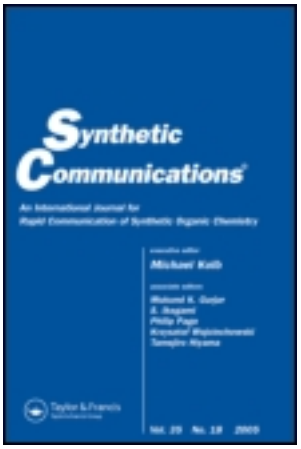

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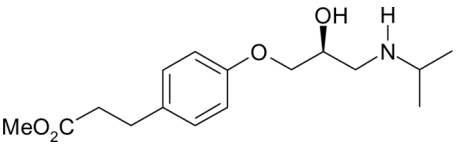
NOVEL ASYMMETRIC SYNTHESIS OF (*S*)-ESMOLOL USING HYDROLYTIC KINETIC RESOLUTION

A. Venkat Narsaiah and J. Kranthi Kumar
Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad, India

GRAPHICAL ABSTRACT



Abstract *An efficient asymmetric synthesis of (*S*)-methyl 3-[4-[2-hydroxy-3-(isopropyl amino) propoxy] phenyl] propanoate is described. The key intermediate (*S*)-methyl 3-[4-(oxiran-2-ylmethoxy) phenyl] propanoate was obtained by hydrolytic kinetic resolution method using Jacobsen catalyst.*

Keywords Amino alcohol; epoxide; isopropyl amine; resolution

INTRODUCTION

Esmolol **1** is a potent cardioselective β_1-receptor blocker and rapidly hydrolyzed by the esterases in the cytosol of red blood cells. Esmolol is a short-acting β-blocker and its pharmacodynamic half-life (10 min) can be attributed to the ester group in the *para*-substituent of the phenoxypropanolamine. Esmolol decreases the force and rate of heart contractions by blocking β-adrenergic receptors of the sympathetic nervous system,[1–3] which are found in the heart and other organs of the body.

RESULTS AND DISCUSSION

As part of our research program in design and synthesis of β-adrenoceptor antagonist,[4,5] herein we report the asymmetric synthesis of (*S*)-esmolol by using hydrolytic kinetic resolution method, which was introduced by Jacobsen and coworkers.[6–9] This protocol provides high eanantioselectivity and is extremely simple compared to other approaches. The reasons to select this route are (1) the ready availability of the catalyst, (2) the catalyst would be used in small quantities

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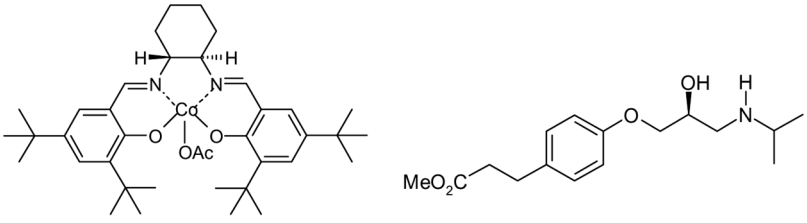
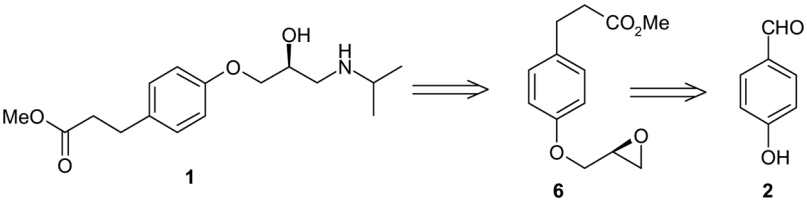


Figure 1.

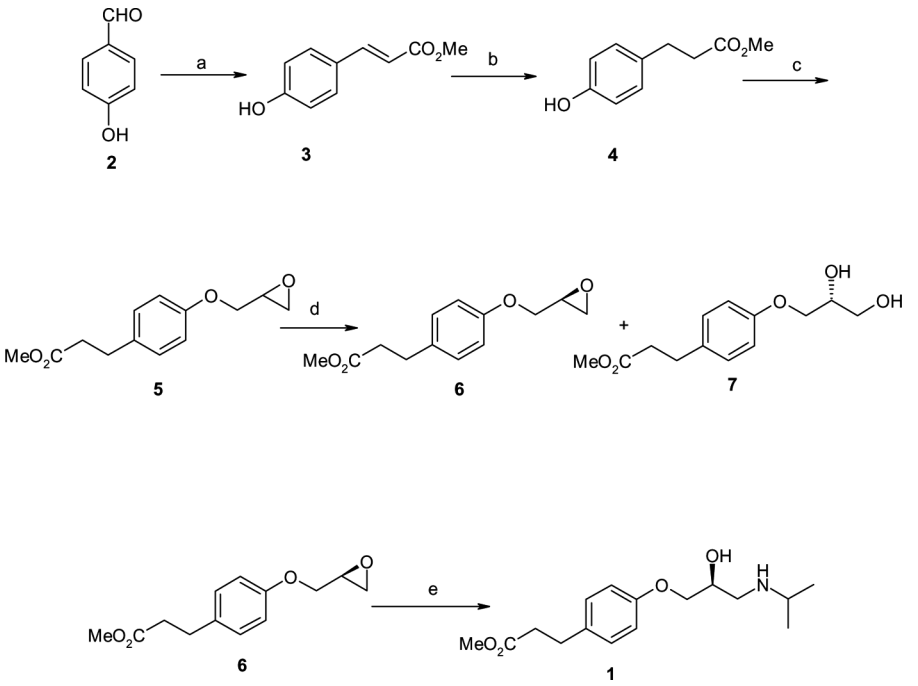
(0.5 mol%), and (3) the recyclability of the catalyst and 0.55 equivalent amount of water as the only solvent as well as reactant (Fig. 1).

The synthetic approach started from the commercially available 4-hydroxy benzaldehyde (**2**), which was subjected to the Wittig reaction and gave the product (*E*)-methyl 3-(4-hydroxyphenyl) acrylate (**3**) in 92% yield. The olefin compound was treated with Pd/C in ethyl acetate under a hydrogen atmosphere to afford methyl 3-(4-hydroxypheny)propanoate (**4**) in quantitative yield. The resulting saturated ester compound was reacted with epichlorohydrin in the presence of K_2CO_3 in acetonitrile at reflux condition to yield the racemic epoxide of methyl 3-[4-(oxiran-2-ylmethoxy)-phenyl] propanoate (**5**) in 82% yield. The racemic epoxide was a free-flowing liquid, and the hydrolytic kinetic resolution method was convenient to apply.

The racemic epoxide was treated with Jacobsen[7–9] catalyst (*R,R*)-(salen Co-(III) OAc) (0.5 mol%) and water (0.55 eq) at room temperature for 8.0 h, and the reaction was monitored by high-performance liquid chromatography (HPLC) (ODS-Column) UV: 225 nm, 60% CH_3CN in H_2O. After completion of the reaction, the reaction mixture was chromatographed on silica gel (60–120 mesh) to give the enantioselective epoxide of (*S*)-methyl 3-[4-(oxiran-2-ylmethoxy)phenyl]propanoate (**6**) in 46% yield with 94% enantiomeric excess. The optical rotation of epoxide **6** shows that $[\alpha]_D^{21} = +4.42$ (*c* 1, $CHCl_3$), and further elution of the column by increasing the polarity of mobile phase gave the (*R*)-methyl 3-[4-(2,3-dihydroxyl propoxy)-phenyl]propanoate (**7**) in 48% yield with 98% ee, the optical rotation of which shows that $[\alpha]_D^{21} = -4.6$ (*c* 1, $CHCl_3$). The enantiomerically pure *R*-diol on further treatment for Mitsunobu[10] conditions with triphenylphosphine and diethyl azodicarboxylate afforded the optically active *R*-epoxide. The first separated enantiomeric pure chiral *S*-epoxide (**6**) was treated with an excess amount of *N*-isopropyl amine in the presence of water to afford the final target product of (*S*)-methyl 3-[4-[2-hydroxy-3-(isopropyl



Scheme 1.



Scheme 2. Reagents and conditions: (a) Wittig ylide, room temperature, 6.0 h, 92%; (b) 10% Pd/C, ethyl acetate, hydrogen atmosphere, room temperature, 12.0 h, 95%; (c) epichlorohydrin, K_2CO_3, CH_3CN, reflux, 6.0 h, 82%; (d) *R,R*-salen Co(III) catalyst, H_2O, 0 °C to room temperature, 8.0 h, 46% of *S*-epoxide and 48% *R*-diol; (e) and isopropyl amine, H_2O, reflux, 5.0 h, 80%.

amino) propoxy] phenyl] propanoate (**1**) in 80% yield. The optical rotation of the *S*-esmolol shows that $[\alpha]_D^{21} = +4.5$ (*c* 1, $CHCl_3$). All the compounds were confirmed by their infrared (IR), ^{1}H NMR, and mass spectroscopic data and optical rotation.

CONCLUSION

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

EXPERIMENTAL

Melting points were recorded in a Buchi capillary melting-point (R-535) apparatus. IR spectra were recorded on a Perkin-Elmer Fourier transform (FT)–IR 240C spectrophotometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer with tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded

on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All chemicals or reagents were purchased from standard commercial suppliers.

Preparation of (*E*)-Methyl 3-(4-hydroxyphenyl)-acrylate (3)

Wittig compound (10.0 g, 1.5 eq) was added to a stirred mixture of 4-hydroxybenzaldehyde **2** (2.44 g, 20 mol) in methylene dichloride (20 ml). The resulting reaction mixture was stirred for a period of 6.0 h room temperature, and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction as indicated by TLC, the reaction mixture was diluted by adding dichloromethane (25 mL) and extracted. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography by using silica gel, 60–120 mesh. The pure product **3** was obtained as white solid, yield 3.3 g (92%), mp 130–132 °C. ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3H), 6.20 (d, 1H, $J = 12.0$ Hz), 6.70 (d, 2H, $J = 7.5$ Hz), 7.35 (d, 2H, $J = 7.5$ Hz), 7.65 (d, 1H, $J = 12.0$ Hz); EIMS m/z (%) 178 (m^+ 55), 163 (10), 147 (100), 133 (10), 119 (28), 107 (10), 91 (24), 65 (18), 51 (10).

Preparation of Methyl 3-(4-Hydroxypheny)propanoate (4)

To a stirred solution of compound **3** (3.3 g, 18.5 mmol) in ethyl acetate (20 mL) was added 10% Pd/C (100 mg). Stirring continued under a hydrogen atmosphere at room temperature, and progress of the reaction was monitored by TLC (12.0 h). The completion of the reaction was confirmed by TLC. The reaction mixture was filtered, and the catalyst was washed with the solvent (2×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **4** was obtained as a colorless liquid, and it was confirmed by spectral data. Yield 3.1 g (95%). ^{1}H NMR ($CDCl_3$): δ 2.58 (t, 2H, $J = 4.5$ Hz), 2.86 (t, 2H, $J = 4.5$ Hz), 3.65 (s, 3H), 6.68 (d, 2H, $J = 7.0$ Hz), 6.99 (d, 2H, $J = 7.0$ Hz).

Preparation of Methyl 3-[4-(Oxiran-2-ylmethoxy)phenyl]propanoate (5)

A mixture of methyl ester compound **4** (3.0 g, 16.6 mmol) and potassium carbonate (4.6 g, 33.3 mmol) in acetonitrile (50 mL) was stirred for some time, and epichlorohydrine (1.53 g 16.6 mmol) was added. The resulting mixture was refluxed for about 6.0 h, and the complete conversion of the starting material was confirmed by TLC. Then the solvent was removed under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate (2×25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh) to obtain a colorless liquid, yield 3.2 g (82%).

Preparation of (*S*)-Methyl-3-(4-(oxiran-2-ylmethoxy)phenyl) propanoate (6)

A mixture of racemic epoxide **5** (3.0 g, 12.7 mmol) and (*R,R*)-salen Co(III)–OAc complex (0.038 g, 0.063 mmol) was vigorously stirred for 15 min at room

temperature. Then reaction mixture was cooled to 0 °C, and water (0.1 mL, 6.9 mmol) was added over a period of 1 h through a syringe pump. After complete addition of water, the cooling was removed, and stirring continued at room temperature (monitored by HPLC [(ODS-column) UV: 225 nm, 60% CH_3CN in H_2O]). After completion of the reaction, the reaction mixture was diluted by adding ethylacetate (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on silica gel (60–120 mesh) using ethyl acetate and petroleum ether mixture in a 1:9 ratio. The less polar epoxide **6** was eluted first as a colorless liquid, yield 1.38 g (46%) and 94% enantiomeric excess. $[\alpha]_D^{21} + 4.42$ (*c* 1, $CHCl_3$). The chiral epoxide **6** was confirmed by its spectral data. IR (KBr) υ 3451, 3000, 2928, 1736, 1612, 1512, 1439, 1362, 1296, 1243, 1176, 1111, 1035, 987, 913, 835, 768 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (t, 2H, $J = 4.0$ Hz), 2.70 (t, 1H, $J = 3.0$ Hz), 2.80–2.90 (m, 3H), 3.25–3.32 (m, 1H), 3.65 (s, 3H), 3.95 (q, 1H, $J = 3.0$ Hz), 4.10 (dd, 1H, $J = 9.0$, 2.0 Hz), 6.80 (d, 2H, $J = 6.0$ Hz), 7.05 (d, 2H, $J = 6.0$ Hz). EIMS *m/z* (%) 236 (100), 221 (12), 203 (10), 194 (15), 177 (25), 159 (22), 147 (10), 132 (15), 118 (35), 102 (18), 96 (12), 76 (42), 51 (25).

Later, the ethyl acetate and petroleum ether ratio was raised to 3:7 to elute the *R*-diol compound **7**, which was obtained as a thick syrup, yield 1.44 g (48%) and 98% enantiomeric excess. The optical rotation shows as $[\alpha]_D^{21} - 4.6$ (*c* 1, $CHCl_3$). IR (KBr) υ 3380, 2928, 1732, 1610, 1513, 1441, 1375, 1280, 1244, 1176, 1109, 1052, 980, 946, 873, 826, 783 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (t, 2H, $J = 6.0$ Hz), 2.89 (t, 2H, $J = 6.0$ Hz), 3.62 (s, 3H), 3.68–3.85 (m, 2H), 3.95–4.15 (m, 3H), 6.80 (d, 2H, $J = 6.0$ Hz), 7.08 (d, 2H, $J = 6.0$ Hz); EIMS *m/z* (%) 254 (10), 242 (100), 186 (22), 142 (15), 124 (20), 104 (10), 76 (30), 51 (15).

Preparation of 3-[4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]propanoate (1)

A mixture of *S*-epoxide **6** (1.0 g, 4.2 mmol), isopropyl amine (3.75 mL, 42.3 mmol), and water (0.13 mL) was refluxed for 5 h, and the unreacted isopropyl amine was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography to afford the final pure product as thick syrup (1.0 gm, 80%). $[\alpha]_D^{21} + 4.5$ (*c* 1, $CHCl_3$). IR (KBr) υ 3318, 2928, 2854, 1735, 1612, 1513, 1441, 1368, 1297, 1244, 1176, 1109, 1045, 832 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (s, 6H), 2.55 (t, 2H, $J = 5.0$ Hz), 2.78 (q, 1H, $J = 5.0$ Hz), 2.85–2.93 (m, 4H), 3.15 (brs, 1H), 3.65 (s, 3H), 3.85–4.10 (m, 3H), 6.80 (d, 2H, $J = 6.0$ Hz), 7.05 (d, 2H, $J = 6.0$ Hz). EIMS *m/z* (%) 297 (40), 296 (100), 277 (15), 254 (10), 219 (20), 193 (12), 163 (10), 145 (25), 118 (15), 102 (12), 96 (18), 76 (35), 51 (22). HRMS calculated for $C_{16}H_{25}NO_4$ 296.1861; found 296.1855.

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