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Asymmetric Syntheses of (R)- and (S)-2-Aminobutanesulfonic Acid and their 3,3-Dimethylderivatives

Daniela Braghiroli and Maria Di Bella*

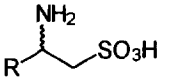
Dipartimento di Scienze Farmaceutiche, University of Modena, Via Campi 183, 41100 Modena, Italy

Abstract: (R)- and (S)-2-aminobutanesulfonic acid, **3a** and **3b**, and (R)- and (S)-2-amino-3,3-dimethylbutanesulfonic acid, **4a** and **4b**, were synthesized from the corresponding N-Boc protected β-amino alcohols in good yields and high enantiomeric purities (>99% ee). Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Recently we reported the syntheses of enantiomerically pure (R)- and (S)-2-aminopropanesulfonic acid, **1a** and **1b**.[1] These enantiomers were submitted to pharmacological tests that showed that only **1b** mimics the hypotensive effect of taurine (2-aminoethanesulfonic acid) **2**,[2] one of the most abundant free amino acid in mammals that seems to exhibit a special affinity for excitable tissues, such as brain, nerve, and muscle.[3]

In order to pursue the study of structure-activity as well as stereochemical requirements for the 2-aminoethanesulfonic acid **2** activities, the asymmetric syntheses of (R)- and (S)-2-aminobutanesulfonic acid, **3a** and **3b**, and of (R)- and (S)-2-amino-3,3-dimethylbutanesulfonic acid, **4a** and **4b**, were performed.



1a: (R) R = CH_3 **2**: R = H **3a**: (R) R = C_2H_5 **4a**: (R) R = $C(CH_3)_3$
1b: (S) R = CH_3 **3b**: (S) R = C_2H_5 **4b**: (S) R = $C(CH_3)_3$

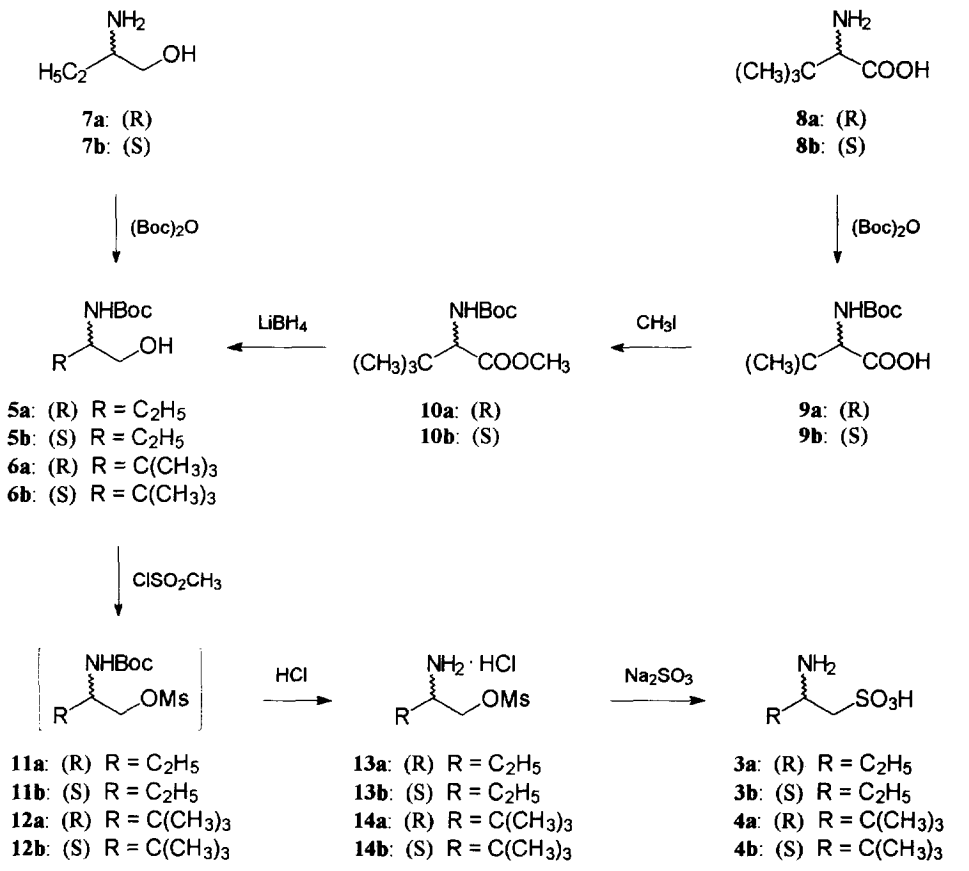
RESULTS AND DISCUSSION

Compounds **3** and **4** were synthesized from the corresponding β-(N-[(1,1-dimethylethoxy)carbonyl)amino alcohols **5** and **6** as outlined in Scheme 1.

2-N-[(1,1-Dimethylethoxy)carbonyl]aminobutanols **5** were obtained from the corresponding β-aminoalcohols **7** by reaction with di-*tert*-butyldicarbonate, $(Boc)_2O$, with the same method used for the racemate.[4] Otherwise 2-N-[(1,1-dimethylethoxy)carbonyl]amino-3,3-dimethylbutanols **6** were synthesized from the corresponding *tert*-leucines **8a** and **8b**. The amino groups of amino acids **8** were protected with di-*tert*-butyldicarbonate according to literature.[5] The N-[(1,1-dimethylethoxy)carbonyl]-*tert*-leucines **9** were then esterified to **10** and reduced to **6**.

Compounds **5** and **6** by treatment with methanesulfonyl chloride afforded unstable intermediates, reasonably compounds **11** and **12**, which were used for the following reactions without further purification. Deprotection of compounds **11** and **12** with hydrochloric acid provided the corresponding hydrochlorides **13** and **14**, which were treated with sodium sulfite to give **3** and **4**.

The above reactions proceed in mild conditions, with high yields, and without racemization. Each pair of enantiomers synthesized has the same $[\alpha]_D^{25}$ value of opposite sign. The enantiomeric purity of **3a** and **3b** and of **4a** and **4b** was assayed by HPLC after derivatization with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC).[6-8]



Scheme 1

EXPERIMENTAL

Melting points were determined with an Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Model 1600 FT-IR spectrometer (KBr pellets) and were consistent with the

assigned structures. ^{1}H NMR spectra were recorded with a Bruker AMX 400 or a Bruker DPX 200 spectrometer using $CDCl_3$ or D_2O as solvent and tetramethylsilane (TMS) as internal or external standard respectively. Chemical shifts are in ppm (δ) and coupling constants (J) in Hz. Multiplicities are abbreviated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; b, indicates a broadening of the signal. HPLC analyses were performed on Perkin Elmer Series 4 chromatograph equipped with ISS-101 automatic sampler, LC-85B spectrophotometric detector, LCI-100 Laboratory Computing Integrator and 7500 Professional Computer with Chromatographics 3 Software (Perkin Elmer Co., Norwalk, CT, USA). The column employed was a LiChrospher 100-RP18-LiChroCART (250 mm x 4 mm I.D.; 5 μm) (E.Merck, Darmstadt, Germany). Optical rotations were measured using a Perkin Elmer 241 polarimeter. Elemental analyses were performed in Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche of Modena University on a Carlo Erba Elemental Analyzer Model 1106 apparatus.

N-Boc-tert-leucine methyl esters **10**

To a stirred solution of **9** (6.50 g, 28 mmoles) in N,N-dimethylformamide[9] (45 ml) was added potassium hydrogen carbonate (5.60 g, 56 mmoles) and dropwise methyl iodide (2.8 ml, 45 mmoles). The mixture was stirred at room temperature under nitrogen for 5 hrs, then diluted with water (100 ml) and extracted with ethyl acetate-benzene 1:1 (3 x 25 ml). The organic extracts were washed with water (2 x 25 ml), 5% aqueous sodium sulfite (25 ml) and brine (25 ml), dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure to give in almost quantitative yields **10** (oils), which were used for the next steps without further purification.

N-Boc-D-tert-leucine methyl ester **10a**: ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J 1.0, 9H), 1.45 (s, 9H), 3.74 (s, 3H), 4.11 (d, J 9.6, 1H), 5.09 (bd, 1H).

N-Boc-L-tert-leucine methyl ester **10b**: ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J 1.0, 9H), 1.45 (s, 9H), 3.74 (s, 3H), 4.11 (d, J 9.6, 1H), 5.09 (bd, 1H).

2-N-[(1,1-Dimethylethoxy)carbonyl]aminobutanols **5**

To a stirred solution of the appropriate 2-aminobutanols **7** (5.29 ml, 56 mmoles) in 50 ml of CH_2Cl_2 and 50 ml of NaOH 1N was added dropwise 128 ml (56 mmoles) of di-*tert*-butyldicarbonate. After stirring overnight at room temperature, the organic layer was separated, washed with water (2 x 25 ml), dried over anhydrous sodium sulfate, and filtered. Removal of the solvent gave **5**, which were used for the next step without further purification.

(R)-2-N-[(1,1-Dimethylethoxy)carbonyl]aminobutanols **5a**: yield 92%. m.p. 45-6°C. $[\alpha]_D^{25}$ = +24.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J 7.4, 3H), 1.48 (s, 9H), 1.50-1.61 (m, 2H), 2.32 (bs, 1H), 3.56-3.73 (m, 3H), 4.65 (bs, 1H). Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.25; H, 10.21;

N, 7.54.

(S)-2-N-[(1,1-Dimethylethoxy)carbonyl]aminobutanols **5b**: yield 94%. m.p. 45-6°C. $[\alpha]_D^{25}$ = -24.4 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.97 (t, J 7.4, 3H), 1.48 (s, 9H), 1.50-1.61 (m, 2H), 2.32 (bs, 1H), 3.56-3.73 (m, 3H), 4.65 (bs, 1H). Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.28; H, 10.22; N, 7.56.

2-N-[(1,1-Dimethylethoxy)carbonyl]amino-3,3-dimethylbutanols **6**

To a stirred solution of the appropriate **10** (7.32 g, 30 mmoles) in 12 ml of anhydrous THF was added dropwise, in atmosphere of nitrogen, a 2M solution of lithium borohydride in THF (30 ml), then 85 ml of ethanol. After stirring overnight at room temperature, the mixture was acidified (pH 4) with 10% aqueous citric acid, and concentrated under reduced pressure. The precipitate lithium salts were removed by filtration and the filtrate was extracted with CH_2Cl_2 (3 x 30 ml). The organic layers were dried over sodium sulfate and evaporated in vacuo. The residue, crystallized from ethyl ether and hexane, gave **6**.

(R)-2-N-[(1,1-Dimethylethoxy)carbonyl]amino-3,3-dimethylbutanols **6a**: yield 92%. m.p. 113-4°C. $[\alpha]_D^{25}$ = +5.5 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.96 (s, 9H), 1.48 (s, 9H), 2.30 (bs, 1H), 3.49-3.57 (m, 2H), 3.84-3.88 (m, 1H), 4.70 (bd, J 6.9, 1H). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.44. Found: C, 60.95; H, 10.79; N, 6.41.

(S)-2-N-[(1,1-Dimethylethoxy)carbonyl]amino-3,3-dimethylbutanols **6b**: yield 90%. m.p. 113-4°C. $[\alpha]_D^{25}$ = -5.5 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.96 (s, 9H), 1.48 (s, 9H), 2.30 (bs, 1H), 3.49-3.57 (m, 2H), 3.84-3.88 (m, 1H), 4.70 (bd, J 6.9, 1H). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.44. Found: C, 60.88; H, 10.75; N, 6.43.

2-Aminobutanolmethanesulfonate hydrochlorides **13** *and 2-amino-3,3-dimethylbutanolmethanesulfonate hydrochlorides* **14**

To a stirred solution of the appropriate **5** or **6** (50 mmoles) and triethylamine[10] (7.6 ml, 55 mmoles) was added at 0°C, in atmosphere of nitrogen, a solution of methanesulfonyl chloride (4 ml, 52 mmoles) in CH_2Cl_2 (100 ml). The reaction mixture was stirred at room temperature for 20 min, then the solvent was evaporated under reduced pressure. The residue was treated with ethyl acetate (50 ml) and water (50 ml). The organic layer was separated, washed with aqueous 5% $NaHCO_3$ (3 x 20 ml) and brine (3 x 20 ml), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give **11** (waxy solids) or **12** (oils) respectively, which were used for the next steps without further purification. Compounds **11** or **12** were treated at room temperature for 60 min with a 4M solution of HCl in dioxane (100 ml). The precipitate was filtered and crystallized from acetonitrile and ethyl ether to give **13** or **14** respectively.

(R)-2-Aminobutanolmethanesulfonate hydrochlorides **13a**: yield 91%. m.p. 110-1°C. $[\alpha]_D^{25}$ = -15.5 (*c* 1.0,

H_2O). ^1H NMR (D_2O): δ 1.04 (t, J 7.5, 3H), 1.72-1.87 (m, 2H), 3.30 (s, 3H), 3.57-3.69 (m, 1H), 4.43 and 4.49 (dd, J 6.1 and 11.4, 1H), 4.56 and 4.62 (dd, J 3.2 and 11.4, 1H). Anal. Calcd for $C_5H_{14}ClNO_3S$: C, 29.48; H, 6.93; N, 6.88. Found: C, 29.40; H, 6.85; N, 6.75.

(S)-2-Aminobutanolmethanesulfonate hydrochlorides **13b**: yield 93%. m.p. 110-1°C. $[\alpha]_D^{25}$ = +15.5 (*c* 1.0, H_2O). ^1H NMR (D_2O): δ 1.04 (t, J 7.5, 3H), 1.72-1.87 (m, 2H), 3.30 (s, 3H), 3.57-3.69 (m, 1H), 4.43 and 4.49 (dd, J 6.1 and 11.4, 1H), 4.56 and 4.62 (dd, J 3.2 and 11.4, 1H). Anal. Calcd for $C_5H_{14}ClNO_3S$: C, 29.48; H, 6.93; N, 6.88. Found: C, 29.37; H, 6.81; N, 6.73.

(R)-2-Amino-3,3-dimethylbutanolmethanesulfonate hydrochlorides **14a**: yield 74%. m.p. 148-9°C. $[\alpha]_D^{25}$ = -25.7 (*c* 1.0, H_2O). ^1H NMR(D_2O): δ 1.09 (s, 9H), 3.30 (s, 3H), 3.48 and 3.52 (dd, J 3.5 and 8.9, 1H), 4.44 and 4.50 (dd, J 8.9 and 11.3, 1H), 4.67 and 4.73 (dd, J 3.5 and 11.3, 1H). Anal. Calcd for $C_7H_{18}ClNO_3S$: C, 36.28; H, 7.83; N, 6.04. Found: C, 36.42; H, 7.91; N, 6.15.

(S)-2-Amino-3,3-dimethylbutanolmethanesulfonate hydrochlorides **14b**: yield 72%. m.p. 148-9°C. $[\alpha]_D^{25}$ = +25.7 (*c* 1.0, H_2O). ^1H NMR(D_2O): δ 1.09 (s, 9H), 3.30 (s, 3H), 3.48 and 3.52 (dd, J 3.5 and 8.9, 1H), 4.44 and 4.50 (dd, J 8.9 and 11.3, 1H), 4.67 and 4.73 (dd, J 3.5 and 11.3, 1H). Anal. Calcd for $C_7H_{18}ClNO_3S$: C, 36.28; H, 7.83; N, 6.04. Found: C, 36.27; H, 7.87; N, 6.25.

2-Aminobutanesulfonic acids **3** *and 2-amino-3,3-dimethylbutanesulfonic acids* **4**

Sodium sulfite (10 g, 80 mmol) was added to a solution of the appropriate **13** or **14** (53 mmol) in water (100 ml) and the mixture was stirred at room temperature for 24 hrs. The resulting solution was passed through columns first of Amberlite IR-120 (H^+ form) then of Dowex 11 (acetate form). The eluate was evaporated to dryness under reduced pressure and the residue was crystallized from water and ethanol to give **3** or **4** respectively.

(R)-2-Aminobutanesulfonic acids **3a**: yield 89%. m.p. dec >300°C. $[\alpha]_D^{25}$ = -22.2 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **3a** with GITC.[8] ^1H NMR(D_2O): δ 1.03 (t, J 7.5, 3H), 1.74-1.89 (m, 2H), 3.07-3.34 (m, 2H), 3.58-3.71 (m, 1H). Anal. Calcd for $C_4H_{11}NO_3S$: C, 31.36; H, 7.24; N, 9.14. Found: C, 31.43; H, 7.38; N, 9.25.

(S)-2-Aminobutanesulfonic acids **3b**: yield 86%. m.p. dec >300°C. $[\alpha]_D^{25}$ = +22.2 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **3b** with GITC.[8] ^1H NMR(D_2O): δ 1.03 (t, J 7.5, 3H), 1.74-1.89 (m, 2H), 3.07-3.34 (m, 2H), 3.58-3.71 (m, 1H). Anal. Calcd for $C_4H_{11}NO_3S$: C, 31.36; H, 7.24; N, 9.14. Found: C, 31.21; H, 7.27; N, 9.10.

(R)-2-Amino-3,3-dimethylaminobutanesulfonic acids **4a**: yield 81%. m.p.290-1°C (dec.). $[\alpha]_D^{25}$ = -30.3 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **4a** with GITC.[8] ^1H NMR (D_2O): δ 1.05 (d, J 0.4, 9H), 3.00-3.13 (m, 1H), 3.32-3.50 (m, 2H). Anal. Calcd for $C_6H_{15}NO_3S$: C, 39.76; H, 8.34; N, 7.73. Found: C, 39.53; H, 8.37; N, 7.68.

(S)-2-Amino-3,3-dimethylaminobutanesulfonic acids **4b**: yield 84%. m.p.290-1°C (dec.). $[\alpha]_D^{25}$ = +30.3 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **4b** with GITC.[8] ^1H NMR (D_2O): δ 1.05 (d, J 0.4, 9H), 3.00-3.13 (m, 1H), 3.32-3.50 (m, 2H). Anal. Calcd for $C_6H_{15}NO_3S$: C, 39.76; H, 8.34; N, 7.73. Found: C, 39.88; H, 8.24; N, 7.77.

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8. *Enantiomeric purity determination of* **3a**, **3b**, **4a** *and* **4b** *by HPLC.* A 5 mg amounts of **3a**, **3b**, **4a**, **4b**, an equimolar mixture of **3a** and **3b**, and an equimolar mixture of **4a** and **4b** were dissolved in 10 ml of 50% (v/v) aqueous acetonitrile containing 0.4% (v/v) triethylamine. To 50 µl of each of these solutions were added 50 µl of a 0.2% (w/v) solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC, Fluka ChiraSelect, e.r. D:L > 99.5:0.5) in acetonitrile. The resulting mixtures were allowed to stand at room temperature for about 60 min. An aliquot of 2 µl of each reaction mixture was directly analysed by HPLC. The mobile phase consisted of a mixture of acetonitrile - 0.010 M potassium phosphate monobasic (pH 4.74) (20:80 v/v). Chromatographic separations were carried out at room temperature and at a flow rate of 1 ml min^{-1}. The detector wavelength was set at 248 nm.
   For the thiourea derivatives of **3a** and **3b**: K'(R) = 6.39, K'(S) = 4.81, α = 1.33, R_s = 6.46.
   For the thiourea derivatives of **4a** and **4b**: K'(R) = 12.99, K'(S) = 10.10, α = 1.29, R_s = 5.66.
9. N,N-Dimethylformamide was dried over calcium sulfate for several hours and then distilled under reduced pressure.
10. Triethylamine was freshly refluxed with phthalic anhydride, distilled, refluxed with potassium hydroxide and again distilled.

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