A Simple and Efficient Asymmetric Synthesis of Anxiolytic Drug Enciprazine

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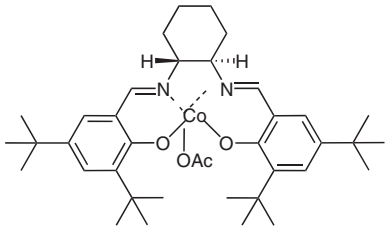
Abstract: A straightforward and efficient asymmetric synthesis of (*S*)-1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(3,4,5-trimethoxyphenoxy)propan-2-ol is described. The key intermediate, (*S*)-2-[(3,4,5-trimethoxyphenoxy)methyl]oxirane, was obtained by a hydrolytic kinetic resolution method using the catalyst (*R*,*R*)-salen–cobalt(III) complex.

Key words: trimethoxyphenol, resolution, chiral epoxide, methoxybenzenamine

The aryloxyaminopropanol moiety is a general feature of various β-adrenoreceptor blocking drugs (β-blockers). Different substitution on the lipophilic or hydrophilic parts of the molecule can modify the pharmacologic profile as well as pharmacokinetics of the compounds. The main clinical indications of β-blockers are in the area of cardiovascular diseases, such as hypertension, angina pectoris, myocardial infarction, and cardiac arrhythmias.[1] However, some β-blockers readily access the brain because of their lipophilicity and can influence some central nervous system functions.



(*R*,*R*)-salen–Co(III) complex

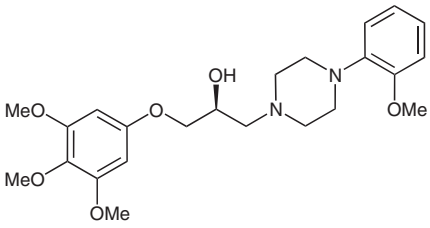


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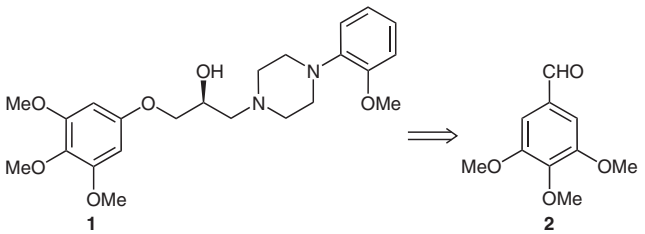
Figure 1

Therefore, propranolol has been used for treatment of anxiety syndromes, prophylaxis of migraine headaches, schizophrenia, alcohol withdrawal, and tremors. In a similar manner, the newly developed aryloxyaminopropanol derivatives with various heterocycles in the hydrophilic part of the molecule have shown the highest anticonvulsive activity. Enciprazine [(*S*)-1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(3,4,5-trimethoxyphenoxy)propan-2-ol, **1**] is a non-benzodiazepine anxiolytic drug. As a (phenoxy)(phenylpiperazinyl)propanol derivative, it exhibits a broad spectrum of pharmacological activity, such as cardiovascular, hypotensive, neurotropic, and local anesthetic properties (Figure 1).[1e,2]

As part of our research program in the design and synthesis of β-adrenoceptor antagonist molecules,[3] herein we report the asymmetric synthesis of (*S*)-enciprazine (**1**) using the hydrolytic kinetic resolution method introduced by Jacobsen.[4] Advantages of this protocol are the ready availability of the catalyst [(*R*,*R*)-salen–Co(III) complex], the catalyst would be used in small quantities (0.5 mol%) and is recyclable, and the use of 0.55 equivalents of water as the solvent as well as reactant (Figure 1).



Scheme 1

As shown in the retrosynthetic analysis (Scheme 1), the synthetic approach started from commercially available 3,4,5-trimethoxybenzaldehyde (**2**), which was treated with 3-chloroperoxybenzoic acid in dichloromethane to afford the 3,4,5-trimethoxyphenyl formate (**3**) in very good yield. The thus obtained formate compound **3** was reacted with potassium hydroxide in methanol to obtain the hydrolysis product, 3,4,5-trimethoxyphenol (**4**), in excellent yield. Phenol compound **4** was reacted with epichlorohydrin in presence of potassium carbonate to yield *rac*-2-[(3,4,5-trimethoxyphenoxy)methyl]oxirane (**5**) in very good yields (Scheme 2). This racemic epoxide is a free-flowing liquid, which is an advantage when using the hydrolytic kinetic resolution method which was used to separate the enantioselective isomers of (*S*)-epoxide **6** and (*R*)-1,2-diol **7** with excellent enantioselectivity.

Thus, the racemic epoxide **5** was treated with Jacobsen catalyst (*R*,*R*)-salen–Co(OAc) (0.5 mol%) and water (0.55 equiv) at room temperature for eight hours; the reac-

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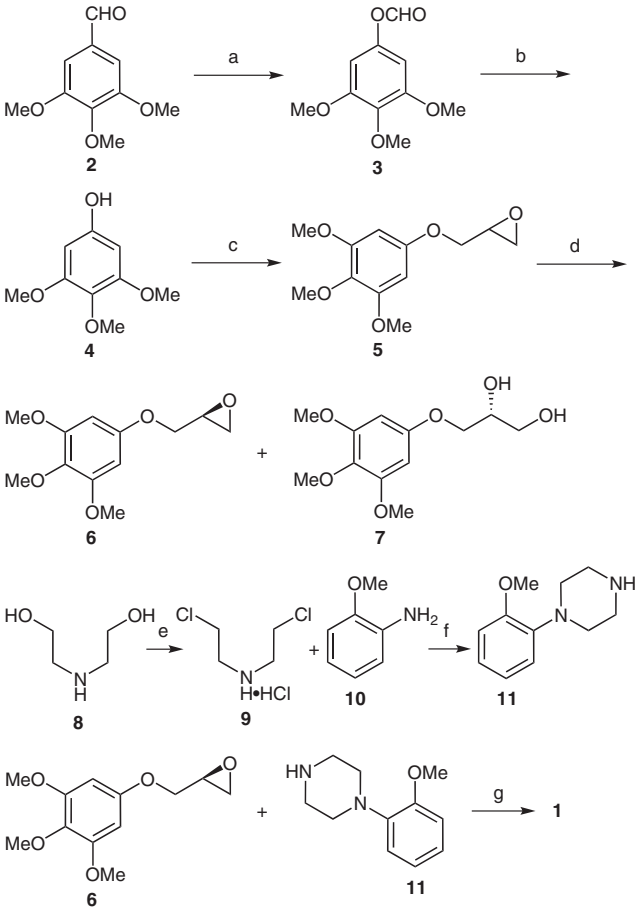

Scheme 2 *Reagents and conditions:* (a) MCPBA, CH_2Cl_2, r.t., 8 h, 93%; (b) KOH, MeOH, r.t., 30 min, 80%; (c) epichlorohydrin, K_2CO_3, TBAB (cat.), MeCN, reflux, 6 h, 90%; (d) (*R*,*R*)-salen–Co(III) catalyst, H_2O, 0 °C to r.t., 10 h, 46% (**6**), 48% (**7**); (e) $SOCl_2$, benzene, reflux, 5 h, 95%; (f) Na_2CO_3, H_2O, reflux 24 h, 90%; (g) *i*-PrOH, reflux, 15 h, 93%.

tion was monitored by HPLC (ODS-Column, UV: 225nm, 60% MeCN–H_2O). When the reaction was complete, the mixture was chromatographed on silica gel (60–120 mesh) to give the enantioselective epoxide (*S*)-2-[(3,4,5-trimethoxyphenoxy)methyl]oxirane (**6**) in 46% yield with 94% ee with $[\alpha]_D^{21}$ +3.5 (*c* 1, $CHCl_3$). On further elution of the column by increasing the polarity of the mobile phase, (*R*)-3-(3,4,5-trimethoxyphenoxy)propane-1,2-diol (**7**) was obtained in 48% yield with 97% ee with $[\alpha]_D^{21}$ –3.6 (*c* 1, $CHCl_3$).

In a similar manner, diethanolamine **8** was treated with thionyl chloride in benzene at reflux condition to afford the corresponding derivative of bis(2-chloroethyl)amine hydrochloride (**9**) in very good yields. This hydrochloride was reacted with *o*-ansidine in presence of a base to yield 1-(2-methoxyphenyl)piperazine (**11**) in good yields. The chiral epoxide, (*S*)-2-[(3,4,5-trimethoxyphenoxy)methyl]oxirane (**6**), and the amine, 1-(2-methoxyphenyl)piperazine (**11**), were refluxed in isopropyl alcohol for 15 hours to afford the desired product (*S*)-1-[4-(2-methylphenyl)piperazin-1-yl]-3-(3,4,5-trimethoxyphenoxy)propan-2-ol (enciprazine, **1**) in excellent yields with $[\alpha]_D^{21}$ +3.0 (*c* 1, $CHCl_3$).[2b] All the products were characterized by their ^1H NMR, IR, and mass spectroscopy data.

In summary, we have described, a concise asymmetric synthesis of (*S*)-enciprazine (**1**) in a highly enantioselective fashion. The key intermediate, the chiral epoxide **6**, was achieved by hydrolytic kinetic resolution method using Jacobsen's catalyst with excellent enantioselectivity. This method can be applied for large-scale preparation of (*S*)-enciprazine.

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR spectra were recorded on Bruker-300 MHz spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

3,4,5-Trimethoxyphenyl Formate (3)

To a stirred soln of 3,4,5-trimethoxybenzaldehyde (**2**, 2 g, 10.2 mmol) in anhyd CH_2Cl_2 (20 mL) was added MCPBA (2.64 g, 15.3 mmol) in portions at 0 °C for a period of 30 min. After 1 h, cooling was removed and the mixture was stirred at r.t. for 8 h (TLC monitoring). When no starting material remained (TLC), the mixture was diluted with CH_2Cl_2 (40 mL) and washed with sat. $NaHCO_3$ (2 × 20 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was obtained as red syrup; yield: 2 g (93%).

3,4,5-Trimethoxyphenol (4)

To a stirred soln of **3** (2 g, 9.43 mmol) in MeOH (10 mL) was added KOH (0.5 g, 9.43 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 30 min. When the reaction was complete (TLC), the solvent was removed under reduced pressure and washed with hexane (20 mL). The residue obtained was dissolved in H_2O (25 mL) and acidified with dilute (1 M) HCl (to pH 5–6) with cooling to give a solid that was filtered and dried; yield: 1.38 g (80%); mp 143–145 °C.

IR (KBr): 3270, 2999, 2957, 2843, 1611, 1515, 1485, 1432, 1342, 1272, 1225, 1184, 1130, 996, 814, 777, 740, 703 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.61 (s, 3 H), 3.80 (s, 6 H), 6.01 (s, 2 H), 8.65 (br s, 1 H, OH).

MS (EI): *m*/*z* (%) = 184 (75) $[M]^+$, 169 (100), 154 (10), 141 (50), 126 (25), 111 (30), 85 (15), 71 (10), 69 (40), 55 (20).

2-[(3,4,5-Trimethoxyphenoxy)methyl]oxirane (5)

To a stirred soln of **4** (1.3 g, 7 mmol) in anhyd MeCN (10 mL) was added anhyd K_2CO_3 (2 g, 14 mmol) and epichlorohydrin (0.65 g, 7 mmol) and TBAB (cat.) at r.t. The resulting mixture was stirred at reflux for 6 h (TLC monitoring). When the reaction was complete, the solvent was removed under reduced pressure. The residue was dissolved in H_2O and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4) and concentrated under reduced pressure. The obtained crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 3:7) to give pure **5** as light-colored liquid; yield: 1.52 g (90%).

IR (neat): 2936, 2838, 1598, 1506, 1459, 1423, 1344, 1231, 1194, 1128, 1056, 1007, 911, 814, 779, 629 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.69 (q, *J* = 2.3 Hz, 1 H), 2.88 (t, *J* = 4.5 Hz, 1 H), 3.20–3.30 (m, 1 H), 3.71 (s, 3 H), 3.80 (s, 6 H), 3.90 (q, *J* = 5.5 Hz, 1 H), 4.12 (dd, *J* = 3.8, 3.8 Hz, 1 H), 6.12 (s, 2 H).

MS (EI): *m*/*z* (%) = 242 (100) $[M + 2]^+$, 223 (10), 183 (10), 168 (12), 152 (20), 121 (15), 90 (22), 65 (20).

(*S*)-2-[(3,4,5-Trimethoxyphenoxy)methyl]oxirane (6)
A mixture of racemic epoxide **5** (3 g, 12.5 mmol) and (*R*,*R*)-salen–Co(III)OAc complex (0.036 g, 0.062 mmol) was vigorously stirred for 15 min at r.t. Then mixture was cooled to 0 °C and H_2O (0.12 mL, 6.86 mmol) was added over a period of 30 min through syringe pump. After complete addition of H_2O, the cooling was removed and stirring was continued at r.t. for 10 h [monitored by HPLC (ODS-column, UV 225 nm, 60% MeCN–H_2O)]. When the reaction was complete, the mixture was diluted with EtOAc (30 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed (silica gel, 60–120 mesh, EtOAc–hexane, 1:9). The less polar epoxide **6** eluted first as light-colored liquid; yield: 1.3 g (46%); 94% ee; $[\alpha]_D^{21}$ +3.5 (*c* 1, $CHCl_3$). The chiral epoxide **6** was confirmed by its spectral data and similar to the racemic epoxide **5**. Changing the column eluent to EtOAc–hexane (4:6) provided the (*R*)-diol **7**, which was obtained as a light-colored thick syrup; yield: 1.5 g (48%); 97% ee.

(*R*)-3-(3,4,5-Trimethoxyphenoxy)propane-1,2-diol (7)
$[\alpha]_D^{21}$ –3.6 (*c* 1, $CHCl_3$).

IR (neat): 3409, 2937, 1599, 1506, 1459, 1423, 1346, 1230, 1194, 1157, 1126, 1056, 1006, 813, 778, 628 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.60 (dd, *J* = 5.3, 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.76 (d, *J* = 3.5 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.92 (d, *J* = 5.4 Hz, 2 H), 3.98–4.12 (m, 1 H), 6.12 (s, 2 H).

MS (EI): *m*/*z* (%) = 259 (100) $[M + 1]^+$, 238 (10), 221 (15), 199 (10), 131 (10), 122 (25), 100 (52), 76 (10).

Bis(2-chloroethyl)amine Hydrochloride (9)
To a stirred mixture of diethanolamine (2 g, 19 mmol) in benzene (10 mL) was added $SOCl_2$ (6.8 g, 57 mmol) at 0 °C. The resulting mixture was refluxed for 5 h and the solvent was distilled off under reduced pressure. To the residue was added benzene (10 mL) and the mixture was stirred for a period and then distilled again. A white solid was obtained (3.23 g, 95%) and used directly.

1-(2-Methoxyphenyl)piperazine (11)
To a stirred mixture of **9** (2.5 g, 14 mmol) and **10** (1.72 g, 14 mmol) was added Na_2CO_3 soln [Na_2CO_3 (3 g) dissolved in H_2O (15 mL)] and TBAB (cat.) at r.t. The resulting mixture was refluxed for 24 h (TLC monitoring). When the reaction was complete, the mixture was cooled to r.t. and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 4:6) to give pure **11** as a light-colored, low-melting solid; yield: 2.42 g (90%).

IR (KBr): 3405, 2931, 1748, 1601, 1519, 1486, 1436, 1364, 1320, 1267, 1223, 1178, 1136, 1096, 1044, 974, 903, 763, 740, 699, 663, 630 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.35–3.45 (m, 2 H), 3.50–3.68 (m, 4 H), 3.84 (s, 3 H), 4.25–4.35 (m, 2 H), 6.55–6.88 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5, 137.3, 120.9, 116.5, 109.3, 61.8, 55.1, 45.7, 44.8, 43.5, 41.3.

MS (EI): *m*/*z* (%) = 192 (10) $[M]^+$, 177 (10), 161 (10), 149 (15), 136 (100), 120 (60), 100 (20), 93 (10), 77 (15), 56 (20), 42 (10).

(*S*)-1-[4-(2-Methylphenyl)piperazin-1-yl]-3-(3,4,5-trimethoxyphenoxy)propan-2-ol ((*S*)-Enciprazine, 1)
To a stirred mixture of **6** (0.2 g, 0.83 mmol) in anhyd *i*-PrOH (5 mL) was added **11** (0.19 g, 1 mmol) at r.t. The resulting mixture was refluxed for 15 h (TLC monitoring). When the reaction was complete, the solvent was removed under reduced pressure and residue was dissolved in a minimal amount of EtOAc and adsorbed on silica gel, and eluted with EtOAc–hexane (4:6). The pure product was obtained as syrup; yield: 0.33 g (93%).

$[\alpha]_D^{21}$ +3.0 (*c* 1, $CHCl_3$).

IR (neat): 3456, 2925, 2854, 1746, 1461, 1375, 1163, 723 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.30–3.40 (m, 2 H), 3.45–3.55 (m, 5 H), 3.70 (s, 3 H), 3.80 (s, 6 H), 3.88 (s, 4 H), 3.90–3.98 (m, 3 H), 4.15 (t, *J* = 6.0 Hz, 2 H), 6.11 (s, 2 H), 6.91 (d, *J* = 6.5 Hz, 2 H), 7.01–7.10 (m, 1 H), 7.20–7.30 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.3, 129.8, 125.4, 124.1, 121.1, 111.7, 96.0, 92.3, 70.3, 67.1, 61.6, 60.7, 57.7, 55.3, 51.3, 44.4, 42.4.

MS (EI): *m*/*z* (%) = 433 (20) $[M + 1]^+$, 418 (12), 326 (25), 250 (100), 242 (25), 184 (15), 169 (10), 154 (15), 138 (10), 123 (0), 92 (20), 84 (10), 76 (15), 56 (20), 42 (10).

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