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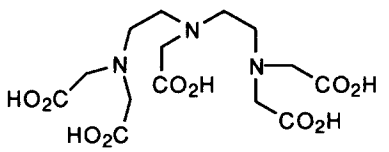
Synthesis of C_2-Symmetric (*S,S*)-1,4-Dibenzyl-DTPA and 1,4-*meso*-Dibenzyl-DTPA *via* Chiral Diamines

Hironao Sajiki*† and Karen Y. Ong

Metasyn, Inc., 71 Rogers St., Cambridge, Massachusetts 02142, USA

Abstract: *Novel routes to C_2-symmetric (S,S)-1,4-dibenzyl-DTPA and 1,4-meso-dibenzyl-DTPA are described. The methodology utilizes readily available starting materials.*

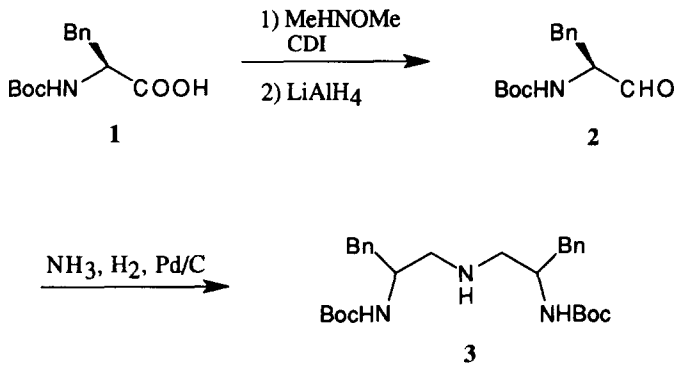
The ability of DTPA (diethylenetriamine pentaacetic acid) **1** and its derivatives to form stable complexes with gadolinium (III) allows for their use as MRI (magnetic resonance imaging) contrast agents.[1] As the MRI provides a safe and potential imaging utility, new medically useful chelates must show great biological interests. Among them, attachment of small molecular weight DTPA chelates to biological macromolecules with non-covalent interaction or covalent bonds, which increase the rotational tumbling time of DTPA chelates, can considerably enhance the water proton relaxation efficiency due to a better match between the frequency of electron-nuclear interactions and the proton Larmor frequency.[1,2] Thus, currently, the search for new contrast agents for MRI is directed toward the synthesis of functionalized derivatives of DTPA ligands without altering their chelating abilities.[3]



1

Introduction of an additional functional group in DTPA at one of the four carbons of the back bone have generally placed the *p*-ethoxybenzyl group[4] or *p*-nitrobenzyl group.[5] The addition of one more benzyl group lead to increase lipophilicity of the chelate and this is certainly one factor in generating the biological structures binding properties [for example: human serum albumin (HSA) binds a wide variety of endogenous metabolites and drugs, particularly anionic molecules with lipophilic groups[6]]. In this paper, we wish to describe the preparation of enantiomerically pure (*S,S*)-1,4-dibenzyl-DTPA **10a** together with the *meso*-analogue **10b** for use in the synthesis of anionic $Gd(DTPA)^{2-}$ derivatives which possess lipophilic benzyl groups. The lack of published synthetic methods for C_2-symmetric chiral DTPA derivatives makes it important to make widely applicable way to prepare them and the C_2-symmetric triamine intermediates **8** can be used as chiral auxiliaries.

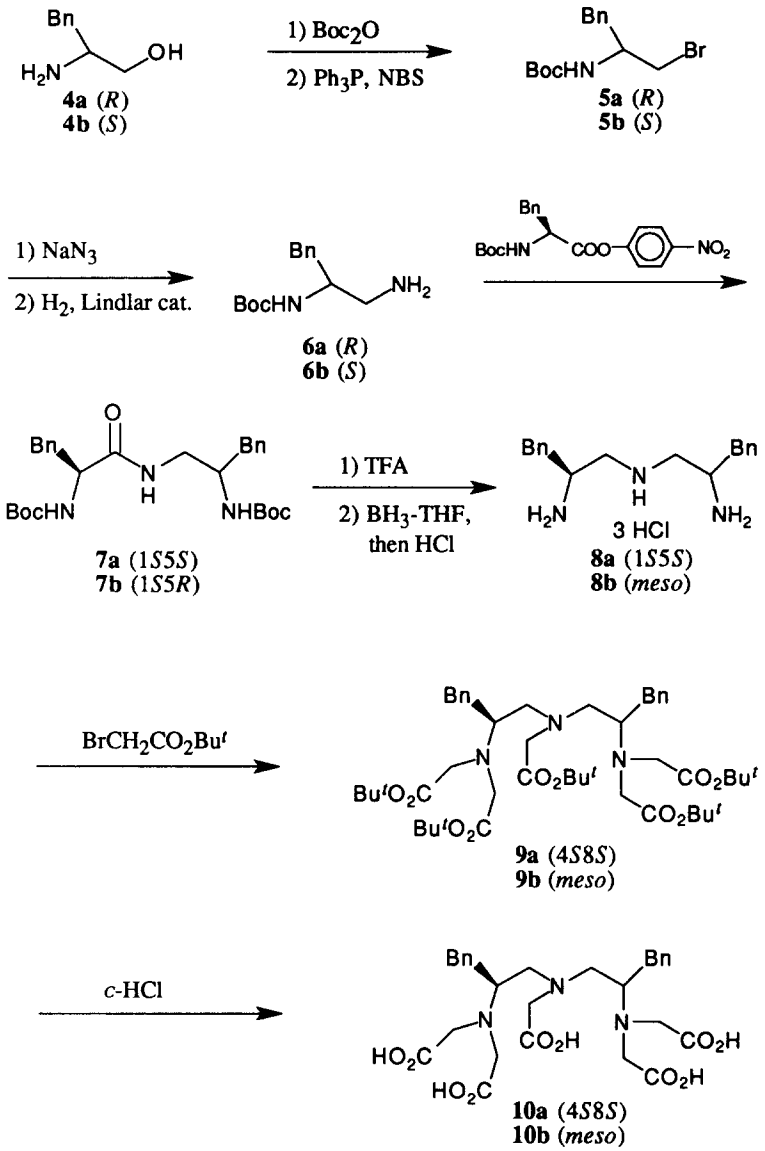
Scheme 1



To synthesize these 1,4-dibenzyl-DTPA derivatives **10a** and **10b**, we first attempted to prepare the homochiral (*S,S*)-dibenzyl-diethylenetriamine **3a** from N-Boc-L-phenylalanal **2**[7] prepared from N-Boc-L-phenylalanine **1**, using standard reductive amination conditions (Pd-C/H_2 and 2M ammonia-MeOH) gave the desired (*S,S*)-product **3a** along with significant amounts of the *meso*-product **3b** (3 : 1 — 2 : 1 mixture) (Scheme 1).[8] Based on this observation, to meet our needs for a enantiomerically pure synthesis of 1,4-dibenzyl-DTPA, we have investigated the synthesis of (*S,S*) and *meso*-dibenzyltriamine derivatives **8a** and **8b** derived from the commercially available (Aldrich Chemical Co.) phenylalaninols **4a** and **4b**[9] which are much more stable to epimerization.[10] In addition, since the benzyl groups originate from the aminoalcohol, access to a variety of functional groups is possible, depending on the aminoalcohol derived from the corresponding amino acid chosen.

2-Boc-amino-3-phenyl-propylbromides **5a** and **5b** were readily prepared from the corresponding phenylalaninols **4a** and **4b** as shown in Scheme 2. Treatment of phenylalaninols **4a** and **4b** with Boc_2O in THF gave the Boc phenylalaninols respectively and then directly treat the crude product with NBS and Ph_3P in CH_2Cl_2 to afford the bromides **5a** and **5b** in 46.7 % and 48.2 % yield, respectively, for two steps. These bromides **5a** and **5b** are stable and could be readily purified by short silica gel flash column chromatography.[11] Treatment of the bromides **5a** and **5b** with sodium azide in DMF at 60 ℃ gave the azides. It is practically convenient to isolate the azides by liquid-liquid extraction and then directly hydrogenated the crude product on Lindlar catalyst[12] in MeOH to afford the diamines **6a** and **6b** in 97 and 94 % yield, respectively, for two steps. After removal of the catalyst, these white waxy products were used in the next peptide coupling reaction with N-Boc-L-phenylalanine *p*-nitrophenyl ester without further purification. The diamines **6a** and **6b** were then converted to the diethylenetriamine derivatives **8a** and **8b**. The coupling reaction of the diamines **6a** and **6b** and the bromides **5a** and **5b** did not deliver the triamine even under heating conditions. Instead, decomposition of the bromides **5a** and **5b** were observed and thus peptide coupling reaction was considered in conversion of **6a** and **6b** to **8a** and **8b** *via* amide intermediates **7a** and **7b**. When commercially available N-Boc-L-phenylalanine *p*-nitrophenyl ester was performed with the diamines **6a** and **6b** in ethyl acetate at room temperature, the reaction gave the amides **7a** and **7b** in 89 and 98 % yield, respectively. Analysis of the amides **7a** and **7b** by ^1H and ^{13}C NMR determined no racemization. After removal of the Boc protecting groups of **7a** and **7b** using trifluoroacetic acid (TFA), the amide moiety may be reduced using BH_3-THF[13] to obtain C_2-symmetric (1*S*5*S*) triamine **8a** (74 %) and *meso*-triamine **8b** (88 %) as trihydrochloride salts. The structural assignment of **8a** and **8b** were readily achieved by their 300 MHz ^1H-NMR, 75 MHz ^{13}C-NMR and LRFABMS spectra analysis and elemental analysis.

Scheme 2



The triamines **8a** and **8b** are readily converted to the DTPA penta-*t*-butyl esters **9a** and **9b** by treatment with 6.8 equiv. of *t*-butyl bromoacetate and 11.8 equiv. of N,N-diisopropylethylamine in 98 % and 95 % yield, respectively, after silica gel column chromatography. Finally, the DTPA penta-*t*-butyl esters **9a** and **9b** were stirred at r.t. in *c*-HCl−ether to produce the deprotected DTPAs **10a** and **10b**. Both **10a** and **10b** are acidic. After removal of ether *in vacuo*, the pH of the aqueous solutions were adjusted to 2 with 2 M NaOH in ice bath to

give thoroughly HCl free **10a** and **10b** as white powder in 82 % and 87 % yield, respectively. Analysis and comparison of the DTPAs **10a** and **10b** by ^1H and ^{13}C NMR determined no racemization.

In summary, we have described the synthesis of C_2-symmetric (*S*,*S*)-1,4-dibenzyl-DTPA **10a** and 1,4-*meso*-dibenzyl-DTPA **10b** starting from readily available chiral phenylalaninols **4a** and **4b**, respectively, without racemization. These nine steps synthesis include only one column chromatography purification process and the crude intermediates were generally used in the next reaction without further purification. These synthetic methods should have some further utility in introduction of variety of substituents at the methylene moieties of diethylenetriamine derivatives, stereoselectively (*i.e.* **8a** and **8b**), which are of great importance in the stereoselective reactions as chiral auxiliaries.

EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. (*R*)-(+)-2-amino-3-phenyl-1-propanol (D-phenylalaninol) **4a**, (*S*)-(-)-2-amino-3-phenyl-1-propanol (L-phenylalaninol) **4b** and anhydrous N,N-dimethylformamide (DMF) were obtained from Aldrich Chemical Co., and N-Boc-L-phenylalanine *p*-nitrophenyl ester was obtained from BACHEM CALIFORNIA. THF was distilled from potassium benzophenone ketyl immediately prior to use. Methylene chloride was distilled over calcium hydride. All column chromatography were carried out under nitrogen by flash method described by Still[11] with silica gel (230-400 mesh, EM SEPARATIONS TECHNOLOGY or Fisher Scientific). All reactions were monitored by thin layer chromatography (TLC) performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (EM SEPARATIONS TECHNOLOGY), and compounds were visualized under Uv light (254 nm), ninhydrin reagent[14] with subsequent heating, or Dragendorff's reagent.[14] Melting points were determined on a Electrothermal digital melting point apparatus and were uncorrected. Routine ^1H-NMR spectra were recorded at 300 MHz, and coupling constants (*J*) were reported in hertz (Hz). ^{13}C-NMR spectra were obtained at 75.5 MHz. Low and high resolution mass spectra were carried out by Mass Spectrometry Lab., University of California, Berkeley, CA and microanalyses were accomplished at ATLANTIC MICROLAB, INC., GA, USA.

(*R*)-2-*t*-Butoxycarbonylamino-3-phenyl-1-propylbromide (5a). Di-*t*-butyl dicarbonate (Boc_2O) (7.27 g, 33.30 mmol) was added portionwise to a suspension of (*R*)-(+)-2-amino-3-phenyl-1-propanol **4a** (4.58 g, 30.29 mmol) in distilled THF (50 ml). The reaction mixture was stirred for 18 h at RT and concentrated *in vacuo*. The residue was partitioned between AcOEt (150 ml) and saturated Na_2CO_3 soln. The organic layer was washed with H_2O (50 ml x 2) and brine (50 ml), dried over $MgSO_4$ and evaporated. The solid residue was triturated with hexanes (70 ml) and filtered to afford a white solid which was used in the next reaction without further purification (6.90 g, 90.6 %). An analytical sample was prepared by recrystallization from hexanes-ether: ^1H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.42 (br, 1H, deuterium exchangeable), 2.84 (d, 2H, J = 7.2), 3.54 (dd, 1H, J = 10.9, 5.3), 3.66 (dd, 1H, J = 10.9, 3.6), 3.78-3.96 (m, 1H), 4,81 (br, 1H, slow deuterium exchangeable), 7.15-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.21, 37.27, 53.47, 63.52, 79.42, 126.24, 128.30, 129.20, 137.86, 156.05; LREIMS m/z 251 (M^+); Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.94; H, 8.42; N, 5.59.

Triphenylphosphine (8.61 g, 32.82 g) was added to a cooled (0 ℃) solution of the phenylalaninol (6.67 g, 26.54 mmol) in distilled CH_2Cl_2 (60 ml). N-Bromosuccinimide (NBS) (5.20 g, 29.19 mmol) was added to the stirring mixture portionwise over 5 min. After 2 h, evaporation of the solvent gave a semisolid residue which was

triturated with ether (150 ml) to a solid and subsequently removed by filtration. The ethereal layer was concentrated in vacuo and passed through a short column of silica gel, eluting with 20 % ether in hexanes to give the bromide **5a** which was used in the next reaction without further purification (4.30 g, 51.6 %): ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.85 (dd, 1H, *J* = 13.4, 8.4), 2.94 (dd, 1H, *J* = 13.4, 5.7), 3.36 (dd, 1H, *J* = 10.3, 3.5), 3.53 (dd, 1H, *J* = 10.3, 3.9), 3.86-4.16 (m, 1H), 4.80 (br, 1H), 7.17-7.24 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.33, 37.42, 38.81, 51.42, 80.03, 126.82, 128.68, 129.26, 137.04, 154.92.

(*S*)-2-*t*-Butoxycarbonylamino-3-phenyl-1-propylbromide (5b). Prepared from (*S*)-(-)-2-amino-3-phenyl-1-propanol **4b** by the same procedure as for **5a** (2 steps total 48.2 %).

(*R*)-2-*t*-Butoxycarbonylamino-3-phenyl-1-propylamine (6a). A mixture of the bromide **5a** (3.00 g, 9.55 mmol) and NaN_3 (0.65 g, 10.02 mmol) in anhydrous DMF (30 ml) was stirred at 60 ℃ under N_2 for 24 h. The solvent was evaporated and the residue was partitioned between AcOEt (30 ml) and saturated $NaHCO_3$ soln. (30 ml). The organic layer was washed with H_2O (30 ml) and brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with hexanes (50 ml) and filtered to give (*R*)-2-*t*-butoxycarbonylamino-3-phenyl-1-propylazide as a white solid which was used in the next reaction without further purification (2.51 g, 95.1 %). An analytical sample was prepared by recrystallization from hexanes-ether: ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.81 (dd, 1H, *J* = 13.6, 8.0), 2.91 (brdd, 1H, *J* = 13.6, 6.6), 3.33 (dd, 1H, *J* = 12.3, 4.5), 3.45 (brdd, 1H, *J* = 12.3, 4.2), 3.82-4.06 (m, 1H), 4.71 (brd, 1H, *J* = 5.4), 7.17-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.29, 38.10, 51.29, 53.06, 79.76, 126.72, 128.64, 129.25, 137.08, 155.03; LREIMS m/z 277 (M^++1); Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.87; H, 7.31; N, 20.37.
The mixture of the azide (2.48 g, 8.97 mmol) was hydrogenated on Lindlar catalyst (Aldrich Chemical Co.) (0.20 g) in MeOH at ordinary pressure and RT for 16 h. The catalyst was filtered off (celite cake), and the filtrate was concentrated *in vacuo*. The white waxy product **6a** (2.17 g, 96.6 %) was used in the next reaction without further purification: ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.62 (dd, 1H, *J* = 13.2, 6.9), 2.67-2.93 (m, 3H), 3.70-3.92 (m, 1H), 4.68 (br, 1H), 7.16-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.31, 38.81, 44.57, 53.95, 79.20, 126.32, 128.39, 129.24, 137.98, 155.74; HRFABMS m/z 251.1758 (M^++1, 95, calcd for $C_{14}H_{23}N_2O_2$ 251.1760).

(*S*)-2-*t*-Butoxycarbonylamino-3-phenyl-1-propylamine (6b). Prepared from **5b** by the same procedure as for **6a** (2 steps total 93.5 %).

3-Aza-1-(*S*)-5-(*S*)-dibenzylpentane-1,5-di-*t*-butoxycarbonylamine-2-one (7a). To a solution of the amine **6b** (2.70 g, 10.79 mmol) in EtOAc (200 ml) was added N-Boc-L-phenylalanine *p*-nitrophenyl ester (4.17 g, 10.79 mmol) at 0 ℃. The reaction mixture was stirred at RT overnight. The resulting precipitate was filtered and washed with AcOEt (25 ml x 5) and ether (25 ml x 2) to give a white solid which was used in the next reaction without further purification (4.78 g, 89.1 %). An analytical sample was prepared by recrystallization from AcOEt: ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.40 (s, 9H), 2.65 (dd, 1H, *J* = 13.5, 7.5), 2.70-2.89 (m, 1H), 3.04 (d, 2H, *J* = 6.6), 3.11-3.25 (m, 1H), 3.31 (dt, 1H, *J* = 13.5, 4.9), 3.66-3.92 (m, 1H), 4.14-4.39 (m, 1H), 4.72 (brd, 1H, *J* = 5.7, slow deuterium exchangeable), 5.02 (br, 1H, slow deuterium exchangeable), 6.21 (br, 1H, slow deuterium exchangeable), 7.07-7.38 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 28.24, 28.34, 38.66, 42.87, 52.16, 55.96, 79.61, 80.15, 126.59, 126.96, 128.56, 128.68, 129.19, 129.27, 136.68, 137.32, 155.32, 155.82, 171.92; LRFABMS m/z 498 (M^++1); Anal. Calcd for $C_{28}H_{39}N_3O_5$: C, 67.58; H, 7.90; N, 8.44. Found: C, 67.44; H, 7.88; N, 8.38.

3-Aza-1-(*S*)-5-(*R*)-dibenzylpentane-1,5-di-*t*-butoxycarbonylamine-2-one (7b). Prepared from the amine **6a** (2.17 g, 8.67 mmol) by the same procedure as for **7a** (4.21 g, 97.6 %): ^{1}H-NMR ($CDCl_3$) δ 1.37 (s, 18 H), 2.56 (dd, 1H, *J* = 13.7, 7.4), 2.68-2.86 (m, 1H), 3.03 (d, 2H, *J* = 6.9), 3.11-3.34 (m, 2H), 3.62-3.84 (m, 1H), 4.16-4.46 (m, 1H), 4.76 (brd, 1H, *J* = 7.5, slow deuterium exchangeable), 4.92 (br, 1H, slow deuterium exchangeable), 6.26 (br, 1H, slow deuterium exchangeable), 7.06-7.45 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 28.24, 28.33, 38.50, 38.64, 42.99, 52.10, 56.01, 79.56, 80.25, 126.63, 127.00, 128.59, 128.71, 129.15, 129.25, 136.61, 137.30, 155.30, 155.91, 171.96; LRFABMS m/z 498 (M^++1); Anal. Calcd for $C_{28}H_{39}N_3O_5$: C, 67.58; H, 7.90; N, 8.44. Found: C, 67.71; H, 7.97; N, 8.43.

3-Aza-1-(*S*)-5-(*S*)-dibenzylpentane-1,5,-diamine Trihydrochloride (8a). The solution of **7a** (4.53 g, 9.10 mmol) in TFA (20 ml) and distilled CH_2Cl_2 (30 ml) was stirred at RT for 1 h, and the solvents were removed *in vacuo*. The residue was taken up in absolute EtOH (25 ml), and evaporated *in vacuo*. The oily residue was dried under vacuum at RT for 4 h to give the deprotected amide (2.51 g, 93.0%) which was used in the next reaction without further purification: ^{1}H-NMR (D_2O) δ 2.52 (dd, 1H, *J* = 14.5, 8.1), 2.64 (dd, 1H, *J* = 14.5, 6.3), 2.92 (dd, 1H, *J* = 13.4, 7.5), 3.00 (dd, 1H, *J* = 13.4, 6.9), 3.23 (brd, 2H, *J* = 2.0), 3.32-3.49 (m, 1H), 4.02 (t, 1H, *J* = 7.7), 7.02-7.33 (m, 10H);
A solution of the deprotected amide (2.50 g, 8.43 mmol) in 1M BH_3-THF (80 ml, 80 mmol) was refluxed under N_2 for 40 h. The reaction mixture was quenched with dry MeOH (5 ml) at 0 ℃, and the solvents were evaporated *in vacuo*. The residue was treated with absolute EtOH (50 ml), and EtOH was evaporated off. The resulting oily product was taken up in absolute EtOH (50 ml), saturated with HCl (gas) at 0 ℃ and raised to a reflux for 24 h. The solution was cooled and then left at 0 ℃ for 0.5 h. The white-powder precipitate **8a** (2.65 g, 80.1%) was collected, washed with EtOH (20 ml) and ether (100 ml), and dried in a vacuum desiccator: ^{1}H-NMR (D_2O) δ 2.83 (dd, 2H, *J* = 14.2, 8.6), 2.98 (dd, 2H, *J* = 14.2, 6.6), 3.20 (dd, 2H, *J* = 13.7, 5.3), 3.26 (dd, 2H, *J* = 13.7, 6.6), 3.72-3.81 (m, 2H), 7.14-7.29 (m, 10H); ^{13}C-NMR (D_2O, CD_3OD as the internal standard) δ 37.35, 50.37, 51.09, 129.09, 130.36, 134.76; LRFABMS m/z 284 (M^++1, as a free triamine); Anal. Calcd for $C_{18}H_{28}N_3Cl_3$: C, 55.04; H, 7.18; N, 10.70; Cl, 27.08. Found: C, 54.81; H, 7.24; N, 10.58; Cl, 26.96.

3-Aza-1,5-*meso*-dibenzylpentane-1,5,-diamine Trihydrochloride (8b). The solution of **7b** (3.97 g, 7.98 mmol) in TFA (20 ml) and distilled CH_2Cl_2 (30 ml) was stirred at RT for 1 h and the solvents were removed *in vacuo*. The residue was taken up in absolute EtOH (25 ml), and evaporated *in vacuo*. The oily residue was dried under vacuum at RT for 4 h to give the deprotected amide (2.31 g, 97.7%) which was used in the next reaction without further purification: ^{1}H-NMR (D_2O) δ 2.53 (brdd, 1H, *J* = 13.8, 9.9), 2.62 (brdd, 1H, *J* = 13.8, 6.9), 2.91-3.09 (m, 2H), 3.12-3.41 (m, 3H), 4.01 (brt, 1H, *J* = 7.8), 7.00-7.29 (m, 10H).
A solution of the deprotected amide (2.30 g, 7.76 mmol) in 1M BH_3-THF (80 ml, 80 mmol) was refluxed under N_2 for 40 h. The reaction mixture was quenched with dry MeOH (5 ml) at 0 ℃ and the solvents were evaporated *in vacuo*. The residue was treated with absolute EtOH (50 ml), and EtOH was evaporated off. The resulting oily product was taken up in absolute EtOH (50 ml), saturated with HCl (g) at 0 ℃, and raised to a reflux for 24 h. The reaction solution was cooled and then left at RT for 2 h. The recrystallized white crystals **8b** (2.76 g, 90.5%) were collected, washed with EtOH (20 ml) and ether (50 ml), and dried in a vacuum desiccator: ^{1}H-NMR (D_2O) δ 2.82 (dd, 2H, *J* = 14.4, 8.7), 2.98 (dd, 2H, *J* = 14.4, 6.3), 3.17-3.29 (m, 4H), 3.72-3.81 (m, 2H), 7.14-7.29 (m, 10H); ^{13}C-NMR (D_2O, CD_3OD as the internal standard) δ 37.31, 50.46, 51.16, 129.09, 130.36, 134.78; LRFABMS m/z 284 (M^++1, as a free triamine); Anal. Calcd for $C_{18}H_{28}N_3Cl_3 \cdot 0.25\ H_2O$: C, 54.42; H, 7.23; N, 10.58; Cl 26.77. Found: C, 54.43; H, 7.23; N, 10.33; Cl, 26.79.

3,6,9-Triaza-3,6,9-tris-(*t*-butoxycarbonylmethyl)-4-(*S*)-8-(*S*)-(dibenzyl)undecanedioic Acid Di-*t*-butyl Diester (9a). To a solution of the dibenzyl diethylenetriamine **8a** (2.32 g, 5.91 mmol) and N,N-diisopropylethylamine (12.19 ml, 70 mmol) in anhydrous DMF (20 ml) at RT under N_2 was added *t*-butyl bromoacetate (6.46 ml, 40 mmol) and allowed to stir for 40 h at RT. Solvents were then evaporated *in vacuo*, and the residue was partitioned between AcOEt (50 ml) and H_2O (50 ml). The AcOEt layer was washed with H_2O (50 ml), saturated $NaHCO_3$ soln. (50 ml), H_2O (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography (hexanes : ether = 10:1 - 1:1) to give the pure product **9a** (pale yellow oil, 4.93 g, 97.6%): ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.41 (s, 36H), 2.34 (brd, 1H, *J* = 8.6), 2.39 (brd, 1H, *J* = 8.6), 2.59 (brd, 1H, *J* = 5.9), 2.63 (brd, 1H, *J* = 5.9), 2.74-2.86 (m, 6H), 3.36 (s, 8H), 3.43 (d, 2H, *J* = 9.3), 7.08-7.21 (m, 10H) ; ^{13}C-NMR ($CDCl_3$) δ 28.10, 36.93, 53.20, 55.73, 56.71, 63.95, 80.29, 80.46, 125.64, 128.11, 129.25, 140.67, 171.27, 171.50; HRFABMS m/z 854.5507 (M^++1, 28, calcd for $C_{48}H_{76}N_3O_{10}$ 854.5531).

3,6,9-Triaza-3,6,9-tris-(*t*-butoxycarbonylmethyl)-4,8-*meso*-(dibenzyl)undecanedioic Acid Di-*t*-butyl Diester (9b). Prepared from **8b** (2.42 g, 6.17 mmol) by the same procedure as for **9a** (pale yellow oil, 5.00 g, 94.9%): ^{1}H-NMR ($CDCl_3$) δ 1.32 (s, 9H), 1.41 (s, 36H), 2.41 (dd, 2H, *J* = 13.6, 5.7), 2.54 (dd, 2H, *J* = 13.6, 7.7), 2.74 (dd, 2H, *J* = 13.6, 7.2), 2.84 (dd, 2H, *J* = 13.6, 5.9), 2.95-3.04 (m, 2H), 3.36 (s, 2H), 3.41 (s, 8H), 7.09-7.22 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 28.11, 37.18, 53.28, 55.51, 56.26, 63.05, 80.43, 125.67, 128.15, 129.23, 140.54, 171.34, 171.44; HRFABMS m/z 854.5515 (M^++1, 52, calcd for $C_{48}H_{76}N_3O_{10}$ 854.5531).

3,6,9-Triaza-3,6,9-tris-(hydroxycarbonylmethyl)-4-(*S*)-8-(*S*)-(dibenzyl)undecanedioic Acid [(*S,S*)-1,4-dibenzyl-DTPA] (10a). To a stirring solution of **9a** (4.80 g, 5.63 mmol) in ether (20 ml) was added *c*-HCl (trace metal grade, 5 ml). Solution was stirred overnight. Ether was removed *in vacuo*, and the pH of the solution was adjusted to between 3.3 and 3.6 with 2M NaOH in ice bath. The resulting off-white semi-solid precipitate **10a** (1.85 g) was filtered, washed with H_2O (50 ml) and ether (50 ml), and dried under a vacuum desiccator. The pH of filtrate was readjusted to 2, and left at RT overnight. The resulting white crystals **10a** were collected (0.78 g), washed with ether (50 ml), and dried in a vacuum desiccator (total yield: 81.7%). m.p. 157.2-161.0 ℃; ^{1}H-NMR (D_2O, pH 2.5-3.0) δ 2.43 (brt, 2H, *J* = 11.4), 2.74-3.06 (m, 8H), 3.29 (d, 4H, *J* = 17.7), 3.49 (d, 4H, *J* = 17.7), 3.62 (d, 1H, *J* = 17.6), 3.97 (d, 1H, *J* = 17.6), 6.99 (brd, 4H, *J* = 7.2), 7.16-7.28 (m, 6H); ^{13}C-NMR (D_2O, CD_3OD as the internal standard, pH 2.2) δ 34.39, 51.20, 53.71, 56.57, 62.45, 128.23, 130.12, 130.34, 137.86, 171.28, 175.06; LRFABMS m/z 574 (M^++1); Anal. Calcd for $C_{28}H_{35}N_3O_{10}(Cl_0)$: C, 58.63; H, 6.15; N, 7.33; Cl, 0.00. Found: C, 57.61; H, 6.19; N, 7.18; Cl, 0.00.

3,6,9-Triaza-3,6,9-tris-(hydroxycarbonylmethyl)-4,8-*meso*-(dibenzyl)undecanedioic Acid (1,4-*meso*-dibenzyl-DTPA) (10b). To a stirring solution of **9b** (4.86 g) in ether (20 ml) was added *c*-HCl (trace metal grade, 5 ml). Solution was stirred overnight. Ether was removed *in vacuo*, and the pH of the solution was adjusted to between 3.3 and 3.6 with 2M NaOH in ice bath. The resulting white powder **10b** (1.30 g) was filtered, washed with H_2O (50 ml) and ether (50 ml), and dried in a vacuum desiccator. The pH of filtrate was adjusted to 2, and the white powder precipitate **10b** (1.52 g) was collected, washed with ether (50 ml), and dried in a vacuum desiccator (total yield: 86.5%). m.p. 202.9-204.4 ℃; ^{1}H-NMR (D_2O, pH 3.0) δ 2.69 (dd, 2H, *J* = 14.1, 8.6), 2.85 (dd, 2H, *J* = 14.1, 5.0), 2.91-2.98 (m, 4H), 3.39-3.46 (m, 2H), 3.48 (d, 4H, *J* = 16.7), 3.55 (s, 2H), 3.58 (d, 4H, *J* = 16.7), 7.07 (brd, 4H, *J* = 7.2), 7.14-7.25 (m, 6H); ^{13}C-NMR (D_2O, CD_3OD as the internal standard, pH 2.2) δ 34.39, 53.03, 55.99, 62.61, 128.10, 130.09, 130.18, 169.77, 175.76; LRFABMS m/z 574 (M^++1); Anal. Calcd for $C_{28}H_{35}N_3O_{10}(Cl_0)$: C, 58.63; H, 6.15; N, 7.33; Cl,

0.00. Found: C, 58.42; H, 6.11; N, 7.29; Cl, 0.00.

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†Present address: Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan, Fax: +81(58)2375979, e-mail: sajiki@gifu-pu.ac.jp.

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