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Enantiodivergent syntheses of (+)- and (−)-1-(2,6-dimethylphenoxy) propan-2-ol: A way to access (+)- and (−)-mexiletine from D-(+)-mannitol

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ABSTRACT

Chiron approach was used to acquire optically pure (*R*)- and (*S*)-1-(2,6-dimethylphenoxy)propan-2-ol, immediate precursors of (*S*)- and (*R*)-mexiletines, respectively. Two different routes were followed from a D-mannitol-derived optically pure common precursor to get the enantiomeric alcohols separately. Comparison of their specific rotation values with the corresponding literature values as well as exact mirror-image relationship between their CD curves proved their high enantiopurity. These alcohols were then transformed to the corresponding amine-drugs in an efficient one-step process instead of two steps described in the literature.

1. Introduction

Mexiletine, **1** and ***ent*-1** (Fig. 1), is 1-(2,6-dimethylphenoxy)-2-propanamine. It is a class I–B antiarrhythmic oral drug [1]. This drug can also be used clinically in many disorders [2] such as myotonic syndromes, sporadic amyotrophic lateral sclerosis, Timothy syndrome. Mexiletine is clinically useful to relieve neuropathic pain and prescribed for treating patients with painful diabetic neuropathy. The therapeutic effect of mexiletine can be correlated with the block of voltage-dependent sodium ion channels present in both cardiac and skeletal muscle fibers. Though this chiral drug is clinically used as racemate, mexiletine enantiomers are found to differ in both pharmacodynamics and pharmacokinetics. The (*R*)-isomer, ***ent*-1** was found to be more potent in experimental arrhythmias [3], in binding studies on cardiac sodium channels [4], and in producing a tonic block of the skeletal muscle channel [5]. On the other hand, the (*S*)-isomer, **1** is superior for the treatment of allodynia [6]. Consequently, development of strategies to access both the enantiomers of mexiletine continues to be at the forefront of organic synthesis. There are reports of many approaches to access mexiletine enantiomers. Racemic mexiletines have been resolved by different methods: (i) classical resolution methods involving formation of diastereomeric salts with di-*p*-toluoyltartaric acid [3], dibenzoyltartaric acid [7]; (ii) derivatization with a chiral auxiliary tetrahydropyranyl-protected (*R*)-(−)-mandelic acid [8]; (iii) chromatographic methods utilizing chiral stationary phase or involving separation of diastereomeric pair produced *via* covalent derivatization and (iv) enzymatic processes [10]. Several synthetic strategies have been reported also. Key reaction involved in many of these was either Williamson's aryl ether formation using 2,6-dimethylphenol or phthalimide substitution under Mitsunobu's condition followed by imide hydrazinolysis. Chiral precursors such as (*S*)-(+)-3-bromo-2-methyl-1-propanol (overall yield 7.2%) [7], (*S*)-(+)- and (*R*)-(−)-2-amino-1-propanol (overall yields [11a]11a 28% and 32%, respectively) [11a,c], (*S*)-(−)- and (*R*)-(+)-propylene oxide (overall yields 24% and 34%, respectively) [11b] and (*R*)-epichlorohydrin (overall yield 34%) [11d] were stereospecifically converted to the corresponding enantiomers of mexiletine. Loughhead and co-workers [11a] reported overall yields (28% and 32%) with reference to the reaction between chiral 2-amino-1-propanol and 1,3-dimethyl-2-fluorobenzenetricarbonylchromium complex. They referred to Mahaffy and Hamilton, who prepared the chromium complex in 28% yield. Hence, overall yields are expected to be lower than the reported values [11c]. Carocci and co-workers' [11c] methodology involving Mitsunobu reaction for the aryl ether bond formation provided (*S*)- and (*R*)-mexiletines in 36–39% and 44–46% overall yields, respectively. Asymmetric syntheses of both the enantiomers of mexiletine have been achieved by Han and co-workers [12] by nucleophilic substitution of two epimeric (sulfonyloxymethyl) aziridines as the key step. The overall yield of (*S*)-mexiletine referred to a relatively expensive chiral hydroxymethylaziridine derivative was 60%; whereas that of (*R*)-mexiletine is expected to be lower as it required isolation of the appropriate intermediate from an epimeric mixture. Chirality transfer agents were utilized by few scientists toward the syntheses of mexiletine and their structural analogs. Huang and co-workers [13] reported use of chiral spiroborate ester as chiral catalyst, whereas Ryan and co-workers [1,14] used chiral *tert*-butanesulfinamide as chiral auxiliary.

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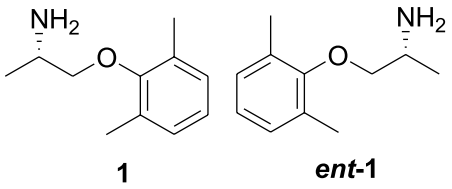


Fig. 1. Enantiomers of mexiletine.

In few synthetic procedures, the two secondary alcohols **2** and ***ent*-2** (Scheme 1) were involved as the immediate precursors of mexiletine enantiomers. In the year 2000, Carocci and co-workers [11b] stereospecifically synthesized these two alcohols from two enantiomeric chiral precursors (*vide supra*). They also reported, for the first time, highly stereoselective conversion of the two secondary alcohols **2** and ***ent*-2** into mexiletines ***ent*-1** (e.e. 96%) and **1** (e.e. 93%), respectively, with inversion of configuration. The overall procedure for this alcohol to amine conversion consisted of two steps, (i) Mitsunobu's Gabriel-type reaction of the alcohol with phthalimide (yield: 68% from alcohol **2**, 84% from alcohol ***ent*-2**) and (ii) hydrazinolysis (yield: 66% for amine ***ent*-1**, 70% for amine **1**). Later on, Sasikumar and co-workers [15a]15a (2009) as well as Sadhukhan and co-workers [15b] (2012) modified slightly the above mentioned two-step procedure to access (*R*)-mexiletine ***ent*-1** from (*S*)-alcohol **2**. They applied hydrolytic kinetic resolution strategy to obtain (*S*)-alcohol **2**. Sasikumar and co-workers [15a] used Jacobsen catalyst, whereas Sadhukhan and co-workers [15b] employed recyclable macrocyclic Co^{III}-salen complex. Both the alcohols, **2** and ***ent*-2**, were also synthesized by Bredikhina and co-workers in 2015 [6]. The key step used by them was the direct resolution of *rac*-3-(2,6-dimethylphenoxy)propane-1,2-diol by entrainment procedure. Recently in 2018, Nagai and co-workers [16] reported enzymatic asymmetric reduction of a suitable ketone to produce alcohols **2** and ***ent*-2**.

The uses of D-mannitol and other sugars in the syntheses of enantiomeric pairs of biologically active compounds are well documented in literature [17]. However, till date, to the best of our knowledge, there is no report of syntheses of both the enantiomers of mexiletine from a carbohydrate molecule. The two enantiomers have not also been synthesized from any common chiral precursor. Since we could recognize latent D-glyceraldehyde carbohydrate symmetry in alcohols **2** and ***ent*-2**, we initiated our project in this direction as part of our continued interest in the chiral pool syntheses of potentially bioactive natural and unnatural molecules using chiron approach [18].

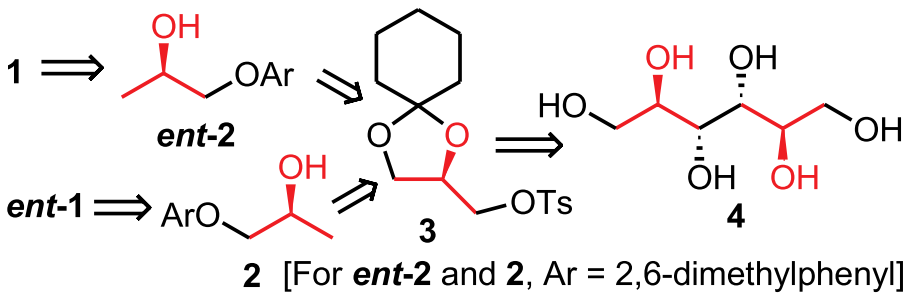
Herein, we wish to report enantiodivergent syntheses of two secondary alcohols **2** and ***ent*-2** (Scheme 1), the evident precursors of mexiletine enantiomers ***ent*-1** and **1**, respectively, from a D-mannitol-derived optically pure known D-glyceraldehyde derivative, the tosylate **3**. The chirality of C-2 stereogenic center of the C_2-symmetric inexpensive chiral pool molecule D-mannitol **4** would be directly and efficiently translated to the chirality of the only stereogenic center of the two enantiomeric target alcohol molecules unaffected. Simple conventional functional group modifications of the two functionally differentiated masked primary hydroxyl groups in **3** were to be carried out without disturbing the chiral center to which they were attached. More obviously we could say that displacement of the two modified primary hydroxyl groups by nucleophilic hydride and 2,6-dimethylphenol in two possible alternative ways would allow us to access both the enantiomeric alcohols in optically pure forms. As optical integrity would be maintained throughout, there would be no ambiguity in the assignment of absolute configurations to the chiral centers of the final products as well as of all the synthetic intermediates.

2. Results and discussion

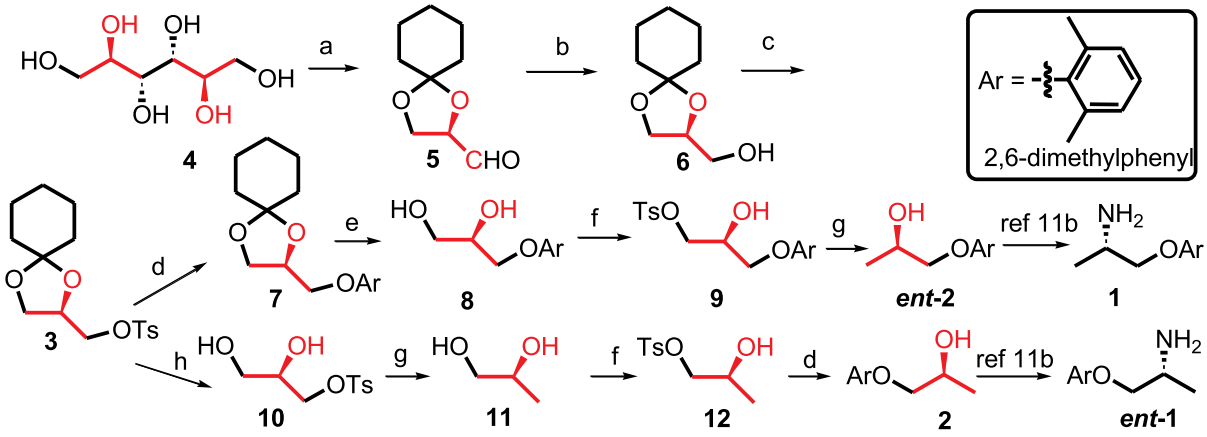
The synthesis was initiated by a reported [19] conversion of D-mannitol **4** into 2,3-di-*O*-cyclohexylidine-(*R*)-(+)-glyceraldehyde **5**, which was then reduced to the corresponding alcohol **6** by following a literature procedure [20] (Scheme 2). Tosylation ($TsCl/Et_3N/DCM$) with slightly modified literature procedure [21] led to the formation of our desired chiral intermediate in almost quantitative yield. Having prepared this chiral template **3**, we paid our attention to its transformation to both the secondary alcohols **2** and ***ent*-2** (see Scheme 2).

To access (*R*)-1-(2,6-dimethylphenoxy)propan-2-ol, ***ent*-2**, the tosyloxy group in the tosylate **3** was substituted by 2,6-dimethylphenol (K_2CO_3/DMF) to obtain the ether **7** in 82% yield. Acid induced deketalization (TFA/H_2O/MeOH) of the compound **7** produced the diol **8** [6] in 80% yield. Deprotection led to regeneration of the primary and the secondary alcoholic OH groups. As per our synthetic plan, the primary hydroxyl group was selectively tosylated ($TsCl/Et_3N$/DCM) to acquire tosylate **9** in moderate yield (70%). It was evident that only a primary tosylate like **9** could lead us unambiguously to our desired secondary alcohol ***ent*-2** *via* substitution of the tosyloxy group by nucleophilic hydride. Treatment of the tosylate **9** with $LiAlH_4$ in THF produced (*R*)-1-(2,6-dimethylphenoxy)propan-2-ol, ***ent*-2**. Specific rotation value (Table 1) as well as ^1H and ^{13}C NMR spectral data [22] of our synthesized molecule were closely comparable to those reported in the literature. As expected its ^{13}C NMR spectrum showed no characteristic peak for the tosyloxy group. Moreover, signal for methylene protons of CH_2OTs group at δ 4.21–4.35 (m) in the spectrum of the tosylate **9** was replaced by a methyl signal at δ 1.27 (d) in ***ent*-2**.

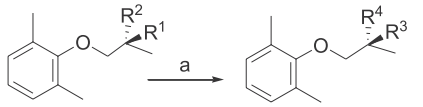
To get the optical antipode of (*R*)-1-(2,6-dimethylphenoxy)propan-2-ol, ***ent*-2** from the same tosylate intermediate **3** without any loss of optical integrity, the tosyloxy group in **3** ought to be substituted by nucleophilic hydride instead of 2,6-dimethylphenol. Toward this end, acid promoted deprotection of the crucial intermediate **3** (*p*-TSA/MeOH) gave the diol **10** [23] in 85% yield. The tosyloxy group was then displaced by nucleophilic hydride ($LiAlH_4$/THF) to get (*S*)-propane-1,2-diol **11** [24]. Selective tosylation ($TsCl/Et_3N$/DCM) of the primary hydroxyl group in **11** generated the primary tosylate **12** [25]. Similar to the compound **9**, here also selective tosylation of the primary hydroxyl group was confirmed *via* its displacement by 2,6-dimethylphenol (K_2CO_3/DMF) leading to formation of our expected (*S*)-1-(2,6-dimethylphenoxy)propan-2-ol, **2**. ^1H and ^{13}C NMR spectral data of our



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (i) cyclohexanone, $HC(OEt)_3$, $BF_3{\cdot}OEt_2$ (cat.), dry DMSO, rt, 12 h, 65%, (ii) $NaIO_4$, $CH_3CN–H_2O$ (3:2), 0 °C- rt, 6 h, 95%; (b) $NaBH_4$, methanol, 0 °C- rt, 3 h, 92%; (c) TsCl, Et_3N, dry DCM, 0 °C- rt, 6 h, 97%; (d) 2,6-dimethylphenol, K_2CO_3 (anhydrous), dry DMF, 60 °C, 12 h, for **3** to **7**: 82%, for **12** to **2**: 72%; (e) 80% TFA-H_2O, methanol, rt, 24 h, 80%; (f) TsCl, Et_3N, dry DCM, 0 °C–5 °C, for **8** to **9**: 2 h, 70%, for **11** to **12**:1 h, 69%.; (g) $LiAlH_4$, dry THF, 0 °C- rt, for **9** to ***ent*-2**: 3 h, 74%, for **10** to **11**: 4 h, 72%; (h) *p*-TSA (cat.), methanol, rt, 24 h, 85%.



2: R^1 = OH, R^2 = H ***ent*-1**: R^3 = H, R^4 = NH_2
***ent*-2**: R^1 = H, R^2 = OH **1**: R^3 = NH_2, R^4 = H

Scheme 3. Reagents and conditions: (a) NaN_3, PPh_3, CCl_4-DMF (1:4), 90 °C, 3 h, 82% for ***ent*-2** to **1**, 79% for **2** to ***ent*-1**.

synthesized molecule showed absence of tosyloxy group and appearance of signals for 2,6-dimethylphenoxy group. Specific rotation value of the molecule synthesized by us in this way was closely comparable to those reported in the literature (Table 1). ^1H and ^{13}C NMR data were also similar [22].

Since, we utilized 'chiron approach' from D-(+)-mannitol to access both the enantiomers **2** and ***ent*-2**, they were enantiomerically pure. It was evident from the almost equal and opposite specific rotation values of these two enantiomers (Table 1), which were synthesized following two different routes from a D-mannitol-derived chiral template **3**. Additionally, CD spectrum of individual enantiomer synthesized by us was acquired with its methanolic solution of concentration 500 μg/mL. The CD curve (Fig. 2a) of the (*S*)-isomer **2** displayed negative Cotton effect whereas that of the (*R*)-isomer ***ent*-2** showed positive Cotton effect (in the wavelength region of 234.5 nm–229 nm). The spectra of the enantiomers exhibited exact mirror image relationship further corroborating their enantiopurity. As expected, their NMR spectra were identical [22].

Now, these two secondary alcohols **2** and ***ent*-2** had already been transformed into mexiletines, ***ent*-1** and **1**, respectively (*vide supra*). Hence, we have achieved for the first time an enantiodivergent formal synthesis of mexiletine enantiomers from a D-(+)-mannitol-derived scaffold.

In the year 2000, Vidya Sagar Reddy and co-workers [26], reported a convenient and efficient one-pot transformation of primary and secondary alcohols to the corresponding amines using sodium azide and triphenylphosphine (two equivalents) in CCl_4-DMF (1:4) solvent (at 90 °C). Their work encouraged us to apply their methodology on our synthesized alcohols **2** and ***ent*-2** so as to access mexiletines in only one step instead of two steps as stated in the literature (*vide supra*). To our utmost satisfaction, our synthesized (*R*)-(+)- and (*S*)-(−)-1-(2,6-dimethylphenoxy)propan-2-ol, i.e. ***ent*-2** and **2** smoothly produced (*S*)-(+)-mexiletine **1** (82% yield) and (*R*)-(−)-mexiletine ***ent*-1** (79% yield), respectively in only one step. The overall yields for the reported two-step procedures were 59% [11b] for (*S*)-mexiletine and 45% [11b], 68% [15b], 71% [15a] for (*R*)-mexiletine. We performed the reactions under the same conditions as reported by Vidya Sagar Reddy and co-workers. However, both our reactions took only 3 h to complete, whereas, as per the literature, primary alcohols require 4 h–6 h and secondary alcohols require 8 h–10 h. To the best of our knowledge, this is the first time when any single step conversion of alcohols to mexiletines has been achieved. HRMS and NMR spectral data of the two pure amines supported this transformation. For instance, upfield shifts of the methine proton (from δ 4.22–4.23 to δ 3.34 for amine **1**, from δ 4.22 to δ 3.37 for amine ***ent*-1**) and methine carbon (from δ 67.1 to δ 47.3 for amine **1**, from δ 67.3 to δ 47.3 for amine ***ent*-1**) were observed as predicted because of replacement of the OH group attached to the methine carbon by a NH_2 group. Both the ^1H and ^{13}C NMR spectra are almost identical and they are closely similar to those reported in the literature [22].

Specific rotation values of the two amines (Table 1) synthesized by us were found to be almost equal; however their signs of rotation were opposite. This demonstrated enantiomeric relationships between them. These values were also very closely similar to the corresponding specific rotation values reported in the literature (Table 1). This is suggestive of inversion of configuration with almost similar type of high stereoselectivity at the stereogenic center as in the two-step transformation by Carocci and co-workers. Here again, CD spectra of our synthesized enantiomeric amines were recorded with their methanolic solutions of same concentration as for the precursor alcohols (500 μg/mL). Similar to the (*S*)-alcohol **2**, the CD curve (Fig. 2b) of the (*S*)-isomer **1** displayed negative Cotton effect; whereas that of the (*R*)-isomer ***ent*-1** exhibited

Table 1
Comparison of specific rotation data of alcohols and mexiletines.

Research work	(*R*)-Mexiletine	(*S*)-Mexiletine	(*R*)-Alcohol	(*S*)-Alcohol
Our work	$[\alpha]_D^{25}$ − 2.86 (*c* 4.61, $CHCl_3$)	$[\alpha]_D^{25}$ +2.64 (*c* 4.82, $CHCl_3$)	$[\alpha]_D^{25}$ +1.21 (*c* 4.8, $CHCl_3$)	$[\alpha]_D^{25}$ − 1.06 (*c* 5.02, $CHCl_3$)
Sasikumar et al. [15a]	$[\alpha]_D^{25}$ − 2.4 (*c* 5, $CHCl_3$)			$[\alpha]_D^{25}$ − 1.3 (*c* 5, $CHCl_3$)
Carocci et al. [11b]	$[\alpha]_D^{20}$ − 2.7 (*c* 4.7, $CHCl_3$)	$[\alpha]_D^{20}$ +2.5 (*c* 4.9, $CHCl_3$)	$[\alpha]_D^{20}$ +0.9 (*c* 5.5, $CHCl_3$)	$[\alpha]_D^{20}$ − 1.1 (*c* 5, $CHCl_3$)

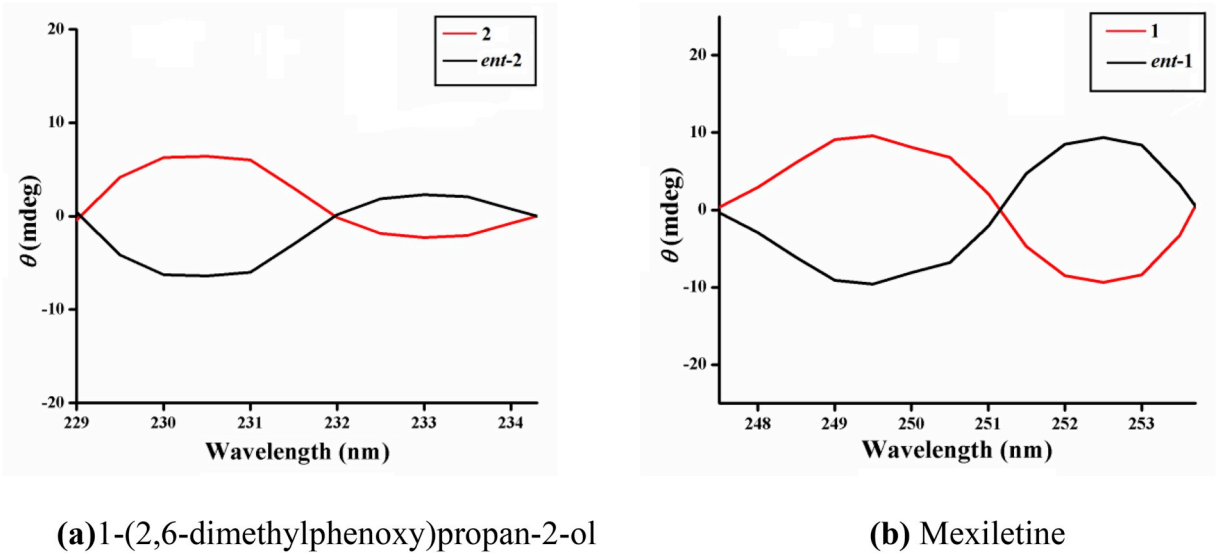


Fig. 2. CD spectra of synthesized molecules **2**, ***ent*-2**, **1** and ***ent*-1**.

positive Cotton effect as in the case of (*R*)-alcohol ***ent*-2** (but in the wavelength region of 253.5 nm–247.5 nm). The CD spectra of the amines **1** and ***ent*-1**, synthesized by us, showed exact mirror image relationship affirming again their enantiomeric relationship.

Our route which started from very inexpensive D-mannitol did give (*S*)- and (*R*)-mexiletine in 15% and 13% overall yields, respectively. However, (*S*)- and (*R*)-mexiletine were obtained in 28% and 24% overall yields, respectively, relative to the known D-mannitol-derived advanced precursor **3** from which two routes toward enantiomeric target molecules were diverted. The overall yields of the reported synthetic procedures, which involved chiral enantiopure molecules as the source of chirality, have already been mentioned (*vide supra*). However, those processes never involved any carbohydrate molecule as chiral source. Even none of those synthetic pathways did produce both the enantiomeric amines from the same chiral molecule.

3. Conclusions

In conclusion, chiron approach has been utilized for the syntheses of both the enantiomers of 1-(2,6-dimethylphenoxy)propan-2-ol separately in optically pure forms from an advanced optically pure precursor **3** having one stereogenic center. The common intermediate was synthesized from D-mannitol in four steps with an overall yield of 55%. The two routes towards two enantiomeric alcohols from the intermediate **3** were different; each consisted of four more steps. Reactions used were conventional and simple. All of them were moderate to high yielding. Starting from this D-mannitol scaffold, the overall yields for (*R*)- and (*S*)-alcohol were 34% and 30%, respectively. Chirality of D-mannitol was efficiently translated to the chirality of the product molecules, leading to unequivocal assignment of their absolute configurations. To the best of our knowledge, ours is the first synthesis of 1-(2,6-dimethylphenoxy)propan-2-ol enantiomers, which are the immediate precursor of mexiletines, from a carbohydrate molecule. Apart from that, first time a one-step protocol was applied successfully on the 1-(2,6-dimethylphenoxy)propan-2-ols for their efficient conversions to the corresponding amine drugs. All the literature procedures available till date regarding this transformation involved two-step protocols. Moreover, synthesis of both the enantiomers of 1-(2,6-dimethylphenoxy)propan-2-ol and subsequently mexiletine enantiomers from 2,3-di-*O*-cyclohexylidine-(*R*)-(+)-glyceraldehyde **5**, which was conveniently derived from D-mannitol **4** in two steps, is significant as the corresponding enantiomer (*S*)-(−)-glyceraldehyde is not readily available.

Additionally, the methodology is flexible. Preparation of several mexiletine analogs, for evaluation of potential biological activities, appears feasible by using various differently substituted phenols as nucleophiles. Even nucleophilic hydride may be replaced by a nucleophilic alkyl group to access various analogs differing in alkyl chain lengths. The extension of the routes reported here to the preparation of above mentioned analogs will be pursued in our laboratory.

4. Experimental

4.1. General considerations

^{1}H NMR spectra were recorded in a Bruker 500/300 (500/300 MHz respectively) spectrometer. Chemical shifts were expressed in parts per million (ppm, δ) with chloroform as an internal standard. The coupling constants are expressed in Hz. Signal description: s = singlet, d = doublet, m = multiplet, dd = doublet of doublet, br s = broad singlet. Proton decoupled ^{13}C NMR spectra were recorded in a Bruker 500/300 (125/75 MHz respectively). Chemical shifts were expressed in parts per million (ppm, δ) and were referred to chloroform as an internal standard. High-resolution mass spectra (HRMS) were recorded on a TOF spectrometer using electrospray (ESI) method. Optical rotations were measured with an ANTON PAR digital polarimeter. Circular dichroism of the enantiomers has been carried out in JASCO J815 spectropolarimeter affixed to a thermal programmer model PFD 425 L/15. Routine monitoring of reactions was carried out using TLC plates Merck Silica Gel 60 and visualization with iodine and vanillin in ethanol as development reagent. All the solvents were purified and dried by standard procedure prior to use. Column chromatographic purification of compounds was done with silica gel 60–120. All of the moisture sensitive reactions were performed using thoroughly washed, oven dried glassware and under argon gas atmosphere.

4.1.1. (R)-1,4-dioxaspiro[4.5]decan-2-ylmethyl 4-methylbenzenesulfonate (3)

To a magnetically stirred ice-cold solution of alcohol **6** (5.0 g, 29.03 mmol) in dry dichoromethane (100 mL) was added triethylamine (8.07 mL, 58.10 mmol). After 15 min of stirring, tosyl chloride (8.3 g, 43.58 mmol) was added to it. The reaction mixture was stirred vigorously at room temperature for 6 h, till the disappearance of starting material (checked by performing TLC). The reaction was quenched with water and extracted with dichoromethane (3 × 15 mL). The combined organic layer was washed with water, brine and dried over anhydrous

sodium sulfate. The solvent was removed under reduced pressure followed by purification procedure by column chromatography (silica gel, ethyl acetate-hexane 1:9) to produce tosylate **3** [21] as a colourless viscous liquid (9.2 g, 97%): R_f = 0.62 (1:9 EtOAc – hexane); $[\alpha]_D^{25}$ − 1.56 (*c* 1.10, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 1420.3, 1172.2, 1102.4; δ_H see **Supplementary Data 1**; δ_C see **Supplementary Data 1**; HRMS (ESI) calcd. for $C_{16}H_{22}O_5SNa$ $[M+Na]^+$, 349.1086; found, 349.1089.

4.1.2. (S)-2-((2,6-dimethylphenoxy)methyl)-1,4-dioxaspiro[4.5]decane (7)

To a stirred solution of 2,6-dimethylphenol (3.4 g, 27.6 mmol) in dry DMF (50 mL) anhydrous K_2CO_3 (3.8 g, 27.6 mmol) was added. After continuous stirring for 1 h tosyl compound **3** (6.0 g, 18.38 mmol) was added to it. The reaction mixture was warmed at 60 °C and stirred for 12 h. After completion of reaction it was quenched with water (30 mL). It was extracted with diethyl ether (3 × 30 mL). The combined organic phase was washed with 2(N) NaOH (2 × 10 mL) to remove excess phenol. It was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified by column chromatography (silica gel, ethyl acetate-hexane 3:17) to obtain the desired product **7** as a viscous liquid (4.2 g, 82%): R_f = 0.56 (1:9 EtOAc – hexane); $[\alpha]_D^{25}$ +1.90 (*c* 0.42, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 1476.2, 1104.5; δ_H ($CDCl_3$, 300 MHz) 1.42 (2H, br s, CH_2), 1.60 (4H, s, CH_2), 1.64 (4H, br s, CH_2), 2.29 (6H, s, CH_3), 3.78–3.84 (2H, m, OCH_2), 3.97 (1H, dd, *J* 8.1, 6.2 Hz, OCH_2), 4.19 (1H, dd, *J* 8.0, 6.7 Hz, OCH_2), 4.47–4.51 (1H, m, OCH), 6.92–7.01 (3H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 16.2 (2 × CH_3), 23.9 (CH_2), 24.0 (CH_2), 25.2 (CH_2), 34.9 (CH_2), 36.5 (CH_2), 66.4 (OCH_2), 72.8 (OCH_2), 74.2 (OCH), 110.1 (C), 124.0 (CH), 128.9 (2 × CH), 130.8 (2 × C) 155.1 (C); HRMS (ESI) calcd. for $C_{17}H_{24}O_3Na$ $[M+Na]^+$, 299.1623; found, 299.1634.

4.1.3. (R)-3-(2,6-dimethylphenoxy)propane-1,2-diol (8)

To a magnetically stirred solution of compound **7** (3.0 g, 10.85 mmol) in methanol (50 mL) catalytic amount (10 drops) of 80% trifluoro acetic acid-water was added. After stirring at room temperature for 24 h, the reaction mixture was quenched with two sodium beads. It was filtered and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane 3:2) to acquire the target molecule **8** [6] as a colourless viscous liquid (1.7 g, 80%): R_f = 0.38 (3:7 EtOAc – hexane); $[\alpha]_D^{25}$ +10.23 (*c* 0.86, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3250.5, 1474.5, 1114.1; δ_H see **Supplementary Data 1**; δ_C see **Supplementary Data 1**; HRMS (ESI) calcd. for $C_{11}H_{16}O_3Na$ $[M+Na]^+$, 219.0997; found, 219.0988.

4.1.4. (S)-3-(2,6-dimethylphenoxy)-2-hydroxypropyl 4-methylbenzenesulfonate (9)

To a magnetically stirred ice-cold solution of the diol **8** (0.8 g, 4.08 mmol) in dry dichloromethane (40 mL) were added triethylamine (0.68 mL, 4.9 mmol) and tosyl chloride (0.78 g, 4.08 mmol) portion wise. Stirring was continued at 0 °C–5 °C for about 2 h till the reaction did not proceed further (checked by performing TLC). Then the reaction mixture was extracted with dichloromethane (3 × 10 mL) and washed with brine followed by drying over anhydrous sodium sulfate. It was then concentrated under reduced pressure and purified by column chromatography (silica gel, ethyl acetate-hexane 1:1) to acquire the desired viscous liquid **9** (1.0 g, 70%): R_f = 0.43 (1:4 EtOAc – hexane); $[\alpha]_D^{25}$ +5.00 (*c* 0.24, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3230.1, 1401.9, 1179.1, 1104.4; δ_H ($CDCl_3$, 300 MHz) 2.13 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.46 (3H, s, CH_3), 2.64 (1H, br s, OH), 3.85 (2H, dd, *J* 16.5, 4.6 Hz, OCH_2), 4.21–4.35 (3H, m, OCH, OCH_2), 6.93–7.01 (3H, m, ArH), 7.31–7.38 (2H, m, ArH), 7.72–7.84 (2H, m, ArH); δ_C ($CDCl_3$, 75 MHz) 16.0 (CH_3), 16.2 (CH_3), 21.7 (CH_3), 67.0 (OCH_2), 68.8 (OCH_2), 70.2 (OCH), 124.5 (CH), 128.0 (2 × CH), 129.0 (2 × CH), 129.9 (2 × CH), 130.6 (2 × C), 132.6 (C), 145.2 (C), 154.4 (C); HRMS (ESI) calcd. for $C_{18}H_{22}O_5SNa$ $[M+Na]^+$, 373.1086; found, 373.1083.

4.1.5. (R)-1-(2,6-dimethylphenoxy)propan-2-ol (ent-2)

To a cooled suspension of lithium aluminium hydride (0.27 g, 7.15 mmol) in dry THF (15 mL) at 0 °C was added dry THF (20 mL) solution of tosyl compound **9** (1.0 g, 2.85 mmol) dropwise. The resulting reaction mixture was then allowed to attain room temperature and stirred for 3 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride at 0 °C and the resulting mixture was filtered and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography (silica gel, ethyl acetate-hexane 2:3) to get ***ent*-2** as a viscous liquid (0.38 g, 74%): R_f = 0.54 (1:4 EtOAc – hexane); $[\alpha]_D^{25}$ +1.21 (*c* 4.8, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3213.2, 1476.5, 1206.8; δ_H see Supplementary Data 1: Table 1; δ_C see Supplementary Data 1: Table 2; HRMS (ESI) calcd. for $C_{11}H_{16}O_2Na$ $[M+Na]^+$, 203.1048; found, 203.1053.

4.1.6. (S)-1-(2,6-dimethylphenoxy)propan-2-amine (1)

Alcohol ***ent*-2** (0.11 g, 0.61 mmol), sodium azide (0.05 g, 0.77 mmol) and triphenylphosphine (0.32 g, 1.22 mmol) in CCl_4-DMF (1:4, 10 mL) were warmed at 90 °C with vigorous stirring. After 3 h when the reaction was completed (checked by TLC) it was brought to room temperature. Finally it was quenched with water (4 mL) and stirred for 30 min. It was then diluted with ether (30 mL) and washed rapidly with water again. The ether fraction was cooled to 0 °C and triturated by glass rod to crystallize out triphenylphosphine oxide. The ether layer was filtered off and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane 9:11) to obtain amine **1** as a viscous liquid (0.09 g, 82%): R_f = 0.52 (1:4 EtOAc – hexane); $[\alpha]_D^{25}$ +2.64 (*c* 4.82, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3120.1, 2981.9, 1587.4, 1476.5, 1206.8; δ_H see Supplementary Data 1: Table 3; δ_C see Supplementary Data 1: Table 4; HRMS (ESI) calcd. for $C_{11}H_{17}NONa$ $[M+Na]^+$, 202.1208; found, 202.1205.

4.1.7. (R)-2,3-dihydroxypropyl 4-methylbenzenesulfonate (10)

To a magnetically stirred solution of the tosyl compound **3** (3.5 g, 10.72 mmol) in methanol (50 mL) was added *p*-toluenesulfonic acid (0.41 g, 2.38 mmol) at once. After stirring the reaction mixture for 24 h at room temperature it was quenched with solid K_2CO_3. It was filtered and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane 4:1) to secure the desired compound **10** [23] as a colourless viscous liquid (2.24 g, 85%): R_f = 0.45 (3:2 EtOAc – hexane); $[\alpha]_D^{25}$ +1.92 (*c* 1.47, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3248.3, 1355.0, 1114.1; δ_H see **Supplementary Data 1**; δ_C see **Supplementary Data 1**; HRMS (ESI) calcd. for $C_{10}H_{14}O_5SNa$ $[M+Na]^+$, 269.0460; found, 269.0460.

4.1.8. (S)-propane-1,2-diol (11)

To an ice cold suspension of lithium aluminium hydride (0.62 g, 16.33 mmol) in dry THF (50 mL) was added dry THF (70 mL) solution of tosyl compound **10** (1.62 g, 6.58 mmol) dropwise at 0 °C. The resulting reaction mixture was then allowed to attain room temperature and stirred for 4 h. After completion of the reaction (checked by TLC) it was quenched with saturated aqueous solution of ammonium chloride at 0 °C and the resulting mixture was filtered off and extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed simultaneously with water, brine and dried over anhydrous sodium sulfate. After evaporating the solvent under reduced pressure the obtained crude product was purified by column chromatography (silica

gel, ethyl acetate-hexane 9:1) to get the product **11** [24] as a viscous liquid (0.36 g, 72%): R_f = 0.31 (3:2 EtOAc – hexane); $[\alpha]_D^{25}$ +4.25 (*c* 0.40, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3408.3, 1114.1; δ_H see **Supplementary Data 1**; δ_C see **Supplementary Data 1**; HRMS (ESI) calcd. for $C_3H_8O_2Na$ $[M+Na]^+$, 99.0422; found, 99.0424.

4.1.9. (S)-2-hydroxypropyl 4-methylbenzenesulfonate (12)

To a magnetically stirred ice-cold solution of the diol **11** (0.11 g, 1.45 mmol) in dry dichloromethane (20 mL) were added triethylamine (0.20 mL, 1.43 mmol) and tosyl chloride (0.28 g, 1.45 mmol) portion wise. Stirring was continued at 0 °C–5 °C for about 1 h till the reaction did not proceed further (checked by performing TLC). Then the reaction mixture was extracted with dichloromethane (3 × 10 mL) and washed with brine followed by drying over anhydrous sodium sulfate. It was then concentrated under reduced pressure and purified by column chromatography (silica gel, ethyl acetate-hexane 11:9) to acquire the desired product **12** [25] as a viscous liquid (0.23 g, 69%): R_f = 0.42 (2:3 EtOAc – hexane); $[\alpha]_D^{25}$ +12.57 (*c* 0.42, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3176.9, 1401.9, 1104.5, 611.9; δ_H see **Supplementary Data 1**; δ_C see **Supplementary Data 1**; HRMS (ESI) calcd. for $C_{10}H_{14}O_4SNa$ $[M+Na]^+$ 253.0510; found, 253.0516.

4.1.10. (S)-1-(2,6-dimethylphenoxy)propan-2-ol (2)

To a stirred solution of 2,6-dimethyl phenol (0.08 g, 0.65 mmol) in dry DMF (10 mL), anhydrous K_2CO_3 (0.09 g, 0.65 mmol) was added. After continuous stirring for 1 h tosyl compound **12** (0.1 g, 0.44 mmol) was added to it. The reaction mixture was warmed at 60 °C and stirred for 12 h. After completion of reaction the solvent was evaporated under reduced pressure. It was extracted with diethyl ether (3 × 10 mL). The combined organic phase was washed with 2(N) NaOH (2 × 5 mL) to remove excess phenol. It was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified by column chromatography (silica gel, ethyl acetate-hexane 2:3) to obtain the desired alcohol **2** as a viscous liquid (0.056 g, 72%): R_f = 0.54 (1:4 EtOAc – hexane); $[\alpha]_D^{25}$ − 1.06 (*c* 5.02, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3219.2, 1480.8, 1208.3; δ_H see **Supplementary Data 1**: Table 1; δ_C see Supplementary Data 1: Table 2; HRMS (ESI) calcd. for $C_{11}H_{16}O_2Na$ $[M+Na]^+$, 203.1048; found, 203.1053.

4.1.11. (R)-1-(2,6-dimethylphenoxy)propan-2-amine (ent-1)

Alcohol **2** (0.05 g, 0.28 mmol), sodium azide (0.02 g, 0.31 mmol) and triphenylphosphine (0.16 g, 0.61 mmol) in CCl_4-DMF (1:4, 8 mL) was warmed at 90 °C with vigorous stirring. After 3 h when the reaction was completed (checked by TLC) it was brought to room temperature. Finally it was quenched with water (4 mL) and stirred for 30 min. It was then diluted with ether (20 mL) and washed rapidly with water again. The ether fraction was cooled to 0 °C and triturated by glass rod to crystallize out triphenylphosphine oxide. The ether layer was filtered off and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, ethyl acetate-hexane 9:11) to obtain amine ***ent*-1** as a viscous liquid (0.039g, 79%): R_f = 0.52 (1:4 EtOAc – hexane); $[\alpha]_D^{25}$ − 2.86 (*c* 4.61, $CHCl_3$); υ_{max}/cm^{-1} (KBr) 3112.8, 2989.4, 1580.5, 1465.7, 1217.2; δ_H see Supplementary Data 1: Table 3; δ_C see Supplementary Data 1: Table 4; HRMS (ESI) calcd. for $C_{11}H_{17}NONa$ $[M+Na]^+$, 202.1208; found, 202.1205.

4.1.12. CD spectroscopy of alcohols 2 and ent-2 (Fig. 2a)

CD spectrum of methanolic solution (500 μg/mL) of individual enantiomer was recorded. The CD curve of the (*S*)-isomer **2** displayed negative Cotton effect whereas that of the (*R*)-isomer ***ent*-2** showed positive Cotton effect in the wavelength region of 234.5 nm–229 nm. The spectra of the enantiomers exhibited exact mirror image relationship.

4.1.13. CD spectroscopy of mexiletines 1 and ent-1 (Fig. 2b)

CD spectrum of methanolic solution (500 μg/mL) of individual enantiomer was recorded. In the wavelength region of 253.5 nm–247.5 nm, the CD curve of the (*S*)-isomer **1** displayed negative Cotton effect, whereas that of the (*R*)-isomer ***ent*-1** exhibited positive Cotton effect. The CD spectra of the enantiomeric amines **1** and ***ent*-1**, synthesized by us, showed exact mirror image relationship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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