature, washed with 5% $NaHCO_3$, water, dried and concentrated. The residue was dissolved in EtOAc and filtered through a silica gel column (60 g) giving **15**, 1.29 g (71%), mp 112°C; $[\alpha]_D^{21}$ - 17.5 (c 2, EtOAc); IR (Nujol): 3333, 1696, 1544 cm^{-1}; ^1H NMR (CD_2Cl_2): δ 1.43 (s, 9H, Me); 1.48, 1.95 (m, 2H, CH_2-3); 2.98 (m, 1H, part of AB of CH_2-4); 3.28 (m, 3H, CH_2-1 and part of AB of CH_2-4); 3.75 (m, 1H, CH-2), 5.07 (s, 4H, CH_2O); 5.19 (br, 1H, NH-4); 5.4 - 5.6 (br, 2H, NH-1 and NH-2); 7.34 (s, 10H, arom); ^{13}C NMR (CD_2Cl_2): δ 23.8 (Me); 33.1 (C-3); 37.1 (C-4); 45.2 (C-1); 49.9 (C-2); 66.7, 66.8 ($\underline{C}H_2O$); 79.0 ($\underline{C}(Me)_3$); 127.9, 128.8, 128.1, 128.6, 136.9 (arom), 156.1, 157.0 (CO_2); Anal. Found: C, 63.64; h, 7.14; N, 8.91. $C_{25}H_{33}N_3O_6$ requires C, 63.67; H, 7.05; N, 8.91%.

(S)-N^1,N^2-Dibenzyloxycarbonyl-1,2,4-triaminobutane hydrochloride (16):

15 (700 mg, 1.48 mmol) was dissolved in EtOH (3 mL) and added to a solution of dry 10% HCl in EtOH (7 mL). After 5 h dry ether was added to precipitate the salt which was washed three times with dry ether and dried in vacuo yielding 485 mg (80%) of **16**, mp 151-5°C; $[\alpha]_D^{21}$ + 4.1 (c 2, EtOH); IR (Nujol): 3333, 1685, 1539 cm^{-1}; ^1H NMR (CD_3OD): δ 1.60 - 1.75 (m, 2H, CH_2-3); 2.89 - 3.05 (m, 2H, CH_2N-4); 3.13 - 3.28 (m, 2H, CH_2N-1); 3.74 (m, 1H, CHN-2); 5.07 (s, 2H, CH_2O); 5.08 (s, 2H, CH_2O); 7.32 (s, 5H, arom); 7.33 (s, 5H, arom); ^{13}C NMR (CD_3OD): δ 31.6 (C-3); 38.0 (C-4); 45.3 (C-1); 50.4 (C-2); 67.6 (CH_2O); 67.7 (CH_2O); 128.8, 128.9, 129.0, 129.5, 138.2, 138.3 (arom); 159.1, 159.2 (CO_2); Anal. Found: C, 56.61; H, 6.90; N, 10.12. $C_{20}H_{27}ClN_3O_4 \cdot H_2O$ requires C, 56.27; H, 6.84; N, 9.84%.

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