

The Absolute Configurations of Emepromium Bromide and Recipavrin, Two Antispasmodics. Stereoselective Syntheses of All Stereoisomers using (*S*)-2-Hydroxypropanoic Acid as Chiral Synthron

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Emepromium bromide [(±)-*N*-ethyl-*N,N*-dimethyl-(1-methyl-3,3-diphenylpropyl)ammonium bromide; (±)-**1**], an anticholinergic with effects similar to those of atropine, is used in the treatment of incontinence to reduce urinary frequency, and after bladder surgery, bladder radiotherapy or prostatectomy.^{1,2} Recipavrin [(±)-*N,N*,1-trimethyl-3,3-diphenylpropylamine; (±)-**2**], a spasmolytic agent exerting both muscurotropic (antibarium) and anticholinergic action, relieves smooth muscle spasms, e.g. dysmenorrhea and pains associated with gallstones.^{1,3,4} Both drugs are administered as racemates, and, to the best of our knowledge, their absolute configurations have not previously been established. Syntheses of the individual enantiomers employing (*S*)-2-hydroxypropanoic acid (L-lactic acid) as chiral synthron constitute the subject of the present communication.

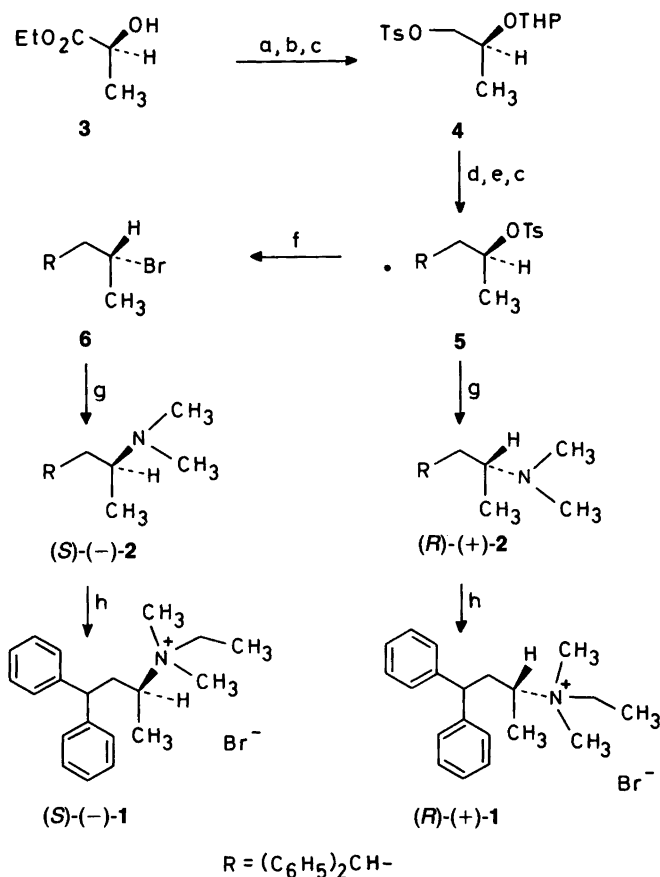
The key intermediate, (*S*)-(-)-1-methyl-3,3-diphenylpropyl *p*-toluenesulfonate (**5**), was prepared by converting ethyl (*S*)-2-hydroxypropanoate (**3**) to the THP-protected *p*-toluenesulfo-

nate (**4**), which was subsequently reacted with diphenylmethyl lithium, deprotected, and, finally, esterified with *p*-toluenesulfonyl chloride according to known procedures⁴⁻⁹ (cf. Scheme 1). The tosylate **5** reacted smoothly with dimethylamine in an S_N2 type reaction giving (*R*)-(+)-recipavrin [(*R*)-(+)-**2**] of high optical purity, as judged from the ¹H NMR spectrum recorded in the presence of the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol)^{10,11} (cf. Fig. 1c). The sign of the optical rotation applies to a solution of (*R*)-recipavrin in methanol; the sign was found to be negative when chloroform was used as solvent.

(*S*)-(-)-Recipavrin [(*S*)-(-)-**2**] was obtained from the tosylate **5** as the result of two consecutive S_N2 reactions in which the tosylate **5** was converted to the bromide **6** which then reacted, somewhat sluggishly, with dimethylamine. The enantiomeric composition of the product was found to be 92:8 as compared to 98:2 for (*R*)-(+)-recipavrin (cf. Fig. 1d).

Quaternization of (*R*)-(+)-**2** and (*S*)-(-)-**2** with bromoethane afforded (*R*)-(+)- and (*S*)-(-)-emepromium bromide [(*R*)-(+)-**1** and (*S*)-(-)-**1**], respectively. Addition of Pirkle's alcohol to a solution of racemic emepromium bromide in

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Scheme 1. Syntheses of the (*S*)-(-)- and (*R*)-(+)-enantiomers of emepronium bromide (1) and recipavrin (2). a: Dihydropyran/H⁺; b: LiAlH₄; c: TsCl; d: (C₆H₅)₂CH⁻Li⁺; e: CH₃OH-water/H⁺; f: LiBr; g: HN(CH₃)₂; h: CH₃CH₂Br.

the NMR tube did not induce ¹H NMR spectral nonequivalence of the diastereomeric solvates. However, racemization during the last step is unlikely and the enantiomeric composition of (*R*)-(+)-emepronium bromide should be 98:2. The [α]_D²⁰ value of +62.0° for this composition implies a numerical value of 64.6° for the [α]_D²⁰ of the pure (*R*)-enantiomer. Thus, the [α]_D²⁰ value of -60.7° for (*S*)-emepronium bromide [(*S*)-(-)-1] infers an enantiomeric ratio of 97:3, which is significantly better than the 92:8 ratio of (*S*)-(-)-recipavrin [(*S*)-(-)-2]. This accidental purification was effected by selective crystallization of racemic emepronium bromide [(±)-1] from an ethanol-acetone solution of the product mixture containing (*S*)-(-)-emepronium bromide.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Optical rotations and mass spectra were recorded on Carl Zeiss, Perkin Elmer 241 and Micromass 7070F instruments, respectively. ¹H NMR and ¹³C NMR spectra were recorded at 270 MHz and 68 MHz, respectively, on a Jeol GX 270 MHz instrument. TMS, or the central solvent peak (¹³C) of CDCl₃ (δ 77.08) were used as internal references.

(*S*)-(-)-1-Methyl-3,3-diphenylpropyl *p*-toluenesulfonate (5). Compound 5 was prepared by methods previously described in the literature for

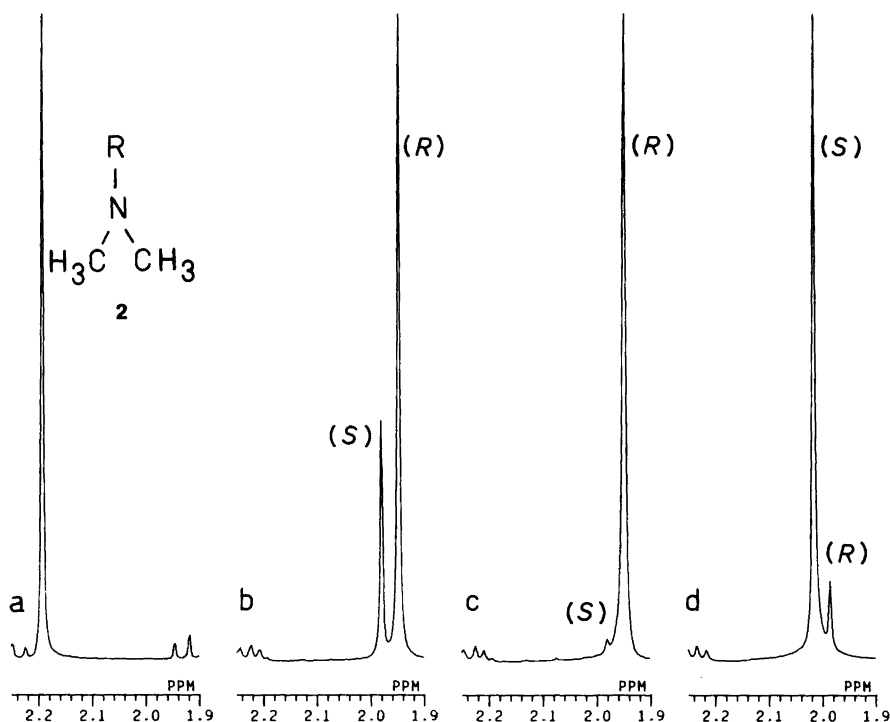


Fig. 1. Partial ^1H NMR spectra of recipavrin (**2**). a: Without Pirkle's alcohol; b: a 1 : 2.5 mixture of (*S*)-**2** and (*R*)-**2** in the presence of Pirkle's alcohol; c and d: (*R*)-**2** and (*S*)-**2**, prepared as described in Scheme 1, in the presence of Pirkle's alcohol.

the enantiomer.⁴⁻⁹ $[\alpha]_{\text{D}}^{25} - 10.1^\circ$ (*c* 4.2, CHCl_3); lit.⁸ $[\alpha]_{\text{D}}^{26} + 8.27 \pm 0.90^\circ$ (*c* 1.874, CHCl_3).

(*R*)-(-)-3-Bromo-1,1-diphenylbutane (**6**). A solution of (*S*)-(-)-1-methyl-3,3-diphenylpropyl *p*-toluenesulfonate (**5**; 2.60 g, 6.84 mmol) and LiBr (0.91 g, 10.48 mmol) in acetone (55 ml) was heated under reflux for a total of 19 h and then kept at ca. 40°C for 12 h. Aliquots (10–20 μl) were periodically withdrawn and diluted with CDCl_3 , and the ratio of **6** to **5** was measured by integration of the ^1H NMR doublets ($\text{CH}-\text{CH}_3$) at δ 1.73 (**6**) and δ 1.31 (**5**), respectively. The reaction was terminated by the addition of EtOAc and aqueous NaHCO_3 when the ratio of **6** to **5** was approximately 4.3 : 1. The EtOAc extract was washed with water, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to a yellow oil (2.02 g). The oil was dissolved in a small volume of hexane, applied to a silica gel column (45 g Kieselgel 60; Merck Art. 7734), and eluted with

hexane. The first fraction (83 mg) contained, as judged from the ^1H NMR spectrum, mainly elimination products [$(\text{C}_6\text{H}_5)_2\text{C}_4\text{H}_6$]. The subsequent fractions furnished (*R*)-(-)-3-bromo-1,1-diphenylbutane (**6**; 1.05 g, 65%). $[\alpha]_{\text{D}}^{22} - 104.4^\circ$ (*c* 1.5, CHCl_3); MS [IP 70 eV; *m/z* (% rel. int.)]: 290 (M^+ , 3), 288 (M^+ , 3), 168 (14), 167 (100), 166 (10), 165 (26), 152 (10), 115 (8); ^1H NMR (CDCl_3): δ 1.73 (3H, d, *J* 6.6 Hz), 2.35–2.6 (2H, m), 3.8–3.9 (1H, m), 4.28 (1H, dd, *J* 5.9 and 9.5 Hz), 7.1–7.3 (10H, m); ^{13}C NMR (CDCl_3): δ 26.80 (q), 46.90 (t), 49.41 (d), 49.76 (d), 126.42 (d), 126.67 (d), 127.72 (d), 128.18 (d), 128.61 (d), 128.74 (d), 143.20 (s), 144.18 (s).

(*R*)-(+)-*N,N*,1-Trimethyl-3,3-diphenylpropylamine; (*R*)-recipavrin [(*R*)-(+)-**2**]. A mixture of (*S*)-(-)-1-methyl-3,3-diphenylpropyl *p*-toluenesulfonate (**5**; 405 mg, 1.06 mmol), 40% aqueous dimethylamine (2 ml) and 2-propanol (2 ml) was heated under reflux for 2 h. The ^1H NMR spec-

trum of an aliquot dissolved in CDCl_3 , then revealed that the resonance at ca. δ 4.45 ($\text{CH}-\text{CH}_3$) for **5** had disappeared. The reaction mixture was acidified with 1M HCl to pH about 2.5, and extracted with hexane to remove neutral and acidic constituents. The application of more polar solvents, e.g. EtOAc or CH_2Cl_2 , led to losses due to unexpected solubility of the hydrochloride of **2**. The aqueous phase was basified with 2M NaOH to pH ca. 10 and extracted with CH_2Cl_2 . The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, leaving a colourless oil which solidified at 5°C (184 mg, 68%). $[\alpha]_{\text{D}}^{20} + 22.1^\circ$ (*c* 3.2, CH_3OH); $[\alpha]_{\text{D}}^{25} - 6.1^\circ$ (*c* 1.3, CHCl_3); MS [IP 70 eV; *m/z* (% rel. int.)]: 253 (M^+ , 3), 167 (8), 165 (4), 72 (100); ^1H NMR (CDCl_3): δ 0.94 (3H, d, *J* 6.6 Hz), 1.8–2.0 (1H, m), 2.20 (6H, s), 2.25–2.35 (1H, m), 2.4–2.5 (1H, m), 4.11 (1H, t, *J* 8.1 Hz), 7.1–7.22 (1H, m), 7.23–7.33 (9H, m); ^{13}C NMR (CDCl_3): δ 12.60 (q), 39.66 (t), 40.07 (2 \times q?), 47.86 (d), 56.12 (d), 126.05, 126.16, 127.00 (d), 128.40, 128.51, 144.86 (s), 145.56 (s). Enantiomeric composition: (R):(S) = 98:2 (cf. Fig. 1c).

(S)-(-)-*N,N,1-Trimethyl-3,3-diphenylpropylamine*; (S)-recipavrin [(S)-(-)-**2**]. A solution of (R)-(-)-3-bromo-1,1-diphenylbutane (**6**; 1.05 g, 3.62 mmol), 40% aqueous dimethylamine (5 ml) and 2-propanol (5 ml) was heated at reflux temperature for 12 h and then left overnight at 40–50°C. Dimethylamine (7 ml) and 2-propanol (5 ml) were added to the reaction mixture, after which the mixture was heated under reflux for another 12 h and left overnight at 40–50°C. The reaction was monitored by recording ^1H NMR spectra of aliquots (10–20 μl) of the reaction mixture dissolved in CDCl_3 . The reaction was discontinued when the integrals of the resonances of the benzylic protons of (S)-(-)-**2** and **6** at δ 4.11 and δ 4.28, respectively, revealed the ratio (S)-(-)-**2**:**6** to be 12:1. Aqueous 1M HCl was added to the mixture, which was then extracted with hexane giving a neutral fraction (214 mg) whose ^1H NMR spectrum indicated the presence of the bromide **6** and elimination products [$(\text{C}_6\text{H}_5)_2\text{C}_4\text{H}_6$]. The aqueous phase was basified with 2M NaOH and extracted with CH_2Cl_2 ; drying of the extract over anhydrous Na_2SO_4 and subsequent concentration *in vacuo* gave a colourless oil which solidified at 5°C (734 mg, 80%). $[\alpha]_{\text{D}}^{25} - 18.4^\circ$ (*c* 7.3, CH_3OH); MS, ^1H NMR and

^{13}C NMR spectra were indistinguishable from those of (R)-recipavrin [(R)-(+)-**2**]. Enantiomeric composition: (S):(R) = 92:8 (cf. Fig. 1d).

Enantiomeric composition of (R)- and (S)-recipavrin (2). Addition of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's alcohol)^{10,11} to the CDCl_3 solution of a 1:2.5 mixture of (S)-(-)-**2** and (R)-(+)-**2** in the NMR tube induced ^1H NMR spectral nonequivalence of the diastereomeric solvates. A 3.6:1 molar ratio of chiral solvating agent to substrate effected complete resolution of the singlets for the $\text{N}(\text{CH}_3)_2$ groups (see Figs. 1a and 1b). (R)-solvate: δ 1.94 [$\text{N}(\text{CH}_3)_2$]; (S)-solvate: δ 1.97 [$\text{N}(\text{CH}_3)_2$].

(R)-(+)-*N-Ethyl-N,N-dimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide*; (R)-emepromonium bromide [(R)-(+)-**1**]. A solution of (R)-(+)-*N,N,1-trimethyl-3,3-diphenylpropylamine* [(R)-(+)-**2**; 1.03 g, 4.07 mmol] and bromoethane (5 ml) was left at ambient temperature for six days, during which a solid mass was formed. Excess bromoethane was removed *in vacuo* and the solid residue was recrystallized first from a mixture of 2-propanol (2 ml) and acetone (5 ml), and subsequently from ethanol/diethyl ether. As judged from ^1H NMR spectra of the needles which were collected from the latter solvent system, extensive drying under reduced pressure at 80–90°C was required to remove residual ethanol. Yield: 728 mg (49%). M.p. 172–173°C; lit.¹ m.p. for the racemate: 204°C; $[\alpha]_{\text{D}}^{20} + 62.0^\circ$, $[\alpha]_{578}^{20} + 64.9^\circ$, $[\alpha]_{546}^{20} + 74.2^\circ$, $[\alpha]_{436}^{20} + 131.5^\circ$, $[\alpha]_{365}^{20} + 219.1^\circ$ (*c* 0.9, ethanol); ^1H NMR (CDCl_3): δ 0.99 (3H, t, *J* 7.3 Hz), 1.54 (3H, d, *J* 5.9 Hz), 2.1–2.2 (1H, m), 2.93 (1H, broad t, *J* 12.5 Hz), 3.0–3.15 (1H, m), 3.24 (3H, s), 3.25 (3H, s), 3.65–3.85 (2H, m), 3.91 (1H, dd, *J* 3.7 and 11.7 Hz), 7.15–7.45 (10H, m); ^{13}C NMR (CDCl_3): δ 7.85 (q), 14.14 (q), 36.18 (t), 48.05 (q), 48.48 (q), 48.81 (d), 58.66 (t), 65.67 (d), 126.94, 127.62, 128.02, 128.89, 129.37, 141.89 (s), 142.86 (s); the NMR spectra were in agreement with those of racemic emepromonium bromide (**1**).

(S)-(-)-*N-Ethyl-N,N-dimethyl(1-methyl-3,3-diphenylpropyl)ammonium bromide*; (S)-emepromonium bromide [(S)-(-)-**1**]. Bromoethane (5 ml) was added to (S)-(-)-*N,N,1-trimethyl-3,3-diphenylpropylamine* [(S)-(-)-**2**; 705 mg, 2.79 mmol]

and the solution was left at room temperature for six days. Excess bromoethane was removed *in vacuo* and the solid residue was recrystallized from a mixture of 2-propanol (1.5 ml) and acetone (5 ml), yielding 869 mg of crystalline material. $[\alpha]_D^{22} - 44.1^\circ$ (c 4.9, ethanol). The subsequent recrystallization from ethanol (0.5 ml)/acetone (5 ml) furnished 124 mg of nearly racemic emepronium bromide; m.p. 207–208 °C; $[\alpha]_D^{20} - 3.0^\circ$ (c 0.7, ethanol); ^1H NMR as for (\pm)-**1**. The mother liquor (667 mg) was concentrated to dryness and the residue recrystallized from ethanol/diethyl ether, furnishing (*S*)-(-)-**1** as colourless needles (462 mg, 46 %). M.p. 172–173 °; $[\alpha]_D^{20} - 60.7^\circ$, $[\alpha]_{578}^{20} - 63.3^\circ$, $[\alpha]_{546}^{20} - 72.3^\circ$, $[\alpha]_{436}^{20} - 128.2^\circ$, $[\alpha]_{365}^{20} - 213.6^\circ$ (c 0.7, ethanol); the ^1H NMR and ^{13}C NMR spectra of the product matched the corresponding spectra of (*R*)-(+)-**1** and (\pm)-**1**.

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