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Asymmetric Synthesis of 2-Methyltaurine

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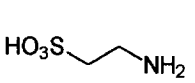
Abstract: Enantiomeric (R)- and (S)-2-aminopropanesulfonic acids, **4a** and **4b**, were prepared in good yields and high enantiomeric purities (>99% ee) from (S)- **5a** and (R)-1-amino-2-propanol **5b** respectively, using a four step synthesis. The absolute configuration of (S)-enantiomer **4b** was established by X-ray analysis.

INTRODUCTION

Recently there is an increased interest in the biological properties of amino sulfonic acids. Some of these compounds, as taurine (2-aminoethanesulfonic acid) **1** and cysteic acid (2-amino-3-sulfopropionic acid) **2**, are endogenous amino acids in mammals and are involved in various and important physiological processes.[1] Taurine derivatives are of interest in enzymological, neurophysiological and amino acid transport studies.[1-4] Cysteic acid derivatives have received attention as analogs of aspartate and homocysteic acid (2-amino-4-sulfobutyric acid) **3** derivatives are also of interest as aspartate or glutamate analogs.[5] Furthermore γ- and β-amino sulfonic acids can be used to synthesized pseudopeptides characterized by sulfonamido groups, that may act as protease inhibitors.[6]



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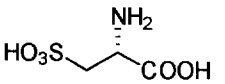

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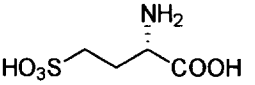

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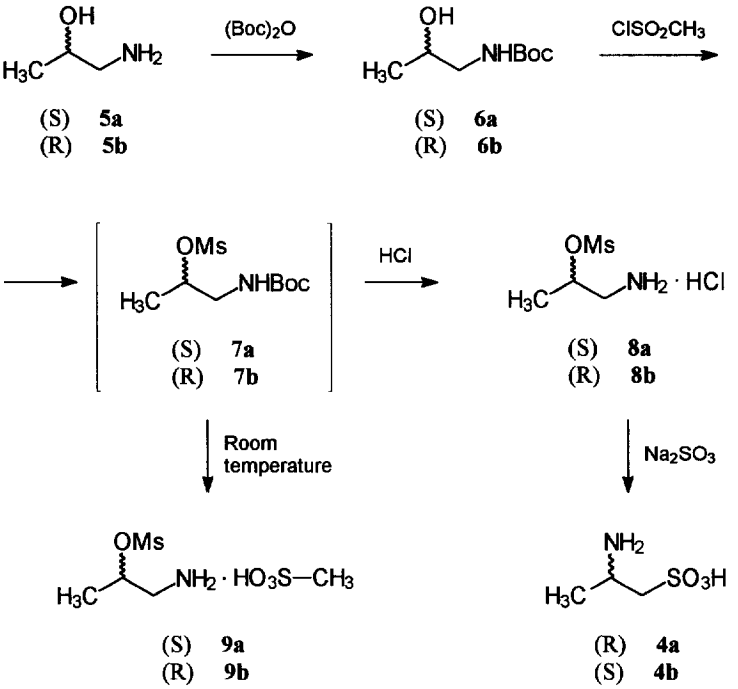
As part of an ongoing program aimed to study the effects on biological activity of systematic variations of substituents on sulfur, nitrogen and carbon atoms of 2-aminoethanesulfonic acid (**1**) and the role of molecular asymmetry of synthesized compounds, a new asymmetric synthesis of (R)- **4a** and (S)-2-aminopropanesulfonic acid **4b** was studied.

RESULTS AND DISCUSSION

The synthesis of (R)- **4a** and (S)-2-aminopropanesulfonic acid **4b** was approached as shown in Scheme 1. 1-N-[(1,1-Dimethylethoxy)carbonyl]amino-2-propanols (1-N-Boc-amino-2-propanols) **6** were obtained from

the corresponding β-aminoalcohols **5** by reaction with di-*tert*-butyldicarbonate according to literature.[7] Compounds **6** by treatment with methanesulfonyl chloride afforded unstable oily intermediates, reasonably compounds **7**, which were used for the following reactions without further purification. Deprotection of compounds **7** with hydrochloric acid provided the 1-amino-2-propanolmethanesulfonate hydrochlorides **8**, which were treated with sodium sulfite to give (R)- **4a** and (S)-2-aminopropanesulfonic acid **4b** in good overall yields.

The unstable oily intermediates **7** by standing at room temperature partially decomposed yielding compounds **9**.



Scheme 1

The key step of this synthesis is the reaction of (S)- **8a** and (R)-1-amino-2-propanolmethanesulfonate hydrochloride **8b** with sodium sulfite, namely a nucleophilic substitution in a molecule with a group with an unshared pair of electrons β to the leaving group, therefore it is possible to occur either by a simple substitution or a rearrangement. Under the reaction conditions used (S)- **8a** and (R)-1-amino-2-propanolmethanesulfonate hydrochloride **8b** afforded (R)-**4a** and (S)-2-aminopropanesulfonic acid **4b** respectively, in high enantiomeric purity. The enantiomeric purity of compounds **4a** and **4b** was assayed by HPLC after derivatization with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC)[8,9]. The absolute configuration of compound **4b** was then determined by single crystal X-ray structure analysis (Figure 1).

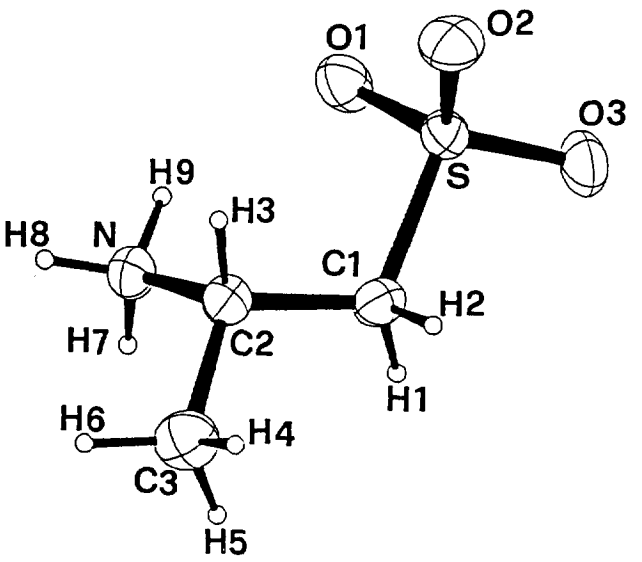


Figure 1. ORTEP view of the **4b** molecule with 40% probability ellipsoids. H atoms are represented as spheres of arbitrary radii.

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 FT-NMR spectrometer using D_2O as solvent and tetramethylsilane (TMS) as external standard. Chemical shifts are in ppm (δ) and coupling constants (J) in Hz. Multiplicities are abbreviated as follows: s, singlet; d, doublet; 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). 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 0.9 ml min^{-1}. The detector wavelength was set at 248 nm. 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.

1-Amino-2-propanolmethanesulfonate hydrochlorides **8** *and methanesulfonates* **9**

To a stirred solution of appropriate 1-N-[(1,1-dimethylethoxy)carbonyl]amino-2-propanol **6** (23.0 g, 131 mmoles) and triethylamine (20 ml, 144 mmoles) was added at 0°C a solution of methanesulfonyl chloride (10.6 ml, 136 mmoles) in CH_2Cl_2 (200 ml).[10] 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 (150 ml) and water (150 ml). The organic layer was separated, washed with aqueous 5% $NaHCO_3$ (3 x 50 ml) and brine (3 x 50 ml), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give **7** (oils), which were used for the next steps without further purification. The colorless oils **7** were treated at room temperature for 60 min with a 4M solution of HCl in dioxane (250 ml). The precipitate was filtered and crystallized from acetonitrile and ethyl ether to give **8** (20.23 g; yield 81.3%).

(S)-1-amino-2-propanolmethanesulfonate hydrochloride **8a**: m.p. 128-9°C. $[\alpha]_D^{25}$ = +18.5 (*c* 1.0, H_2O). ^1H NMR: δ 1.58 (d, J = 6.5, 3H), 3.31 to 3.45 (m, 5H), 5.16 to 5.24 (m, 1H). Anal. Calcd for $C_4H_{12}ClNO_3S$: C, 25.33; H, 6.38; N, 7.39. Found: C, 25.22; H, 6.15; N, 7.35.

(R)-1-amino-2-propanolmethanesulfonate hydrochloride **8b**: m.p. 128-9°C. $[\alpha]_D^{25}$ = -18.5 (*c* 1.0, H_2O). ^1H NMR: δ 1.58 (d, J = 6.5, 3H), 3.31 to 3.45 (m, 5H), 5.16 to 5.24 (m, 1H). Anal. Calcd for $C_4H_{12}ClNO_3S$: C, 25.33; H, 6.38; N, 7.39. Found: C, 25.21; H, 6.31; N, 7.40.

The colorless oils **7** by standing at room temperature changed into a white waxy solids, from which by crystallization from ethanol and ethyl ether were obtained **9**:

(S)-1-amino-2-propanolmethanesulfonate methanesulfonate **9a**: m.p. 112-3°C. $[\alpha]_D^{25}$ = +13.2 (*c* 1.0, H_2O). ^1H NMR: δ 1.59 (d, J = 6.5, 3H), 2.88 (s, 3H), 3.31 to 3.45 (m, 5H), 5.17 to 5.24 (m, 1H). Anal. Calcd for $C_5H_{15}NO_6S_2$: C, 24.09; H, 6.06; N, 5.62. Found: C, 23.96; H, 5.97; N, 5.56.

(R)-1-amino-2-propanolmethanesulfonate methanesulfonate **9b**: m.p. 112-3°C. $[\alpha]_D^{25}$ = -13.2 (*c* 1.0, H_2O). ^1H NMR: δ 1.59 (d, J = 6.5, 3H), 2.88 (s, 3H), 3.31 to 3.45 (m, 5H), 5.17 to 5.24 (m, 1H). Anal. Calcd for $C_5H_{15}NO_6S_2$: C, 24.09; H, 6.06; N, 5.62. Found: C, 23.98; H, 6.06; N, 5.63.

2-Aminopropanesulfonic acids **4**

To a solution of the appropriate **8** (10 g, 53 mmol) in water (100 ml) was added sodium sulfite (10 g, 80 mmol). 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 **4.**

(R)-2-aminopropanesulfonic acid **4a**: m.p. dec >300°C. $[\alpha]_D^{25}$ = -18.5 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **4a** with GITC. ^1H NMR: δ 1.52 (d, J = 6.9, 3H),

3.22 to 3.29 (m, 2H), 3.85 to 3.94 (m, 1H). Anal. Calcd for $C_3H_9NO_3S$: C, 25.89; H, 6.52; N, 10.06. Found: C, 25.71; H, 6.39; N, 9.83.

(S)-2-aminopropanesulfonic acid **4b**: m.p. dec >300°C. $[\alpha]_D^{25}$ = +18.5 (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **4b** with GITC. ^1H NMR: δ 1.52 (d, J = 6.9, 3H), 3.22 to 3.29 (m, 2H), 3.85 to 3.94 (m, 1H). Anal. Calcd for $C_3H_9NO_3S$: C, 25.89; H, 6.52; N, 10.06. Found: C, 25.61; H, 6.50; N, 9.98.

X-ray structure determination.

$C_3H_9NO_3S$ MW= 139.2. A suitable crystal of compound **4b** was mounted on a Nonius CAD4 diffractometer (Mo Kα radiation λ = 0.71069 Å graphite monocromator). Orthorombic space group $P2_12_12_1$, Z = 4, a = 7.960(2), b = 10.526(3), c = 7.005(2)Å, V = 586.9 Å^3, d_c = 1.57 gcm^{-3}, F(000) = 296, μ = 4.50 cm^{-1}. 2420 reflections up to 2θ = 56° of which 1308 unique with I>3σ(I) were kept in refinement calculation. The structure was solved using Patterson and Fourier methods and refined by least-squares calculations using SHELX76[11] minimizing the quantity $\Sigma_w(F_o-F_c)^2$. All non hydrogen atoms were refined anisotropically, hydrogen atoms were located in a difference Fourier map and refined with constant isotropic factors. Final $R=\Sigma(F_o-F_c)/\Sigma F_o$ = 0.028. $R_w = [\Sigma_w(F_o-F_c)^2/ \Sigma_w F_o^2]^{1/2}$ = 0.024 with $w = 1/\sigma^2(F_o)$. The final difference density shows no features up to 0.49 e·Å^{-3} and down to -0.42 e·Å^{-3}.

Supplementary material available: lists of the fractional atomic coordinates, isotropic thermal parameters, bond lengths and angles, observed and calculated structure factors.

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