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An Efficient Synthesis of Optically Active Eprozinol[1]

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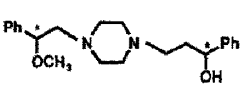
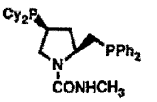
Abstract: A synthetic route to optically active eprozinol has been developed by efficient asymmetric hydrogenations of α- and β-amino ketone hydrochloride derivatives with MCCPM-rhodium catalyst.

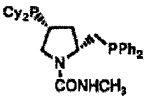
Eprozinol[1-(2-methoxy-2-phenylethyl)-4-(3-hydroxy-3-phenylpropyl)piperazine] (**1**) was prepared by three groups in the 1970s[2] and is used therapeutically as bronchodilator. Duchene-Marullaz *et al.* reported that eprozinol was effective against histamine- and acetylcholine-induced bronchospasm, possesses antitussive activity, and does not depress respiration.[3] Eprozinol has two chiral atoms, therefore the number of optical isomers is four. To our knowledge, however, asymmetric synthesis of (**1**) has not been reported. Now we report first synthesis of the four chiral forms of (**1**). The key step in the synthesis involves the efficient catalytic asymmetric hydrogenations of α- and β-amino ketone hydrochloride derivatives using MCCPM (**2**)-Rh(I) complex.[4]



Eprozinol (1)



(2*S*,4*S*)-MCCPM (2a)

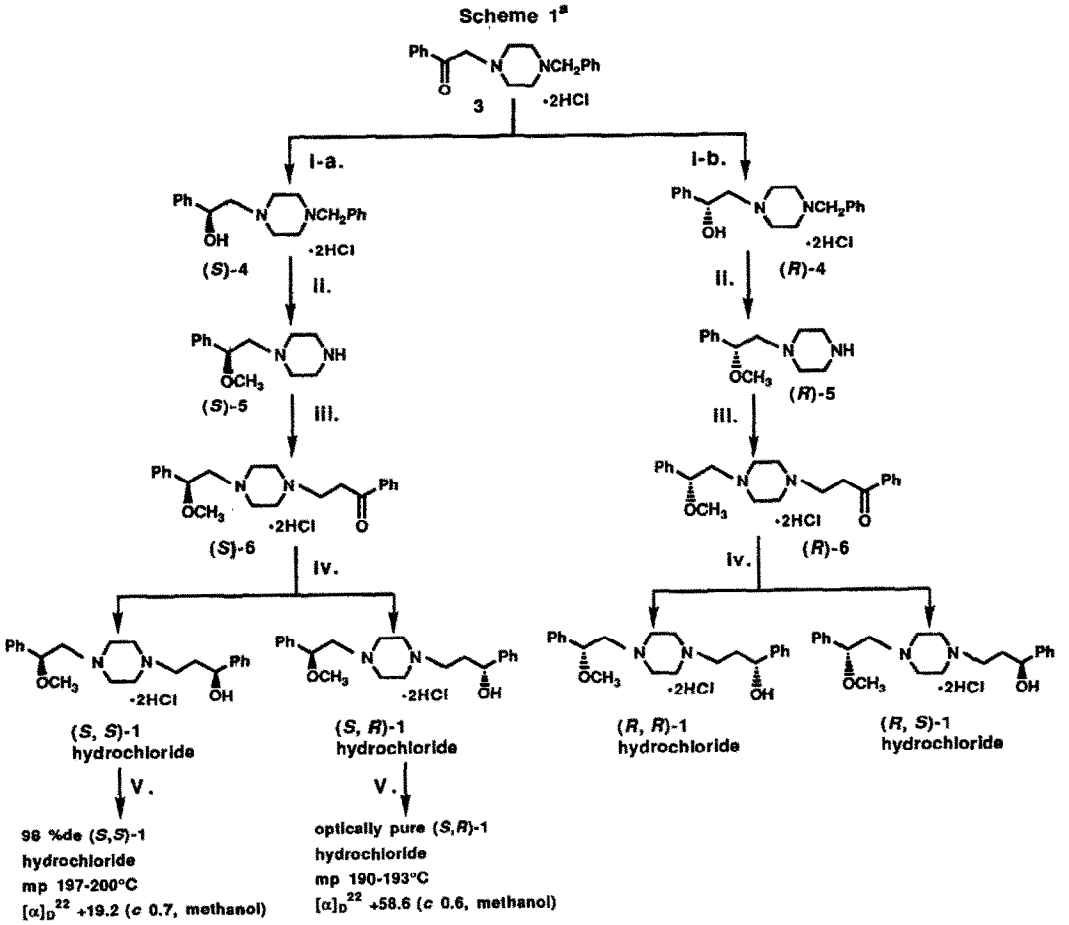


(2*R*,4*R*)-MCCPM (2b)

Our approach is summarized in Scheme 1. Asymmetric hydrogenation of α-amino ketone hydrochloride **3**, prepared from α-bromoacetophenone and *N*-benzylpiperazine, proceeded smoothly in the presence of 0.4 mol% of (2*S*, 4*S*)-MCCPM (**2a**)-Rh(I) and triethylamine in methanol at 50 °C for 24 h under initial hydrogen pressure of 30 atm. Usual work up gave (*S*)-β-amino alcohol hydrochloride (**4**) in >99 % yield and 88.2 %ee. Recrystallization of (*S*)-**4** from methanol afforded enantiomerically pure (*S*)-**4** (61.8 %), mp 226 °C decomp., $[\alpha]_D^{22}$ +34.6 (*c* 1.0, methanol). Optically pure (*R*)-**4** , mp 226 °C decomp., $[\alpha]_D^{22}$ -34.3 (*c* 1.0, methanol), was prepared by a similar procedure using (2*R*, 4*R*)-MCCPM (**2b**). The absolute configuration of **4** was determined by comparison of the specific rotation with an authentic sample prepared from (*R*)-styrene oxide and *N*-benzylpiperazine. The enantiomeric purity of **4** was measured by reaction with benzoyl chloride followed by HPLC analysis (Daicel, Chiralcel OJ, hexane/2-propanol=4/1) of resulting benzoate.

(*S*)-**4** was converted to β-amino ketone hydrochloride (**6**) in the following way. The sodium alkoxide of (*S*)-**4** free base was generated in *N*, *N*-dimethylacetamide using sodium hydride by reaction initially at 0°C and then, after warming at 70 °C for 2 h. Iodomethane was added and the mixture was stirred at room temperature overnight. Extractive isolation afforded (*S*)-*O*-methylated product as a yellow oil which was hydrogenated with

Scheme 1[a]



[a]*Reagents and conditions:* (i-a) H_2(30atm), $[Rh(COD)Cl]_2$, (2*S*,4*S*)-MCCPM, Et_3N, methanol, 50°C, 24h, >99% (88.2% ee); then recrystallization from methanol, 62% (~100% ee); (i-b) H_2(30atm), $[Rh(COD)Cl]_2$, (2*R*,4*R*)-MCCPM, Et_3N, methanol, 50°C, 24h, >99% (91.7% ee); then recrystallization from methanol, 60.0% (~100% ee); (ii) (1) NaOHaq. (2) NaH, *Iodomethane*, *N*,*N*-dimethylacetamide, 0~r.t., overnight; (3) H_2, 5% Pd-C, methanol, r.t., overnight; (iii) (1) 3-iodopropiophenone, ether, 0~r.t., 10h; (2) HCl gas, ether; (iv) H_2(30atm), $[Rh(COD)Cl]_2$, (2*S*,4*S*)- or (2*R*,4*R*)-MCCPM, methanol, 50°c, 72h; (v) recrystallization from methanol-hexane.

Table 1 Asymmetric Hydrogenations of 6

		condition			product 1	
subst.	ligand	atm/°C/h	[subst.]/[Rh]	convn[a](%)	(*S*, *S*)/(*S*, *R*)[b]	(*R*, *R*)/(*R*, *S*)[b]
(*S*)-6	(2*S*,4*S*)-MCCPM	30/50/72	250	100	10.4/89.6	-
(*S*)-6	(2*R*,4*R*)-MCCPM	30/50/72	250	100	89.7/10.3	-
(*R*)-6	(2*S*,4*S*)-MCCPM	30/50/72	250	100	-	90.9/9.1
(*R*)-6	(2*R*,4*R*)-MCCPM	30/50/72	250	100	-	8.6/91.4

[a]Determined by ^{1}H-NMR analysis. [b]Determined by HPLC analysis of its free amine.

5 % Pd-C in methanol to yield (*S*)-**5** (80.8 %). Reaction of (*S*)-**5** in ethyl ether and 3-iodopropiophenone, prepared from 3-chloropropiophenone and sodium iodide, produced the free base form of β-amino ketone (*S*)-**6** followed by treating with hydrogen chloride in ethyl ether provided (*S*)-**6** (56.7 %), mp 153-155 °C, $[\alpha]_D^{22}$ +37.3 (*c* 1.5, methanol). In a completely analogous manner we synthesized (*R*)-**6**, mp 151-153 °C, $[\alpha]_D^{22}$ -38.9 (*c* 1.0, methanol), starting with optically pure (*R*)-**4**.

Optically active eprozinol hydrochloride was obtained by asymmetric hydrogenation of **6** in a quantitative yield. The results of the asymmetric hydrogenations of (*S*)- and (*R*)-**6** with MCCPM-Rh(I) complex are summarized in Table 1. In all cases diastereomeric excess were approximately 80 %. These results indicate that the product stereoselectivity is insensitive to the chirality of stereogenic carbon atom of **6**. Recrystallization of (*S*, *R*)- and (*S*, *S*)-**1** hydrochloride from hexane-methanol afforded optically pure (*S*, *R*)- and (*S*, *S*)-eprozinol hydrochloride, (*S*, *S*)-**1** hydrochloride: 64 %, mp 197-200 °C, $[\alpha]_D^{22}$ +19.2 (*c* 0.7, methanol); (*S*, *R*)-**1** hydrochloride: 50 %, mp 190-193 °C, $[\alpha]_D^{22}$ +58.6 (*c* 0.6, methanol). Optically pure (*R*, *S*)- and (*R*, *R*)-eprozinol hydrochloride can be available in a similar manner. The synthetic substances were analyzed as the free base form and found to be identical with authentic samples[5] by 270 MHz ^{1}H-NMR, HPLC, gas chromatography and FAB mass spectrometric comparisons.

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5) Authentic samples of (*S*, *R*)- and (*S*, *S*)-eprozinol were prepared from (*S*)-styrene oxide.
(*S*, *R*)-eprozinol: mp 87-89°C, $[\alpha]_D^{22}$ +59.3 (*c* 0.9, methanol), ^{1}H-NMR(270 MHz, $CDCl_3$)δ 1.85(2H, m, NCC$\underline{H_2}$CPh), 2.41(1H, dd, J=13.4, 3.1 Hz, Ha of PhCC$\underline{H_2}$N), 2.55-2.71(10H, m, NC$\underline{H_2}$C$\underline{H_2}$Nx2, NC$\underline{H_2}$CCPh), 2.80(1H, dd, J=13.4, 9.2 Hz, Hb of PhCC$\underline{H_2}$N), 3.22(3H, s, OC$\underline{H_3}$), 4.36(1H, dd, J=3.1, 9.2 Hz, Ph$\underline{C}$H(OMe)CN), 4.92(1H, bt, NCC$\underline{C}$H(OH)Ph), 7.22-7.37(10H, m, Ar-H), FABMASS: m/z$(M+H)^+$ 355.
(*S*, *S*)-eprozinol: colorless oil, $[\alpha]_D^{22}$ +19.3 (*c* 1.1, methanol), ^{1}H-NMR(270 MHz, $CDCl_3$)δ 1.84(2H, m, NCC$\underline{H_2}$CPh), 2.41(1H, dd, J=13.4, 3.1 Hz, Ha of PhCC$\underline{H_2}$N), 2.55-2.72(10H, m, NC$\underline{H_2}$C$\underline{H_2}$Nx2, NC$\underline{H_2}$CCPh), 2.79(1H, dd, J=13.4, 8.9 Hz, Hb of PhCC$\underline{H_2}$N), 3.22(3H, s, OC$\underline{H_3}$), 4.36(1H, dd, J=3.1, 8.9 Hz, Ph$\underline{C}$H(OMe)CN), 4.93(1H, bt, NCC$\underline{C}$H(OH)Ph), 7.22-7.37(10H, m, Ar-H), FABMASS: m/z$(M+H)^+$ 355.