Synthesis of (*R*)- and (*S*)-isomers of 1-methylspermidine

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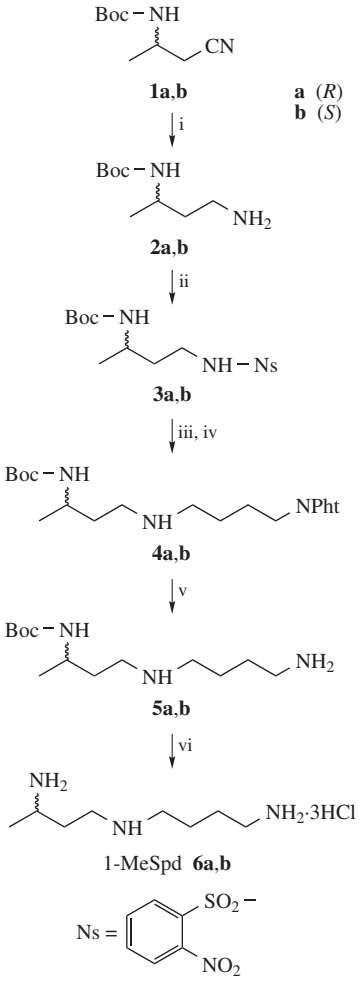
Previously unknown (*R*)- and (*S*)-isomers of 1,8-diamino-5-azanonane were prepared starting from (*R*)- and (*S*)-2-aminopropanols.

The biogenic polyamines spermidine (Spd, 1,8-diamino-4-azaoctane) and spermine (Spm, 1,12-diamino-4,9-diazadodecane) occur in significant amounts in all mammalian cells and are essential for their normal growth. A deficiency of Spm and Spd leads to serious disorders of cellular metabolism and, finally, to cell death.[1] The consequences of the depletion of a polyamine pool *in vivo* are quite complex.[2] For example, the activation of polyamine catabolism in transgenic rats dramatically reduces Spd and Spm pools mainly in the pancreas and provokes acute pancreatitis.[3] Racemic 1,8-diamino-5-azanonane (1-methylspermidine, 1-MeSpd) is metabolically stable, and it is the only known polyamine analogue to completely prevent acute pancreatitis caused by polyamine depletion *in vivo*.[4]

However, it is unclear which of the two enantiomers of 1-MeSpd is the exact biochemical equivalent of Spd. Here we describe the synthesis of earlier unknown (*R*)- and (*S*)-1-MeSpds.



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, –5 °C; ii, NsCl, Et_3N, CH_2Cl_2; iii, $PhtN(CH_2)_4I$, K_2CO_3, DMF; iv, PhSH, K_2CO_3, DMF; v, $N_2H_4·H_2O$, EtOH, Δ; vi, HCl, MeOH.

Boc-protected aminonitriles **1a** and **1b** were prepared according to a published procedure[5] starting from commercial enantiomerically pure 2-aminopropanol *via* its *N*-Boc-protected mesylate. The cyano group in **1a** and **1b** was smoothly reduced by $LiAlH_4$ at –5 °C and afforded **2a** and **2b**† without racemization. The above compounds were converted into *o*-nitrophenylsulfonyl (Ns) derivatives **3a** and **3b**,‡ which were alkylated with *N*-(4-iodobutyl)phthalimide. Subsequent removal of the Ns group led to bis(protected) 1-MeSpds **4a** and **4b**, which were isolated by flash chromatography§. The target hydrochlorides of **6a** and **6b** were obtained after the removal of Pht and Boc[t] groups¶ with

† To the cooled (–5 °C) suspension of $LiAlH_4$ (0.96 g, 25 mmol) in Et_2O (20 ml), a solution of **1a** (1.7 g, 9.2 mmol) in Et_2O (15 ml) was added with stirring for 20 min, and stirring was continued for 45 min at –5 °C. The reaction was quenched with aqueous NaOH. The organic phase was separated, the residue was treated with Et_2O, combined Et_2O extracts were washed with brine and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography [60 g SiO_2, 1,4-dioxane–25% NH_4OH (98:2)] affording 1.56 g (90%) of (*R*)-N^3-(*tert*-butyloxycarbonyl)-1,3-diaminobutane **2a**; R_f 0.33 [1,4-dioxane–25% NH_4OH (95:5)]; $[\alpha]_D^{20}$ –12.0° (*c* 2.0, $CHCl_3$; lit.,[5] $[\alpha]_D^{20}$ –12.0°). ^1H NMR ($CDCl_3$) δ: 4.65 (br. s, 1H), 3.72 (m, 1H), 2.69 (m, 2H), 1.50 (m, 1H), 1.44 (m, 1H), 1.38 (s, 9H), 1.31 (br. s, 2H), 1.08 (d, 3H, J_{HH} 6.54 Hz). ^{13}C NMR ($CDCl_3$) δ: 155.51, 78.89, 44.26, 40.99, 38.81, 28.34, 21.43. Starting from **1b** and following the same procedure, **2b** was obtained (91%); $[\alpha]_D^{20}$ +12.0° (*c* 2.0, $CHCl_3$; lit.,[5] $[\alpha]_D^{20}$ +12.0°).

‡ To the cooled (0 °C) solution of **2a** (1.43 g, 7.6 mmol) and Et_3N (1.21 ml, 8.8 mmol) in dry CH_2Cl_2 (15 ml) a solution of NsCl (1.77 g, 8.0 mmol) in dry CH_2Cl_2 (7 ml) was added with stirring for 30 min, and stirring was continued for 1 h at 0 °C and for 3 h at 20 °C. The reaction mixture was washed with H_2O, 10% citric acid and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford (*R*)-N^1-(*o*-nitrophenylsulfonyl)-N^3-(*tert*-butyloxycarbonyl)-1,3-diaminobutane **3a** (2.78 g, 98%); R_f 0.21 [EtOAc–*n*-hexane (1:2)]; $[\alpha]_D^{20}$ –13.0° (*c* 5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 8.09 (m, 1H), 7.80 (m, 1H), 7.70 (m, 2H), 6.23 (br. s, 1H), 4.33 (br. s, 1H), 3.71 (m, 1H), 3.24 (m, 1H), 3.01 (m, 1H), 1.69 (m, 1H), 1.37 (m, 10H), 1.07 (d, 3H, J_{HH} 6.54 Hz). ^{13}C NMR ($CDCl_3$) δ: 155.91, 148.07, 134.24, 133.28, 132.49, 130.70, 125.06, 79.59, 43.81, 40.81, 38.10, 28.26, 21.37. Found (%): C, 48.28; H, 6.33; N, 11.35. Calc. for $C_{15}H_{23}N_3O_6S$ (%): C, 48.25; H, 6.21; N, 11.25. Starting from **2b** and following the same procedure, **3b** was obtained (99%); $[\alpha]_D^{20}$ +13.0° (*c* 5, $CHCl_3$). Found (%): C, 48.17; H, 6.26; N, 11.28. Calc. for $C_{15}H_{23}N_3O_6S$ (%): C, 48.25; H, 6.21; N, 11.25.

§ The mixture of **3a** (2.7 g, 7.2 mmol), *N*-(4-iodobutyl)phthalimide (2.6 g, 7.9 mmol) and K_2CO_3 (2.98 g, 21.5 mmol) in dry DMF (20 ml) was stirred for 20 h at 20 °C, then PhSH (1.13 ml, 11.0 mmol) and K_2CO_3 (1.52 g, 11.0 mmol) were added and stirring was continued for 3 h at 20 °C. The reaction mixture was evaporated to dryness *in vacuo*, the residue was treated with a mixture of EtOAc and H_2O (3:2, 50 ml) and the organic layer was separated and washed with brine. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography [60 g of SiO_2, $CHCl_3$–MeOH–25% NH_4OH (100:2:0.2 to 100:4:0.4)] to afford (*R*)-N^1-(phthaloyl)-N^8-(*tert*-butyloxycarbonyl)-1,8-diamino-5-azanonane **4a** (2.49 g, 89%) as a white solid; R_f 0.37 ($CHCl_3$–MeOH–25% NH_4OH, 100:4:0.4); $[\alpha]_D^{20}$ –6.2° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.79 (m, 2H), 7.67 (m, 2H), 4.90 (br. s, 1H), 3.67 (t, 3H, J_{HH} 7.16 Hz), 2.61 (m, 4H), 1.65 (m, 3H), 1.48 (m, 4H), 1.38 (s, 9H), 1.09 (d, 3H, J_{HH} 6.54 Hz). ^{13}C NMR ($CDCl_3$) δ: 168.31, 155.52, 133.78, 132.14, 123.09, 78.80, 49.35, 46.50, 45.03, 37.77, 37.11, 28.37, 27.26, 26.35, 21.34. Starting from **3b** and following the same procedure, **4b** was obtained (92%); $[\alpha]_D^{20}$ +6.4° (*c* 1.0, $CHCl_3$).

overall yields of 43 and 45%, respectively, based on starting 2-aminopropanols. Thus, (*R*)- and (*S*)-1-MeSpds were obtained in 99+% purity, as determined by standard HPLC for polyamines.[6]

¶ The solution of **4a** (2.4 g, 6.2 mmol) and $N_2H_4·H_2O$ (0.4 g, 8.0 mmol) in 95% EtOH (30 ml) was refluxed for 3 h, the solvent was evaporated *in vacuo*, the residue was dissolved in 25% NH_4OH (20 ml) at 40 °C and extracted with $CHCl_3$. The combined extracts were washed with brine, the $CHCl_3$ was removed *in vacuo*, the residue was dissolved in MeOH (15 ml) and 11 M HCl in EtOH (4 ml) was added and the mixture was stirred for 4 h at 20 °C. The solvent was evaporated *in vacuo*, and the residue was crystallised from H_2O–MeOH–EtOH to give (*R*)-1,8-diamino-5-azanonane trihydrochloride [(*R*)-1-MeSpd] **6a** (1.15 g, 93%); R_f 0.45 (Bu^nOH–AcOH–Py–H_2O, 4:2:1:2); mp 191 °C; $[\alpha]_D^{20}$ +5.6° (*c* 5.0, H_2O). ^1H NMR ($CDCl_3$) δ: 3.53 (m, 1H), 3.21 (m, 2H), 3.15 (m, 2H), 3.07 (m, 2H), 2.16 (m, 1H), 2.02 (m, 1H), 1.86–1.74 (m, 4H), 1.36 (d, 3H, *J* 6.52 Hz). ^{13}C NMR ($CDCl_3$) δ: 50.03, 48.36, 46.89, 41.85, 33.34, 26.85, 25.69, 20.38. Found (%): C, 35.90; H, 9.12; N, 15.80. Calc. for $C_8H_{24}N_3Cl_3$ (%): C, 35.76; H, 9.00; N, 15.64. Starting from **5b** and following the same procedure, **6b** was obtained (96%); $[\alpha]_D^{20}$ –5.6° (*c* 5.0, H_2O). Found (%): C, 35.88; H, 9.10; N, 15.63. Calc. for $C_8H_{24}N_3Cl_3$ (%): C, 35.76; H, 9.00; N, 15.64.

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