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Concise synthesis of β-blockers (*S*)-metoprolol and (*S*)-betaxolol using hydrolytic kinetic resolution

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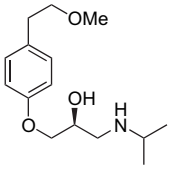
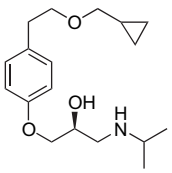
Abstract—Enantiopure (*S*)-metoprolol and (*S*)-betaxolol were prepared in an extremely simple and practical way using Jacobsen's hydrolytic kinetic resolution of terminal epoxides in isopropanol.

1. Introduction

Hypertension is a growing medical concern worldwide. With an increasing number of patients suffering from hypertension every year, the use of antihypertensive medications such as β-blockers has increased. β-Blockers[1] are a group of compounds that competitively inhibit the effects of catecholamines at β-adrenergic receptors and have a diverse range of clinical applications in the treatment of cardiovascular disorders.[2] Metoprolol (**1**) and betaxolol (**2**) are important drugs in this series, the former is widely used in the treatment of angina and hypertension[3] and the latter one is a strong antiglaucoma agent.[4] Although these drugs possess one stereogenic carbon center, they are generally administered as racemates. The biological activity in a racemic drug often resides in a single enantiomer.[5] For instance, the *S*-isomers of metoprolol (**1**) and betaxolol (**2**) are associated with β-blocking activity, while the *R*-isomers are responsible for side effects.[3a,4a] The synthesis of drugs in enantiomerically pure form is very important for pharmaceutical industries,[6] due to increased demand for more effective, safe single isomers.



(*S*)-Metoprolol **1**



(*S*)-Betaxolol **2**

Although a number of approaches have been described in the literature for the asymmetric synthesis of (*S*)-metoprolol[7] and (*S*)-betaxolol,[8] most of the methods require lengthy reaction sequences coupled with low yield and enantioselectivity. Synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for drug preparation.

In this context, the phenomenal success of the hydrolytic kinetic resolution (HKR) technique developed by Jacobsen and co-workers using chiral (salen) Co complex catalyst has provided a powerful tool for the generation of enantioenriched terminal epoxide and vicinal diols in excellent yields.[9] The other salient features of this method include extraordinarily high levels of selectivity, easy availability of racemic terminal epoxides, low loadings, and easy recyclability of the commercially available catalyst, which makes it extremely simple to work with compared to other approaches.[9,10] Generally, the HKR reaction has been performed in water medium, which is not suitable for water immiscible/insoluble solid epoxides. Although alternative solvents such as Et_2O,[11] THF,[12] and isopropanol[13] have been suggested for the HKR reaction, this approach was not attempted for the synthesis of any drug targets. The synthetic potential inherent in the efficiency and excellent enantioselectivity of the HKR reaction combined with the possible use of organic solvents as a medium inspired us to explore the preparation of different β-blockers using this versatile methodology. As part of our ongoing program on improving the process for the preparation of β-blockers for industrial applications,[14] herein, we report a concise and simple synthesis of (*S*)-metoprolol (**1**) and (*S*)-betaxolol (**2**) from a common intermediate (*S*)-1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane (**3**) employing HKR as the key step and isopropanol as the reaction medium.

Keywords: β-Blockers; Metoprolol; Betaxolol; Hydrolytic kinetic resolution.
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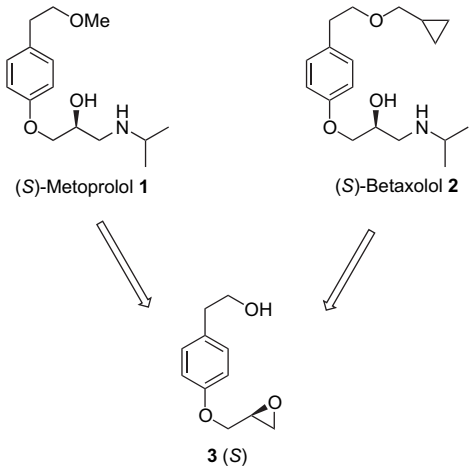
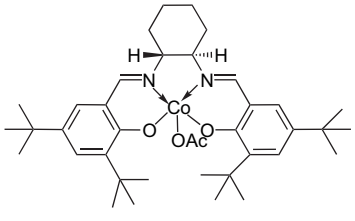
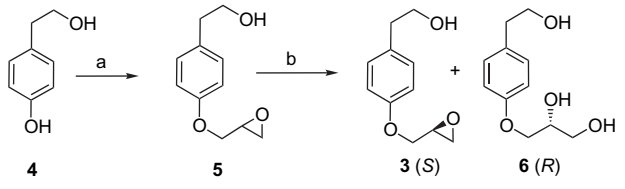
2. Results and discussion

Based on the retrosynthetic disconnection (Scheme 1), we felt that (*S*)-1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane (**3**) is a substrate of special interest as it serves as a common intermediate for (*S*)-metoprolol and (*S*)-betaxolol and can be easily converted to compounds **1** and **2** by a simple reaction sequence in high enantiopurity and good yields (Schemes 2 and 3). The substrate for the HKR, the racemic epoxide **5** was obtained from alkylation of 2-(4-hydroxyphenyl)-ethanol (**4**) with (±)-epichlorohydrin in anhydrous 2-butanone in the presence of K_2CO_3 and a phase transfer catalyst under reflux temperature for 15 h in 86% yield. Subsequently, the HKR of racemic epoxide **5** was performed with Jacobsen catalyst (*R*,*R*) (salen Co(III)OAc) (0.5 mol %) and water (0.55 equiv) in isopropanol at ambient temperature for 30 h and the reaction was monitored by HPLC (SS-Wakosil; UV: 225 nm, 70% MeOH in H_2O). After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give the (*S*)-epoxide **3** from the racemic mixture in 42% yield and 99% ee {selectivity factor, E=429; $[\alpha]_D$ +2.72 (*c* 1, MeOH)} and (*R*)-diol **6** in 47% yield and 92% ee. The use of isopropanol in the HKR of epoxides offers the advantage that the reaction mixture becomes a one-phase system whereas the use of Et_2O results in a two-phase system. This is one reason why the reaction in isopropanol proceeds faster than that in Et_2O. A disadvantage of the use of isopropanol as solvent is the faster deactivation of the Co(III)-Jacobsen catalyst compared to Et_2O but the deactivated Co(II)-Jacobsen catalyst can be easily reactivated by acid treatment in the presence of air.[12] Subsequently, the selective O-alkylation of the hydroxyl group of (*S*)-epoxide **3** was carried out with methyl iodide and bromomethylcyclopropane separately in the presence of KO^{t}Bu in DMA to provide (*R*)-iodohydrin **7** (98% yield, 96% ee) and (*S*)-epoxide **8** (96% yield, 99% ee), respectively. An interesting observation was made while using methyl iodide for O-alkylation: a regiospecific epoxide ring opening took place by the iodide nucleophile and 2% of racemization was observed. The reaction conditions were optimized such that self-polymerization with the epoxide was eliminated.

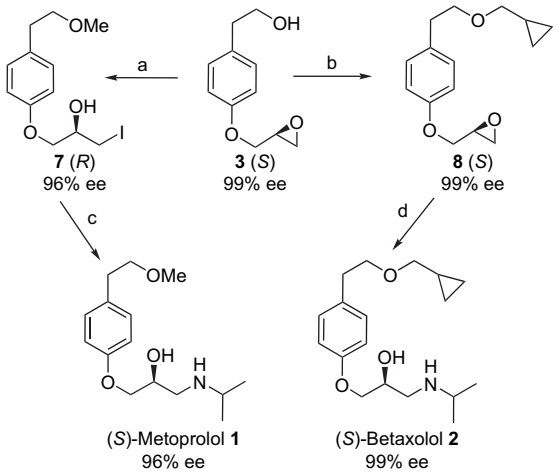


Scheme 1.





Scheme 2. Reagents and conditions: (a) (±)-epichlorohydrin, K_2CO_3, 2-butanone, 86%; (b) (*R*,*R*) salen Co(III)-A, isopropanol.



Scheme 3. Reagents and conditions: (a) CH_3I, KO^{t}Bu, *N*,*N*-dimethylacetamide, 98%; (b) bromomethylcyclopropane, KO^{t}Bu, *N*,*N*-dimethylacetamide, 96%; (c) isopropylamine, water, reflux, 97%; (d) isopropylamine, water, reflux, 96%.

Subsequently, the (*R*)-iodohydrin **7** and (*S*)-epoxide **8** were treated separately with an excess amount of *N*-isopropyl amine at reflux temperature for 2–10 h to afford crude (*S*)-metoprolol hydroiodide salt and (*S*)-betaxolol free base, respectively. The crude (*S*)-metoprolol hydroiodide salt was made free using 6% ammonia solution. The crude (*S*)-metoprolol (**1**) and (*S*)-betaxolol (**2**) were further purified by silica gel column chromatography to afford pure (*S*)-metoprolol in 97% yield and excellent enantioselectivity (96% ee) $[\alpha]_D$ −8.10 (*c* 10, $CHCl_3$) {lit.[7g] $[\alpha]_D$ −8.70 (*c* 10, $CHCl_3$)} and (*S*)-betaxolol in 96% yield and excellent enantioselectivity (99% ee) $[\alpha]_D$ −7.13 (*c* 1, $CHCl_3$) {lit.[8b] $[\alpha]_D$ −5.4 (*c* 1, $CHCl_3$)}.

3. Conclusion

In summary, a concise asymmetric synthesis of (*S*)-metoprolol and (*S*)-betaxolol with high enantioselectivity has been achieved using Jacobsen's HKR technique (in isopropanol) as the key step and source of chirality. The extension of

the synthetic strategy described here employing the versatile intermediate **3** is being investigated for other chiral β-blockers.

4. Experimental

4.1. General methods

Melting points were measured on a BUCHI Melting Point B-540 melting point apparatus. ^{1}H NMR spectra were recorded on a BRUKER 200 MHz and 500 MHz NMR spectrometers. Chemical shifts were given in parts per million (ppm). Spectra were obtained in $CDCl_3$. Elemental analysis was performed using Karlo-Erba elemental analyzer. Monitoring of reactions was carried out using TLC plates Merck Silica gel 60 F_{254} and visualization with UV light (254 and 365 nm), I_2 and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a JASCO DIP 370 digital polarimeter. IR spectra were obtained from Perkin–Elmer 68515 PC-FTIR spectrophotometer. GCMS analysis was carried out using SHIMADZU-QP5050 system. HPLC analyses were performed on 'SHIMADZU SCL-10A. Unit' system controller and UV monitor as detector. Chiral compounds were analyzed on Daicel Chiralcel OD column and reaction monitoring was performed on SS-Wakosil column. All reagents and solvents were obtained from commercial suppliers and were used as such without further purification. The selectivity factor (E) for the product was calculated using the equation $E=\ln[1-c(1+ee)]/\ln[1-c(1-ee)]$, where c is the conversion of (*S*)-epoxide and ee is the enantiomeric excess of (*S*)-epoxide.[15]

4.1.1. 1-[4-(2-Hydroxyethyl)phenoxy]-2,3-epoxypropane (racemic) (5). To a stirred solution of 2-(4-hydroxyphenyl)-ethanol **4** (10 g, 0.073 mol) and K_2CO_3 (30 g, 0.218 mol) in anhydrous 2-butanone (100 mL) was added (±)-epichlorohydrin (6.2 mL, 0.080 mol) and the reaction mixture was refluxed until all of the 2-(4-hydroxyphenyl)-ethanol had been consumed (15 h; TLC). The reaction mixture was filtered, solvent was removed under vacuum, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 70/30) to yield **5** as a white solid (11.9 g; 86%). Mp 57–58 °C (lit.[16] mp 56–58 °C); IR (neat): ν 3300, 3078, 3004, 2928, 2861, 1723, 1612, 1583, 1512, 1454, 1378, 1297, 1243, 1179, 1096, 1037, 937, 828 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.73–2.77 (m, 1H), 2.80 (t, J=8.0 Hz, 2H), 2.88–2.93 (m, 1H), 3.31–3.38 (m, 1H), 3.75–3.87 (m, 1H), 3.94 (dd, J=12.0 and 4.0 Hz, 1H), 4.20 (dd, J=11.0 and 4.0 Hz, 1H), 6.87 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 157.0, 131.1, 128.9, 114.7, 68.7, 63.6, 50.1, 44.6, 38.1; MS *m*/*z*: 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; O, 24.71. Found: C, 68.22; H, 7.48; O, 24.46.

4.1.2. (*S*)-1-[4-(2-Hydroxyethyl)phenoxy]-2,3-epoxypropane (3). A mixture of 1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane **5** (10 g, 0.052 mol) and (*R*,*R*) salen Co(III)OAc complex-A (0.085 g, 0.00013 mol) in isopropanol (100 mL) were vigorously stirred for 15 min, then cooled to 0 °C, and added water (0.5 mL, 0.028 mol) over a period of 15 min, through syringe. The reaction mixture was stirred at room temperature for 20 h and additional (*R*,*R*) salen Co(III)OAc complex-A (0.085 g, 0.00013 mol) was added, stirring was continued for additional 10 h, monitored by HPLC (SS-Wakosil column, UV: 225 nm, 70% MeOH in H_2O). The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 70/30). The less polar epoxide **3** eluted first as a white solid (4.2 g; 42%), mp 51 °C; $[\alpha]_D$ +2.72 (*c* 1, MeOH), ee>99% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/isopropanol=95/5; flow rate: 0.5 mL/min; detector: 220 nm (t_R=60.39 min) (t_S=63.59 min)], followed by the diol **6** as a pale brown solid (5.1 g; 47%), mp 67–68 °C; ee 92% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/isopropanol=95/5; flow rate: 1 mL/min; detector: 220 nm (t_R=58.36 min) (t_S=59.72 min)]; IR (neat): ν 3328, 3019, 2926, 2865, 1611, 1583, 1512, 1457, 1383, 1298, 1241, 1215, 1177, 1111, 1038, 950, 821 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.70–2.75 (m, 1H), 2.80 (t, J=6.5 Hz, 2H), 2.88–2.93 (m, 1H), 3.28–3.36 (m, 1H), 3.81 (t, J=6.5 Hz, 2H), 3.95 (dd, J=11.1 and 5.5 Hz, 1H), 4.15 (dd, J=11.1 and 3.2 Hz, 1H), 6.91 (d, J=8.7 Hz, 2H), 7.15 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.0, 131.8, 128.5, 114.1, 75.5, 65.1, 50.1, 43.0, 38.7; MS *m*/*z*: 212 (M^+). Anal. Calcd for $C_{11}H_{16}O_3$: C, 62.25; H, 7.60; O, 30.15. Found: C, 62.45; H, 7.38; O, 30.46.

4.1.3. (*R*)-1-Iodo-3-[4-(2-methoxy ethyl)phenoxy]propan-2-ol (7). A reaction flask was charged with (*S*)-1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane **3** (1 g, 0.005 mol), methyl iodide (0.36 mL, 0.006 mol), and *N*,*N*-dimethylacetamide (10 mL). The mixture was blanketed under nitrogen and stirred at room temperature for 15 min and then cooled to −5 °C. Potassium *tert*-butoxide (0.87 g, 0.007 mol) was slowly added. After the addition was completed, the reaction mixture was maintained at 0 °C for 3 h. The reaction mixture was diluted with aqueous hydrochloric acid (7 N, 5 mL). The aqueous mixture was extracted three times with 25 mL portions of ether. The combined organic extracts were washed twice with 10 mL of water, dried over Na_2SO_4, evaporated, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc=98/2) to provide **7** as a colorless liquid (1.65 g; 98%). ee 96% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.4×25 cm) column; eluent: hexane/isopropanol=97.5/2.5; flow rate: 1.0 mL/min; detector: 254 nm (t_R=36.93 min) (t_S=41.42 min)]; IR (neat): ν 3078, 3004, 2928, 2861, 1723, 1612, 1583, 1512, 1454, 1378, 1297, 1243, 1179, 1096, 1037, 937, 828 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.84 (t, J=8.0 Hz, 2H), 3.36 (s, 3H), 3.40–3.53 (m, 2H), 3.58 (t, J=8.0 Hz, 2H), 3.93–3.97 (m, 1H), 4.02–4.05 (m, 2H), 6.85 (d, J=8.0 Hz, 2H), 7.15 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.6, 131.7, 129.7, 114.4, 73.6, 70.4, 69.3, 58.5, 35.1, 9.1; MS *m*/*z*: 336 (M^+). Anal. Calcd for $C_{12}H_{17}IO_3$: C, 42.87; H, 5.10; I, 37.75. Found: C, 42.68; H, 5.22; I, 37.62.

4.1.4. (*S*)-Metoprolol (1). A solution of (*R*)-**7** (1 g, 0.003 mol) in *i*-$PrNH_2$ (2.5 mL) and H_2O (2–3 drops) was refluxed until TLC showed the reaction had gone to completion (2 h). Removal of the solvent yielded the crude (*S*)-metoprolol hydroiodide salt, which was made free using

6% ammonia solution (5 mL). The crude (*S*)-metoprolol **1** free base was purified by column chromatography (silica gel, DCM/MeOH=98/2) (0.77 g; 97%), colorless solid; $[\alpha]_D$ −8.10 (*c* 10, $CHCl_3$) {lit.[7g] $[\alpha]_D$ −8.70 (*c* 10, $CHCl_3$)}; ee 96% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/ethylalcohol/diethylamine=70/30/0.1; flow rate: 0.5 mL/min; detector: 254 nm (t_R=9.7 min) (t_S=11.77 min)]; IR (neat): ν 3327, 3045, 2981, 2866, 1611, 1585, 1512, 1472, 1383, 1298, 1243, 1216, 1178, 1092, 930, 828, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.15 (d, *J*=6 Hz, 6H), 2.73–2.96 (m, 5H), 3.35 (s, 3H), 3.57 (t, *J*=8 Hz, 2H), 3.94–3.97 (m, 2H), 4.02–4.10 (m, 1H), 6.84 (d, *J*=8.0 Hz, 2H), 7.13 (d, *J*=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.9, 131.0, 129.5, 114.2, 75.3, 71.5, 70.6, 68.2, 49.5, 48.7, 35.0, 22.7; MS *m*/*z*: 267 (M^+). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.51; H, 9.74; N, 5.15.

4.1.5. (*S*)-2-[4-(2-Cyclopropylmethoxy ethyl)phenoxymethyl]oxirane (8). A reaction flask was charged with (*S*)-1-[4-(2-hydroxyethyl)phenoxy]-2,3-epoxypropane **3** (1 g, 0.005 mol), bromomethylcyclopropane (0.83 g, 0.006 mol), and *N*,*N*-dimethylacetamide (10 mL). The mixture was blanketed under nitrogen and stirred at room temperature for 15 min and then cooled to −5 °C. Potassium *tert*-butoxide (0.87 g, 0.007 mol) was slowly added. After the addition was completed, the reaction mixture was maintained at 0 °C for 3 h. The reaction mixture was diluted with aqueous hydrochloric acid (7 N, 5 mL). The aqueous mixture was extracted three times with 25 mL portions of ether. The combined organic extracts were washed twice with 10 mL of water, dried over Na_2SO_4, evaporated, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc=98/2) to provide **8** as a colorless oil (1.29 g; 96%); $[\alpha]_D$ +2.05 (*c* 1, $CHCl_3$); ee >99% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/isopropanol=97.5/2.5; flow rate: 1.0 mL/min; detector: 254 nm (t_R=9.25 min) (t_S=10.25 min)]; IR (neat): ν 3078, 3004, 2928, 2861, 1723, 1612, 1583, 1512, 1454, 1378, 1297, 1243, 1179, 1096, 1037, 937, 828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.54 (m, 2H), 1.06 (m, 1H), 2.70–2.75 (m, 1H), 2.83 (t, *J*=7.3 Hz, 2H), 2.88–2.93 (m, 1H), 3.26 (d, *J*=6.8 Hz, 2H), 3.28–3.36 (m, 1H), 3.61 (t, *J*=7.3 Hz, 2H), 3.95 (dd, *J*=11.1 and 5.5 Hz, 1H), 4.15 (dd, *J*=11.1 and 3.2 Hz, 1H), 6.87 (d, *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.8, 131.5, 129.8, 114.4, 75.5, 71.6, 68.6, 50.1, 44.6, 35.3, 10.5, 2.9; MS *m*/*z*: 248 (M^+). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.70; H, 8.42.

4.1.6. (*S*)-Betaxolol (2). A solution of (*S*)-**8** (0.7 g, 0.003 mol) in *i*-$PrNH_2$ (2.5 mL) and H_2O (2–3 drops) was refluxed until TLC showed the reaction had gone to completion (10 h). Removal of the solvent yielded the crude (*S*)-betaxolol **2** as a free base, which was purified by column chromatography (silica gel, DCM/MeOH=98/2) (0.83 g; 96%), colorless solid; $[\alpha]_D$ −7.13 (*c* 1, $CHCl_3$) {lit.[8b] $[\alpha]_D$ −5.4 (*c* 1, $CHCl_3$)}; ee >99% [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/isopropanol/diethylamine=60/40/0.1; flow rate: 0.5 mL/min; detector: 228 nm (t_R=8.53 min) (t_S=10.61 min)]; IR (neat): ν 3327, 3045, 2981, 2866, 1611, 1585, 1512, 1472, 1383, 1298, 1243, 1216, 1178, 1092, 930, 828, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.20 (m, 2H), 0.52 (m, 2H), 1.06 (m, 8H), 2.70–2.75 (m, 1H), 2.83–2.93 (m, 3H), 3.27 (d, *J*=7.2 Hz, 2H), 3.61 (t, *J*=7.3 Hz, 2H), 3.90 (d, *J*=5.6 Hz, 3H), 3.98–4.02 (m, 1H), 6.84 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 156.9, 131.0, 129.5, 114.2, 75.3, 71.5, 70.6, 68.2, 49.5, 48.7, 35.0, 22.7, 10.4, 2.7; MS *m*/*z*: 307 (M^+). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 69.91; H, 9.74; N, 4.15.

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