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A DETAILED INVESTIGATION OF THE PREPARATION OF 2,7-DIAMINOSUBERIC ACID AND 2,5-DIAMINOADIPIC ACID DERIVATIVES USING KOLBE ELECTROLYSIS

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Abstract: The yield of protected 2,7- diaminosuberic acid (DAS) prepared by Kolbe reaction of N-protected α-glutamic acid esters is dependent on solvent, temperature, concentration of carboxylate anion, and protecting groups. The highest yield of protected *L,L*-2,7-diaminosuberic acid is obtained with Boc-Glu-OMe as starting material using MeOH/pyridine/NaOMe as electrolyte.
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2,7-*L,L*-Diaminosuberic acid (**1**, *L,L*-DAS, see Scheme 1) is an unnatural amino acid which is obtained formally by replacing the sulfur atoms of cystine **2** by methylene groups. Diaminodicarboxylic acid **1** has been used as replacement for cystine in the peptide hormone oxytocin[1] and in an analogue of somatostatin.[2] The resulting dicarba analogues of these peptides have shown high biological activity and enhanced metabolic and chemical stability due to the absence of reducible disulfide linkages.

Recently compound **3** (SK&F 107647, see Scheme 1), a nonapeptide with hematoregulatory activity, has demonstrated significant protection in animal models of bacterial[3], fungal[4] and viral[5] diseases and bone marrow transplantation.[6] Compound **3** is the dicarba analogue of the dimer[7] of the hemoregulatory peptide **4** (HP-5b, see Scheme 1) isolated by Laerum and Paukovits from mature human leukocytes.[8]

The 2,7-*L,L*-diaminosuberic acid used for structure-activity-relationship studies[9] of **3** was synthesized by either Kolbe electrolysis[10] of Boc-Glu-OBn [1, 9, 11] (**5**) or by alkylation of a chiral bislactimether (Schöllkopf technology)[12,13] in almost the same overall yield.[14] We decided to further evaluate the synthesis of protected 2,7-diaminosuberic acid by the Kolbe electrolysis of Boc-Glu-OBn (**5**). This electrochemical reaction allows the preparation of diaminodicarboxylic acids bearing the required protecting groups for the synthesis of peptides (e.g. **3**) in just one step from an appropriate protected amino acid. This is a big

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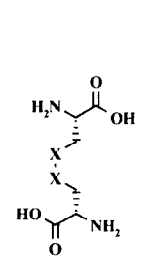
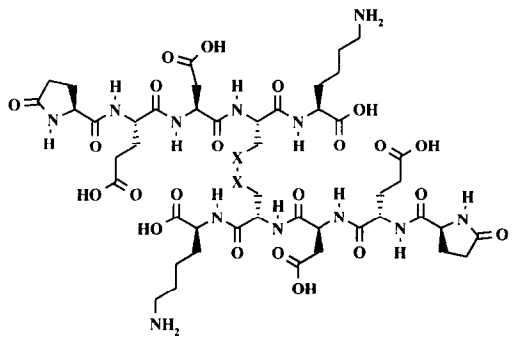
advantage over the Schöllkopf route[13] and other multi-step synthetic routes.[15] Diaminodicarboxylic acid derivatives have been used recently as peptidomimetics[16] and chiral ligands for catalysts.[17] As they contain two amino and two carboxylic groups they are interesting new building blocks for combinatorial chemistry.

In this paper we present a detailed investigation of the Kolbe electrolysis of Boc-Glu-OBn. We investigated the influence of temperature, solvent, concentration of the carboxylate anion and of the protecting groups on the yield. For the first time the main side products were isolated and characterized. The results obtained for 2,7-diaminosuberic acid can be useful for the preparation of other diaminodicarboxylic acids by Kolbe electrolysis.



1 X = CH_2, DAS
2 X = S, cystine



3 X = CH_2, SK&F 107647
4 X = S, HP-5b

Scheme 1

Mechanism of the Kolbe reaction of Boc-Glu-OBn

The moderate isolated yield (20%) of di-Boc-DAS-di-OBn (**7**) by the Kolbe reaction of Boc-Glu-OBn forced us to isolate and characterize the main side products. The formation of the main side products **8**, **9**, **10** and **11** can be explained by the different reaction possibilities of the intermediate alkyl radical. The mechanism of the electrolysis of Boc-Glu-OBn (**5**) is shown in Scheme 2.

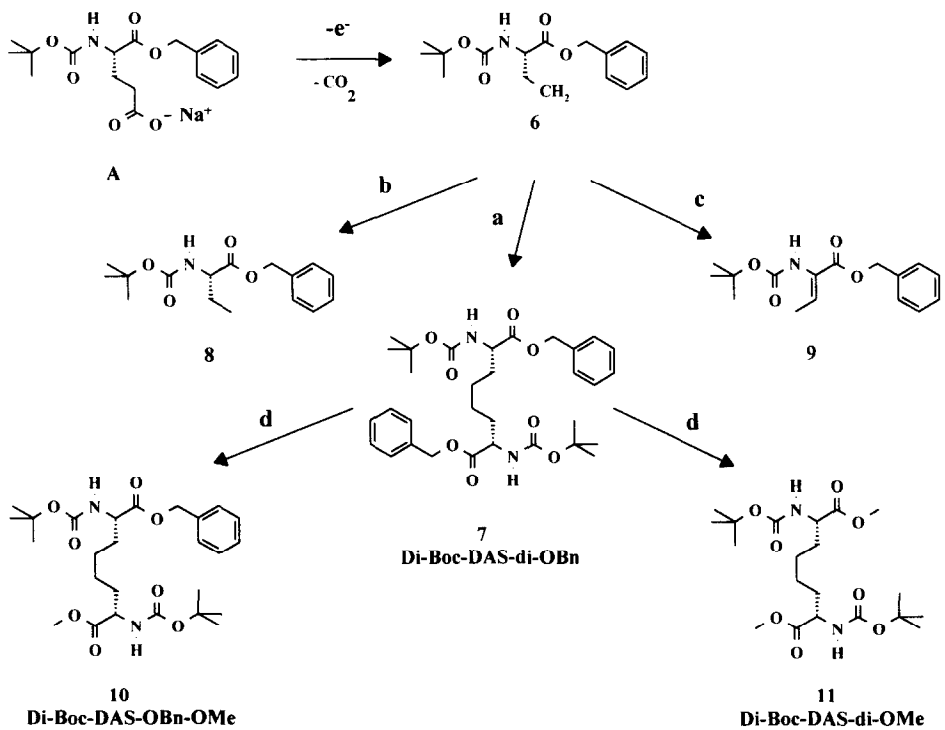
In the presence of $NaOCH_3$ the anion **A** of Boc-Glu-OBn (**5**) is formed. This is oxidized at the anode to the carboxyl radical which fragments into carbon dioxide and the corresponding alkyl radical **6**. The following reaction paths of radical intermediate **6** are possible.

a) Dimerization. Combination of two radicals **6** gives the desired diaminosuberic acid derivative **7** (di-Boc-DAS-di-OBn). In our hands **7** was obtained under optimized reaction conditions (see experimental part) in 20 % yield after recrystallization.

b) Abstraction of a hydrogen atom. Abstraction of a hydrogen atom from another molecule, e.g. solvent or other reaction component, results in the formation of a saturated side chain. The protected 2-aminobutyric acid derivative **8** is formed when Boc-Glu-OBn (**5**) is the starting material. The yield of this side product was approximately 25% (HPLC).

c) Formation of a double bond. Further oxidation of the intermediate radical **6** results in the corresponding cation which undergoes rearrangement to the more stable ß-carbenium ion. Deprotonation yields the unsaturated derivative of 2-acylaminocrotonate derivative **9** in ca. 25% (HPLC) yield. The Z-configuration of the double bond was determined by comparison with literature ^{1}H NMR data.[18]

d) Transesterification. In addition to 2-aminobutane carboxylic acid derivatives (**8** and **9**) we isolated monomethyl ester **10** (up to 15% yield (HPLC) depending on the reaction conditions) and dimethyl ester **11** (up to 3% yield (HPLC)) bearing the skeleton of 2,7-diaminosuberic acid whose formation can be explained by transesterification.



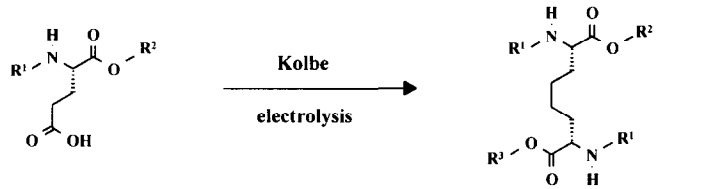
Scheme 2: Mechanism and side products of the Kolbe electrolysis of Boc-Glu-OBn

The ratio of these products (**7**, **8**, **9**, **10**, **11**) depends on the reaction conditions (temperature, solvent, concentration of carboxylate anion, electrode surface area, and material of the electrodes). The highest yields

of the Kolbe product **7** were obtained under the following conditions: a) using platinum gauze electrodes; b) running the electrolysis in a mixture of methanol / pyridine (3 / 1) containing a 10% solution of the carboxylate anion formed by addition of sodium methoxide to the reaction mixture; c) keeping the temperature between 18-24°C. Higher concentration of the anion of Boc-Glu-OBn, a higher temperature or using methanol as solvent increased the amount of side products **10** and **11**. This process not only reduced the yield of **7** (di-Boc-DAS-di-OBn) but also made the purification more difficult. The isolated yield of pure **7** was 20%. The cleavage of the benzyl esters of **7** by hydrogenolysis in the presence of Pd/C yielded di-Boc-DAS-di-OH (**12**) in 90%. The overall yield in the conversion of Boc-Glu-OBn (**5**) to **12** was 18%.

Based on this careful investigation we realized that the use of Boc-Glu-OMe (**13**) should avoid these problems. Transesterification still takes place but the resulting products are identical with the desired product di-Boc-DAS-di-OMe (**11**). We were pleased to obtain the diaminosuberic acid derivative **11** in 34% yield from the Kolbe reaction of Boc-Glu-OMe (**13**). Compound **11** was transformed into di-Boc-DAS-di-OH (**12**) by hydrolysis with LiOH in 80% yield. This gave an overall yield for **12** of 27% starting with Boc-Glu-OMe (**13**). This was more than 50% higher compared to the analogous conversion using Boc-Glu-OBn (**5**) as the starting material.

The formation of side product **10** during the electrolysis of Boc-Glu-OBn (**5**) demonstrates that the selection of the protecting groups is important. The results obtained with other protecting groups[19] are summarized in Table 1. In general the yield of the Kolbe electrolysis of Glu-derivatives bearing a benzyl ester or a benzyloxycarbonyl protecting group is lower compared with those having a methyl, or tert-butyl ester or tert.-butyloxycarbonyl group. The reason is the sensitivity of the benzyl groups to electrochemical oxidation.



5 R^1 = Boc, R^2 = Bn
13 R^1 = Boc, R^2 = Me
14 R^1 = Boc, R^2 = tBu
17 R^1 = Boc, R^2 = EtTos
19 R^1 = Z, R^2 = Bn
22 R^1 = Z, R^2 = Me

7 R^1 = Boc, R^2 = Bn, R^3 = Bn
10 R^1 = Boc, R^2 = Bn, R^3 = Me
11 R^1 = Boc, R^2 = Me, R^3 = Me
12 R^1 = Boc, R^2 = H, R^3 = H
15 R^1 = Boc, R^2 = tBu, R^3 = tBu
18 R^1 = Boc, R^2 = EtTos, R^3 = EtTos
20 R^1 = Z, R^2 = Bn, R^3 = Bn
21 R^1 = Z, R^2 = H, R^3 = H
23 R^1 = Z, R^2 = Me, R^3 = Me

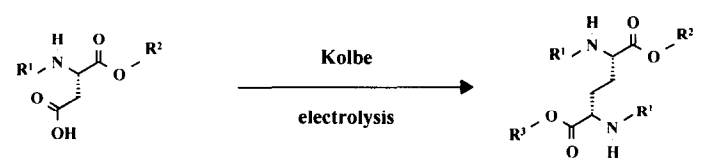
Scheme 3: Synthesis of 2,7-diaminosuberic acid derivatives by Kolbe electrolysis

Table 1: Preparation of Protected 2,7-Diaminosuberic Acid Derivatives by Kolbe Electrolysis

Starting material	Electrolsis product	Yield (%)	Comments
Boc-Glu-OBn (**5**)	di-Boc-DAS-di-OBn (**7**)	20	18% overall yield from **5** to di-Boc-DAS-di-OH (**12**)
Boc-Glu-OMe (**13**)	di-Boc-DAS-di-OMe (**11**)	34	27% overall yield from **13** to di-Boc-DAS-di-OH (**12**)
Boc-Glu-OtBu (**14**)	di-Boc-DAS-di-OtBu (**15**)	38	isolated by HPLC
Boc-Glu-OEtTos (**17**)	di-Boc-DAS-di-OEtTos (**18**)	17	-
Z-Glu-OBn (**19**)	di-Z-DAS-di-OBn (**20**)	11	9% overall yield from **19** to di-Z-DAS-di-OH (**21**)
Z-Glu-OMe (**22**)	di-Z-DAS-di-OMe (**23**)	18	15% overall yield from **22** to di-Z-DAS-di-OH (**21**)
Boc-*D*-Glu-OBn	di-Boc-*D*,*D*-DAS-di-OBn (**29**)	20	-
Z-*D*-Glu-OBn	di-Z-*D*,*D*-DAS-di-OBn (**36**)	11	-

Kolbe reaction of Boc-Asp-OBn (24)

Bhatnagar *et al.*[9] showed that an analogue of **3** containing 2,5-*L*,*L*-diaminoadipic acid (DAA) instead of 2,7-*L*,*L*-diaminosuberic acid is more potent than **3**. 2,5-Diaminoadipic acid derivatives are not available by dialkylation of Schöllkopf's bislactimether with dibromoethane.[20] In contrast to the Schöllkopf route the protected 2,5-diaminoadipic acid derivative di-Boc-DAA-di-OBn (**26**) could be successfully prepared by Kolbe electrolysis of Boc-Asp-OBn (**24**) in 17% yield. We also isolated the corresponding monomethyl ester di-Boc-DAA-OBn-OMe (**27**) as side product. Starting with Z-Asp-OMe (**25**) we isolated di-Z-DAA-di-OMe (**28**) in 25% yield. Based on the results obtained in the glutamic acid series we would expect that Boc-Asp-OMe[21] should give the highest yields of protected 2,5-diaminoadipic acid derivatives.



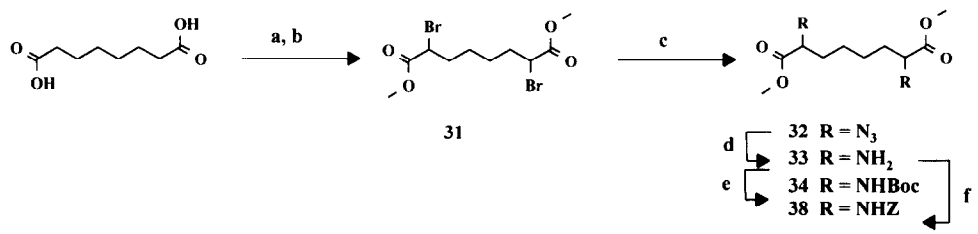
24 R^1 = Boc, R^2 = Bn
25 R^1 = Z, R^2 = Me

26 R^1 = Boc, R^2 = Bn, R^3 = Bn
27 R^1 = Boc, R^2 = Bn, R^3 = Me
28 R^1 = Z, R^2 = Me, R^3 = Me

Scheme 4: Synthesis of 2,5-diaminoadipic acid derivatives by Kolbe electrolysis

Optical purity of di-Boc-*L,L*-DAS-di-OH (12) and di-Z-*L,L*-DAS-di-OH (21)

Di-Boc-*D,D*-DAS-di-OH (**30**) was obtained by Kolbe reaction of Boc-*D*-Glu-OBn and subsequent cleavage of the benzyl ester of the Kolbe product di-Boc-*D,D*-DAS-di-OBn (**29**) by hydrogenolysis. An analytical sample containing the mixture of the three stereoisomers [di-Boc-*L,L*-DAS-di-OH (**12**), di-Boc-meso-DAS-di-OH (**35**), and di-Boc-*D,D*-DAS-di-OH (**30**)] was available in a ratio of 1 : 2 : 1 from optically inactive di-Boc-DAS-di-OMe (**34**) by saponification with LiOH. Optically inactive compound **34** was obtained from suberic acid as shown in Scheme 5. The corresponding di-Z-*D,D*-DAS-di-OH (**37**) was prepared by Kolbe electrolysis of Z-*D*-Glu-OBn followed by saponification of the benzyl esters of di-Z-*D,D*-DAS-di-OBn (**36**) with LiOH. The corresponding analytical sample containing the mixture of the three stereoisomers [di-Z-*L,L*-DAS-di-OH (**21**), di-Z-meso-DAS-di-OH (**39**), and di-Z-*D,D*-DAS-di-OH (**37**)] in a ratio of 1 : 2 : 1 was obtained by treating the free amine **33** with benzyloxycarbonyl chloride followed by saponification of **38** with LiOH.



Scheme 5: Preaparation of optically inactive 2,7-diaminosuberic acid derivatives: a) $SOCl_2$, reflux, 1.5h; b) i) Br_2, 45-50°C, 50h; ii) MeOH; c) NaN_3, MeOH, reflux, 17h; d) H_2, Pd/C, dioxane; e) $(Boc)_2O$, dioxane/water; f) benzyloxycarbonyl chloride, $NaHCO_3$, dioxane/water.

The optical purity di-Boc-*L,L*-DAS-di-OH (**12**) and di-Z-*L,L*-DAS-di-OH (**21**) was determined by chiral capillary electrophoresis. In all cases no racemization was detectable.

In conclusion we have investigated the Kolbe reaction of protected glutamic acid derivatives for the preparation of protected 2,7-diaminosuberic acid. The results of this study are of general importance for the synthesis of other diaminodicarboxylics acids by Kolbe electrolysis. The highest yields were obtained with N-protected a-methyl esters of glutamic acid in MeOH/pyridine in the presence of a catalytic amount of sodium methoxide.

EXPERIMENTAL PROCEDURES

General

Protected amino acids were purchased from Bachem Feinchemikalien AG, Bubendorf, Switzerland, and Senn Chemicals AG, Dielsdorf, Switzerland. 2-[(4-methylphenyl)sulfonyl]ethanol[22, 23] (HOEtTos) was purchased from Loba Feinchemie AG, Fischamend, Austria. Rotary evaporations were performed at 30-35°C and 20 torr. Melting points were obtained on a Kofler apparatus and are uncorrected. NMR spectra were recorded on a Bruker ARX 400 spectrometer at 400MHz for ^{1}H and 100 MHz for ^{13}C. All chemical shifts are reported in parts per million (ppm, d) downfield from tetramethylsilane. Mass spectra were obtained on a Hewlett Packard 5989A mass spectrometer at 70eV using 59987A electrospray unit. Optical rotations were measured with a Perkin-Elmer 341 polarimeter in a 1 dm cell. Elemental analysis was performed at Chemserv, Linz, Austria. Thin layer chromatography (TLC) was performed on silica gel $KG60_{F254S}$ precoated plates or $RP18_{F356S}$ (E. Merck). Visualization was done by spraying with ninhydrin solution (0.5g ninhydrin, 1.5 mL glacial acetic acid, 12.5 mL water, 236mL n-butanol) or Hannessian's dip (12.5g $H_{24}Mo_7N_6O_{24}.4H_2O$, 5g $Ce(SO_4)_2$, 28 mL conc. H_2SO_4 and topped it up to 500 mL with water) and heating to 250°C. Product purities were analyzed on Hewlett Packard 1050 or 1090 HPLC systems. The Kolbe electrolysis was performed with a power supply SM120-25D from Delta Electronika. Capillary electrophoresis (CE) was done with a P/ACE 2000 from Beckman Instruments. *CE-Method A for the investigation of the optical purity of di-Boc-L,L-DAS-di-OH (**12**):* Capillary: fused silica untreated, 56 cm; inside diameter: 50µm. Column temperature: 15°C. Puffer: Phosphoric acid (100mM, adjusted with NaOH to pH 6.0), hydroxypropyl-b-cyclodextrine (25 mmol); acetonitrile (5%v/v). Separation: constant field. Electric field: 375V/cm. Injection: 20 mbar, 10.0 sec. Detection: UV 200nm. *CE-Method B for the investigation of the optical purity of di-Z-L,L-DAS-di-OH (**21**):* Capillary: fused silica untreated, 56 cm; inside diameter: 50µm. Column temperature: 10°C. Puffer: Phosphoric acid (120mM, adjusted with NaOH to pH 6.0), hydroxypropyl-b-cyclodextrine (25 mmol); methanol (5%v/v). Separation: constant voltage. Electric field: 470V/cm. Injection: 20 mbar, 10.0 sec. Detection: UV 205nm.

General method for Kolbe electrolysis

CAUTION: The electrolysis has to be carried out under an N_2 atmosphere! The starting material (1250 mmol) was dissolved in 3 / 1 (v/v) mixture of MeOH / pyridine (2100 mL). The cryostat was cooled earlier to -40°C with the feed to the electrolysis cell being shut off. The reaction solution was transferred to the electrolysis cell. The electrolysis cell was filled with MeOH until the gauze electrodes (arranged in cylinder form) were totally submerged. Then 6 mL of $NaOCH_3$ (30 % in MeOH) was added and the feed to the electrolysis cell was opened. When the reaction solution reached 15°C the power supply was turned on. The reaction

temperature was recorded initially about every 15min, later every 30min. The reaction temperature was kept between +18°C and +24°C by temperature regulation with the cryostat. The reaction was monitored by TLC (RP18, acetonitrile/water = 4/1). After 8h the reaction was finished, the reaction solution was transferred to two 2-L round-bottom flasks, the reaction vessel and the electrodes were rinsed thoroughly with MeOH and this was combined with the reaction solution. This solution was rotary evaporated at 40°C. The residue was dissolved in 1000 mL of ethyl acetate and transferred to a separatory funnel. The organic phase was washed first with HCl solution (60mL of conc. HCl was diluted with water to 600 mL), with saturated $NaHCO_3$ (600 mL) and than washed to neutral with brine (several times 200 mL). The organic phase was dried with Na_2SO_4, filtered, the filtrate was concentrated and degassed. The residue was then filtered through silica gel (1400g KG 60F 254, 20-45μ, toluene/ethyl acetate = 30/1). The fractions were pooled on the basis of TLC and concentrated. The crude material was purified by crystallization or flash chromatography.

Di-Boc-*L,L*-DAS-di-OBn (7)

Starting material: Boc-Glu-OBn. Yield: 20%. mp 104-105°C (cyclohexane/petroleum ether = 1/1); $[\alpha]^{20}_D$ = -3.2° (5% in $CHCl_3$). ^1H NMR($CDCl_3$, 400MHz): 1.15-1.38(m, 4, 2 CH_2), 1.43(s, 18, 2 $C(CH_3)_3$), 1.58(m, 2, CH_2), 1.72(m, 2, CH_2), 4.29(br s, 2, 2 CH), 4.98(br s, 2, 2 NH), 5.15(AB system, 4, J = 12.3Hz, 2 benzyl-CH_2), 7.33(m, 10, aromatic-H). ^{13}C NMR($CDCl_3$, 100MHz): 24.83, 28.32, 32.48, 53.40, 66.96, 79.87, 128.31, 128.42, 128.59, 135.48, 155.31, 172.55. Anal. ($C_{32}H_{44}N_2O_8$, MW: 584.708): Calculated: C 65.73; H 7.58; N 4.79; Found: C 65.8; H 7.5; N 4.7.

(*L*)-2-(tert.-butyloxycarbonyl)butanoic acid benzylester (8)

Compound **8** was isolated as an oil from the mother liquor of **7** by chromatography (silica gel, eluent: petroleum ether / ethyl acetate = 10 / 1). $[\alpha]^{20}_D$ = -9.4° (5% in $CHCl_3$, content: 89.8 area% by HPLC). ^1H NMR($CDCl_3$, 400MHz): 0.90(t, 3, J = 7.6Hz, CH_3), 1.43(s, 9, $C(CH_3)_3$), 1.68 and 1.85(m, 1, CH_2), 4.29(br s, 1, NH), 5.04(br s, 1, CH), 5.13 and 5.20(d, 1, J = 12 Hz, benzyl-CH_2), 7.35(m, 5, aromatic-H). ^{13}C NMR($CDCl_3$, 100MHz): 9.50, 25.88, 28.29, 54.63, 66.87, 79.75, 128.20, 128.34, 128.40, 128.45, 128.55, 135.51, 155.35, 172.57. Anal. ($C_{16}H_{23}NO_4$, MW: 293.362): Calculated: C 65.51; H 7.90; N 4.75; Found: C 65.9; H 7.8; N 4.7.

(Z)-2-(tert. Butyloxycarbonylamino)-but-2-enoic acid benzylester (9)

Compound **9** was isolated from the mother liquor of **7** by chromatography (silica gel, eluent: petroleum ether / ethyl acetate = 10 / 1). mp 84-85°C. ^1H NMR($CDCl_3$, 400MHz): 1.45(s, 9, $C(CH_3)_3$), 1.80(d, 3, J = 7.2 Hz,

CH_3), 5.20(s, 2, benzyl-CH_2), 5.98(br s, 1, NH), 6.720(q, 1, J = 7.2 Hz, CH), 7.30(m, 5, aromatic-H). ^{13}C NMR($CDCl_3$, 100MHz): 14.20, 28.17, 66.96, 80.41, 126.79, 128.17, 128.25, 128.52, 132.40, 135.71, 153.11, 164.68. Anal. ($C_{16}H_{21}NO_4$, MW: 291.346): Calculated: C 65.96; H 7.26; N 4.81; Found: C 66.0; H 7.2; N 4.7.

Di-Boc-*L,L*-DAS-OBn-OMe (10)

Compound **10** was isolated by chromatography from the motherliquor of **7**. First the desired compound was enriched using silica gel (eluent: petroleum ether / ethyl acetate = 10 / 1). The fractions containing the desired compound were pooled and the resulting residue was purified by reversed phase chromatography with acetonitrile / water = 4 / 1 (Rf (**7**) =0.2; Rf (**10**) =0.3). mp 55-59°C; $[\alpha]^{20}_D$ = -24.9° (1% in DMF).

^1H NMR($CDCl_3$, 400MHz): 1.20-1.40(m, 4, 2 CH_2), 1.43 and 1.44(s, 9, $C(CH_3)_3$), 1.60(m, 2, CH_2), 1.75(m, 2, CH_2), 3.72(s, 3, OCH_3), 4.26(br s, 1, CH), 4.32(br s, 1, CH), 5.00(br s, 2, 2 NH), 5.17(AB system, 2, J=12.3Hz, benzyl-CH_2), 7.32(m, 5, aromatic-H). ^{13}C NMR($CDCl_3$, 100MHz): 24.82, 28.31, 32.49, 32.54, 52.18, 53.38, 66.99, 79.89, 128.31, 128.42, 128.59, 135.46, 155.32, 172.57, 173.20. Anal. ($C_{26}H_{40}N_2O_8$, MW: 508.610): Calculated: C 61.40; H 7.93; N 5.51; Found: C 61.0; H 7.7; N 5.4.

Di-Boc-*L,L*-DAS-di-OMe (11)

Starting material: Boc-Glu-OMe. Yield: 34%, mp 65-68°C; MS: 433(M+1); $[\alpha]^{20}_D$ = +18.6° (5% in $CHCl_3$). ^1H NMR($CDCl_3$, 400MHz): 1.32(m, 4, 2 CH_2), 1.43(s, 18, 2 $C(CH_3)_3$), 1.59(m, 2, CH_2), 1.76(m, 2, CH_2), 3.72(s, 6, 2 OCH_3), 4.27(br s, 2, 2 NH), 4.99(br s, 2, 2CH). ^{13}C NMR($CDCl_3$, 100MHz): 24.86, 28.30, 32.53, 52.17, 53.29, 79.87, 155.31, 173.20. Anal. ($C_{20}H_{36}N_2O_8$, MW: 432.513): Calculated: C 55.54; H 7.97; N 6.92; Found: C 55.1; H 8.4; N 6.5.

Di-Boc-*L,L*-DAS-di-OH (12)

Method A: Hydrogenolysis of 7: Di-Boc-DAS-di-OBn (**7**, 21.22 g, 36.29 mmol) was dissolved in 200mL methanol, treated with 2,1 g Norit and stirred for 15 min. The solution was filtered, the residue was washed with 20 mL methanol. 2,12 g 10 % Pd/C (type K-0225) was added to the solution under a nitrogen atmosphere. The solution was hydrogenated in a Parr apparatus at 4bar at ambient temperature for 3 h. TLC (acetonitrile/water 1 : 1, RP-18, ninhydrin) showed complete reaction. The solution was filtered from the catalyst by suction, the catalyst was washed with 50 mL methanol and the filtrate was concentrated. The residue was crystallized from 85mL acetonitrile yielding 13.21 (90 %) of **12**. This gives an overall yield of 18% calculated on Boc-Glu-OBn.

Method B: Saponification of 11: Compound **12** was obtained in 80% yield using method B described for compound **21** with di-Boc-DAS-di-OMe (**11**) as starting material. This gives an overall yield of 27% starting from Boc-Glu-OMe. mp 148-150°C; MS : 405.6 (M+1); $[\alpha]^{20}_D$ = -15.2° (5%in DMF). ^{1}H NMR(d_6-DMSO, 400MHz): 1.20-1.60(m, 8, 4 CH_2), 1.38(s, 18, 2 $C(CH_3)_3$), 3.82(br s, 2, 2 CH), 6.95(br s, 2, 2 NH). ^{13}C NMR(d_6-DMSO, 100MHz): 25.30, 28.32, 30.79, 53.51, 78.02, 155.69, 174.25. Anal. ($C_{18}H_{32}N_2O_8$, MW: 404.459): Calculated: C 53.45; H 7.97; N 6.92; Found: C 53.9; H 7.9; N 6.9.

Di-Boc-*L,L*-DAS-di-OtBu (15)

Starting material: Boc-Glu-OtBu (**14**). The product **15** was isolated by HPLC. Yield: 38.5%; mp 68-70°C; $[\alpha]^{20}_D$ = +14.3° (3% in $CHCl_3$). ^{1}H NMR($CDCl_3$, 400MHz): 1.23-1.47(m, 4, 2 CH_2), 1.43 and 1.45(s, 9, 2 $C(CH_3)_3$), 1.58(m, 2, CH_2), 1.72(m, 2, CH_2), 4.13(br s, 2, 2 NH), 4.98(br s, 2, 2CH). ^{13}C NMR($CDCl_3$, 100MHz): 24.91, 28.01, 28.33, 32.76, 53.91, 79.55, 81.69,155.34, 171.89. Anal. ($C_{26}H_{48}N_2O_3$, MW: 516.674): Calculated: C 60.44; H 9.36; N 5.42; Found: C 60.3; H 9.2; N 5.1.

Boc-Glu-(OBn)-OEtTos (16)

Boc-Glu-(OBn)-OH (407.24g, 1200mmol) and 2-[(4-methylphenyl)sulfonyl]ethanol[22, 23] (HOEtTos, 250.86g, 1250mmol) were dissolved in pyridine (2L) and cooled to 0°C (ice-bath). A solution of dicyclohexyl carbodiimide (260.01g, 1250mmol) in pyridine (1L) was added in such a way to keep the temperature below 5°C. The reaction was kept at 0°C for 1h. Then the ice bath was removed and the reaction was stirred mechanically at ambient temperature overnight. The precipitated urea was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate (500 mL) and stored at 4°C for 30min. The precipitated urea was filtered off and the filtrate was washed with diluted HCl solution (10% in water), saturated $NaHCO_3$ solution and finally with brine until neutral. The organic phase was dried with Na_2SO_4, filtered and the filtrate was concentrated. The residue was crystallized from petroleum ether /ethyl acetate = 1 / 5 to yield 470g (75%) of **16**. mp 82-85°C; $[\alpha]^{20}_D$ = +2.0° (5% in $CHCl_3$). ^{1}H NMR($CDCl_3$, 400MHz): 1.42(s, 9, $(CH_3)_3C$), 1.82 and 2.03(m, 1, CH_2), 2.38(m, 2, CH_2), 2.44(s, 3, tolyl-CH_3), 3.42(m, 2, $OCH_2CH_2SO_2C_7H_7$), 4.11(m, 1, CH), 4.44(m, 2, $OCH_2CH_2SO_2C_7H_7$), 4.96(br s, 1, NH), 5.11(s, 2, benzyl-CH_2), 7.29-7.39(m, 7, 5 phenyl-H, 2 tolyl-H), 7.78(d, 2, J = 8.2Hz, 2 tolyl-H). ^{13}C NMR($CDCl_3$, 100MHz): 21.60, 27.20, 28.29, 30.13, 52.79, 54.93, 58.49, 66.50, 80.12, 128.13, 128.26, 128.31, 128.59, 130.08, 135.78, 136.31, 145.24, 155.25, 171.50, 172.37. Anal. ($C_{26}H_{33}NO_8S$, MW: 519.38): Calculated: C 65.73; H 7.58; N 4.79; Found: C 65.8; H 7.5; N 4.7.

Boc-Glu-OEtTos (17)

Compound **16** (20g, 38.5mmol) was dissolved in MeOH (200mL). 10% Pd/C (2.03g) was added under a nitrogen atmosphere and hydrogenated in a Parr apparatus at 4bar at room temperature for 3h. The catalyst was filtered, the filtrate was concentrated and the product was crystallized from diisopropyl ether to yield 13.24g (80%) of **17**, mp 96-100°C; $[\alpha]^{20}_D$ = +1.6° (5% in $CHCl_3$). ^1H NMR($CDCl_3$, 400MHz): 1.44(s, 9, $(CH_3)_3C$), 1.83 and 2.05(m, 1, CH_2), 2.40(m, 2, CH_2), 2.46(s, 3, tolyl-CH_3), 3.45(t, 2, J = 6.1Hz, $OCH_2CH_2SO_2C_7H_7$), 4.14(m, 1, CH), 4.47(t, 2, $OCH_2CH_2SO_2C_7H_7$), 5.04(br s, 1, NH), 7.38(d, 2, J = 8.1Hz, 2 tolyl-H), 7.80(d, 2, 2 tolyl-H). ^{13}C NMR($CDCl_3$, 100MHz): 21.61, 27.09, 28.26, 29.88, 52.67, 54.90, 58.51, 80.33, 127.75, 128.12, 129.84, 130.10, 136.21, 145.31, 155.43, 171.47, 177.33. Anal. ($C_{19}H_{27}NO_8S$, MW: 429.488): Calculated: C 53.14; H 6.37; N 3.26; Found: C 53.4; H 6.4; N 3.3.

Di-Boc-*L,L*-DAS-di-OEtTos (18)

Starting material: Boc-Glu-OEtTos (**17**). Yield: 17%; mp 94-96°C; $[\alpha]^{20}_D$ = +4.3° (3% in $CHCl_3$).

^1H NMR($CDCl_3$, 400MHz): 1.24(m, 4, 2 CH_2), 1.49 and 1.64(m, 2, CH_2), 2.43(s, 6, 2 tolyl-CH_3), 3.41(dt, 4, J = 6.2Hz, J = 0.9Hz, $OCH_2CH_2SO_2C_7H_7$), 4.04(m, 2, 2 CH), 4.41(t, 4, $OCH_2CH_2SO_2C_7H_7$), 4.93(m, 2, 2 NH), 7.35 and 7.75(d, 4, J = 8.2Hz, 4 tolyl-H). ^{13}C NMR($CDCl_3$, 100MHz): 21.62, 24.74, 28.30, 31.96, 53.16, 54.95, 58.24, 79.95, 128.09, 128.15, 130.08, 136.32, 145.21, 155.28, 172.12. Anal. ($C_{36}H_{52}N_2O_{12}S_2$, MW: 768.941): Calculated: C 56.23; H 6.82; N 3.64; Found: C 56.5; H 7.0; N 3.7.

Di-Z-*L,L*-DAS-di-OBn (20)

Starting material: Z-Glu-OBn (**19**). . Yield: 11% of **20**. mp 107-109°C (MeOH); $[\alpha]^{20}_D$ =-1.2° (5% in $CHCl_3$). ^1H NMR($CDCl_3$, 400MHz): 1.21 and 1.30(m, 2, CH_2), 1.60 and 1.74(m, 2, CH_2), 4.38(m, 2, 2 CH), 5.10(s, 4, 2 benzyl-CH_2), 5.16(AB-system, 4, J = 12.2Hz, 2 benzyl-CH_2), 5.28(m, 2, 2 NH), 7.26-7.44(m, 20, phenyl-H). ^{13}C NMR($CDCl_3$, 100MHz): 24.66, 32.42, 53.81, 67.03, 67.15, 128.11, 128.19, 128.36, 128.52, 128.54, 128.65, 135.34, 136.30, 155.86, 172.18. Anal. ($C_{38}H_{40}N_2O_8$, MW: 652.743): Calculated: C 69.92; H 6.18; N 4.29; Found: C 70.0; H 6.2; N 4.3.

Di-Z-*L,L*-DAS-di-OH (21)

*Method A: Hydrolysis of **20***: Di-Z-*L,L*-DAS-di-OBn (**20**) (10.06g, 15.41mmol) was dissolved in a mixture of dioxane (108mL) and water (30mL). 2N LiOH solution (19.23mL, 38.47mmol, 1.25 equivalents) was added. This was stirred at ambient temperature for 2h. TLC control (RP18, acetonitrile/water = 1/1) showed that all

starting material was consumed. The solution was concentrated to 1/3 of the volume and 5% $KHSO_4$ solution was added under stirring till pH=2-3. The precipitate was filtered and stirred with ethyl acetate (250mL). The aqueous phase was extracted with ethyl acetate, the combined organic phases were dried with Na_2SO_4, filtered and concentrated. The resulting residue was crystallized from CH_3CN (125mL) to yield 6.63g (91%) of **21**. The overall yield calculated on Z-Glu-OBn was 9%.

Method B: Hydrolysis of 23: Di-Z-*L,L*-DAS-di-OMe (**23**) (2g, 4mmol) was dissolved in a mixture of water (6mL) and MeOH (15mL). 2N LiOH solution (5mL, 10mmol, 1.25 equivalents) was added followed by MeOH (4mL) to obtain a clear solution. This reaction mixture was stirred at ambient temperature overnight. The solution was concentrated, 5% $KHSO_4$ solution was added with stirring till pH=2-3. The aqueous phase was extracted with ethyl acetate (3x 50mL), the organic phase was dried with Na_2SO_4, filtered and concentrated. The resulting residue was crystallized from CH_3CN (10mL) to yield 1.6g (84%) of **21**. The overall yield calculated on Z-Glu-OMe was 15%. mp 152-154°C, $[\alpha]^{20}_D$ = -9.8° (5% in DMF). ^1H NMR (d_6-DMSO, 400 MHz): 1.30(m, 4, 2 CH_2), 1.60(m, 4, 2 CH_2), 3.28 (br s, 2, D_2O-exchangeable, 2 COOH), 3.92(m, 2, 2 CH), 5.02(s, 4, 2 benzyl-CH_2), 7.28-7.40(m, 10, aromatic-H), 7.50(d, 2, J = 7.9Hz, 2 NH). ^{13}C NMR (d_6-DMSO, 100 MHz): 24.53, 30.05, 53.21, 64.79, 126.46, 127.10, 127.18, 127.74, 136.48, 155.59, 173.29. Anal. ($C_{24}H_{28}N_2O_8$, MW: 472.499): Calculated: C 61.00; H 5.97; N 5.93; Found: C 60.8; H 6.0; N 6.0.

Di-Z-*L,L*-DAS-di-OMe (23)

Starting material: Z-Glu-OMe (**22**). Yield: 18% mp 72-78°C; $[\alpha]^{20}_D$ = +14.6° (5% in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.30(m, 4, 2 CH_2), 1.64 and 1.80(m, 2, CH_2), 3.73(s, 6, 2 OMe), 4.35(br s, 2, 2 CH), 5.10(s, 4, 2 benzyl-CH_2), 5.25 (br s, 2, 2 NH), 7.28-7.35(m, 10, aromatic-H). ^{13}C NMR ($CDCl_3$, 100 MHz): 24.68, 32.39, 52.28, 53.68, 66.97, 128.05, 128.13, 128.47, 136.25, 155.81, 172.76. Anal. ($C_{26}H_{32}N_2O_8$, MW: 500.548): Calculated: C 62.38; H 6.44; N 5.60; Found: C 61.9; H 6.3; N 5.8.

Di-Boc-*L,L*-DAA-di-OBn (26)

Starting material: Boc-Asp-OBn (**24**). Yield: 17%, mp 119°C. $[\alpha]^{20}_D$ = +9.7° (0.8% in $CHCl_3$). ^1H NMR ($CDCl_3$, 400MHz): 1.42(s, 18, 2 $C(CH_3)_3$), 1.58(m, 2, CH_2), 1.89(m, 2, CH_2), 4.32(br s, 2, 2 CH), 4.95(br d, 2, 2NH), 5.13(AB-system, 4, J = 12.7Hz, 2 benzyl-CH_2), 7.32(m, 10, aromatic-H). ^{13}C NMR ($CDCl_3$, 100MHz): 28.25, 28.67, 53.01, 67.11, 79.98, 128.31, 128.46, 128.60, 135.28, 155.26, 172.07. Anal. ($C_{30}H_{40}N_2O_8$, MW: 556.665): Calculated: C 64.73; H 7.24; N 5.03; Found: C 64.5; H 7.1; N 4.9.

Di-Boc-*L*,*L*-DAA-OMe-OBn (27)

Compound **27** was isolated as a side product by chromatography from the mother liquor of **26** using the method described for **10**, mp 94-99°C. $[\alpha]^{20}_D$ = +12.1° (5% in $CHCl_3$). ^1H NMR($CDCl_3$, 400MHz): 1.43(s, 9, $C(CH_3)_3$), 1.42(s, 9, 2 $C(CH_3)_3$), 1.57 and 1.68(m, 1, CH_2), 1.90(m, 2, CH_2), 3.69(s, 3, OCH_3), 4.28(br s, 1, CH), 4.37(br s, 1, CH), 4.99(br s, 1, NH), 5.10(br s, 1, NH), 5.15(AB-system, 2, J = 12.2Hz, benzyl-CH_2), 7.35(m, 5, aromatic-H). ^{13}C NMR ($CDCl_3$, 100MHz): 28.27, 28.66, 28.73, 52.26, 52.96, 67.14, 79.98, 128.33, 128.47, 128.61, 135.33, 155.29, 172.13, 172.75. Anal. ($C_{24}H_{36}N_2O_8$, MW: 480.557): Calculated: C 59.99; H 7.55; N 5.83; Found: C 60.0; H 7.2; N 5.9.

Di-*Z*-*L*,*L*-DAA-di-OMe (28)

Starting material: Z-Asp-OMe (**25**). Yield: 23%. mp 111-112°C (MeOH); $[\alpha]^{20}_D$ = +21.4° (5% in $CHCl_3$).
^1H NMR (400 MHz, $CDCl_3$) δ 1.60-1.72(m, 2, CH_2), 1.93(m, 2, CH_2), 3.71(s, 6, OCH_3), 4.37(m, 2, 2 CH), 5.09(s, 4, 2 benzyl-CH_2), 5.28 (m, 2, 2 NH), 7.27-7.38(m, 10, aromatic-H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 28.75, 52.51, 53.43 67.13, 128.10, 128.22, 128.54, 136.15, 155.87, 172.32.
Anal. Cacld for $C_{24}H_{28}N_2O_8$ (MW: 472.50): C, 61.01; H, 5.98; N, 5.93. Found: C, 61.22; H, 6.0; N, 5.7.

Di-Boc-*D*,*D*-DAS-di-OBn (29)

Starting material: Boc-*D*-Glu-OBn. Yield: 20%; mp 102-103°C; $[\alpha]^{20}_D$ = +3.3° (2% in $CHCl_3$). Anal. ($C_{32}H_{44}N_2O_8$, MW: 584.708): Calculated: C 65.73; H 7.58; N 4.79; Found: C 65.8; H 7.4; N 4.7

Di-Boc-*D*,*D*-DAS-di-OH (30)

Compound **30** was prepared in the same manner as described for **12** with **29** as starting material. Yield: 80%. mp 143.5-144.5°C; MS : 405.6 (M+1). $[\alpha]^{20}_D$ = +14.0° (5% in DMF). Anal. ($C_{18}H_{32}N_2O_8$, MW: 404.459): Calculated: C 53.45; H 7.97; N 6.92; Found: C 53.0; H 8.0; N 6.9.

(±)-2,7-Dibromosuberic acid dimethyl ester (31)

31 was prepared as described in the literature[24] for 2,5-dibromoadipic acid diethyl ester with suberic acid as starting material. Suberic acid (10.00g, 57.41mmol) was suspended in 25mL thionyl chloride and heated to reflux. After 30min a clear solution was obtained and reflux was maintained for an additional 0.5h. Then the solvent was evaporated at the water jet pump, the residue was treated once with 25mL chloroform and again brought to dryness. Bromine (5.88mL, 229.63mmol) was added dropwise to the oily residue at 50°C (ca. 15

min.) and the solution was stirred at 45 - 50°C for 7h whereafter additional 2mL bromine was added and heating to 45 - 50°C was continued for further 43h. (Note: To avoid problems in the following steps it is important that no monobromosuberic acid is present in the reaction mixture. In our hands no monobromo compound was detectable by ^{1}H NMR spectroscopy after 50h of treatment with bromine). Then 100mL methanol was cautiously dropped in at this temperature (ca. 25min). After complete addition the resulting dark brown solution was heated to reflux for 20min. The solvent was evaporated and degassed. Yield: 16.66g orange-red oil (80.5 %). ^{1}H NMR($CDCl_3$, 400MHz): 1.50(m, 4, 2 CH_2), 2.01(m, 4, 2 CH_2), 3.79(s, 6, 2 OMe), 4.23(dd, 2, J = 6.8Hz, J = 8.0Hz, 2 CH). Anal. ($C_{10}H_{16}Br_2O_4$, MW: 360.042): Calculated: C 33.36; H 4.48; Found: C 33.5; H 4.6.

(±)-2,7-Diazidosuberic acid dimethyl ester (32)

Ester **31** (15.00g, 41.655mmol) and sodium azide (5.96g, 91.605mmol) were refluxed in 150mL methanol for 17h. The reaction solution was then concentrated to about one third of the original volume, poured on 500mL deionized water, extracted three times each with 50mL ethyl acetate, the combined organic layers were washed once with 250mL deionized water, dried over sodium sulfate with addition of activated charcoal, filtered and evaporated to dryness. The residue was degassed at the oil pump for two hours. Yield: 10.23g (86% of theory) brownish oil. The resulting crude product can be used directly for the next step. An analytical sample was obtained by chromatography (silica gel, petroleum ether/ethyl acetate = 10/1). ^{1}H NMR($CDCl_3$, 400MHz): 1.37(m, 4, 2 CH_2), 1.72(m, 4, 2 CH_2), 3.72(s, 6, 2 OMe), 3.78(dd, 2, J = 5.3Hz, J = 8.2Hz, 2 CH). Anal. ($C_{10}H_{16}N_6O_4$, MW: 284.274): Calculated: C 42.25; H 5.67; N 29.56; Found: C 42.3; H 5.7; N 30.0.

(±)-2,7-Bis-(tert. butyloxycarbonylamino)-suberic acid dimethyl ester (34)

(±)-2,7-Diazidosuberic acid dimethyl ester **32** (10g, 35.18mmol) was dissolved in dioxane (100mL) and stirred with activated carbon (Norit, 0.5g) for 10min. The solution was filtered and the activated carbon was washed with dioxane (2x10mL). Pd/C (10%, 3.9g) was added to the solution under an atmosphere of nitrogene. The mixture was hydrogenated in a Parr apparatus at 4bar for 2h at ambient temperature to yield diamino derivative **33**. TLC control (petroleum ether / ethyl acetae = 2 / 1, detection ninhydrin) showed no remaining starting material. The catalyst was removed by filtration. Water (50mL) was addded to the filtrate followed by Boc-anhydride (16.9g, 77.40mmol). The solution was stirred at ambient temperature overnight. Then the reaction was concentrated. Water (100mL) was added. The resulting mixture was extracted with ethyl acetate (3x50mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to yield

16.44g of an oil which was crystallized from 30mL of acetonitrile to yield 5.7g of **34**. mp 110-122°C. Anal. ($C_{20}H_{36}N_2O_8$, MW: 432.513): Calculated: C 55.54; H 7.97; N 6.92; Found: C 55.3; H 8.0; N 6.9.

Di-Z-*D,D*-DAS-di-OBn (36)

Starting material: Z-D-Glu-OBn. Yield: 12%. mp 84-87°C; $[\alpha]^{20}_D$ = +1.1° (5% in $CHCl_3$). Anal. ($C_{38}H_{40}N_2O_8$, MW: 652.742): Calculated: C 69.92; H 6.18; N 4.29; Found: C 69.7; H 6.3; N 4.2.

Di-Z-*D,D*-DAS-di-OH (37)

Compound **37** was prepared in the same manner as described for **30** with **36** as starting material. Yield 85%; mp 170-174°C. $[\alpha]^{20}_D$ = +9.7° (5% in DMF). Anal. ($C_{24}H_{28}N_2O_8$, MW: 472.499): Calculated: C 61.00; H 5.97; N 5.93; Found: C 61.1; H 6.0; N 6.0.

(±)-2,7-Bis-(benzyloxycarbonylamino)-suberic acid dimethyl ester (38)

(±)-2,7-Diazidosuberic acid dimethyl ester **32** (8.97g, 31.554mmol) was dissolved in dioxane (100mL) and was transformed into the diamino compound **33** as decribed above (see **34**). The catalyst was removed by filtration. Water (50mL) and $NaHCO_3$ (2g) was added to the filtrate followed by benzyloxycarbonyl chloride (12mL). The solution was stirred at ambient temperature overnight. More water (1000mL) was added and the product was extracted with ethyl acetate (3x150mL). The combined organic phases were dried with sodium sulfate, filtered and the filtrate was concentrated. The residue was crystallized from 100mL diisopropyl ether to yield 6.2g of **38**. mp 93-133°C. Anal. ($C_{26}H_{32}N_2O_8$, MW: 500.548): Calculated: C 62.38; H 6.44; N 5.60; Found: C 62.5; H 6.6; N 5.8.

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