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C_3-Symmetric tripodal tetra-amines — preparation from chiral amino alcohols via aziridines

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Abstract: Enantiopure *N*-sulfonylaziridines, conveniently obtained from readily available enantiopure amino alcohols, undergo smooth ring opening reactions using ammonia as a nucleophile to yield tripodal tetradentate C_3-symmetric amines. *N*-alkylation and subsequent removal of the sulfonyl groups provide access to alkyl-substituted analogs.
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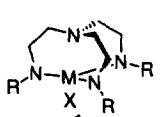
Introduction

Transition metal catalysis is a highly attractive method to obtain chiral enantiopure compounds since the chirality may be transferred from a catalytic amount of a chiral compound to a stoichiometric amount of product.[1] To achieve this, efficient chiral ligands are required, and extensive current interest is therefore devoted to the design of new types of ligands.[2] An analysis of the stereochemistry of a proposed chemical process, taking into account relevant symmetry considerations, constitutes an important part of the ligand design.[3]

Chiral molecules may contain rotational axes as their sole symmetry elements. Following the successful applications of ligands with C_2 symmetry,[4] interest has recently been directed towards chiral ligands containing a threefold rotational axis.[5–8] Whereas bidentate ligands of the former type may reduce the number of transition states in a square planar environment, tripodal ligands with a threefold rotational axis may have advantageous properties in an octahedral situation.[3] C_3-Symmetric tripodal tetradentate ligands are also expected to give highly symmetrical trigonal bipyramidal complexes.

Extensive interest has recently been devoted to metal complexes of tetradentate as well as tridentate tripodal amines, represented by **1**[9,10] and **2**,[11] respectively. Both types of ligands form complexes with a variety of transition and main group metal ions, and the complexes obtained usually exhibit threefold rotational symmetry. Ligands carrying large R groups (for example *t*-butyldimethylsilyl) have the ability to kinetically stabilize early transition metal centers having one remaining reactive site by steric shielding.[9a,10d,11b]



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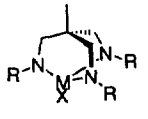

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Our interest in C_3-symmetric ligands[6] prompted us to investigate routes to chiral analogs of the tripodal amines for use in asymmetric catalysis. We were particularly interested in chiral analogs of **1**, since a variety of trigonal monopyramidal[9b] transition metal complexes with this class of ligands have been shown to have the ability to bind Lewis bases.[9f,10e] Furthermore, cationic complexes of **1** with Mo(IV), W(IV),[9d] and Ti(IV)[9e] have been isolated. Chiral complexes were therefore thought to have potential application in asymmetric Lewis-acid catalyzed transformations.

Some chiral C_3-symmetric amines, both acylic such as **3**[7] and cyclic such as **4**,[8] have already been reported. These compounds, having the stereogenic centers residing in the R groups of the amine, are

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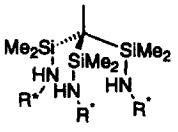
accessible by substitution of the amino function with chiral electrophiles. However, in order to have the stereogenic center in the chelate ring, a situation believed to be advantageous for efficient chirality transfer in catalytic applications, a totally different synthetic procedure had to be developed. Such a procedure, involving nucleophilic ring opening of chiral enantiopure aziridines obtained from amino alcohols,[12] is presented here.



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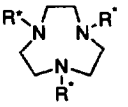

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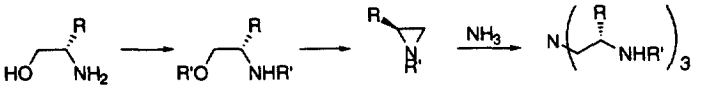
Results and discussion

For the preparation of chiral analogs of **1**, alaninol **5a** or valinol **5b** was first reacted with two equivalents of mesityl chloride to afford substituted derivatives **6a** and **6b**, respectively. The analogous reaction of **5a** with tosyl chloride yielded **6c**. Treatment of these compounds with a weak base resulted in the formation of aziridines **7a–c** (30–63% yields based on the amino alcohol). Use of triflic anhydride in place of mesityl chloride in the reaction with valinol afforded the aziridine **7d** directly (96% yield), without isolation of intermediate **6**.

Since the aziridines carry electron-withdrawing groups, they were expected to be susceptible to nucleophilic attack. Ring opening by amines has, indeed, previously been found to take place, but only in the presence of ytterbium (III) triflate; the reaction was sluggish in the absence of Lewis acid.[13] However, nucleophilic ring opening without Lewis acid occurs readily when methanol is used as solvent.[14] Thus, reaction with ammonia in methanol resulted in formation of the desired tripodal C_3-symmetric sulfonamides **8a–d** in moderate to good yields (53–80%).



5a R=Me
5b R=^{i}Pr

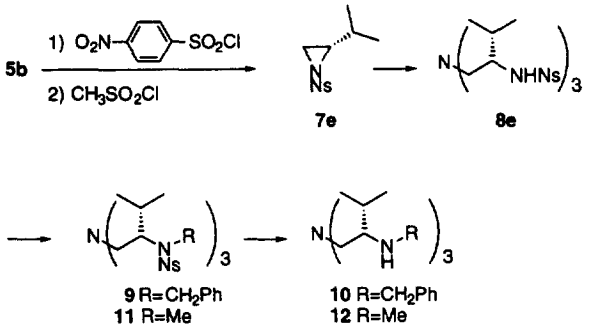
6a R=Me; R'=Ms
6b R=^{i}Pr; R'=Ms
6c R=Me; R'=Ts

7a R=Me; R'=Ms
7b R=^{i}Pr; R'=Ms
7c R=Me; R'=Ts
7d R=^{i}Pr; R'=Tf

8a R=Me; R'=Ms
8b R=^{i}Pr; R'=Ms
8c R=Me; R'=Ts
8d R=^{i}Pr; R'=Tf

It was also desirable to have access to derivatives lacking the sulfonyl group, since alkylation of such compounds would constitute a route to a variety of chiral tripodal tetra-amines. To achieve this, a *p*-nitrophenylsulfonyl (nosyl) derivative would be desired since the nosyl group could be readily removed under mild conditions.[15] Therefore, **5b** was reacted with one equivalent of nosyl chloride followed by 1.1 equivalents of mesityl chloride to directly yield aziridine **7e** (73%), which was transformed into C_3-symmetric **8e** (85%) using ammonia in methanol. Attempts to remove the nosyl group from **8e**, using mercaptoacetic acid, were unsuccessful, affording only recovered starting material, probably via deprotonation of the sulfonamide. The amino function of **8e** was therefore protected by reaction with benzyl bromide, and the compound obtained, **9**, was treated with mercaptoacetic acid/NaOH to give the desired compound **10**. Attempts to debenzylate this compound using palladium on carbon and formic acid[16] gave a tetraamine which was difficult to purify.

We have also demonstrated that other alkyl-substituted derivatives are accessible by the route described. Thus, **8e** was methylated to afford compound **11**. This compound was not isolated, but transformed directly into **12** (85% yield based on **8e**).



The ability of these C_3-symmetric tripodal tetradentate amines to form complexes with metal ions, and the use of the metal complexes obtained as catalysts in asymmetric reactions is presently under investigation.

Conclusions

The nucleophilic ring opening of aziridines using ammonia as a nucleophile constitutes an efficient method for the preparation of C_3-symmetric tripodal tetraamines. A large variety of chiral amino alcohols **5**, derived from naturally occurring amino acids, serve as useful starting materials.

Experimental section

General

Chemicals were purchased from Aldrich and used as received. (*S*)-Valinol was prepared according to a literature procedure.[17] All solvents except diethyl ether and methanol were distilled before use. CH_2Cl_2 was distilled from P_2O_5 and THF from benzophenone ketyl. MPLC (Medium Pressure Liquid Chromatography) was carried out using silica gel 60 (Merck 230–400 mesh). Melting points are uncorrected. Microanalyses were performed by INSA, Rouen, France, and by Analytische Laboratorien, Lindlar, Germany. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, with the solvent as reference.

(S)-N,O-Dimesitylalaninol ***6a***[18]

Mesityl chloride (1.7 mL, 22 mmol) was added dropwise over 1.5 h to (*S*)-alaninol (**5a**, 751 mg, 10 mmol) and triethylamine (2.8 mL, 20 mmol) in dry CH_2Cl_2 (80 mL) under nitrogen at −20°C. Stirring was continued at that temperature for an additional 30 min, whereafter the flask was kept at −30°C overnight. The cold solution was then washed with 0.1 M HCl (2×10 mL) and saturated aqueous $NaHCO_3$ (15 mL). The organic phase was dried ($MgSO_4$) and the solvent evaporated, leaving 1.54 g (66%) of **6a** as a white solid, which was used without further purification. ^1H NMR ($CDCl_3$) δ 4.79 (1H, br d, *J*=8.1 Hz), 4.25 (1H, dd *J*=10.4 and 4.2 Hz), 4.15 (1H, dd *J*=10.4 and 5.6 Hz), 3.88–3.83 (1H, m), 3.08 (3H, s), 3.02 (3H, s), 1.33 (3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 72.2, 48.9, 42.0, 37.5, 18.4.

(S)-N-Mesityl-2-methylaziridine ***7a***[18]

Sulfonamide **6a** (3.20 g, 13.8 mmol) in dry THF (50 mL) was added dropwise to a suspension of sodium hydride (20.7 mmol, washed with dry hexane) in dry THF (20 mL). The resulting mixture was stirred for 3 h at room temperature. The reaction was then quenched by adding EtOH (10 mL) followed by cold water (20 mL). The resulting mixture was diluted with brine (70 mL) and diethyl ether (100 mL). The phases were separated and the aqueous phase was extracted with another 100 mL of diethyl ether. The combined ether phases were dried ($MgSO_4$), and the solvent evaporated, leaving 1.11 g (60%) of **7a** as a colorless liquid, which was used without further purification. ^1H NMR ($CDCl_3$) δ 3.04 (3H, s), 2.83–2.76 (2H, m), 2.59 (1H, d, *J*=7.0 Hz), 1.34 (3H, d, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 39.6, 35.2, 34.3, 16.8.

(S,S,S)-Tris(N-mesityl-2-aminopropyl)amine ***8a***

Aziridine **7a** (1.12 g, 8.26 mmol) was added to a 2.0 M solution of ammonia in methanol (1.4 mL, 2.8 mmol) and the reaction mixture was stirred at 40°C for 4 days. More methanol (8 mL) was added, and the resulting mixture was refluxed for 2.5 h. Evaporation of the solvent, followed by recrystallisation from hot methanol, afforded 810 mg (71%) of **8a** as white crystals: mp 161–163°C; $[\alpha]_D^{21}$ +97 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.77 (3H, br d, *J*=5.8 Hz), 3.84–3.77 (3H, m), 3.04 (9H, s), 2.60 (3H, dd, *J*=13.0 and 11.7 Hz), 2.20 (3H, dd, *J*=13.1 and 4.0 Hz), 1.20 (9H, d, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 57.7, 45.0, 42.5, 20.6; Anal. Calcd. for $C_{12}H_{30}N_4O_6S_3$: C, 34.11; H, 7.16; N, 13.26. Found: C, 34.25; H, 7.06; N, 13.32.

(S)-N,O-Dimesitylvalinol ***6b***

Mesityl chloride (2.55 mL, 33 mmol) was added dropwise over 90 min to a solution of (*S*)-valinol (**5b**, 1.55 g, 15 mmol) and triethylamine (4.18 mL, 30 mmol) in dry CH_2Cl_2 (70 mL) under nitrogen at −20°C. After stirring for another 60 min at −20°C, the mixture was kept at −30°C overnight. The cold mixture was washed with 0.1 M HCl (2×20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$) and the solvent evaporated, leaving 4.17 g of crude **6b** as a yellow oil, which was purified by liquid chromatography on silica (column 4×6 cm, eluent: 500 mL of hexane:EtOAc 1:1) to give 3.01 g (72%) of **6b** as a clear oil, which solidified after a few minutes. ^1H NMR ($CDCl_3$) δ 4.69 (1H, bd, *J*=8.0 Hz), 4.30 (1H, dd, *J*=10.2 and 4.0 Hz), 4.27 (1H, dd, *J*=10.2 and 5.5 Hz), 3.50–3.44 (1H, m), 3.06 (3H, s), 3.03 (3H, s), 1.92 (1H, octet, *J*=6.9 Hz), 1.02 (6H, t, *J*=7.0 Hz).

(S)-N-Mesityl-2-isopropylaziridine ***7b***

Na_2CO_3 (1.23 g, 11.6 mmol) was added to sulfonamide **6b** (3.01 g, 11.6 mmol) in methanol (60 mL), and the mixture was refluxed overnight. The methanol was evaporated, leaving a white solid, which was mixed with water and CH_2Cl_2 (50 mL of each). The phases were separated and the aqueous phase was extracted with more CH_2Cl_2 (2×50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated to give 1.65 g (87%) of **7b** as a clear liquid. NMR showed peaks from traces of starting material, but the liquid was used without further purification: ^1H NMR ($CDCl_3$) δ 3.05 (3H, s), 2.58–2.51 (2H, m), 2.14 (1H, d, *J*=4.3 Hz) 1.53 (1H, octet, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.7 Hz), 1.00 (3H, d, *J*=6.8 Hz).

(S,S,S)-Tris-(N-mesityl-2-amino-3-methylbutyl)amine ***8b***

Aziridine **7b** (1.43 g, 8.76 mmol) was stirred together with a 2.0 M solution of ammonia in methanol (1.46 mL, 2.92 mmol) at 50°C for 5 days. A white precipitate appeared after a few hours. After 5 days, hot methanol (ca. 12 mL) was added to completely dissolve the precipitate. The solution was refluxed overnight, and upon cooling a white microcrystalline precipitate appeared, which was collected by filtration and washed with diethyl ether, leaving 1.19 g (80%) of **8b**: mp 200–202°C; $[\alpha]_D^{21}$ +84 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.93 (3H, br d, *J*=6.4 Hz), 3.79–3.76 (3H, m), 3.05 (9H, s), 2.85 (3H, t, *J*=12.4 Hz), 2.04 (3H, dd, *J*=12.7 and 4.2 Hz), 1.88 (3H, d of septet, *J*=6.9 and 4.2 Hz), 0.98 (9H, d, *J*=6.9 Hz), 0.93 (9H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 54.1, 52.2, 42.7, 34.7, 18.3, 18.2; Anal. Calcd for $C_{18}H_{42}N_4O_6S_3$: C, 42.67; H, 8.35; N, 11.06. Found: C, 42.98; H, 8.36; N, 11.02.

(S)-N,O-Ditosylalaninol ***6c***

Tosyl chloride (9.53 g, 40 mmol) was added in portions over 40 min to (*S*)-alaninol (**5a**, 1.50 g, 20 mmol) in pyridine (50 mL) at 0°C. Stirring was continued for another 3 h, then the flask was placed at −30°C overnight. Ice (200 g) was added followed by concd HCl (60 mL). The water/pyridine solution was extracted twice with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$, water and brine, and finally dried ($MgSO_4$). The solvent was evaporated, leaving a sticky yellow substance. Recrystallisation from hot ethanol yielded 4.77 g (62%) of **6c** as a yellow powder. ^1H NMR ($CDCl_3$) δ 7.73 (2H, d, *J*=8.6 Hz), 7.70 (2H, d, *J*=8.2 Hz), 7.35 (2H, d, *J*=7.9 Hz), 7.28

(2H, d, J=7.8 Hz), 4.63 (1H, br d, J=7.9 Hz), 3.92 (1H, dd, J=10.2 and 4.2 Hz), 3.84 (1H, dd J=10.2 and 4.6 Hz), 3.59–3.51 (1H, m), 2.46 (3H, s), 2.43 (3H, s), 1.08 (3H, d, J=6.7 Hz).

(S)-N-Tosyl-2-methylaziridine 7c

Sulfonamide **6c** (4.77 g, 12.4 mmol) in dry THF (40 mL) was added dropwise to a suspension of washed (hexane) sodium hydride (18.6 mmol) in dry THF (10 mL). The resulting mixture was stirred for 2 h at room temperature, with a lot of foaming. The reaction was quenched by adding water (50 mL) and brine (50 mL). The aqueous phase was extracted 3 times with diethyl ether, the combined ether phases were washed with 2 M NaOH and dried ($MgSO_4$), and the solvent evaporated, leaving a yellow liquid. The liquid was filtered through silica (6 cm column, eluent: hexane:EtOAc 80:20). Evaporation left 1.24 g (47%) of **7c** as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.1 Hz), 2.80 (1H, ddq, J=7.1, 5.7 and 4.7 Hz), 2.59 (1H, d, J=7.1 Hz), 2.42 (3H, s), 2.00 (1H, d, J=4.7 Hz), 1.23 (3H, d, J=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 144.4, 135.5, 129.7, 127.8, 35.9, 34.8, 21.7, 16.8.

(S,S,S)-Tris-(N-tosyl-2-aminopropyl)amine 8c

Aziridine **7c** (1.14 g, 5.4 mmol) and a 2.0 M solution of ammonia in methanol (0.90 mL, 1.8 mmol) were stirred at 40°C for 4 days. More methanol (7 mL) was added, and the resulting mixture refluxed for 2 h. Evaporation of the methanol left an oil. The crude product was dissolved in CH_2Cl_2, silica (3 g) added, and the solvent evaporated. MPLC (10 g of silica, continuous gradient from hexane to pure EtOAc) gave 825 mg (70%) of **8c** as white crystals: mp 106–109°C; $[\alpha]_D^{21}$ +48 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J=8.2 Hz, 6H), 7.23 (d, J=7.9 Hz, 6H), 5.74 (br d, J=5.6 Hz, 3H), 3.67–3.64 (m, 3H), 2.51 (dd, J=12.9 and 11.1 Hz, 3H), 2.38 (s, 9H), 2.13 (dd, J=13.0 and 3.8 Hz, 3H), 0.96 (d, J=6.4 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 143.0, 138.7, 129.5, 127.0, 58.4, 46.2, 21.5, 19.9; Anal. Calcd. for $C_{30}H_{42}N_4O_6S_3$: C, 55.36; H, 8.61; N, 6.50. Found: C, 55.38; H, 8.60; N, 6.52.

(S)-N-Triflic-2-isopropylaziridine 7d

Triflic anhydride (3.6 mL, 22 mmol) was added dropwise over 1 h to a solution of (*S*)-valinol (**5b**, 1.03 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol) in dry CH_2Cl_2 (40 mL) under N_2 at −78°C, whereafter the mixture was kept at −30°C overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed twice with 0.1 M HCl and twice with saturated aqueous Na_2CO_3. The organic phase was dried ($MgSO_4$) and the solvent evaporated leaving 2.08 g (96%) of a yellow liquid of essentially pure **7d**. ^{1}H NMR ($CDCl_3$) δ 2.90 (1H, dt, J=7.0 and 4.9 Hz), 2.86 (1H, d, J=7.0 Hz), 2.45 (1H, d, J=4.9 Hz), 1.65 (1H, octet, J=6.8 Hz), 1.06 (3H, d, J=6.7 Hz), 1.03 (3H, d, J=6.7 Hz).

(S,S,S)-Tris-(N-triflic-2-amino-3-methylbutyl)amine 8d

A 2.0 M solution of ammonia in methanol (1.28 mL, 2.6 mmol) was added to aziridine **7d** (1.66 g, 7.6 mmol) at 0°C. The resulting mixture was stirred overnight at room temperature followed by 3 days at 40°C, and the methanol was evaporated. MPLC (20 g of silica, continuous gradient from hexane to pure EtOAc) yielded 915 mg (53%) of **8d** as a solid compound: mp 183–185°C; $[\alpha]_D^{21}$ −40 (c 1.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.82 (3H, br d, J=7.9 Hz), 3.78–3.72 (3H, m), 2.91 (3H, dd, J=13.1 and 11.0 Hz), 2.24 (3H, dd, J=13.1 and 4.6 Hz), 2.03–1.90 (3H, m), 1.00 (9H, d, J=7.0 Hz), 0.96 (9H, d, J=7.0 Hz); ^{13}C NMR (MeOH-d_4) δ 121.4 (q, J_{CF}=320 Hz), 59.9, 59.2, 29.0, 20.9, 15.2.

(S)-N-Nosyl-2-isopropylaziridine 7e

Nosyl chloride (7.92 g, 35 mmol) was added in portions to (*S*)-valinol (**5b**, 3.61 g, 35 mmol) and triethylamine (19.5 mL, 140 mmol) in dry CH_2Cl_2 (300 mL) while cooling the flask with an ice bath. The resulting mixture was stirred for 60 min at room temperature. Mesityl chloride (3.0 mL, 38.5 mmol) was then added dropwise while cooling with an ice bath. The reaction mixture was stirred for another 2 h in the cooling bath, and then kept at −30°C overnight. The cold mixture was washed with 0.1 M HCl (2×60 mL) and saturated Na_2CO_3 (2×60 mL). The organic phase was dried ($MgSO_4$)

and the solvent evaporated to give 9.2 g of crude **7e** which was evaporated on silica (27 g). Liquid chromatography on silica (column 4×8 cm, eluent: 800 mL of hexane:EtOAc 80:20) yielded 6.91 g (73%) of **7e** as a white solid: TLC (silica) hexane:EtOAc 50:50, R_f 0.64; mp 73–75°C; $[\alpha]_D^{21}$ +11 (*c* 2.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.39 (2H, AA′ part of AA′BB′ spectrum), 8.16 (2H, BB′ part of AA′BB′ spectrum), 2.72–2.66 (2H, m), 2.20 (1H, d, *J*=4.3 Hz), 1.48 (1H, octet, *J*=6.8 Hz), 0.93 (3H, d, *J*=7.0 Hz), 0.84 (3H, d, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 150.6, 144.1, 129.3, 124.2, 47.0, 33.6, 30.1, 19.5, 19.0.

*(S,S,S)-Tris-(*N*-nosyl-2-amino-3-methylbutyl)amine* ***8e***

A 2.0 M solution of ammonia in methanol (4.2 mL, 8.4 mmol) was added to aziridine **7e** (6.81 g, 25.2 mmol). The flask was sealed and heated at 50°C for 3 days and then diluted with methanol (30 mL) and the reaction mixture refluxed for 3 h. The solid was filtered off and washed with methanol, leaving 5.94 g (85%) of **8e** as a white powder: mp 248–250°C; $[\alpha]_D^{21}$ +154 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.33 (6H, AA′ part of AA′BB′ spectrum), 8.14 (6H, BB′ part of AA′BB′ spectrum), 6.41 (3H, bd, *J*=7.0 Hz), 3.98–3.91 (3H, m), 3.01 (3H, t, *J*=12.4 Hz), 2.25 (3H, dd, *J*=12.8 and 4.3 Hz), 1.67 (3H, octet, *J*=7.0 Hz), 0.80 (9H, d, *J*=7.0 Hz), 0.77 (9H, d, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 149.7, 147.7, 127.6, 124.2, 55.8, 51.6, 31.7, 18.7, 18.0; Anal. Calcd. for $C_{33}H_{45}N_7O_{12}S_3$: C, 47.87; H, 5.48; N, 11.84. Found: C, 48.08; H, 5.50; N, 11.80.

(S,S,^{S}*)-Tris-(*N*-nosyl-*N*-benzyl-2-amino-3-methylbutyl)amine* ***9***

Benzyl bromide (1.24 mL, 10.4 mmol) was added to **8e** (1.44 g, 1.74 mmol) and K_2CO_3 (2.82 g, 20.4 mmol) in DMF (10 mL). The resulting dark orange suspension was stirred overnight at room temperature, and then water (50 mL) was added. The light yellow suspension obtained was extracted with diethyl ether (3×40 mL). The combined organic phases were washed with brine and dried (Na_2SO_4), and solvent was evaporated, leaving a yellow oil, which solidified upon standing. The solid was recrystallized from ethanol (90 mL), leaving 1.63 g (85%) of **9** as a yellow solid: mp 120–123°C; $[\alpha]_D^{21}$ −76 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.16 (6H, AA′ part of AA′BB′ spectrum), 7.72 (6H, BB′ part of AA′BB′ spectrum), 7.27–7.18 (15H, m), 4.31 (3H, d, *J*=15.3 Hz), 4.24 (3H, d, *J*=15.3 Hz), 3.76 (3H, bm), 3.06 (3H, bm), 2.13 (3H, bd, *J*=12.8 Hz), 2.05 (3H, bm), 0.99 (9H, d, *J*=6.7 Hz), 0.81 (9H, d, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 149.5, 146.8, 135.7, 129.2, 129.0, 128.5, 128.0, 123.9, 62.5, 59.5, 50.2, 31.1, 20.6, 19.6.

*(S,S,S)-Tris-(*N*-benzyl-2-amino-3-methylbutyl)amine* ***10***

Mercaptoacetic acid (580 μL, 8.1 mmol) was added dropwise to a suspension of trisulfonamide **9** (1.49 g, 1.35 mmol) and NaOH (972 mg, 24 mmol) in DMF (45 mL) at 0°C. After stirring at room temperature for 3 days, water (100 mL) was added, and then solid NaOH added until pH>11. The water phase was extracted with diethyl ether (4×40 mL). The combined organic phases were washed with saturated aqueous Na_2CO_3 and then extracted with 4 M HCl (4×30 mL). The combined acidic water phases were washed with ether and made alkaline with solid NaOH and extracted with diethyl ether (4×40 mL). The combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was evaporated leaving 620 mg (85%) of **10** as a yellow oil, which solidified upon standing: mp 70–72°C; $[\alpha]_D^{21}$ +124 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.17–7.13 (9H, m), 7.09–7.06 (6H, m), 3.66 (3H, d, *J*=13.1 Hz), 3.45 (3H, d, *J*=12.8 Hz), 2.53 (3H, dt, *J*=7.0 and 3.2 Hz), 2.38 (3H, dd, *J*=12.8 and 10.1 Hz), 2.19 (3H, dd, *J*=12.5 and 2.4 Hz), 1.90 (3H, d of septet, *J*=7.0 and 3.7 Hz), 0.89 (9H, d, *J*=7.0 Hz), 0.88 (9H, d, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 141.2, 128.2, 128.1, 126.5, 65.8, 56.1, 52.3, 28.4, 18.9, 16.6.

*(S,S,S)-Tris-(2-*N*-methylamino-3-methylbutyl)amine* ***12***

Methyl iodide (750 μL, 12 mmol) was added to **8e** (1.66 g, 2.0 mmol) and K_2CO_3 (3.32 g, 24 mmol) in DMF (10 mL). The resulting dark orange suspension was stirred overnight at room temperature and then water (50 mL) was added to the suspension. The water phase was extracted with diethyl

ether (3×40 mL) and the combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was evaporated, yielding a mixture of DMF and methylated sulfonamide **11** as a yellow oil. The oil was dissolved in DMF (30 mL), and NaOH (1.44 g, 36 mmol) was added. The resulting suspension was cooled with ice and mercaptoacetic acid (850 μL, 12 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 days and then water (100 mL) was added followed by solid NaOH until pH>11. The water phase was extracted with diethyl ether (5×40 mL). The combined organic phases were washed with a saturated solution of Na_2CO_3 and then extracted with 4 M HCl (4×40 mL). The combined acidic water phases were washed with ether and made alkaline with solid NaOH and extracted with diethyl ether (4×50 mL). The combined organic phases were washed with brine and dried (Na_2SO_4), and solvent was evaporated leaving 535 mg (85%) of **12** as a yellow liquid. $[\alpha]_D^{21}$ +174 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.40 (9H, s), 2.29–2.18 (9H, m), 1.83 (3H, d of septet, *J*=6.9 and 3.5 Hz), 1.70 (3H, bs), 0.91 (9H, d, *J*=6.7 Hz), 0.85 (9H, d, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 62.6, 56.3, 34.9, 28.2, 19.1, 17.0; Anal. Calcd. for $C_{18}H_{42}N_4$: C, 68.73; H, 13.46; N, 17.81. Found: C, 67.75; H, 13.61; N, 17.34.

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