An Improved Synthesis of (3*S*,12*S*)-N^1,N^{14}-Diethyl-3,12-dihydroxyhomospermine, a Polyamine Analogue Therapeutic Agent

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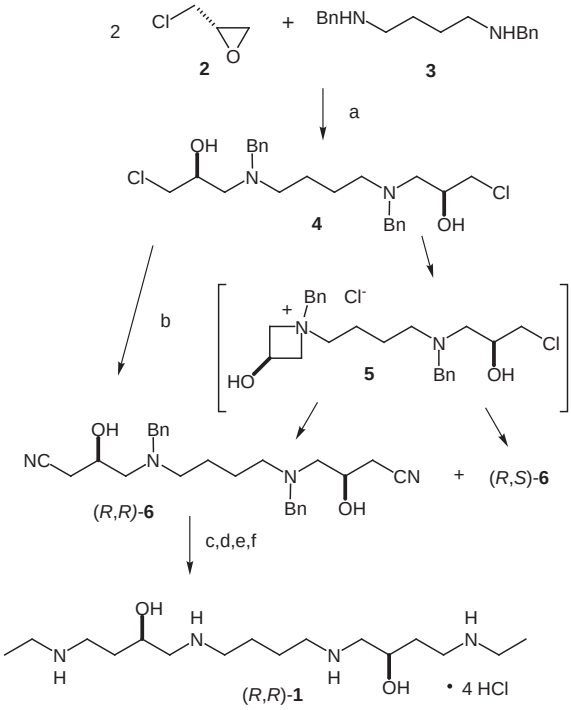
Abstract: The synthesis of a hydroxylated analogue of N^1,N^{14}-diethylhomospermine, (3*S*,12*S*)-N^1,N^{14}-diethyl-3,12-dihydroxyhomospermine, is described. The key step in the assembly of this homospermine derivative involves alkylation of *N*,*N*'-dibenzylputrescine with two equivalents of *N*-[(3*S*)-3,4-epoxybutyl]-*N*-ethyltrifluoromethanesulfonamide.

Key words: antitumor agents, chiral alcohols, epoxides, Mitsunobu reaction, polyamine analogue

Because of the role polyamines play in a number of physiological events, the polyamine metabolic network has attracted considerable attention as a target in many therapeutic strategies.[1–3] A series of terminally N-alkylated polyamine analogues, which exhibit antineoplastic activity against a number of murine and human tumor lines both in vitro and in vivo, were assembled in our laboratories.[4–8]

In the course of our clinical studies with these analogues as antineoplastics, we found N^1,N^{14}-diethylhomospermine (DEHSPM), a polyamine analogue designed and synthesized in these laboratories, to be a very potent gastrointestinal antitransit and antisecretory agent.[9,10] In one attempt to ameliorate some metabolic problems associated with DEHSPM,[11] we raised the oxidation state of two of the methylene groups of DEHSPM by introducing a single hydroxyl in the (*R*) configuration at each of the external aminobutyl fragments, resulting in (3*R*,12*R*)-N^1,N^{14}-diethyl-3,12-dihydroxyhomospermine[(*R*,*R*)-$(HO)_2$DEHSPM, (*R*,*R*)-**1**].[12]

Three synthetic routes to chiral N^1,N^{14}-diethyl-3,12-dihydroxyhomospermines [$(HO)_2$DEHSPMs] have been published from this laboratory. The first access to (*R*,*R*)-**1** began with ring opening of (*S*)-(+)-epichlorohydrin (**2**) (2 equivalents) by *N*,*N*'-dibenzylputrescine (**3**) (Scheme 1).[12] The homospermine chain was completed by elaboration of the resulting dichloride **4** to the dinitrile **6**. During scale-up of this step, varying amounts of racemization were observed, depending on the reaction conditions. Loss of optical purity could arise from nonstereoselective attack by cyanide ion at the 2-position of an azetidinium intermediate such as **5**.[13] Transformation of the cyano groups of **6** to terminally ethylated amines



Scheme 1 Synthesis of (*R*,*R*)-$(HO)_2$DEHSPM [(*R*,*R*)-**1**] from (*S*)-(+)-Epichlorohydrin (**2**)[12]; Reagents and conditions: (a) $MgSO_4$, MeOH, 68%; (b) KCN, 18-crown-6, MeCN, 65%; (c) H_2, Ra Ni, NH_3, MeOH, 86%; (d) Ac_2O, CH_2Cl_2, 73%; (e) $LiAlH_4$, THF, 44%; (f) H_2, Pd-C, HCl, EtOH, 72%

and hydrogenolysis of the benzyls furnished (*R*,*R*)-**1** in only 9% overall yield. Clearly, this sequence does not lend itself to efficient scale-up.

A pivotal step in the second synthesis of (*R*,*R*)-**1**[14] was the regiospecific alkylation of *N*-ethylmesitylenesulfonamide (**7**) (NaH/DMF) by the ditosylate of (*R*)-2-benzyloxy-1,4-butanediol (**8**), which was obtained from dimethyl D-malate (Scheme 2). The resulting monotosylate (**9**) (2 equivalents) was used in the bis-alkylation of *N*,*N*'-bis(mesitylenesulfonyl)-1,4-butanediamine (**10**), providing fully protected polyamine **11** in 50% yield. Although catalytic cleavage of the *O*-benzyl protecting groups of **11** occurred efficiently, deprotection of the amines of **12** by sodium naphthalide gave (*R*,*R*)-**1** in only 21% yield.

In our first route to (3*S*,12*S*)-N^1,N^{14}-diethyl-3,12-dihydroxyhomospermine [(*S*,*S*)-$(HO)_2$DEHSPM, (*S*,*S*)-**1**], L-malic acid was transformed into (3*S*)-*N*-(benzyloxycarbo-

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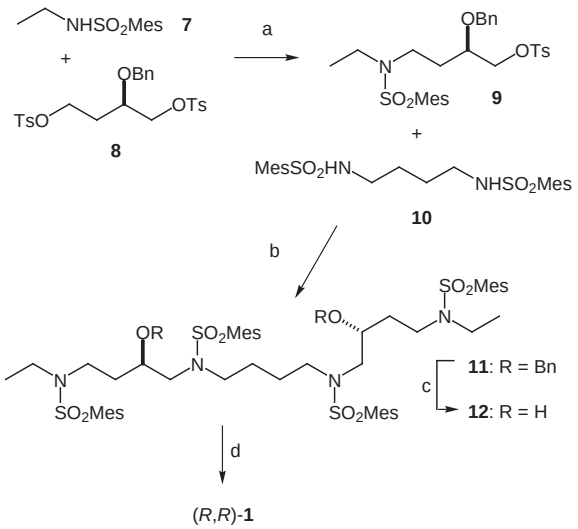
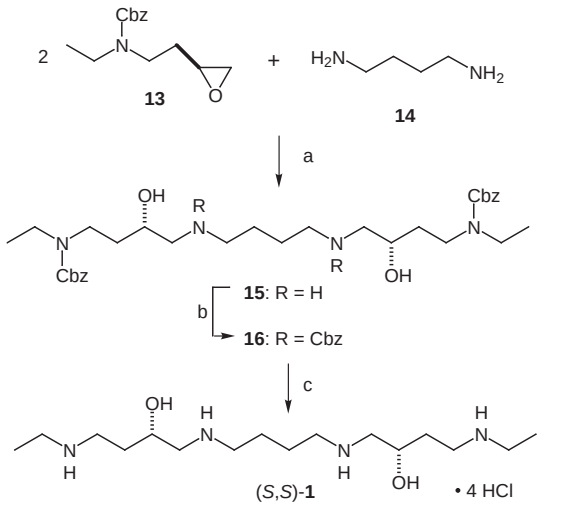


Scheme 2 Synthesis of (*R*,*R*)-$(HO)_2$DEHSPM [(*R*,*R*)-**1**] from Ditosylate **8**[14]; Reagents and conditions: (a) NaH, DMF, 77%; (b) NaH, DMF, 50%; (c) H_2, Pd-black, HOAc, H_2O, 86%; (d) Na/naphthalene, DME, then EtOH, HCl, 21%



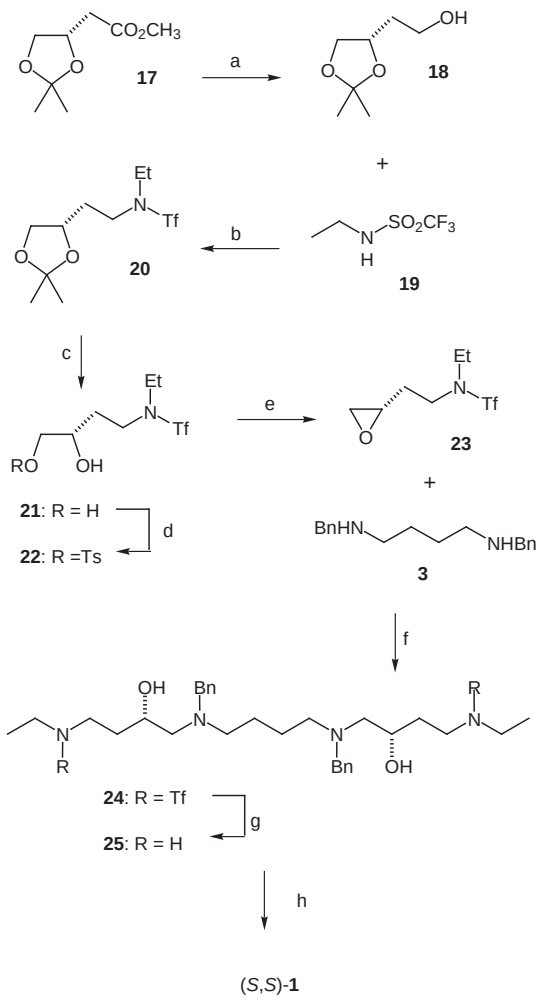
Scheme 3 Synthesis of (*S*,*S*)-$(HO)_2$DEHSPM [(*S*,*S*)-**1**] from Epoxide **13**[14]; Reagents and conditions: (a) EtOH; (b) benzyl chloroformate, Et_3N, $CHCl_3$, 22%; (c) H_2, Pd-C, EtOH, HCl, 85%

nyl)-*N*-ethyl-3,4-epoxybutylamine (**13**) (13% yield),[14] which was used to alkylate putrescine (**14**) (0.5 equivalent) (Scheme 3). Trapping the internal nitrogens of resulting diol **15** with benzyl chloroformate gave tetra-Cbz polyamine **16** in only 22% yield for the two steps. Facile unmasking of the amines by hydrogenolysis provided (*S*,*S*)-**1**.

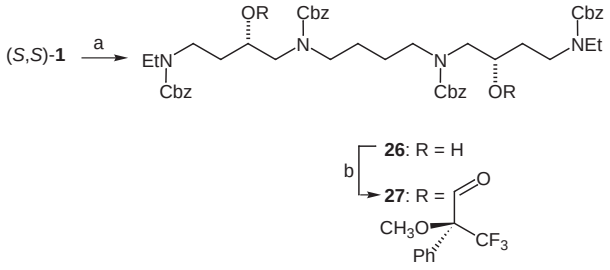
Although both (*R*,*R*)- and (*S*,*S*)-**1** could now be synthesized in enantiomerically pure states (Schemes 2 and 3), as verified by ^{19}F NMR spectral analysis of the bis-Mosher's esters of their N^1,N^5,N^{10},N^{14}-tetra-Cbz derivatives, the overall yields were only 7% and 2%, respectively.[14] The low yields of these routes to the $(HO)_2$DEHSPMs may be due to the stability of amine protecting groups: they were either too labile during elaboration of the molecule or too resistant to removal. The synthetic sequences to date are certainly unsuitable for producing large quantities of $(HO)_2$DEHSPMs sufficient for biological evaluation.

The current investigation describes the improvements in accessing analogue (*S*,*S*)-**1**. The goal of the present route to this polyamine was to increase the overall yield while maintaining enantiomeric purity. Specifically, benzyl and trifluoromethanesulfonyl (Tf)[15] groups, which were utilized for the synthesis of (2*S*,10*S*)-N^1,N^{11}-diethyl-2,10-dihydroxynorspermine,[14] were selected as the amine protecting groups. Methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate (**17**) was reduced to known primary alcohol **18** with lithium aluminum hydride in THF in 84% yield (Scheme 4).[16] Alkylation of ethyl trifluoromethanesulfonamide (**19**) under Mitsunobu conditions (diisopropyl azodicarboxylate, triphenylphosphine, THF)[17–19] with carbinol **18** gave *N*,*N*-dialkyl sulfonamide **20** in 93% yield. Hydrolysis of acetonide **20** (acetone, 1 N HCl, reflux) provided *N*-[(3*S*)-3,4-dihydroxybutyl]-*N*-ethyltrifluoromethanesulfonamide (**21**) in 88% yield. Reaction of diol **21** with TsCl (1.1 equivalents) in pyridine at 0 °C provided primary tosylate **22** in 86% yield. Ring closure of **22** was promoted by K_2CO_3 in methanol, generating *N*-[(3*S*)-3,4-epoxybutyl]-*N*-ethyltrifluoromethanesulfonamide (**23**) in 79% yield. Triflate-protected epoxide derivative **23** was thus synthesized in 56% yield from compound **18**, a sequence with over 40% higher efficiency than that of the Cbz-protected derivative.[13] Alkylation of *N*,*N*'-dibenzylputrescine (**3**) with epoxide **23** (2 equivalents) in refluxing ethanol produced the protected tetraamine **24** in virtually quantitative yield. Unmasking of the amines in **24** was accomplished in two steps. Removal of the Tf groups in **24** was achieved with lithium aluminum hydride in refluxing THF,[20] giving (3*S*,12*S*)-N^5,N^{10}-dibenzyl-N^1,N^{14}-diethyl-3,12-dihydroxyhomospermine (**25**) in 62% yield. Hydrogenolysis of **25** at 1 atmosphere over 10% Pd-C in ethanol and 1 N HCl (8 equivalents) cleaved the *N*-benzyl moieties, providing (*S*,*S*)-$(HO)_2$DEHSPM as its crystalline tetrahydrochloride salt [(S,S)-**1**] in 88% yield. The proton NMR spectrum of (*S*,*S*)-**1** matched published values, and its optical rotation was within 5% error of the literature value.[14] The two-stage unmasking to the target molecule proceeded in 36% higher yield than the corresponding sequence to (*R*,*R*)-**1**.[14]

Evaluation of the optical purity of (*S*,*S*)-**1** was carried out as before,[14] by functionalizing the nitrogens with Cbz, giving **26**, and then making the bis-Mosher's ester **27** (Scheme 5). The ^{19}F NMR spectrum showed approximately 3% contamination by the (*R*) stereocenter. Therefore, the enantiomeric purity of (*S*,*S*)-**1** as accessed by the present route was 94%. Assuming that no racemization occurred in the final two steps, two-fold addition of epoxide **23** to *N*,*N*'-dibenzylputrescine (**3**) led to 94% (97% × 97%) of (*S*,*S*)-**1**, 6% (97% × 3% × 2) of the *meso*-compound, and only 0.1% (3% × 3%) of (*R*,*R*)-**1**. The spec-



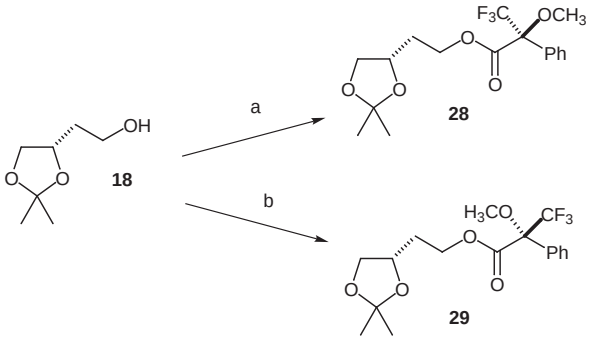
Scheme 4 Synthesis of (*S*,*S*)-$(HO)_2$DEHSPM [(*S*,*S*)-**1**]; Reagents and conditions: (a) $LiAlH_4$, THF, 84%; (b) PPh_3, diisopropyl azodicarboxylate, THF, 93%; (c) 1 N HCl, acetone, 90 °C, 88%; (d) TsCl, pyridine, 86%; (e) K_2CO_3, MeOH, 79%; (f) EtOH, reflux, 98%; (g) $LiAlH_4$, THF, 62%; (h) H_2, 10% Pd-C, 1 M HCl (8 equiv), EtOH, 88%



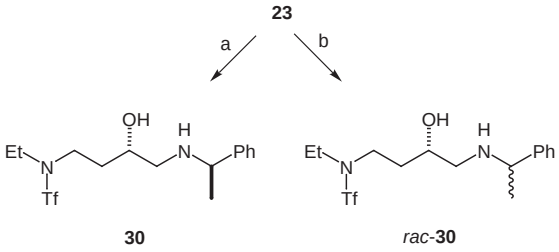
Scheme 5 Reagents and conditions: (a) *N*-(benzyloxycarbonyloxy)succinimide, $KHCO_3$, Et_2O (aq), 83%; (b) (*R*)-(–)-Mosher's acid chloride, pyridine, CCl_4, quantitative

trum of Mosher's ester **27** indicates only 3% epimerization because the chemical shift of the stereogenic center in the (*S*)-configuration in the *meso*-compound would likely be identical to that of the Mosher's ester of **26**, due to the distance between the carbinol stereocenters.

We took measures to find the reaction step at which epimerization occurred. Alcohol **18** was acylated with (*R*)-(–)- and (*S*)-(+)-Mosher's acid chlorides (Scheme 6), and ^{1}H NMR analysis showed that **18** was not stereochemically compromised. Note, however, that the chiral centers in respective derivatives **28** and **29** are separated by four atoms; thus, the small amount of racemization in the final product could have originated from the first step. Epoxide **23** was reacted with chiral and racemic α-methylbenzylamine (Scheme 7), and ^{1}H NMR analysis of the products **30** and *rac*-**30** indicated approximately 1% epimerization of the chiral center in **23**. This level of racemization was slightly less than that in final product (*S*,*S*)-**1**. Therefore, the diastereomeric derivatives of Schemes 6 and 7 do not pinpoint the origin of minor optical contamination from Scheme 4.



Scheme 6 Reagents and conditions: (a) (*R*)-(–)-Mosher's acid chloride, pyridine, CCl_4, 79%; (b) (*S*)-(+)-Mosher's acid chloride, Et_3N, DMAP



Scheme 7 Reagents and conditions: (a) (*R*)-(+)-α-methylbenzylamine, EtOH, reflux, 79%; (b) α-methylbenzylamine, EtOH, reflux, 90%

The key to the improved synthesis of (*S*,*S*)-**1** is in the choice of protecting groups. Construction of a tetra protected polyamine from Tf-containing epoxide **23** (Scheme 4) occurred in 76% higher yield than that from Cbz-protected amino epoxide **13**[14] (Scheme 3), likely due to the greater stability of the Tf functionality. Removal of the Tf blocking groups to make **25** was accomplished 41% more efficiently than cleavage of the mesitylenesulfonyls of **12** to generate (*R*,*R*)-**1**.[14] Whereas the latter protecting group has been effectively used in this laboratory in the synthesis of terminally alkylated polyamine analogues,[21] conditions of its removal using sodium naphthalide had to be carefully controlled to avoid cleavage of the chiral al-

cohols, which need not be protected during the present route (Scheme 4).

Thus, the synthesis of the hydroxylated polyamine analogue (*S*,*S*)-**1** in 30% overall yield and in gram quantities has been completed 15 times more efficiently than its previous synthesis.[14] Also, this route is flexible in that (*R*,*R*)-**1** could be made, starting with the (*R*) enantiomer of **18**.[22] Moreover, the length of the central polyamine chain could be varied by reacting *N*,*N*'-dibenzyldiamines other than **3** with the oxirane **23**.

Methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-acetate (**17**) was obtained from Synthon Co., Lansing, MI. Other reagents were purchased from the Aldrich Chemical Co. (Milwaukee, WI). Fisher Optimagrade solvents (Fisher Scientific, Pittsburgh, PA) were routinely used, and THF was distilled from Na and benzophenone. Organic extracts were dried over Na_2SO_4 unless otherwise indicated, and silica gel 32–63 (40 μm "flash") from Selecto Scientific, Inc. (Suwanee, GA) was used for flash column chromatography. ^{1}H NMR spectra were run at 300 MHz in a deuterated organic solvent ($CDCl_3$ not indicated) or in D_2O on a Varian Unity 300 with chemical shifts in ppm downfield from TMS or 3-(trimethylsilyl)propionic-*2,2,3,3-d*$_4$ acid, sodium salt, respectively. A ^{19}F NMR spectrum was run at 282 MHz in $CDCl_3$ on the same instrument with chemical shifts in ppm downfield from $CFCl_3$. Optical rotations were measured at 589 nm (Na D line) with a Perkin−Elmer 341 polarimeter. High resolution FAB mass spectra were run in a glycerol (**26**) or 3-nitrobenzyl alcohol (**30**) matrix. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

(*S*)-2,2-Dimethyl-1,3-dioxolane-4-ethanol (18)

Compound **17** (19.28 g, 0.111 mol) was reacted with $LiAlH_4$ (1.0 M in THF, 60 mL, 60 mmol) under Ar by a literature method.[16] Distillation (bp 72–73 °C/1.0 mbar) [Lit.[16] bp 49–50 °C/0.47 mbar] gave 13.61 g (84%) of **18** as a colorless oil.

$[\alpha]^{28}_D$ –2.16 (*c* 9.80, MeOH) [Lit. $[\alpha]_D$ –2.23 (*c* 9.8, MeOH);[23] $[\alpha]^{21}_D$ –1.49 (*c* 9.83, MeOH);[16] $[\alpha]^{22}_D$ –3.2 (*c* 1.0, MeOH)[22]].

^{1}H NMR data was essentially identical to reported values.[22]

***N*-{2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]ethyl}-*N*-ethyltrifluoromethanesulfonamide (20)**

Compound **18** (13.93 g, 95.3 mmol), PPh_3 (dried in vacuo over P_2O_5, 30.00 g, 0.114 mol), and **19**[18] (16.90 g, 95.4 mmol) were dissolved in THF (430 mL) under N_2. Diisopropyl azodicarboxylate (22.5 mL, 0.114 mol) was added dropwise over 35 min with intermittent ice cooling, and the reaction mixture was stirred for 3.3 h at r.t. Solids were filtered and washed with Et_2O (3 × 50 mL). After solvent removal in vacuo, purification by flash chromatography (5% EtOAc–cyclohexane) furnished 27.07 g of **20** (93%) as a liquid.

$[\alpha]^{26}_D$ –2.5 (*c* 1.18, $CHCl_3$).

^{1}H NMR: δ = 1.27 (t, 3H, *J* = 7.3 Hz), 1.34 (s, 3H), 1.42 (s, 3H), 1.83–1.94 (m, 2H), 3.42–3.62 (m, 5H), 4.05–4.16 (m, 2H).

Anal. Calcd for $C_{10}H_{18}F_3NO_4S$: C, 39.34; H, 5.94; N, 4.59. Found: C, 39.63; H, 6.05; N, 4.71.

***N*-[(3*S*)-3,4-Dihydroxybutyl]-*N*-ethyltrifluoromethanesulfonamide (21)**

HCl (1 N, 210 mL) was added to a solution of **20** (27.04 g, 88.56 mmol) in acetone (105 mL). The reaction mixture was heated at 95 °C for 1 h and partially concentrated in vacuo. Brine (50 mL) was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (75 mL). After solvent removal in vacuo, purification by flash chromatography (88% MeOH–$CHCl_3$) gave 20.60 g of **21** (88%) as an oil.

$[\alpha]^{23}_D$ –9.0 (*c* 1.88, $CHCl_3$).

^{1}H NMR: δ = 1.19 (t, 3H, *J* = 7.2 Hz), 1.68 (m, 2H), 3.41 (m, 5H), 3.56 (dd, 1H, *J* = 11.7, 3.0 Hz), 3.66 (m, 1H), 3.98 (br s, 2H).

Anal. Calcd for $C_7H_{14}F_3NO_4S$: C, 31.70; H, 5.32; N, 5.28. Found: C, 32.03; H, 5.40; N, 5.20.

***N*-Ethyl-*N*-[(3*S*)-3-hydroxy-4-*p*-toluenesulfonatobutyl]-trifluoromethanesulfonamide (22)**

A solution of **21** (20.12 g, 75.9 mmol) in pyridine (120 mL) was cooled to 0 °C under N_2, and TsCl (15.91 g, 83.45 mmol) in CH_2Cl_2 (80 mL) was added dropwise. The reaction mixture was stirred at r.t. for 12 h, diluted with $CHCl_3$ (600 mL), and extracted with 1 N HCl (3 × 700 mL). The organic phase was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (5% acetone–$CHCl_3$) to yield 27.21 g of **22** (86%) as a liquid.

$[\alpha]^{24}_D$ –5.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (CD_3OD): δ = 1.21 (t, 3H, *J* = 7.0 Hz), 1.64 (m, 1H), 1.76 (m, 1H), 2.45 (s, 3H), 3.44 (q, 2H, *J* = 7.0 Hz), 3.35–3.60 (m, 2H), 3.74 (m, 1H), 3.92 (dd, 1H, *J* = 10.3, 5.2 Hz), 3.95 (dd, 1H, *J* = 10.3, 4.8 Hz), 7.45 (m, 2H), 7.82 (m, 2H).

Anal. Calcd for $C_{14}H_{20}F_3NO_6S_2$: C, 40.09; H, 4.81; N, 3.34. Found: C, 40.19; H, 4.78; N, 3.27.

***N*-[(3*S*)-3,4-Epoxybutyl]-*N*-ethyltrifluoromethanesulfonamide (23)**

K_2CO_3 (4.48 g, 32.4 mmol) was added to a solution of **22** (12.35 g, 29.44 mmol) in MeOH (100 mL). The suspension was vigorously stirred at r.t. for 3 h under Ar and was poured into a mixture of H_2O (200 mL), brine (200 mL), and CH_2Cl_2 (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (10% EtOAc–cyclohexane) gave 5.78 g of **23** (79%) as a colorless oil.

$[\alpha]^{25}_D$ –15.9 (*c* 1.22, $CHCl_3$).

^{1}H NMR: δ = 1.27 (t, 3H, *J* = 7.3 Hz), 1.72 (m, 1H), 2.05 (m, 1H), 2.53 (dd, 1H, *J* = 4.8, 2.6 Hz), 2.82 (dd, 1H, *J* = 4.8, 4.0 Hz), 2.96 (m, 1H), 3.48 (q, 2H, *J* = 7.3 Hz), 3.54 (m, 2H).

Anal. Calcd for $C_7H_{12}F_3NO_3S$: C, 34.01; H, 4.89; N, 5.67. Found: C, 34.22; H, 4.86; N, 5.59.

(3*S*,12*S*)-*N*^{1},*N*^{14}-Bis(trifluoromethanesulfonyl)-*N*^{5},*N*^{10}-dibenzyl-*N*^{1},*N*^{14}-diethyl-3,12-dihydroxyhomospermine (24)

A solution of **23** (5.74 g, 23.2 mmol) and **3** (3.10 g, 11.5 mmol) was heated in EtOH (200 mL) at reflux for 44 h under N_2. The solvent was removed under reduced pressure. Purification by flash chromatography (23% acetone–toluene) gave 8.58 g of **24** (98%) as a colorless oil.

$[\alpha]^{24}_D$ +44.8 (*c* 1.32, $CHCl_3$).

^{1}H NMR: δ = 1.24 (t, 6H, *J* = 7.3 Hz), 1.42 (m, 4H), 1.50–1.78 (m, 4H), 2.30–2.60 (m, 8H), 3.36–3.67 (m, 14H), 3.78 (d, 2H, *J* = 13.5 Hz), 7.15–7.37 (m, 10H).

Anal. Calcd for $C_{32}H_{48}F_6N_4O_6S_2$: C, 50.38; H, 6.34; N, 7.34. Found: C, 50.25; H, 6.16; N, 7.30.

(3*S*,12*S*)-*N*^{5},*N*^{10}-Dibenzyl-*N*^{1},*N*^{14}-diethyl-3,12-dihydroxyhomospermine (25)

A solution of $LiAlH_4$ (1.0 M in THF, 67 mL, 67 mmol) was cautiously added to **24** (8.48 g, 11.1 mmol) in THF (340 mL) by syringe under N_2. The reaction mixture was heated to reflux for 2.8 days, cooled to 0 °C, and carefully hydrolyzed with H_2O (8 mL), 15% NaOH (8 mL), and H_2O (23 mL). The solids were filtered and

washed with Et_2O (2 × 125 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (5%, then 10% concd NH_4OH–MeCN), generating 3.43 g of **25** (62%) as a white solid.

$[\alpha]^{22}_D$ +41.3 (*c* 1.15, $CHCl_3$).

^1H NMR (CD_3OD): δ = 1.09 (t, 6H, *J* = 7.3 Hz), 1.38–1.52 (m, 6H), 1.65–1.77 (m, 2H), 2.37–2.47 (m, 8H), 2.59 (q, 4H, *J* = 7.3 Hz), 2.65 (m, 4H), 3.54 (d, 2H, *J* = 13.4 Hz), 3.61 (d, 2H, *J* = 13.4 Hz), 3.69 (m, 2H), 7.15–7.34 (m, 10H).

Anal. Calcd for $C_{30}H_{50}N_4O_2$: C, 72.25; H, 10.10; N, 11.23. Found: C, 72.02; H, 9.96; N, 11.36.

(3*S*,12*S*)-*N*^{1},*N*^{14}-Diethyl-3,12-dihydroxyhomospermine Tetrahydrochloride [(*S*,*S*)-1]

HCl (1 N, 27 mL) and 10% Pd-C (480 mg) were introduced into **25** (1.73 g, 3.47 mmol) in EtOH (150 mL). The reaction mixture was stirred under H_2 (1 atm) for 5 h, filtered through Celite, and concentrated in vacuo. Recrystallization of the concentrate from aq EtOH gave 1.42 g of (*S*,*S*)-**1** (88%) as white crystals.

$[\alpha]^{23}_D$ +8.33 (*c* 1.14, 1 N HCl) [Lit.[14] $[\alpha]^{23}_D$ +8.7 (*c* 1.05, 1 N HCl)].

^1H NMR (D_2O): δ = 1.29 (t, 6H, *J* = 7.3 Hz), 1.72–2.02 (m, 8H), 2.98–3.30 (m, 16H), 4.05 (tt, 2H, *J* = 9.6, 3.2 Hz); essentially identical to lit.[14] (*S*,*S*)-**1**.

Anal. Calcd for $C_{16}H_{42}Cl_4N_4O_2$: C, 41.39; H, 9.12; N, 12.07. Found: C, 41.61; H, 9.22; N, 12.26.

(3*S*,12*S*)-*N*^{1},*N*^{14}-Diethyl-3,12-dihydroxy-*N*^{1},*N*^{5},*N*^{10},*N*^{14}-tetrakis(benzyloxycarbonyl)homospermine (26)

$KHCO_3$ (228 mg, 2.28 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (128 mg, 0.51 mmol) were added to a mixture of **(S,S)-1** (39.8 mg, 86 μmol) in H_2O (5 mL) and Et_2O (5 mL) at 0 °C, and the reaction mixture was stirred at r.t. for 5 h. H_2O (20 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (75% EtOAc–cyclohexane) gave 61 mg of **26** (83%) as a colorless, viscous oil.

$[\alpha]^{22}_D$ +2.8 (*c* 1.00, MeOH) [Lit.[14] $[\alpha]^{21}_D$ +3.3 (*c* 0.97, MeOH)].

^1H NMR (CD_3OD): δ = 1.08 (m, 6H), 1.47 (m, 6H), 1.69 (m, 2H), 2.98–3.48 (m, 16H), 3.73 (m, 2H), 5.08 (m, 8H), 7.22–7.40 (m, 20H).

HRMS: calcd for $C_{48}H_{63}N_4O_{10}$ (M + H): 855.4544. Found: 855.4625.

(3*S*,12*S*)-3,12-Bis[(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetoxy]-*N*^{1},*N*^{14}-diethyl-*N*^{1},*N*^{5},*N*^{10},*N*^{14}-tetrakis-(benzyloxycarbonyl)homospermine (27)

The reaction was carried out in an oven-dried 5- × 175-mm NMR tube, fitted with a rubber septum, under an Ar atm. The reagents were injected via syringe in the following order: anhyd pyridine (300 μL), (*R*)-(–)-Mosher's acid chloride (37 μL, 0.20 mmol), CCl_4 (200 μL), and a solution of **26** (45 mg, 53 μmol) in CCl_4 (500 μL). The reaction mixture was shaken and allowed to stand at r.t. for 20 h. $CHCl_3$ (20 mL) was added, and the solution was washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (33% EtOAc–cyclohexane) gave 68 mg of **27** (quantitative) as a colorless oil.

$[\alpha]^{20}_D$ –8.8 (*c* 1.28, $CHCl_3$) [Lit.[14] $[\alpha]^{22}_D$ –7.7 (*c* 1.35, $CHCl_3$)].

^1H NMR (45 °C): δ = 1.05 (t, 6H, *J* = 7.3 Hz), 1.32 (m, 4H), 1.70–1.95 (m, 4H), 2.80–3.52 (m, 16H), 3.43 (s, 6H), 5.09 (m, 8H), 5.22 (m, 2H), 7.20–7.54 (m, 30H).

^{19}F NMR (45 °C): δ = –71.57 (97 %), –71.81 (3%).

Anal. Calcd for $C_{68}H_{76}F_6N_4O_{14}$: C, 63.44; H, 5.95; N, 4.35. Found: C, 63.66; H, 6.00; N, 4.45.

2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]ethyl (*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (28)

The reaction was carried out in an oven-dried 5- × 175-mm NMR tube, fitted with a rubber septum, under an Ar atmosphere. The reagents were injected via syringe in the following order: anhyd pyridine (300 μL), (*R*)-(–)-Mosher's acid chloride (50 mg, 0.20 mmol), CCl_4 (200 μL), and a solution of **18** (24.5 mg, 0.17 mmol) in CCl_4 (500 μL). The reaction was run and worked up by the method of **27**. The residue was purified by flash chromatography (10% EtOAc–cyclohexane) to give 48 mg of **28** (79%) as a colorless oil.

^1H NMR: δ = 1.31 (s, 3H), 1.39 (s, 3H), 1.94 (m, 2H), 3.50 (dd, 1H, *J* = 8.1, 7.0 Hz), 3.54 (q, 3H, *J* = 1.2 Hz), 3.95 (dd, 1H, *J* = 8.1, 5.9 Hz), 4.08 (quintet, 1H, *J* = 6.4 Hz), 4.44 (t, 2H, *J* = 6.6 Hz), 7.40 (m, 3H), 7.52 (m, 2H).

2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]ethyl (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (29)

Et_3N (11 mg, 0.11 mmol), DMAP (trace), and (*S*)-(+)-Mosher's acid chloride (13 mg, 51 μmol) were added to **18** (6.4 mg, 44 μmol) in $CDCl_3$ (400 μL). The reaction mixture was stirred for 1 h at r.t. and was transferred to an NMR tube.

^1H NMR: δ = 3.99 (dd, 1H, *J* = 8.1, 6.0 Hz) (absent in the spectrum of crude **28**).

N-Ethyl-*N*-[(3*S*)-3-hydroxy-4-[(1*R*)-1-phenylethylamino]-butyl]trifluoromethanesulfonamide (30)

A solution of **23** (25.1 mg, 0.10 mmol) and (*R*)-(+)-α-methylbenzylamine (24.6 mg, 0.20 mmol) in EtOH (5 mL) was heated to reflux for 1 day under Ar. The solvent was removed, and the crude product was purified by flash chromatography (5% MeOH–$CHCl_3$) to give 29 mg of **30** (79%) as a colorless oil.

$[\alpha]^{24}_D$ +39.3 (*c* 1.14, $CHCl_3$).

^1H NMR ($CDCl_3/D_2O$): δ = 1.23 (t, 3H, *J* = 7.0 Hz), 1.37 (d, 3H, *J* = 6.6 Hz), 1.50–1.75 (m, 2H), 2.28 (dd, 1H, *J* = 12.1, 9.2 Hz), 2.62 (dd, 1H, *J* = 12.1, 3.1 Hz), 3.36–3.57 (m, 4H), 3.63 (tt, 1H, *J* = 9.0, 3.3 Hz), 3.77 (q, 1H, *J* = 6.6 Hz), 7.22–7.38 (m, 5H); δ = 2.38 (dd, integrates to 1% of dd at δ = 2.28, *J* = 12, 10 Hz).

HRMS: calcd for $C_{15}H_{24}F_3N_2O_3S$ (M + H): 369.1460. Found: 369.1463.

N-Ethyl-*N*-[(3*S*)-3-hydroxy-4-(1-phenylethylamino)butyl]-trifluoromethanesulfonamide (*rac*-30)

A solution of **23** (25.0 mg, 0.10 mmol) and α-methylbenzylamine (24.5 mg, 0.20 mmol) in EtOH (5 mL) was heated to reflux for 19 h under N_2. The product was purified by the method of **30** to produce 33 mg of *rac*-**30** (90%) as a colorless oil.

^1H NMR ($CDCl_3/D_2O$): δ = 2.28 (dd, 0.5H, *J* = 12.1, 9.5 Hz), 2.38 (dd, 0.5H, *J* = 12.3, 9.2 Hz).

HRMS: calcd for $C_{15}H_{24}F_3N_2O_3S$ (M + H): 369.1460. Found: 369.1484.

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