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Use of the Mitsunobu Reaction In The Synthesis of Polyamines

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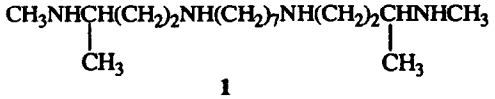
Abstract. The Mitsunobu reaction has been used in the synthesis of polyamine analogues. The synthesis of the (R,R), (S,S) and meso- isomers of a tetraamine are described. The chemistry was used to synthesize a fluorinated polyamine analog and a hexaamine.

INTRODUCTION

Analogues of the naturally occurring polyamines spermine and spermidine inhibit tumor growth in experimental tumor models[1]. As a result of these observations we made a major commitment to the synthesis of this class of compounds. In the course of this work, we have developed a stereospecific synthesis of secondary amines which has proven particularly versatile for the preparation of chiral as well as achiral polyamines. A preliminary communication of this work has been published[2]; this report presents a full account of the application of this synthesis to prepare both chiral and achiral polyamines and compares our methodology with that reported by the Weinreb group[3] for the synthesis of racemic secondary amines. Specifically, we report the stereospecific synthesis of all stereoisomers of the polyamine **1** [**1a** (R,R), **1b** (S,S), and **1c** (meso)], the synthesis of **24**, a fluorine containing spermine analog and the synthesis of **31**, a hexamine containing a repeating diaminobutane moiety.



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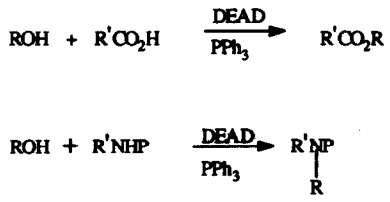
RESULTS AND DISCUSSION

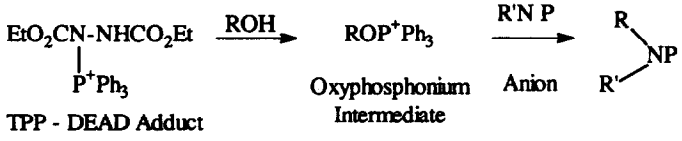
Chiral Amine. The racemic target molecule (**1**) has broad spectrum antitumor activity in animal models. Since diastereomers of polyamine analogs often display differing biological activities[4], it was of interest to synthesize the stereoisomers of **1**. We rationalized that the Mitsunobu reaction between an alcohol and an activated amine (see Scheme I) would provide a route to the desired chiral polyamines as well as a new route to secondary amines. Mitsunobu reported that alcohols react with carboxylic acids to give esters in the presence of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD)[5]. This reaction was expanded to include a variety of acidic compounds including phthalimide, which provided a useful synthesis of protected primary amines from alcohols. When this work was initiated only primary amines had been prepared from alcohols via the Mitsunobu reaction,[5,6] but we felt that the methodology could be expanded to secondary amines to provide a route to the stereoisomers (**1a-c**) of polyamine **1**.

Modifying the Mitsunobu reaction to include the synthesis of secondary amines (Scheme 1) would require the acidic component (**2**) to be an activated primary amine (where P is an electron withdrawing protecting



Scheme 1

group), with a pKa of 11 or less. This minimum pKa value has been established; malononitrile (pKa 11.2) will react with alcohols but diethyl malonate (pKa 13.3) will not under Mitsunobu reaction conditions[7a], (a recent report by Tsunoda, et al has reported new reaction conditions under which malonate esters can be utilized[7b]). We reasoned that an activated primary amine with a relatively low pKa would provide the desired product in higher yield than one with a pKa closer to 11. N-Methyltrifluoromethanesulfonamide ($TfNHCH_3$, **3**) pKa 7.5[7] was selected and yields were compared with those obtained with the reagent N-methyl-p-toluenesulfonamide ($TsNHCH_3$, **4**),pKa 11.7[8], used by Weinreb[3]. Interestingly, Mitsunobu reported an attempt to use p-toluenesulfonamide as the acidic component for a modification of his reaction, but obtained the triphenylphosphine imine [$TsN=P(Ph)_3$] as the only product[6].

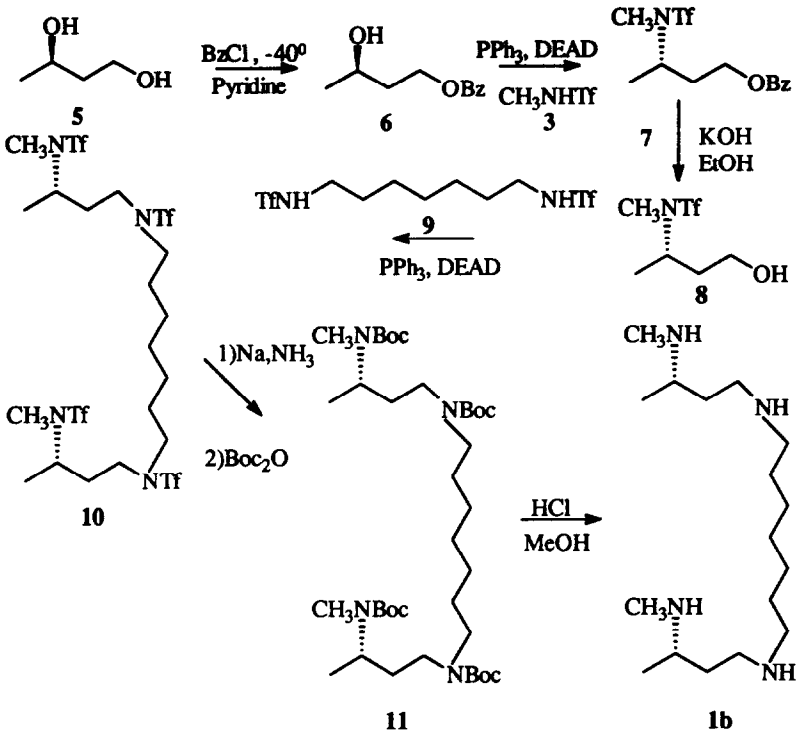


The importance of the pKa of the acidic component in the Mitsunobu reaction has been the subject of a group of mechanistic papers[9], and a correlation between pKa_a and yield has been reported[9c,d]. The reaction sequence is shown in the figure above: the step most influenced by the pKa of the acidic component is reaction of the anion of the acidic component with the oxyphosphonium intermediate[9b]. At the pKa of **3** and **4** this S_N2 reaction is the rate determining step. The higher yield of product from the more acidic **3** comes from the enhancement of the rate of this step decreasing the time for the oxyphosphonium intermediate to undergo side reactions such as elimination[9b].

The synthesis followed the sequence shown in Scheme 2, as shown for the (S,S)-isomer (**1b**). (R)-1,3-Butanediol (**5**)[10] was selected as the starting material for the proposed chiral synthesis.Benzoylation of **5** by the procedure of Seebach, et al.[11] gave the mono-benzoate (**6**) in 72 % yield. Compound **6** was treated with N-methyltriflamide (**3**) under Mitsunobu conditions (PPh_3, DEAD, THF) to provide **7** with inversion of configuration (vide infra). N-Methyltriflamide (**3**) was synthesized by reaction of triflic anhydride with methylamine.

Debenzoylation of **7** provided **8**, the four carbon unit of desired chirality for use in subsequent steps of the proposed sequence. The bistriflamide of 1,7-diaminoheptane (**9**) was prepared by reaction of the diamine with triflic anhydride as described for compound **3**. In this case, however, the product contained compounds in which two trifluoromethanesulfonyl groups had added to one nitrogen atom. This mixture was converted to the desired 1,7-bistriflamide by the use of Claisen's alkali as described by Musser, et al.[12] Reaction of **8** with the bistriflamide (**9**) gave the fully protected tetraamine (**10**). The triflate activating groups were removed from compound **10** with sodium / liquid ammonia. Isolation of the highly polar tetraamine from the reaction mixture was best accomplished by reaction of the tetraamine with di-t-butyldicarbonate to give the tetra-Boc derivative (**11**). which was readily purified by conventional flash chromatography. The Boc groups were removed with anhydrous HCl in methanol to provide **1b** as the tetrahydrochloride salt. Synthesis of the (R,R)-isomer (**1a**) began with (S)-**5** while the meso compound **1c** required stepwise reaction of (R)- then (S)-

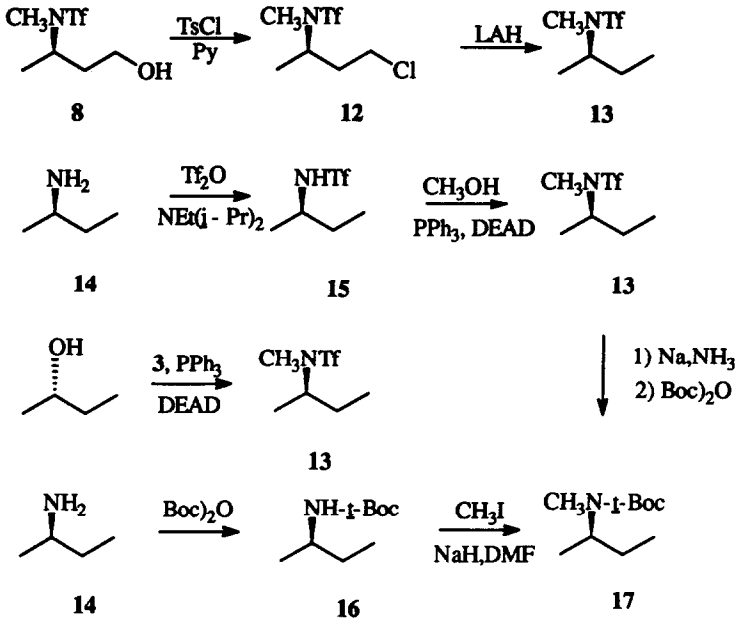
isomers of **8** with compound **9**. The chirality of the products (**1a-c**) was assigned based on the chirality



Scheme 2

of the terminal amine portion (see below and Scheme 3).

N-Methyl-p-toluenesulfonamide (**4**), used by Weinreb[3] for the synthesis of secondary amines, could be substituted for **3** in the Mitsunobu reactions illustrated in Scheme 2, but lower yields were obtained. For the conversion of **6** to **7**, yields were 58% with **3** vs 48% with **4**, and for the conversion of **8** to **10** yields were 72% vs 35%, respectively. The stereochemical outcome of these reactions was established by interconversion of model systems (Scheme 3) and was consistent with the inversion of configuration usually observed with the Mitsunobu reaction[13]. The inter-conversions gave derivatives that were compared to the same compounds prepared from the commercially available (R)-(-)-2-aminobutane (**14**). Intermediate **8**, used in the synthesis of **1a** was prepared from (S)-(+)-1,3-butanediol and was converted in two steps to (R)-(-)-2-(N-methyltrifluoromethanesulfonamido)butane (**13**). This was established unequivocally by preparing **13** from (R)-(-)-2-aminobutane (**14**). The two samples of **13** gave optical rotation values of -13.1 and -15.0°, respectively. In addition, compound **13** was synthesized from (S)-2-butanol, which provided material with an optical rotation of -14.5°. To demonstrate that removal of the triflate activating group did not cause racemization, **13** was converted to the Boc derivative (**17**); **17** was also prepared from (R)-(-)-2-aminobutane. Optical rotations for the two samples of **17** were -16.0 and -15.1°, respectively. These data establish that inversion occurs at the chiral center and that the reaction conditions for removal of the activating triflate group do not result in the loss of chirality at this center.



Scheme 3

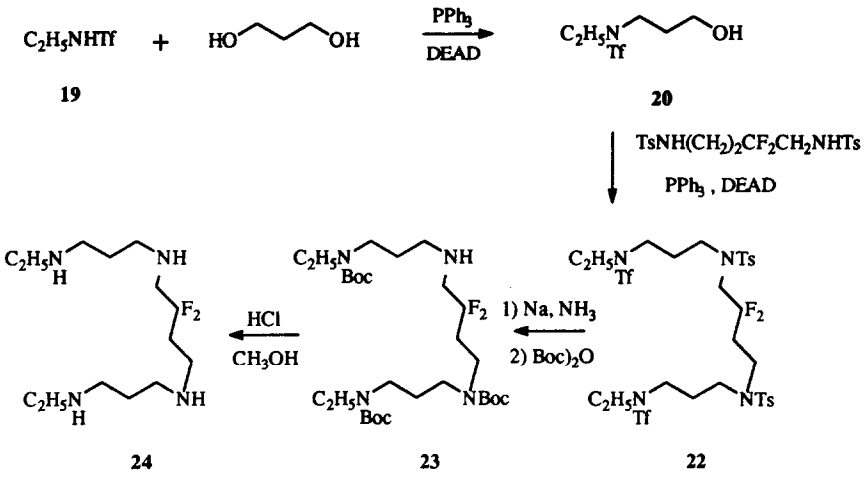
FLUORINATED SPERMINE ANALOG

The difluoro spermine analog (**24**) was synthesized to determine the effect of fluorine substitution on the antitumor agent N^1,N^9-diethylspermine (**18**)[14]. The synthesis followed the route outlined in Scheme 4. Treatment of N-ethyltriflamide (**19**) with excess 1,3-propanediol under Mitsunobu reaction conditions

$$C_2H_5NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NHC_2H_5$$

18

gave acceptable yields of the monosubstituted product (**20**). Reaction of **20** with the bis-tosylamide of difluoroputrescine (**21**) gave the fully protected tetraamine (**22**). The tosylamide activating group, rather than the triflamide, was utilized because reaction of difluoroputrescine with triflic anhydride, as described for the preparation of **3**, did not give isolable amounts of the desired bistriflamide. The yields in this case were variable - in the case where two equivalents of **20** were utilized the reaction gave a mixture of mono and di-substituted products in a ratio of 2:1. Use of three equivalents of **20** resulted in improved yield of the desired di-substituted product (72%). Removal of protecting groups from **22** was accomplished with sodium-ammonia and the tetraamine was isolated as the tri-Boc derivative (**23**) in 29% overall yield.
Isolation of a tri-Boc derivative is consistent with low reactivity at the poorly basic nitrogen atom beta to the difluoromethylene group. The tetrahydrochloride (**24**) final product proved difficult to characterize due to contamination with trihydrochloride, again illustrating the weakly basic nitrogen atom. The low yield reflects in part the repeated recrystallizations of **24** in an attempt to obtain pure tetrahydrochloride.



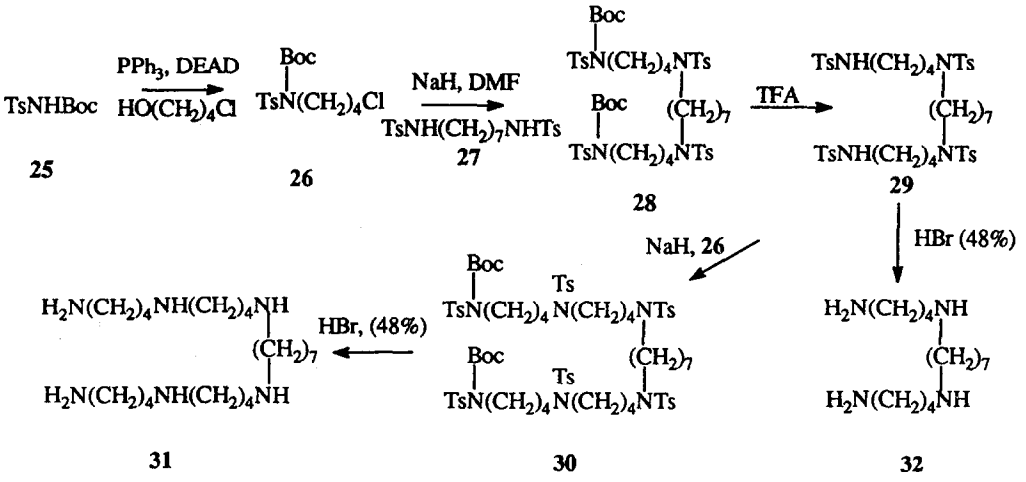
Scheme 4

LINEAR REACTION

Addition of 3-aminopropane groups to an amine can be achieved by the sequence of addition to acrylonitrile followed by reduction[15]. A more complicated synthesis enabling introduction of 4-aminobutane groups has been reported.[16] However, a general procedure for introduction of the aminoalkyl functionality was unavailable. This section describes a process for introduction of a 4-aminobutane chain that should be general for any chain length. The procedure utilizes N-Boc-p-toluenesulfonamide (**25**), reported as a reagent for the synthesis of primary amines.[3] We used this reagent for the synthesis of tetraamine **32** and hexaamine **31** (Scheme 5).

For this synthesis a 4-aminobutane group must be introduced to a central diamine. A useful synthon to effect this transformation through Mitsunobu chemistry would be a protected aminobutanol. Analogous to the synthesis of **20**, compound **25** was reacted with 1,4-butanediol (PPh_3, DEAD). Unreacted **25** was the only product isolated from this reaction, probably due to formation of tetrahydrofuran from the 1,4-butanediol. Use of 4-chloro-1-butanol in the reaction with **25** yielded the product **26** which proved satisfactory for the synthesis of **31** and **32**. Alkylation of tosyl protected amines with alkyl halides by use of DMF/NaH has been reported to proceed in high yield[16]. These conditions were utilized in the reaction of **26** with the bis-p-toluenesulfonamide of 1,7-diaminohexane (**27**) to give the fully protected tetraamine (**28**) in 51% yield. The Boc and Ts protecting groups were removed from **28** to give the desired tetraamine (**32**).

The Boc protecting groups of **28** can be selectively removed[3] and by treatment with TFA the tetra-tosylamide **29** was obtained. Reaction of this product with **26** gave the fully protected hexaamine (**30**) which, on treatment with 48% aqueous HBr, afforded the hexaamine **31**. It should be noted that this sequence can be repeated to give extended polyamine analogs.



Scheme 5

In summary, a new synthesis of chiral secondary amines has been developed and applied to the synthesis of **1a, 1b, 1c**. This chemistry was also used in the synthesis of the achiral compounds **24** and **31** and should prove useful as a general synthesis of a wide variety of secondary amines from alcohols.

EXPERIMENTAL SECTION

General Procedures. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Marion Merrell Dow Research Institute Analytical department and, unless otherwise indicated, agree with theoretical values within ±0.4%. NMR spectra were obtained on a Varian VXR-300 or EM-360L spectrometer. Chemical shifts are reported downfield from TMS in spectra obtained in $CDCl_3$ and from DSS in spectra obtained in D_2O. IR spectra were obtained on a Perkin-Elmer 1800 FT IR spectrometer. Thin-layer chromatography (TLC) were developed on Merck silica gel F254 analytical plates, visualized with I_2, UV light, phosphomolybdic acid or $KMnO_4$. Optical rotation values were determined at 20° C. Where elemental analyses indicate solvent to be present, the values for amount of solvent present in the sample are supported by nmr (toluene, methanol) or loss on heating (hydration).

N-Methyltrifluoromethanesulfonamide (3). Methylamine (15.5 g, 0.5 mole) was added to chilled (-70°) CH_2Cl_2 (250 mL). A solution of triflic anhydride (28.2 g, 0.1 mole) in CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred at -70° for 3 h. The mixture was washed with 1N HCl (2 x 250 mL) and the organic layer was separated and dried ($MgSO_4$). The solvent was removed at atmospheric pressure by slow distillation through a column (500 x 20 cm) packed with glass helices (product codistills with solvent, and evaporation of solvent on a rotary evaporator gives very low yields). The product was distilled to give 9.3 g (57%) of a clear liquid, bp 95 - 98° C / 30 mm (lit[7] bp 90 - 94° C / 20 mm). IR ($CHCl_3$) 3332, 1442, 1366, 1234, 851 and 608 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.90 (broad s, 1H), 2.97 (s, 3H) ^{19}F ($CDCl_3$) δ -77.54 (s). MS (CI/CH_4) 164 (M + H). Anal. Calcd for $C_2H_4F_3NO_2S$: C, 14.72; H, 2.47; N, 8.59; S, 19.66. Found: C, 14.82; H, 2.92; N, 8.68; S, 19.64.

Similarly prepared was **19**, bp 95 - 97 ° C / 0.3 mm.

(R)-(-)-1,3-Butanediol 1-Benzoate (6). A solution of (R)(-)-1,3-butanediol (Wako Chemical $[\alpha]_D^{20}$ -24.0 (c = 1.11, ethanol) (10 g, 0.11 mole) and pyridine (12.5 mL, 0.11 mole) in dichloromethane (100 mL) was chilled to -40° C and a solution of benzoyl chloride (12.9 mL, 0.11 mole) in dichloromethane (30 mL) was added dropwise over 1 h. The reaction temperature was maintained at -40° C for 3 h, and the mixture was stirred an additional 18 h at ambient temperature. The mixture was diluted to 500 mL (CH_2Cl_2) and extracted with 1N HCl and aq. $NaHCO_3$. The organic layer was dried, evaporated, the residue was chromatographed and the product distilled to give 15.3 g (72%) of a clear liquid, bp 125 - 127° C / 0.5 mm. IR (film) 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 7.5 Hz, 3H), 1.8 - 2.0 (m, 2H), 2.12 (d, J = 7.5 Hz, 1H), 3.9 - 4.05 (m, 1H), 4.32 - 4.42 (m, 1H), 4.58 - 4.68 (m, 1H), 7.4 - 7.5 (m, 1H), 7.53 - 7.6 (m, 1H) and 8.01 - 8.05 (m, 2H). MS (CI/CH_4) 195 (M + H). OR: $[\alpha]_D^{20}$ -18.1 (c=1.08, $CHCl_3$). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.30.

By the same procedure was prepared (S)-(+)-1,3-butanediol 1-benzoate, bp 140-45° C / 1.0 mm, $[\alpha]_D^{20}$ +21.7 (c = 1.02, EtOH). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.18; H, 7.35.

(S)-(+)-3-[(N-Methyl-N-trifluoromethanesulfonyl)amino]-1-butanol Benzoate (7). A solution of DEAD (11.2 g, 64 mmol) in THF (40 mL) was added dropwise to a solution of R-(-)-(6) (12.5 g, 64 mmol), 3 (10.9 g, 64 mmol) and PPh_3 (16.8g, 64 mmol) in THF (190 mL). The mixture was stirred 30 min, evaporated and the residue was chromatographed (toluene/hexane, 1/1). The product (12.7 g, 58%) was utilized without further purification. Bp 165° C / 0.75 Torr. IR (film) 1722, 1388, 1278, 1186, 1124, 714 and 596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 7.5 Hz, 3H), 1.9 - 2.12 (m, 2H), 2.95 (s, 3H), 4.29 - 4.45 (m, 3H), 7.4 - 7.48 (m, 2H), 7.55 - 7.6 (m, 1H) and 8.0 - 8.08 (m, 2H). MS (CI/CH_4) 236 (M + H). OR: $[\alpha]_D^{20}$ +17.1 (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{16}F_3NO_4S$: C, 46.01; H, 4.75; N, 4.12. Found: C, 45.74; H, 4.73; N, 4.01.

Similarly prepared was the (R)- isomer, bp 150 - 155° C / 0.5 mm, $[\alpha]_D^{20}$ -17.2 (c = 1.05, $CHCl_3$). Anal. Calcd for $C_{13}H_{16}F_3NO_4S$: C, 46.01; H, 4.75; N, 4.12. Found: C, 46.01; H, 4.75; N, 4.18.

(S)-(+)-3-[(N-Methyl-N-trifluoromethanesulfonyl)amino]-1-butanol (8). Compound 7 (10.2 g, 30 mmol) was dissolved in ethanol (100 mL), a solution of KOH in ethanol (1N, 65 mL) was added and the mixture was stirred for 3 h. The mixture was poured into CH_2Cl_2/H_2O (500 mL each) and the organic layer was separated, dried and evaporated. The residue was chromatographed (toluene/ethyl acetate 4/1) and the product was distilled to give a clear liquid (3.8 g, 54%) bp 100° C/ 1 mm. IR (film) 1386, 1374, 1227, 1184, 1123, 1055, 964 and 597 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 7.5 Hz, 3H), 1.75 (m, 2H), 2.1 (bs, 1H), 2.91 (s, 3H), 3.7 (m, 2H) and 4.28 (m, 1H). MS (CI/CH_4) 236 (M + H). OR: $[\alpha]_D^{20}$ +19.0 (c = 1.0, $CHCl_3$). Anal. Calcd for $C_6H_{12}F_3NO_3S$: C, 30.63; H, 5.14; N, 5.96. Found: C, 30.43; H, 5.04; N, 5.91.

Similarly prepared was the (S)- isomer, bp 124 - 28 / 0.8 mm, $[\alpha]_D^{20}$ -18.8 (c = 0.97, $CHCl_3$). Anal. Calcd for $C_6H_{12}F_3NO_3S$: C, 30.63; H, 5.14; N, 5.96. Found: C, 30.50; H, 5.25; N, 5.73.

1,7-(Bis)-Trifluoromethanesulfonamidoheptane (9). A solution of 1,7-diaminoheptane (1.52 g, 11.7 mmol) in CH_2Cl_2 (117 mL) was chilled to -70° C. Dropwise, from separate funnels, was added di-isopropylethylamine (6.21 mL, 35 mmol) and triflic anhydride (10 g, 35 mmol) at a rate which maintained the reaction temperature below -70° C. Two hours after addition was complete, the mixture was warmed to 0° C and 60 mL of Claisen's alkali[18] was added dropwise over 15 min, while maintaining a reaction temperature below 5° C. The mixture was stirred an additional 1 h, diluted with water (200 mL) and the aqueous layer was separated. The organic layer was washed with two 200 mL portions of 1N NaOH. The combined aqueous layers were acidified and extracted with CH_2Cl_2 (2 x 400 mL). The combined organic extracts were dried, evaporated and the residue was recrystallized (hexane / CH_2Cl_2) to give 2.0 g (43%) of a white solid, mp 43.5 - 45.0° C. IR (KBr) 2942, 1430, 1368 and 1148 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.30 (br. s, 2H), 3.15

(t, J = 7.5 Hz, 4H), 1.50 (m, 4H), 1.30 (m, 6H). MS (CI/CH_4) 395 (M + H). Anal: Calcd for $C_9H_{16}F_6N_2O_4S_2$: C, 27.41; H, 4.09; N, 7.10. Found: C, 27.44; H, 4.21; N, 7.12.

(S,S)-2,6,14,18-Tetraaza-3,17-dimethyl-2,6,14,18-tetra-(trifluoromethane-sulfonyl)nonadecane (10). A solution of **8** (2.35 g, 10 mmol), PPh_3 (2.6 g, 10 mmol) and **9** (2 g, 5 mmol) in THF (50 mL) was stirred at ambient temperature while a solution of DEAD (1.74 g, 10 mmol) in THF (5 mL) was added dropwise. After one hour, tlc (toluene/ethyl acetate 4/1) indicated reaction still contained significant amounts of mono-adduct; another 5 mmol of **10**, PPh_3 and DEAD were added and the reaction mixture was stirred an additional 18 h. The mixture was evaporated and the residue was chromatographed (toluene) to give the product (3g, 72%) as a thick oil. Distillation gave 2.7 g, bp 234 - 38° C/ 0.015 mm. IR (film) 1388, 1226, 1186, 1126, 925 and 596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.3 (d, J = 7.5 Hz, 6H), 1.35 (m, 6H), 1.62 (m, 4H), 1.9 (m, 4H), 2.92 (s, 6H), 3.35 (m, 8H) and 4.02 (m, 2H). MS (CI/CH_4) 829 (M + H). OR: $[\alpha]_D^{20}$ +1.8 (c = 0.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}F_{12}N_4O_8S_4$: C, 30.43; H, 4.38; N, 6.78; S, 15.48. Found: C, 30.50; H, 4.46; N, 6.84; S, 15.24.

Similarly prepared was the (R,R)- isomer, bp 230 - 34° C / 0.015 mm, $[\alpha]_D^{20}$ -1.4 (c = 0.7, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}F_{12}N_4O_8S_4$: C, 30.43; H, 4.38; N, 6.78; S, 15.48. Found: C, 30.31; H, 4.27; N, 6.69; S, 15.50.

Similarly prepared was the meso compound, $[\alpha]_D^{20}$ 0.0 (c = 1.2, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}F_{12}N_4O_8S_4 \cdot 0.1\ C_7H_7$: C, 31.09; H, 4.42; N, 6.60. Found: C, 31.37; H, 4.42; N, 6.47.

(S,S)-2,6,14,18-Tetraaza-3,17-dimethylnonadecane (1b). A mixture of NH_3 (106 mL), 2-methyl-2-propanol (53 mL), THF (53 mL) and **10** (2.48 g, 3 mmol) was stirred at -70° C while sodium metal was added in portions until a persistent blue color was obtained. Water was added dropwise to decompose excess sodium and the mixture was evaporated. The residue was taken up in water (100 mL) and THF (200 mL), di-t-butyldicarbonate (3,26 g, 15 mmol) was added and the mixture was stirred overnight. Ethyl acetate (500 mL) was added and the organic layer was dried and evaporated. Chromatography (20% ethyl acetate/hexane) gave the tetra-Boc derivative (**11**) (1.43 g, 68%) as a thick oil. ^1H NMR ($CDCl_3$) δ 4.05 (br. m, 2H), 3.10 (br. m, 8H), 2.70 (s, 6H), 1.68 (m, 4H), 1.28 (m, 6H) and 1.11 (d, J = 7.4 Hz, 6H).
The tetra-Boc derivative (**11**) (1.43 g, 2 mmol) was dissolved in methanolic HCl (40 mL, 0.5 N) and the solution was stirred overnight. The solution was evaporated and the residue was recrystallized (methanol/acetonitrile) to give the product as a white solid (0.5 g, 54 %), mp 241 - 43° C. IR (KBr) 2964, 2792, 2742, 1438 and 1020 cm^{-1}. ^1H NMR (D_2O) δ 3.36 (m, 2H), 3.15 (m, 4H), 3.06 (m, 4H), 2.71 (s, 6H), 2.17 (m, 2H), 1.94 (m, 2H), 1.69 (m, 4H), 1.38 (m, 6H) and 1.34 (d, J = 6.5 Hz, 6H). MS (CI/CH_4) 301 (M + H).OR $[\alpha]_D^{20}$ -10.3 (c = 0.62, H_2O). Anal. Calcd for $C_{17}H_4N_4 \cdot 4HCl \cdot 3/4\ H_2O$: C, 44.39; H, 9.97; N, 12.18; Cl, 30.84. Found: C, 44.43; H, 10.06; Cl, 30.69.

Similarly prepared was the (R,R)- isomer (**1a**), mp 241 - 42° C, $[\alpha]_D^{20}$ +11.1 (H_2O, c = 1.0). Anal. Calcd for $C_{17}H_{40}N_4 \cdot 4HCl \cdot 1/4\ H_2O$: C, 45.28; H, 9.95; N, 12.43. Found: C, 45.05; H, 10.20; N, 12.36.

Similarly prepared was the meso compound (**1c**), mp 237 -38° C, $[\alpha]_D^{20}$ 0.0 (c = 1.04, H_2O). Anal. Calcd for $C_{17}H_{40}N_4 \cdot 4HCl \cdot 0.1\ CH_3OH$: C, 45.68; H, 9.95; N, 12.46. Found: C, 45.51; H, 9.79; N, 12.32.

(R)-4-Chloro-2-methylamino-N-trifluoromethanesulfonylbutane (12). A solution of **8** (5.74 g, 24.2 mmol) and p-toluenesulfonyl chloride (4.65 g, 24.4 mmol) in pyridine (24 mL) was stirred overnight at ambient temperature. The mixture was evaporated and the residue was chromatographed (20% ethyl acetate/hexane), the product was distilled to give a clear liquid (2.27 g, 37%), bp 108 - 10° C/ 10 mm. MS (CI/CH_4) 254 (M + H). ^1H NMR ($CDCl_3$) δ 4.25 (m, 1H), 3.53 (m, 2H), 2.92 (s, 3H), 2.09 (m, 1H), 1.94 (m, 1H) and 1.30 (d, J = 6.7 Hz, 3H). OR: $[\alpha]_D^{20}$ -11.7 (c = 1.10, $CHCl_3$). Anal. Calcd for $C_6H_{11}ClF_3NO_2S$: C, 28.41; H, 4.37; N, 5.52. Found: C, 28.78; H, 4.51; N, 5.38.

(R)-2-Methylamino-N-trifluoromethanesulfonylbutane (13). A solution of compound **12** (0.8 g, 4 mmol) and LAH (152 mg, 4 mmol) in THF (50 mL) was heated at reflux for 18 h. The LAH was decomposed by addition of water and aq KOH, the mixture was filtered and the precipitate was washed with THF. The filtrate was evaporated through a column packed with glass helices and the residue was distilled to give a clear liquid (0.64 g, 92%) bp 65 - 67° C/12 mm. IR ($CHCl_3$) 2978, 1386 and 1126 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.95 (m, 1H), 2.88 (s, 3H), 1.55 (m, 2H), 1.25 (d, J = 6.7 Hz, 3H) and 0.95 (t, J = 7.8 Hz, 3H). ^{19}F NMR ($CDCl_3$) δ -76.85 (s). OR: $[\alpha]_D^{20}$ -14.5 (c = 1.07, $CHCl_3$). Anal. Calcd for $C_6H_{12}F_3NO_2S$: C, 32.89; H, 5.59; N, 6.39. Found: C, 32.79; H, 5.52; N, 6.08.

(R)-N-Boc-2-aminobutane (16). A mixture of (R)-2-aminobutane (1.0 g, 13.6 mmol), di-t-butyldicarbonate (2.9 g, 13.6 mmol) and CH_2Cl_2 (50 mL) was stirred at ambient temperature for 1h. The solution was washed with aq HCl, dried and evaporated. Distillation of the residue gave 1.82 g (77%) of a clear liquid, bp 102-07° C/0.25 mm. IR ($CHCl_3$) 2970, 1690, 1366 and 1084 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.32 (br. m, 1H), 3.58 (br. m, 1H), 1.45 (s, 9H), 1.42 (m, 2H), 1.12 (d, 3H) and 0.91 (t, 3H). MS (CI/CH_4) 174 (M + H). OR: $[\alpha]_D^{20}$ -11.2 (c = 1.03, $CHCl_3$). Anal: Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 61.71; H, 10.77; N, 7.10.

(R)-N-Boc-2-methlyaminobutane (17). Compound **16** (1.6 g, 9.2 mmol) was dissolved in DMF (40 mL) and NaH (0.37 g, 9.2 mmol) was added. The mixture was stirred for 1 h, iodomethane (0.6 mL, 9.2 mmol) was added and the mixture was stirred an additional 18 h. The solution was evaporated and the residue was chromatographed (gradient, hexane to 20% toluene/hexane). The product was distilled (Kugelrohr) to give a clear liquid (0.96 g, 56%) bp 65 - 70° C/0.25 mm). IR ($CHCl_3$) 2972, 1694 and 1140 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.08 (br. m, 1H), 2.68 (br. s, 3H), 1.45 (s, 9H), 1.40 (m, 2H), 1.06 (d, J = 6.9 Hz, 3H) and 0.85 (t, J = 7.3 Hz, 3H). MS (CI/CH_4) 188 (M + H). OR: $[\alpha]_D^{20}$ -15.1 (c = 1.04, $CHCl_3$). Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.02; H, 11.31; N, 7.35.

3-Ethylamino-1-propanol-N-trifluoromethanesulfonamide (20). A solution of DEAD (15.6 g, 0.09 mole) in THF (30 mL) was added dropwise to a solution of PPh_3 (23 g, 0.088 mole), **19** (15.6 g, 0.088 mole), and 1,3-propanediol (13.4 g, 0.176 mole, 2 eq) in THF (250 mL). The mixture was stirred for 18 h, evaporated, and the residue was chromatographed (toluene/ethyl acetate, 4/1). Distillation of the product gave an oil (6.1 g, 29%), bp 95-97° C / 0.3 mm. IR (film) 1384, 1226, 1190, 1140, 1128, 1060, 1008 and 596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 1.75 (t, J = 7.5 Hz, 1H, exch. D_2O), 1.83 - 1.92 (m, 2H), 3.48 - 3.55 (m, 4H), 4.7 - 4.8 (m, 2H, becomes t, J = 7.5 Hz on D_2O exchange). MS CI/CH_4) 355 (M + H). Anal. Calcd for $C_6H_{12}F_3NO_3S$: C, 30.63; H, 5.14; N, 5.96. Found: C, 30.95; H, 5.18; N, 5.75.

2,2-Difluoro-N,N'-bis-p-toluenesulfonylputrescine (21). A mixture of 2,2-difluoroputrescine dihydrochloride (200 mg, 1 mmol) and triethylamine (410 mg, 4 mmol) in dichloromethane (4 mL) was stirred for 15 min, a solution of tosyl chloride (387 mg, 2 mmol) in dichloromethane (3 mL) was added dropwise, and the mixture was stirred 18 h at ambient temperature. The mixture was diluted with dichloromethane (20 mL), extracted with 1N HCl, water. The organic layer was dried, evaporated, and the residue was recrystallized (hexane/acetone) to give the product (290 mg, 65%) as a white solid, mp 144 - 45° C. IR (KBr) 3288, 1330,1306, 1156, 1092, 704, 666, 560 and 552 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.95 - 2.15 (m, 2H), 2.39 (closely spaced singlets, 6H), 2.85 (q, J = 7.5, 2H), 3.17 (dt, J_1 = 30 Hz, J_2 = 7.5 Hz, 2H), 7.3 - 7.4 (m, 4H), 7.6 - 7.7 (m, 5H) and 8.12 (t, J = 7.5 Hz, 1H). ^{19}F NMR (DMSO-d_6) δ -101.88 - -102.10 (multiplet). MS (CI/CH_4) 433 (M + H). Anal. Calcd for $C_{18}H_{22}F_2N_2O_4S_2$: C, 49.98; H, 5.12; N, 6.48. Found: C, 50.02; H, 5.19: N, 6.50.

3,7,12,16-Tetraaza-9,9-difluoro-7,12-bis-p-toluenesulfonamido-3,16-bis-trifluoromethanesulfonamidooctadecane (22). A solution of DEAD (1.74 g, 10 mmol) in THF (20 mL) was added to a solution of PPh_3 (2.6g, 10 mmol), **20** (2.4 g, 10 mmol) and **21** (2.16 g, 5 mmol) in THF (100 mL). The reaction mixture was evaporated and the residue was chromatographed (toluene/ethyl acetate 9/1) to give the product (1.1 g, 25%) as a thick oil and a second material (2.2 g, 63%) determined to be the monoadduct. IR (film) 1384, 1344, 1226, 1184, 1162 and 1132 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.2 - 1.3 (m, 6H), 1.9 - 2.1 (m, 4H), 2.25 - 2.4 (m, 2H), 2.46 (s, 6H), 3.08 - 3.2 (m, 4H), 3.32 - 3.55 (m, 12 H), 7.32 - 7.4 (m, 4H) and 7.65 - 7.78 (m, 4H). ^{19}F NMR ($CDCl_3$) δ -76.573, -76.612, -101.037 and -101.078. MS (CI/CH_4) 867 (M + H). Anal. Calcd for $C_{30}H_{42}F_2N_4O_8S_4$: C, 41.56; H, 4.88; N, 6.46. Found: C, 41.83; H, 4.97; N, 6.22.

In a similar reaction, a solution of DEAD (2.84 g, 16.3 mmol) in THF (25 mL) was added to a solution of PPh_3 (4.3 g, 16.3 mmol), **20** (3.8 g, 16.3 mmol) and **21** (2.35 g, 5.4 mmol) in THF (60 mL) to give **22** as an oil (3.4 g, 72%). Anal. Calcd for $C_{30}H_{42}F_2N_4O_8S_4$: C, 41.56; H, 4.88; N, 6.46. Found: C, 42.02; H, 5.09; N, 6.18.

3,7,12,16-Tetraaza-9,9-difluorooctadecane Tetrahydrochloride (24). Ammonia (60 mL) was distilled from lithium wire into a flask containing **22** (1 g, 1.15 mmol), THF (40 mL) and 2-methyl-2-propanol (30 mL). At a reaction temperature of -70° C, sodium metal was added until a blue color formed which persisted for 30 min. The reaction was slowly heated to 60° C and maintained at this temperature for 90 min to remove NH_3. To the residue was added THF (80 mL), H_2O (80 mL) and di-t-butyldicarbonate and the mixture was stirred for 18 h. The THF was removed and the aqueous residue was extracted with $CHCl_3$. The extracts were evaporated and the residue was chromatographed (toluene/ethyl acetate 1/1) to give 0.2 g (29%) of a thick oil which was found to be the tri-Boc derivative (**23**). IR (film) 2976, 1694, 1480, 1418, 1366, 1288, 1254 and 1164 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.1 (t, J = 7.5 Hz, 6H), 1.45 (s, 27H), 1.5 - 1.8 (m, 10H), 2.08 - 2.27 (m, 3H), 2.65 (t, J = 7.5 Hz, 2H), 2.9 (t, J = 30 Hz, 2H), 3.1 - 3.3 (m, 10H) and 3.3 - 3.4 (m, 2H). MS (CI/CH_4) 595 (M + H). Anal. Calcd for $C_{29}H_{56}F_2N_4O_6$: C, 58.56; H, 9.49; N, 9.42. Found: C, 58.57; H, 9.84; N, 9.17.

Compound **23** (200 mg, 0.3 mmol) was dissolved in methanolic HCl (3 mL, 1N), the mixture was stirred overnight at ambient temperature and filtered. The precipitated hydrochloride salt was recrystallized three times from 2-propanol/H_2O/methanolic HCl to give a white solid (46 mg, 30%), mp 305 - 07° C. IR (KBr) 2956, 2774, 2484 and 2428 cm^{-1}. ^1H NMR (D_2O) δ 1.38 (t, J = 7.5 Hz, 6H), 2.1 - 2.23 (m, 4H), 2.45 - 2.65 (m, 2H), 3.08 - 3.3 (m, 14 H), 3.4 (t, J = 7.5 Hz, 2H) and 3.75 (t, J = 22.5 Hz, 2H). MS (CI/CH_4) 295 (M + H). Anal. Calcd for $C_{14}H_{32}F_2N_4 \cdot 4HCl$: C, 38.19; H, 8.78; N, 12.72. Found: C, 39.07; H, 8.78; N, 12.48. The product appears to contain some tri-HCl salt.

N-t-Butyloxycarbonyl-N-4-chlorobutyl-p-toluenesulfonamide (26). A solution of DEAD (17.4 g, 0.1 mole) in THF (20 mL) was added dropwise to a solution of **25**[3] (27.1 g, 0.1 mole), PPh_3 (26.2 g, 0.1 mole) and 4-chloro-1-butanol (10.8 g, 0.1 mole) (distilled to remove HCl) in THF (600 mL). After 4h at ambient temperature the mixture was evaporated and the residue was chromatographed (toluene) to give the product (29.4 g, 81%) as an oil. IR (film) 2980, 1728, 1456, 1394, 1356, 1292, 1186, 1156, 1088, 1000, 814, 772, 722, 6764, 598, 576 and 546 cm^{-1}. NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.8 - 2.0 (m, 4H), 2.45 (s, 3H), 3.6 (t, J = 7.5 Hz, 2H), 3.86 (t, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H) and 7.78 (d, J = 7.5 Hz, 2H). MS (CI/CH_4) 362 (M + H). Anal. Calcd for $C_{16}H_{24}ClNO_4S \cdot 1/8$ Toluene: C, 54.28; H, 6.75; N, 3.75. Found: C, 54.39; H, 6.94; N, 3.70.

1,7-bis-p-Toluenesulfonamidoheptane (27). A mixture of dichloromethane (600 mL), aq $NaHCO_3$ (600 mL) and 1,7-diaminoheptane (25 g, 0.19 mole) was stirred while p-toluenesulfonyl chloride (109 g, 0.57 mole) was added in portions over 1 h. The layers were separated, the organic layer was extracted with 1N HCl and evaporated. The residue was triturated with toluene to give the product (58 g, 70%) as a white solid, mp 140-141° C. IR (KBr) 3256, 2942, 2864, 1430, 1328, 1306, 1160, 1094, 1078, 808, 706, 668, 578, 552 and 533

cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.1 - 1.2 (m, 6H), 1.25 - 1.30 (m, 4H), 2.4 (s, 6H), 2.6 - 2.7 (m, 4H), 7.37 (d, J = 7.5 Hz, 4H), 7.45 (t, J = 7.5 Hz, 2H) and 7.75 (d, J = 7.5 Hz, 4H). MS (CI/CH_4) 439 (M + H). Anal. Calcd for $C_{21}H_{30}N_2O_4S_2$: C, 57.50; H, 6.89; N, 6.39. Found: C, 57.87; H, 7.13; N, 6.20.

1,6,14,19-Tetraaza-1,19-bis-t-butyloxycarbonyl-1,6,14,19-tetra-p-toluenesulfonyl-nonadecane (28). Sodium hydride (0.8 g of 50% mineral oil dispersion, 16.8 mmol) was added in portions to a solution of **27** (3 g, 8.4 mmol) in DMF (300 mL) and the mixture was stirred for 1 h at ambient temperature. Sodium iodide (0.1 g) and a solution of **26** (5.2 g, 16.8 mmol) in DMF (50 mL) were added and the mixture was heated at 55 ° C for 18 h. The mixture was cooled, methanol (10 mL) was added to decompose any unreacted NaH, and the mixture was evaporated to dryness. Dichloromethane (300 mL) and water (300 mL) were added, the organic layer was separated, dried and evaporated. Chromatography (toluene/ethyl acetate 6/1) gave the product (4.4 g, 51%) as a thick oil. IR (film) 2980, 2934, 1726, 1458, 1394, 1348, 1306, 1286, 1258, 1186, 1156, 1090, 1006, 814, 756, 722, 674, 654, 598, 576 and 548 cm^{-1}. NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.32 (s, 18H), 1.42 - 1.53 (m, 4H), 1.55 - 1.65 (m, 4H), 1.7 - 1.8 (m, 4H), 2.55 and 2.56 (s, together 12H), 3.02 - 3.18 (m, 8H), 4.82 (t, J = 7.5 Hz, 4H), 7.25 - 7.35 (m, 8H), 7.68 (d, J = 7.5 Hz, 4H) and 7.77 (d, J = 7.5 Hz, 4H). MS (FAB) 1089 (M^+). Anal. Calcd for $C_{53}H_{76}N_4O_{12}S_4$: C, 58.42; H, 7.03; N, 5.14. Found: C, 60.50; H, 7.25; N, 5.08.

1,6,14,19-Tetraaza-1,6,14,19-tetra-p-toluenesulfonylnonadecane (29). A solution of **28** (20 g, 18 mmol) in a mixture of dichloromethane (500 mL) and TFA (20 mL) was stirred overnight at ambient temperature. The mixture was evaporated, toluene (400 mL) was added and the mixture was evaporated to dryness. The residue was chromatographed (toluene/ethyl acetate 3/1) to give the product (14.3 g, 89%) as an oil. IR (film) 3286, 2936, 2864, 1598, 1454, 1426, 1330, 1306, 1290, 1268, 1158, 1092, 1040, 816, 736, 704, 656, 570 and 550 cm^{-1}. NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.45 - 1.60 (m, 12H), 2.42 (s, 12H), 2.86 - 2.95 (m, 4H),3.0 - 3.1 (m, 8H), 4.88 (t, J = 7.5 Hz, 2H), 7.15 - 7.3 (m, 8H), 7.43 (d, J = 7.5 Hz) and 7.72 (d, J = 7.5 Hz, 4H). MS (CI/CH_4) 889 (M + H). Anal. Calcd for $C_{43}H_{60}N_4O_8S_4$•3/4 Toluene: C, 60.38; H, 7.15; N, 5.70. Found: C, 60.48; H, 7.17; N, 5.57.

1,6,14,19-Tetraazanonadecane Tetrahydrobromide (32). A solution of **29** (12.2 g, 13.7 mmol) in 48% aq HBr (500 mL) was heated in a 100° C oil bath for 24 h, cooled and evaporated to dryness. The residue was recrystallized (ethanol/H_2O) to give the product (5.2 g, 63%) as a white solid, mp 303° C. IR (KBr) 2952, 2874 and 2810 cm^{-1}. NMR (D_2O) δ 1.4 (s, 6H), 1.6 - 1.85 (m, 12H) and 3.0 - 3.1 (m, 12H). MS (CI/CH_4) 273 (M + H). Anal. Calcd for $C_{15}H_{36}N_4$•4 HBr: C, 30.22; H, 6.76; N, 9.40. Found: C, 30.60; H, 6.90; N, 9.09.

1,6,11,19,24,29-Hexaaza-1,29-bis-t-butyloxycarbonyl-1,6,11,19,24,29-hexa-p-toluenesulfonylhenicosane (30). Sodium hydride (0.5 g of 50% mineral oil dispersion, 10 mmol) was added to a solution of **29** (2.9 g, 3.3 mmol) in DMF (100 mL) and the mixture was stirred at ambient temperature for 2 h. Sodium iodide (0.1 g) and a solution of **26** (3.6 g, 9.9 mmol) in DMF (20 mL) was added and the mixture was heated in a 60° C oil bath for 24 h. The mixture was cooled, methanol (20 mL) was added and the mixture was evaporated to dryness. The residue was taken up in ethyl acetate/water, the organic layer was isolated, dried and evaporated. The residue was chromatographed (toluene/ethyl acetate 6/1) to give the product (2.1 g, 41%) as an oil. IR (film) 2934, 1726, 1340, 1305, 1286, 1157, 1090, 815, 731, 674, 654, 566 and 548 cm^{-1}. NMR ($CDCl_3$) δ 1.15 - 1.22 (m, 6H), 1.3 (s, 18H), 1.42 - 1.65 (m, 16H), 1.65 - 1.8 (m, 4H), 2.4 - 2.45 (m, 18H), 3.0 - 3.2 (m, 16H), 3.8 (t, J = 7.5 Hz, 4H), 7.1 - 7.35 (m, 12H), 7.65 - 7.7 (m, 8H) and 7.75 (d, J = 7.5 Hz, 4H). MS (FAB-TG/DTT/DTE) 1561.5 (M + Na). Anal. Calcd for $C_{75}H_{106}N_6O_{16}S_6$•Toluene: C, 60.34; H, 7.04; N, 5.15. Found: C, 60.78; H, 7.20; N, 5.17.

1,6,11,19,24,29-Hexaazahenicosane Hexahydrobromide (31). A mixture of **30** (2 g, 1.3 mmol) and 48% aq HBr (300 mL) was heated at 100° C for 24 h. The mixture was evaporated and the residue was recrystallized

from aqueous ethanol to give the product (0.4 g, 34%) as a white solid, mp>315° C. IR (KBr) 2951, 2872 and 2815 cm^{-1}. NMR (D_2O) δ 1.2 (s, 6H), 1.6 - 1.82 (m, 20H) and 3.0 - 3.2 (m, 20H). MS (EI) 415 (M + H). Anal. Calcd for $C_{23}H_{54}N_6$•6HBr: C, 30.68; H, 6.72; N, 9.34. Found: C,31.30; H, 6.77; N, 9.33.

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