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Asymmetric synthesis of (*R*)- and (*S*)-2-pyrrolidinemethanesulfonic acid

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Abstract: (*R*)- and (*S*)-2-Pyrrolidinemethanesulfonic acid, **3a** and **3b**, were synthesized from the corresponding N-Boc-2-(hydroxymethyl)-1-pyrrolidine, **6a** and **6b**. This asymmetric synthesis proceeds in mild conditions, with good overall yields and high enantiomeric purities (>99% ee). © 1997 Elsevier Science Ltd

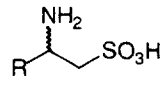
Introduction

Taurine (2-aminoethanesulfonic acid) **1** occurs in high concentration in many mammalian tissues and is involved in various and important physiological processes, but the mechanisms underlying its actions are still unclear.[1,2] This β-amino acid is essential for mammalian development and its low levels are associated with various pathological lesions, especially if deficiency occurs during development.[3] Most of mammals take taurine requirements with the diet and the interest in nutritional aspects of this β-amino acid is growing rapidly. Much recent research has been in this area.[2,4–7]

Taurine **1** shows a considerable degree of conformational flexibility as a result of free rotation around the C–C bond, and therefore its conformational preferences in aqueous solution may be of importance in investigating its functional activity. Indeed conformational study of **1** and of its methyl derivatives in aqueous solution showed that the rotation around the C–C bond is in part hindered at room temperature and at pH 7, implying conformational preferences of these compounds at conditions near to physiological environment.[8]

Recently the study of the two enantiomers of 2-methyltaurine (2-aminopropanesulfonic acid) **2** showed that the (*S*) enantiomer **2b** is the most effective in mimicking the hypotensive activity of taurine **1**, thus suggesting that this effect could be receptor mediated.[9] Therefore also the study of chiral taurine analogs seems to provide information for understanding the mechanism underlying the many-sided biological effects of this important amino acid.

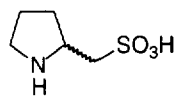
As part of an ongoing program aimed to study the effects on biological activity of systematic variations of the substituents on sulfur, nitrogen and carbon atoms of 2-aminoethanesulfonic acid **1**,[10–12] the asymmetric synthesis of (*R*)- and (*S*)-2-pyrrolidinemethanesulfonic acid, **3a** and **3b**, was performed. These cyclic analogs of taurine are conformationally more restricted than parent compound. Moreover **3a** and **3b** may be interesting pharmacological tools as cyclic amino acid related to the GABA analogue 3-pyrrolidineacetic acid **4**.



1: R = H

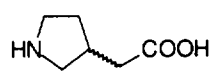
2a: (R) R = CH_3

2b: (S) R = CH_3



3a: (R)

3b: (S)



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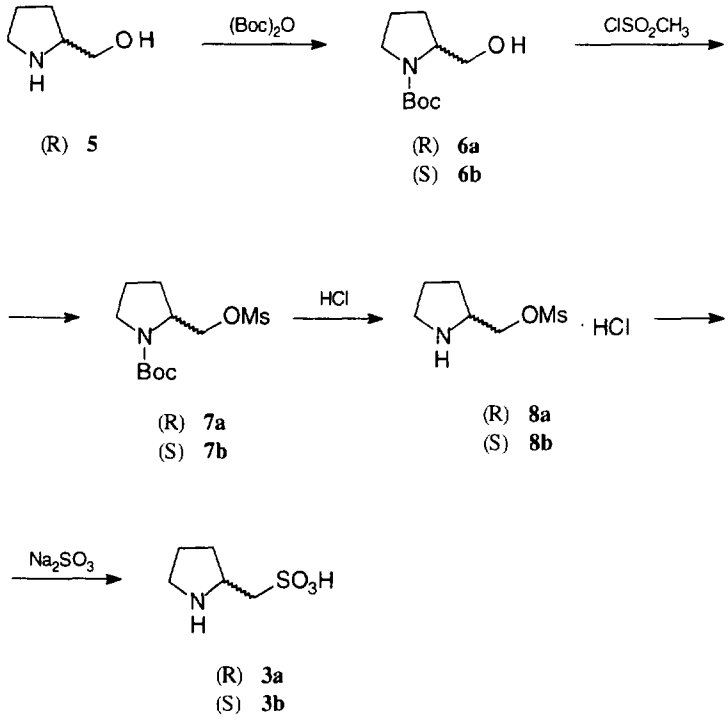
Results and discussion

Compounds **3a** and **3b** were synthesized from the corresponding N-Boc-2-(hydroxymethyl)-1-pyrrolidine **6**, as outlined in Scheme 1.



Scheme 1.

N-Boc-(*R*)-2-(Hydroxymethyl)-1-pyrrolidine **6a**, not available from commercial sources, was obtained from (*R*)-2-pyrrolidinemethanol **5** by treatment with di-*tert*-butyldicarbonate, $(Boc)_2O$.

The N-protected pyrrolidinols **6** by treatment with methanesulfonyl chloride were converted to the corresponding methanesulfonate esters **7**. After removal of the Boc protecting group with hydrochloric acid, the resulting hydrochlorides **8** were treated with sodium sulfite to give 2-pyrrolidinemethanesulfonic acids **3**.

This synthesis proceeds in mild conditions and with high yields; the asymmetric centers are not directly involved in the reactions and there is no racemization. Each pair of enantiomers synthesized has the same $[\alpha]_D^{20}$ value of opposite sign and the enantiomeric purity of compounds **3a** and **3b**, assayed by HPLC after derivatization with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC),[13–15] was determined to be >99%.

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 (neat or KBr pellets) and were consistent with the assigned structures. ^1H NMR spectra were recorded with a Bruker DPX 200 spectrometer using $CDCl_3$ or D_2O as solvent and tetramethylsilane (TMS) as internal or external standard. Chemical shifts are in ppm (δ) and coupling constants (J) in Hz. Multiplicities are abbreviated as follows: s, singlet; dd, double doublet; t, triplet; m, multiplet; b, indicates a broadening of the signal. HPLC analyses were performed on a liquid chromatographic system consisting of a Millipore Waters model 510 HPLC pump, Millipore Waters Automated Gradient Controller, Degasys DG-1210 Uniflows, CMA/200 automatic sampler, Millipore Waters Lambda-max model 481 LC

Spectrophotometer, Spectra-Physics SP 4270 Integrator. The column employed was a LiChrospher 100-RP18-LiChroCART (250 mm × 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-t-Butoxycarbonyl-(R)-2-(hydroxymethyl)-1-pyrrolidine ***6a***

To a stirred solution of (*R*)-2-pyrrolidinemethanol **5** (49 mmoles) in 50 ml of CH_2Cl_2 and 50 ml of NaOH 1 N was added dropwise 11.3 ml (49 mmoles) of di-*tert*-butyldicarbonate. After stirring overnight at room temperature, the organic layer was separated, washed with water (2×25 ml) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave **6a** as an oil which crystallized when freeze-dried. The crude was recrystallized from hexane.

Yield 95.7%. m.p. 59–60°C. $[\alpha]_D^{20}$=+47.5 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 1.61–2.06 (m, 4H), 3.29–3.49 (m, 2H), 3.59–3.62 (m, 2H), 3.91–4.14 (m, 1H), 4.70 (bs, 1H). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.55; H, 9.41; N, 7.14.

1-[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinemethanolmethanesulfonates 7

To a stirred solution of the appropriate 2-(hydroxymethyl)-1-pyrrolidinecarboxilic acid 1,1-dimethylethyl ester **6** (30 mmoles) and triethylamine[16] (33 mmoles) in CH_2Cl_2 (120 ml) was added dropwise a solution of methanesulfonyl chloride (31 mmoles) in CH_2Cl_2 (50 ml) at −10°C and in nitrogen atmosphere. The reaction mixture was stirred at room temperature for additional 30 min, then the solvent was evaporated in vacuo. The residue was dissolved in water and extracted with ethyl acetate (2×30 ml). The organic phase was separated, washed with aqueous 5% $NaHCO_3$ (3×30 ml) and brine (3×30 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the methanesulfonate esters **7** as oils which were used without further purification.

(R)-1-[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinemethanolmethanesulfonate ***7a***

Yield 94%. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H); 1.88–2.11 (m, 4H), 3.03 (s, 3H), 3.38 (t, J 6.1, 2H), 3.58–3.72 (m, 1H); 4.06–4.32 (m, 2H). Anal. Calcd for $C_{11}H_{21}NO_5S$: C, 47.30; H, 7.58; N, 5.01. Found: C, 47.38; H, 7.62; N, 5.14.

(S)-1-[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinemethanolmethanesulfonate ***7b***

Yield 96%. ^1H NMR ($CDCl_3$): δ 1.50 (s, 9H); 1.88–2.11 (m, 4H), 3.03 (s, 3H), 3.38 (t, J 6.1, 2H), 3.58–3.72 (m, 1H); 4.06–4.32 (m, 2H). Anal. Calcd for $C_{11}H_{21}NO_5S$: C, 47.30; H, 7.58; N, 5.01. Found: C, 47.08; H, 7.38; N, 4.85.

2-Pyrrolidinemethanolmethanesulfonate hydrochlorides ***8***

1-[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinemethanolmethanesulfonates **7** (30 mmoles) were treated at room temperature for 60 min with a 4 M solution of HCl in dioxane (60 ml). The precipitates were filtered and crystallized from ethanol and ethyl ether to give **8**.

(R)-2-Pyrrolidinemethanolmethanesulfonate hydrochloride ***8a***

Yield 74%. m.p. 134–5°C. $[\alpha]_D^{20}$= −14.8 (*c* 1.0, H_2O). ^1H NMR (D_2O): δ 1.90–2.44 (m, 4H), 3.40 (s, 3H), 3.51 (t, J 7.2, 2H), 4.12–4.18 (m, 1H), 4.55 and 4.61 (dd, J 7.8 and 11.6, 1H), 4.75 and 4.81 (dd, J 3.5 and 11.6, 1H). Anal. Calcd for $C_6H_{14}ClNO_3S$: C, 33.41; H, 6.54; N, 6.49. Found: C, 33.43; H, 6.42; N, 6.49.

(S)-2-Pyrrolidinemethanolmethanesulfonate hydrochloride ***8b***

Yield 76%. m.p. 134–5°C. $[\alpha]_D^{20}$=+14.8 (*c* 1.0, H_2O). ^1H NMR (D_2O): δ 1.90–2.44 (m, 4H), 3.40 (s, 3H), 3.51 (t, J 7.2, 2H), 4.12–4.18 (m, 1H), 4.55 and 4.61 (dd, J 7.8 and 11.6, 1H), 4.75 and 4.81

(dd, J 3.5 and 11.6, 1H). Anal. Calcd for $C_6H_{14}ClNO_3S$: C, 33.41; H, 6.54; N, 6.49. Found: C, 33.35; H, 6.40; N, 6.47.

2-Pyrrolidinemethanesulfonic acids 3

To a stirred solution of the appropriate 2-pyrrolidinemethanolmethanesulfonate hydrochloride **8** (30 mmoles) in water (40 ml) was added sodium sulfite (80 mmol). The reaction mixture was stirred for 24 h at room temperature, then 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**.

*(R)-2-Pyrrolidinemethanesulfonic acid **3a***

Yield 81%. m.p. dec >300°C. $[\alpha]_D^{20} = -8.3$ (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **3a** with GITC.[15] ^1H NMR (D_2O): δ 1.76–2.54 (m, 4H), 3.04–3.54 (m, 4H), 3.78–4.14 (m, 1H). Anal. Calcd for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; N, 8.48. Found: C, 36.28; H, 6.64; N, 8.38.

*(S)-2-Pyrrolidinemethanesulfonic acid **3b***

Yield 83%. m.p. dec >300°C. $[\alpha]_D^{20} = +8.3$ (*c* 1.0, H_2O). >99% ee by HPLC analysis of the thiourea derivative obtained by reaction of **3b** with GITC.[15] ^1H NMR (D_2O): δ 1.76–2.54 (m, 4H), 3.04–3.54 (m, 4H), 3.78–4.14 (m, 1H). Anal. Calcd for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; N, 8.48. Found: C, 36.42; H, 6.54; N, 8.56.

Acknowledgements

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15. *Enantiomeric purity determination of* **3a** *and* **3b** *by HPLC.* 5 mg amounts of **3a**, **3b**, and of an equimolar mixture of **3a** and **3b** 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. The 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) (15:85 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 250 nm.

16. Triethylamine was freshly refluxed with phthalic anhydride, distilled, refluxed with potassium hydroxide and again distilled.

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