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Synthesis of (*R*)- and (*S*)-isomers of 2-methylspermidine

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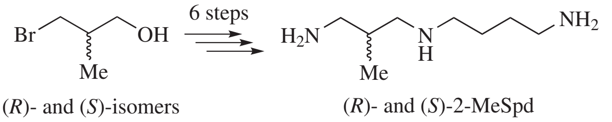
The title compounds, (*R*)- and (*S*)-isomers of 1,8-diamino-2-methyl-4-azaoctane, were prepared from commercially available enantiomers of 3-bromo-2-methylpropan-1-ol, each in six steps and good overall yields.



The biogenic polyamines, spermidine and spermine, are organic polycations present at millimolar concentrations in all eukaryotic cells. Spermine and spermidine participate in the regulation of many essential cellular functions including proliferation and differentiation.[1] Biological evaluation of rationally designed polyamine analogues and chemical regulators of polyamine metabolism is one of cornerstones of polyamine research during the past decades.[2] C-monomethylated analogues of spermidine (MeSpd) are important functionally active mimetics of Spd, because biochemical properties of MeSpds are determined by both properly positioned amino groups protonated at physiological pH and the position of the methyl group.[3] Testing of these analogues provides important information about cellular functions of spermidine and the peculiarities of action of the enzymes of polyamine metabolism.[4] Biochemical properties of MeSpds can be precisely regulated by changing configuration of the chiral center. Enantiomers of 1,8-diamino-5-azanonane (1-MeSpd)[5] and their N-8 acetylated derivatives, 1,8-diamino-3-methyl-4-azaoctane[6] and diastereomers of 2,13-diamino-5,10-diazatetradecane,[7] were synthesized. It was demonstrated that the enzymes of polyamine metabolism, *i.e.* acetylpolyamine oxidase, spermine oxidase, and deoxyhypusine synthase,[4,8] as well as spermidine transporter of prostate carcinoma cells DU145[9] have stereospecificity though their natural substrates are achiral. Moreover, with the use of 1-MeSpd isomers it turned possible to regulate stereospecificity of acetylpolyamine oxidase supplementing the substrate mixture with the required aromatic aldehyde.[4]

Here we describe a synthesis of earlier unknown (*R*)- and (*S*)-isomers of 1,8-diamino-2-methyl-4-azaoctane (2-MeSpd), compounds (*R*)-**1** and (*S*)-**1**, which seem to be useful for studying cellular functions of polyamines, the enzymes of their metabolism and the peculiarities of the regulation of polyamine homeostasis in the living cell.

Syntheses of (*R*)-**1** and (*S*)-**1** were started from commercially available isomers of 3-bromo-2-methylpropan-1-ol,[†] which were converted into the corresponding 3-phthaloylamino-2-methylpropan-1-ols (*R*)-**2** and (*S*)-**2**, as reported.[10] Subsequent hydrazinolysis gave (*R*)- and (*S*)-3-amino-2-methylpropan-1-ols which were converted into the corresponding Cbz-derivatives (*R*)-**3** and (*S*)-**3** (Scheme 1). Signals of C*H*$_2$OH protons in ^{1}H NMR spectra of compounds (*R*)-**3** and (*S*)-**3** are shifted

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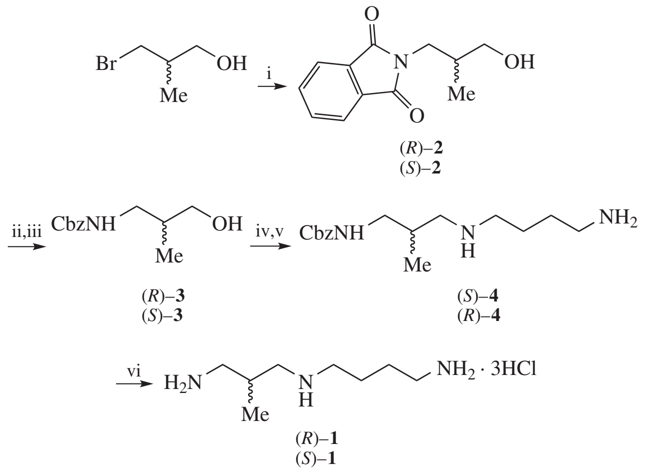
[†] 3-Phthaloylamino-2-methylpropan-1-ols *(R)*- and (*S*)-**2** were prepared from the corresponding freshly distilled *(S)*- and (*R*)-3-bromo-2-methylpropan-1-ols (Aldrich, both 97%) as reported.[10] TLC was performed on Merck Kieselgel 60 F$_{254}$ plates. Merck silica gel (Kieselgel, 40–63 μm) was used for column chromatography. Melting points are uncorrected. The values of optical rotation were measured on a Perkin Elmer 341 polarimeter at 21±2 ºC. High resolution mass spectra (HRMS) were measured with a Bruker micrOTOF II instrument using electrospray ionization (ESI)[11] in a positive ion mode (interface capillary voltage of 4500 V); mass range from *m*/*z* 50 to *m*/*z* 3000; internal calibration was done with ESI Tuning Mix, Agilent. A syringe injection was used for solutions in water for trihydrochlorides (*R*)- and (*S*)-**1** and MeOH for (*R*)- and (*S*)-**3** and (*R*)- and (*S*)-**4** (flow rate of 5 μl min^{-1}), nitrogen was as a nebulizer gas; interface temperature was 180 ºC.

3-Benzyloxycarbonylamino-2-methylpropan-1-ols (*R*)- *and* (*S*)-**3**. A solution of (*S*)-**2** (4.58 g, 20.9 mmol) and hydrazine hydrate (1.4 ml, 28 mmol) in EtOH (75 ml) was refluxed for 2 h, then 20% HCl (10 ml) was added, and refluxing was continued for additional 30 min. The precipitated material was filtered off, the filtrate was concentrated *in vacuo*, the residue was co-evaporated with water (2 x 15 ml), dry EtOH (2 x 20 ml), suspended in dry EtOH and the precipitated hydrazine hydrochloride was filtered off. The filtrate was concentrated *in vacuo*, the residue, 3-amino-2-methylpropan-1-ol hydrochloride (R_f 0.16, dioxane : 25% NH_4OH, 9:1) was dried *in vacuo* over KOH and reacted with benzyl chloroformate (3.72 g, 21.8 mmol) in the mixture of THF (40 ml), 2 M Na_2CO_3 (30 ml) and 1 M $NaHCO_3$ (20 ml) following the known method for amino alcohols.[12] The product (*S*)-**3** was triturated with Et_2O/hexane (1 : 3) mixture and left overnight at +4 °C to afford (*S*)-**3** [3.65 g, 75% as calculated from (*S*)-**2**] as a white solid, R_f 0.17 (CH_2Cl_2 : MeOH, 100 :1), $[\alpha]_D^{20}$ +8.4° (*c* 5.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (d, 3H, Me, *J* 7.0 Hz), 1.71–1.88 (m, 1H, CH), 2.69 (br.s, 1H, OH), 3.03–3.16 (m, 1H, NHC*H*$_2$), 3.22–3.44 (m, 2H, NHC*H*$_2$ + C*H*$_2$OH), 3.55 (dd, 1H, C*H*$_2$OH, $^2J_{HH}$ 11.3 Hz, *J* 4.5 Hz), 5.10 (s, 2H, C*H*$_2$Ph), 5.28 (br.s, 1H, NH), 7.30–7.40 (m, 5H, Ph). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.43, 36.17, 43.61, 64.89, 66.98, 128.15, 128.23, 128.61, 136.55, 157.67. HRESIMS, *m*/*z*: 224.1289 [M + H]$^+$ (calc. for $C_{12}H_{18}NO_3$, *m*/*z*: 224.1281).

Compound (*R*)-**3** was obtained (4.62 g, 71%) starting from (*R*)-**2** (6.38 g, 29 mmol) as above and purified on a silica gel (elution with CH_2Cl_2 : MeOH, 100 : 0.75), $[\alpha]_D^{20}$ –8.6° (*c* 5.0, $CHCl_3$). HRESIMS, *m*/*z*: 224.1284 [M + H]$^+$ (calc. for $C_{12}H_{18}NO_3$, *m*/*z*: 224.1281).



Scheme 1 *Reagents and conditions*: i, PhthNK, DMF, K_2CO_3, 70 °C (ref. 10); ii, $H_2NNH_2{\cdot}H_2O$, EtOH, Δ; iii, CbzCl, H_2O, THF, $NaHCO_3$; iv, MsCl, CH_2Cl_2, Et_3N; v, $H_2N(CH_2)_4NH_2$, THF, 0→20 °C; vi, H_2/Pd, AcOH, MeOH. (*R*)-**3** gives (*S*)-**4** and *vice versa*; (*S*)-**4** gives (*R*)-**1** and *vice versa* (substituent priority change).

downfield probably because C*H*$_2$OH group is close to the aromatic ring of the Cbz-group. Compounds (*R*)-**3** and (*S*)-**3** were O-mesylated, and the crude mesylates were reacted with the excess of 1,4-diaminobutane in THF to give (*S*)-**4** and (*R*)-**4**. The alkylation was carried out at 0→20 °C to diminish the number of minor byproducts inseparable by flash chromatography on SiO_2 and to provide good (66–77%) yields. Subsequent removal of Cbz-protective group and crystallization of the resulting trihydrochlorides afforded target products (*R*)-**1** and (*S*)-**1** in 47 and 34% overall yields [from (*R*)-**2** and (*S*)-**2**], respectively.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.025.

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1-Benzyloxycarbonylamino-8-amino-2-methyl-4-azaoctanes (*R*)- *and* (*S*)-**4**. Compound (*S*)-**3** (1.8 g, 8 mmol) was converted to its *O*-mesylate (*cf.* ref. 12), R_f 0.35 (CH_2Cl_2 : MeOH, 100 : 1), which without isolation was reacted with 1,4-diaminobutane (7.05 g, 80 mmol) in THF (25 ml) at 0 °C for 12 h and then at 20 °C for 96 h. The reaction mixture was concentrated (1 Torr), the residue was taken into 2 M NaOH (12 ml), extracted with CH_2Cl_2 (3 x 20 ml), washed with brine (15 ml) and dried ($MgSO_4$). Purification on silica gel (elution with dioxane/25% NH_4OH, 98 : 2) gave (*R*)-**4** (1.73 g, 77%) as a viscous oil, R_f 0.17 (dioxane : 25% NH_4OH, 9 : 1), $[\alpha]_D^{20}$ –3.2° (*c* 5.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, 3H, Me, *J* 6.8 Hz), 1.23 (br.s, 3H, NH + NH_2), 1.40–1.59 (m, 4H, $NHCH_2CH_2CH_2$), 1.73–1.91 (m, 1H, C*H*Me), 2.44–2.77 (m, 6H, CH_2NHCH_2+ CH_2NH_2), 2.98–3.15 (m, 1H, CH_2NHCbz), 3.24–3.40 (m, 1H, CH_2NHCbz), 5.10 (s, 2H, CH_2Ph), 6.29 (br.s, 1H, NHCbz), 7.30–7.43 (m, 5H, Ph). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 16.70, 27.51, 31.66, 33.39, 42.19, 47.05, 50.00, 55.54, 66.51, 128.08, 128.13, 128.56, 137.01, 156.66. HRESIMS, *m/z*: 294.2183 [M + H]$^+$ (calc. for $C_{16}H_{28}N_3O_2$, *m/z*: 294.2176).

Compound (*S*)-**4** was obtained (2.0 g, 66%) starting from (*R*)-**3** (2.28 g, 10.5 mmol) as above. (*S*)-**4**, $[\alpha]_D^{20}$ +3.3° (*c* 5.0, $CHCl_3$), HRESIMS, *m/z*: 294.2179 [M + H]$^+$ (calc. for $C_{16}H_{28}N_3O_2$, *m/z*: 294.2176).

1,8-Diamino-2-methyl-4-azaoctane trihydrochlorides (*R*)- *and* (*S*)-**1**. Cbz-derivative (*R*)-**4** (1.6 g, 5.5 mmol) was catalytically hydrogenated over Pd black in MeOH/AcOH (1 : 1) mixture (20 ml), the catalyst was filtered off and the filtrate was eveporated to dryness *in vacuo* after the addition of 7 M aq. HCl (3 ml). The residue was coevaporated with H_2O, dried *in vacuo* over P_2O_5/KOH, and recrystallized from MeOH/EtOH to give (*S*)-**1** (1.03 g, 73%), mp 180–181°C, R_f 0.23 (*n*-BuOH : AcOH : Py : H_2O, 4 : 2 : 1 : 2), $[\alpha]_D^{20}$ –6.2° (*c* 5.0, H_2O). ^{1}H NMR (300 MHz, D_2O) δ: 1.14 (d, 3H, Me, *J* 6.8 Hz), 1.68–1.85 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.24–2.40 (m, 1H, C*H*Me), 2.91 (dd, 1H, $CHCH_2NH$, $^2J_{HH}$ 13.1 Hz, $^3J_{HH}$ 8.8 Hz), 2.97–3.20 (m, 7H, $CHCH_2NH$ + $CHCH_2NHCH_2$ + H_2NCH_2CH + CH_2NH_2). ^{13}C NMR (75.4 MHz, D_2O) δ: 14.85, 23.26, 24.58, 30.06, 39.47, 43.03, 48.38, 51.28. HRESIMS, *m/z*: 160.1810 [M + H]$^+$ (calc. for $C_8H_{22}N_3$, *m/z*: 160.1808).

Compound (*R*)-**1** was obtained (1.25 g, 83%) starting from (*S*)-**4** (1.65 g, 5.6 mmol) as above. (*R*)-**1**, $[\alpha]_D^{20}$ +6.1° (*c* 5.0, H_2O). HRESIMS, *m/z*: 160.1809 [M + H]$^+$ (calc. for $C_8H_{22}N_3$, *m/z*: 160.1808).