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A convenient synthesis of enantiomerically pure (*R*)-mexiletine using hydrolytic kinetic resolution method

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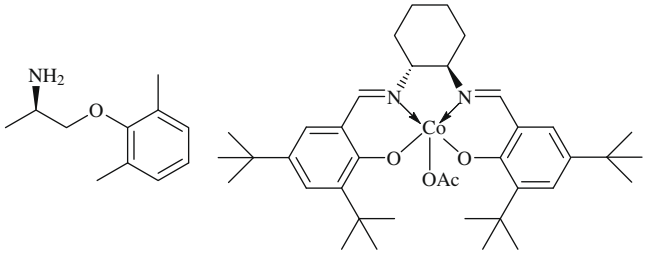
ABSTRACT

Enantiopure (*R*)-mexiletine was prepared in a simple and practical way using hydrolytic kinetic resolution method of terminal epoxide by Jacobsen catalyst. High enantiomeric purity (98% ee) was achieved and the method is well amenable to industrial scale-up.

1. Introduction

Mexiletine is an important β-amino aryl ether class of drug used in the treatment of arrhythmia, allodynia and myotonic syndromes, etc and available in the market with the trade name Mexitil.[1] Although it contains one stereogenic centre, it is generally administered as a racemate. However, the (*R*)-isomer of mexiletine is more potent than the (*S*)-isomer in experimental arrhythmias and in binding studies on cardiac sodium channels.[2] Moreover, the use of mexiletine as a racemate in the treatment of neuromuscular disorders is limited due to its possible side effects.[3] As a result, numerous reports describing the preparation of mexiletine enantiomers and their analogues have been published.[4–6] Generally, the methods include resolution of racemic intermediates,[4] chemoenzymatic routes,[5] or using stereospecific procedures.[6] However, most of these methods have several drawbacks such as tedious and time consuming experiments, unavailability or expensive chiral starting materials, low yield and lower enantiomeric purity, etc. Synthetic efforts now need to be directed at short, practical routes that are amenable to scale-up for drug preparation.

In this context, the success of the hydrolytic kinetic resolution (HKR) technique developed by Jacobsen et al. using a chiral (salen) Co complex catalyst has provided a powerful tool for the generation of enantioenriched terminal epoxides and vicinal diols in excellent yields.[7] The other salient features of this method include extraordinarily high levels of selectivity, easy availability of racemic terminal epoxides, and the low loadings and easy recyclability of the commercially available catalyst, which makes it extremely simple to work with compared to other approaches.[8] The synthetic potential inherent in the efficiency and excellent enantioselectivity of the HKR reaction inspired us and many others[9] to explore this versatile synthetic methodology for the preparation of many drug molecules and natural products. As part of our ongoing program aimed at improving the process for the preparation of various pharmaceutically important compounds for industrial applications,[10] we herein report a concise and simple synthesis of (*R*)-mexiletine employing HKR as the key step (see Fig. 1).



(*R*)-mexiletine **1** (*R*,*R*)-Salen Co (III) catalyst-**A**

Figure 1.

2. Results and discussion

A retrosynthetic analysis of (*R*)-mexiletine **1** is outlined in Scheme 1. As shown in Scheme 1, we envisaged that (*S*)-epoxide **4** would be an ideal key intermediate for the synthesis of (*R*)-mexiletine, which can be easily obtained from its racemic epoxide **3** with high enantiopurity using Jacobsen's HKR method. The key intermediate **4** can be easily converted to the target molecule **1** by simple regioselective reductive ring opening and Mitsunobu reaction protocols.

Accordingly, the substrate for HKR, the racemic epoxide **3**, was obtained from the alkylation of commercially available 2,6-dimethyl phenol **2** with (±)-epichlorohydrin in anhydrous acetone

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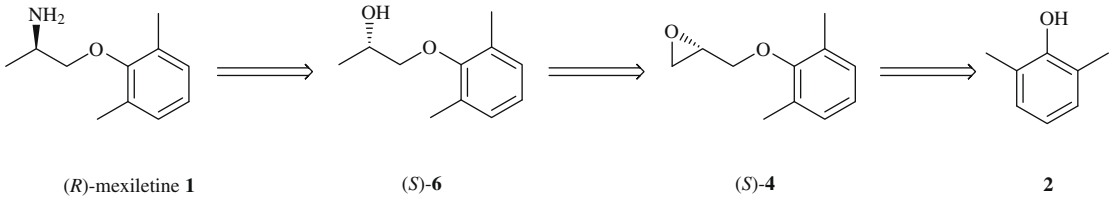
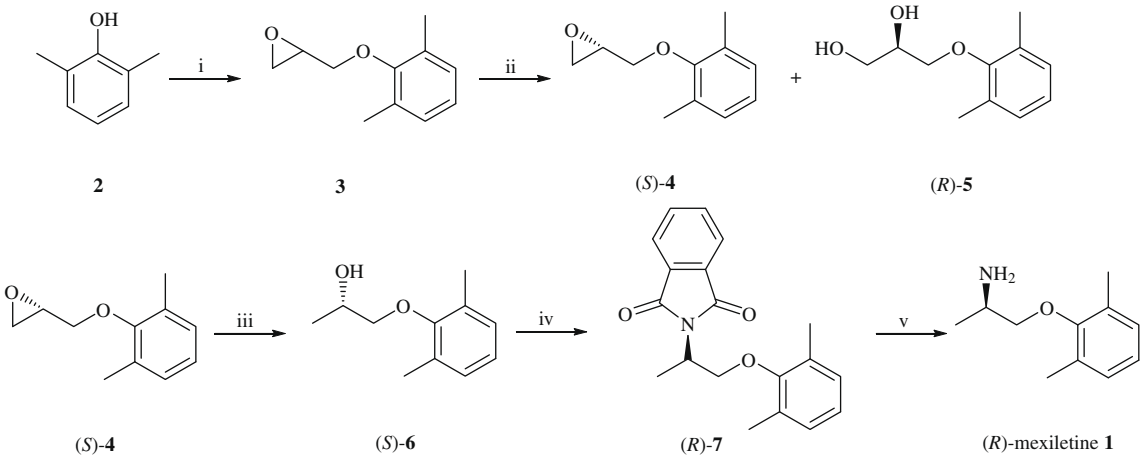


Scheme 1. Retrosynthetic analysis of (*R*)-mexiletine.



Scheme 2. Reagents and conditions: (i) (±)-epichlorohydrin, K_2CO_3, acetone, reflux, 20 h, 80%; (ii) (*R*,*R*) salen Co(III)-A, 0 °C–rt, 30 h; (iii) $LiAlH_4$, THF, 0 °C, 30 min, 91%; (iv) Ph_3P, phthalimide, DIAD, THF, rt, 4 h, 83%; (v) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 3 h; 86%.

in the presence of potassium carbonate at reflux for 20 h in 80% yield as a colorless oil (Scheme 2). The HKR of racemic epoxide **3** was performed with Jacobsen's catalyst (*R*,*R*) salen Co(III)OAc (0.5 mol %) and water (0.55 equiv) at ambient temperature for 30 h. After completion of the reaction, the reaction mixture was chromatographed over a silica gel column to give the (*S*)-epoxide **4** from the racemic mixture in 43% yield and >99% ee, $[\alpha]_D^{25} = +2.5$ (*c* 2, $CHCl_3$) and (*R*)-diol **5** in 47% yield $[\alpha]_D^{25} = -3$ (*c* 2, $CHCl_3$). Subsequently, the regioselective reductive ring opening of (*S*)-epoxide **4** was carried out with lithium aluminium hydride in anhydrous THF at 0 °C to provide secondary alcohol **6** in 91% yield. The regioselective reductive ring opening on the terminal side of the epoxide **4** was ascertained by the appearance of a sharp doublet at δ 1.27 ppm (J = 6.0 Hz) in its ^{1}H NMR spectrum and δ 18.5 ppm in its ^{13}C NMR spectrum corresponding to the terminal methyl group. The secondary alcohol **6** was readily transformed into a phthalimido ether **7** by stereospecific substitution of the hydroxyl group with phthalimide employing a typical Mitsunobu procedure.[1b] Finally, a facile hydrazinolysis[6d] of phthalimido ether **7** with hydrazine hydrate in ethanol afforded the crude target molecule, which was further purified over silica gel column to afford pure (*R*)-mexiletine **1** in 86% yield and 98% ee; $[\alpha]_D^{25} = -2.4$ (*c* 5, $CHCl_3$) {Lit.[1b] $[\alpha]_D^{25} = -2.7$ (*c* 4.7, $CHCl_3$)}. The structure of (*R*)-mexiletine **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy analysis. The enantiomeric purity of (*R*)-mexiletine **1** and the key intermediate **4** was determined by chiral HPLC analysis.

3. Conclusion

In conclusion, a practical and highly enantioselective synthesis of (*R*)-mexiletine **1** has been achieved using Jacobsen's HKR method as the key step and source of chirality. The main advantages of this method were the high enantioselectivity, the ready availability of the catalyst and the use of water (0.55 equiv) as the medium and reactant in the key step. Moreover, the Jacobsen catalyst can be regenerated by treatment with acetic acid and recycled. We envisage that this simple protocol may be a viable alternative for the large scale production of (*R*)-mexiletine in the pharmaceutical industry.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. 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 P 1020 digital polarimeter. Mass spectra were recorded at an ionization energy 70 eV on API Q Star Pulsar spectrometer using electrospray ionization. Enantiomeric excess was determined by chiral HPLC.

4.2. 2-((2,6-Dimethylphenoxy)methyl)oxirane (racemic) 3

To a stirred solution of 2,6-dimethylphenol **2** (6 g, 50 mmol) and K_2CO_3 (17 g, 125 mmol) in dry acetone (50 mL) was added (±)-epichlorohydrin (7 g, 75 mmol) and the reaction mixture was refluxed until all of the 2,6-dimethylphenol had been consumed (20 h, TLC). The reaction mixture was filtered, and the solvent was removed under reduced pressure, after which the residue was purified by column chromatography (silica gel, petroleum ether/acetone, 97:3) to yield **3** as a colorless oil (7.1 g, 80%); IR (Neat): γ 3019, 2925, 1477, 1264, 1216, 1092, 1021, 832, 756. ^{1}H

NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 6H, 2CH_3), 2.70–2.74 (dd, J = 6.0, 2.0 Hz, 1H, OCH_2), 2.88–2.92 (apparent t, J = 4.0 Hz, 1H, OCH_2), 3.33–3.41 (m, 1H, OCH), 3.75 (dd, J = 10.0, 6.0 Hz, 1H, OCH_2), 4.01–4.08 (dd, J = 11.0, 4.0 Hz, 1H, OCH_2), 6.89–7.03 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 155.5 (C), 130.8 (C, 2 carbons), 128.8 (CH, 2 carbons), 124.0 (CH), 72.9 (CH_2), 50.5 (CH), 44.5 (CH_2), 16.2 (CH_3, 2 carbons); MS: m/z 201 $[M+Na]^+$; HRMS calcd for $C_{11}H_{14}O_2$: 178.0993. Found: 178.1002.

4.3. (*S*)-2-(2,6-Dimethylphenoxymethyl)oxirane 4

A mixture of 2-(2,6-dimethyl-phenoxymethyl)oxirane **3** (5 g, 28 mmol) and (*R,R*) salen Co(III)OAc complex-A (0.046 g, 0.07 mmol) were vigorously stirred for 15 min, then cooled to 0 °C, and water added (0.3 mL, 15 mmol) over a period of 15 min, through a micro-syringe. The reaction mixture was stirred at room temperature for 20 h, and additional (*R,R*) salen Co(III)OAc complex-A (0.046 g, 0.07 mmol) was added, and stirring was continued for additional 10 h. 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/acetone (97:3). The less polar epoxide **4** eluted first as a colorless oil (2.15 g, 43%); $[\alpha]_D^{25} = +2.5$ (c 2, $CHCl_3$); ee >99% [chiral HPLC analysis; DAICEL CHIRALCEL OD-H (250 × 4.6 mm) column; eluent: hexane/ethanol = 99.9/0.1; flow rate: 0.5 mL/min; detector: 254 nm [(*R*)-isomer t_R = 30.17 min; (*S*)-isomer t_R = 33.22 min], followed by diol **5** as a pale brown semi solid (2.5 g, 47%); $[\alpha]_D^{25} = -3$ (c 2, $CHCl_3$); IR (Neat): γ 3361, 2924, 1592, 1477, 1377, 1264, 1203, 1023, 931, 768; NMR (200 MHz, $CDCl_3$): δ 1.74 (br s, 1H, OH), 2.30 (s, 6H, 2CH_3), 2.92 (br s, 1H, OH), 3.77–3.93 (m, 4H, 2OCH_2), 4.07–4.14 (m, 1H, CH), 6.91–7.04 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 154.9 (C), 130.6 (C, 2 carbons), 128.9 (CH, 2 carbons), 124.1 (CH), 72.9 (CH_2), 71.2 (CH), 63.8 (CH_2), 16.1(CH_3, 2 carbons); MS: m/z 219 $[M+Na]^+$; HRMS calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1056.]

4.4. (*S*)-1-(2,6-Dimethylphenoxy) propan-2-ol 6

To a solution of epoxide **4** (1.0 g, 5.6 mmol) in dry THF (10 mL) at 0 °C was added slowly a pre-cooled solution of Lithium aluminum hydride (0.25 g, 6.7 mmol) in THF (5 mL) with stirring under nitrogen. After 30 min, the reaction mixture was quenched with 1 mL of water and 1 mL of 15% NaOH solution and the content stirred for 15 min. The inorganic precipitate was filtered, washed with ethyl acetate and the solvent evaporated under reduced pressure. The residue was purified by a short filtration column to yield **6** as a colorless oil (0.91 g, 91%); $[\alpha]_D^{25} = -1.3$ (c 5, $CHCl_3$) {Lit.[1b] $[\alpha]_D^{25} = -1.1$ (c 5, $CHCl_3$)], IR (Neat): γ 3584, 3019, 2924, 1518, 1477, 1215, 1092, 1021, 756. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (d, J = 6.0 Hz, 3H, CH_3), 2.30 (s, 6H, CH_3-Ar), 3.60–3.78 (dd, J = 10.0, 4.0 Hz, 2H, OCH_2), 4.16–4.27 (m, 1H, CH), 6.90–7.05 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 155.1 (C), 130.7 (C, 2 carbons), 128.9 (CH, 2 carbons), 124.0 (CH), 76.9 (CH_2), 67.0 (CH), 18.5 (CH_3), 16.2 (CH_3, 2 carbons); MS: m/z 203 $[M+Na]^+$.

4.5. (*R*)-2-(1-(2,6-dimethylphenoxy)propan-2-yl)isoindoline-1,3-dione 7

A solution of DIAD (0.97 mL, 4.8 mmol) in dry THF (10 mL) was added dropwise to a solution of **6** (0.8 g, 4.4 mmol), phthalimide (0.78 g, 5.3 mmol) and triphenylphosphine (1.26 g, 4.8 mmol) in dry THF (25 mL) under N_2 atmosphere at room temperature. The stirring was continued until all of the alcohol had been consumed (4 h, TLC). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 97:3) to yield **7** as a pale yellow oil (1.13 g, 83%); $[\alpha]_D^{25} = -59$ (c 2.4, $CHCl_3$) {Lit.[1b] $[\alpha]_D^{25} = -55$ (c 2.2, $CHCl_3$)} IR (Neat): γ 3053, 2925, 2985, 2254, 1774, 1711, 1469, 1265, 1209, 1092, 909, 829. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56 (d, J = 8.0 Hz, 3H, CH_3), 2.20 (s, 6H, 2CH_3-Ar), 3.91 (dd, J = 8.0, 6.0 Hz, 1H, OCH_2), 4.38 (apparent t, J = 10.0 Hz, 1H, OCH_2), 4.79–4.97 (m, 1H, CH), 6.84–6.98 (m, 3H, H_{arom}), 7.71–7.75 (m, 2H, H_{arom}), 7.85–7.89 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 168.5 (CO, 2 carbons), 155.1 (C), 133.9 (CH, 2 carbons), 131.9 (C, 2 carbons), 130.7 (C, 2 carbons), 128.7 (CH, 2 carbons), 123.9 (CH, 2 carbons), 123.1 (CH), 71.5 (CH_2), 47.1(CH), 16.2 (CH_3, 2 carbons), 15.1 (CH_3).

4.6. (*R*)-Mexiletine 1

To a stirred solution of **7** (0.92 g, 3 mmol) in ethanol (20 mL) was added hydrazine hydrate (80%) solution (1.4 mL, 24 mmol) and the resulting mixture was refluxed for 3 h. The precipitated solid was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in ether and extracted with 2 N HCl, and the aqueous phase was treated with 2 M NaOH until pH >12. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 97:3) to afford (*R*)-mexiletine **1** as a colorless oil (0.46 g, 86%); $[\alpha]_D^{25} = -2.4$ (c 5, $CHCl_3$) {Lit.[1b] $[\alpha]_D^{25} = -2.7$ (c 4.7, $CHCl_3$)}; IR (Neat): γ 3019, 2400, 1667, 1476,, 1263, 1215, 1092, 1028, 928, 853. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (d, J = 6.0 Hz, 3H, CH_3), 1.82 (br s, 2H, NH_2), 2.29 (s, 6H, 2CH_3-Ar), 3.32–3.42 (m, 1H, CH), 3.50–3.58 (apparent t, J = 10.0 Hz, 1H, OCH_2), 3.63–3.70 (dd, J = 10.0, 4.0 Hz, 1H, OCH_2), 6.89–7.03 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 155.3 (C), 130.7 (C, 2 carbons), 128.8 (CH, 2 carbons), 123.8 (CH), 77.9 (CH_2), 47.2 (CH), 19.8 (CH_3), 16.2 (CH_3, 2 carbons); MS: m/z 180 $[M+1]^+$; ee >98% [The ee of **1** was determined by chiral HPLC analysis of the corresponding *N*-acetyl derivative;[1b] DAICEL CHIRALCEL OD (250 × 4.6 mm) column; eluent: pet. ether/isopropanol = 90/10; flow rate: 0.6 mL/min; detector: 254 nm [(*R*)-isomer t_R = 16.35 min; (*S*)-isomer t_R = 23.07 min].

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