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Nucleophilic substitution of (sulfonyloxymethyl)aziridines: an asymmetric synthesis of both isomers of mexiletine

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ABSTRACT

The nucleophilic substitution reactions of 1-[1′(*R*)-α-methylbenzyl]-(2*R*)- and (2*S*)-(sulfonyloxymethyl)aziridines were carried out with various nucleophiles including N_3^-, MeO^-, CN^-, SCN^-, and diarylcuprates. The reaction pathway is influenced by the stereochemistry of the substrates, nucleophiles, and also the structure of the leaving groups. When the reaction site is less sterically hindered for the reactive nucleophiles to approach to the substrate 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(*p*-toluenesulfonyloxymethyl)aziridines, product is obtained as a single isomer while all the other starting materials afford a mixture of two isomers from two different reaction pathways. Application of this method enabled us to prepare both isomers of orally effective antiarrhythmic agent mexiletine.

1. Introduction

A nitrogen containing three-membered ring compound aziridine can act as a molecular building block to provide various cyclic and heterocyclic compounds including synthetically and biologically important molecules.[1] Their representative synthetic manipulations include the modification of the side chain attached to the aziridine and regioselective ring openings.[1] Since we successfully prepared both enantiomers of aziridine-2-carboxylates, many nitrogen containing molecules were elaborated in optically pure forms using regio- and stereoselective side-chain modifications and ring openings.[2] One of the most efficient side-chain modification methods is the substitution reactions of 2-(sulfonyloxymethyl) aziridines with various nucleophiles to introduce diverse functional groups to the aziridine side chain.[3] However, the possible chemical pathway can be complicated by the electron rich ring nitrogen of the aziridine, which also has good nucleophilicity.[4] Therefore, competition would be expected between an external nucleophile and the ring nitrogen under the reaction condition. Herein we would like to describe the characteristics of nucleophilic substitution of 1-[1′(*R*)-α-methylbenzyl]-(2*R*)- and (2*S*)-(sulfonyloxymethyl)aziridines with various nucleophiles including N_3^-, MeO^-, CN^-, SCN^-, and diarylcuprates and also the application of the methodology to the efficient syntheses of both isomers of mexiletine.

2. Results and discussion

The possible competition between an external nucleophile and the aziridine ring nitrogen during the substitution reaction of 2-(sulfonyloxymethyl)aziridines provides two different pathways, i and ii, shown in Scheme 1. The pathway i is the direct displacement of the leaving group by the nucleophile and the pathway ii involves regioselective nucleophilic ring opening of the aziridine ring followed by the ring closure by the nitrogen resulting in configurational inversion at C2 of the aziridine. The results of substitution reactions would be influenced by several factors including characteristics of nucleophiles and the configuration at C-2 of the substrate aziridines (Table 1).

We carried out the substitution reaction of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-toluenesulfonyloxymethylaziridine (2*S*)-**1** with sodium azide to afford 2-azidomethylaziridne (2*S*)-**4a** in 72% yield whose stereochemistry was identified by its derivatization of the known compound (2*S*)-aminomethylaziridine[5] with retention of the configuration at C-2 of the aziridine (entry 1). This tells us that the reaction gives the direct substitution product without ring opening reaction. The same result was reported with NaOMe in

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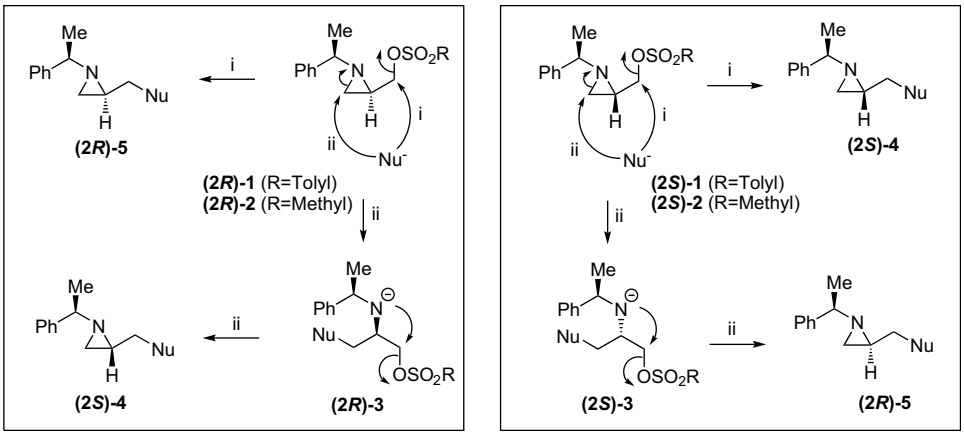


Scheme 1.

Table 1
The schematized results for the substitution reactions of the substrate (2*S*)-**1**, (2*R*)-**1**, (2*S*)-**2** and (2*R*)-**2** with various nucleophiles including N_3^-, OMe^-, CN^-, SCN^- and diphenylcuprate

Entry	Substrate	Nucleophile (reagents)[a]	Medium	Time (h)	Yield[b]	Products[c]
1	(2*S*)-**1**	N_3^- (NaN_3)	DMF	6	72	(2*S*)-**4a**
2	(2*S*)-**1**	MeO^- (NaOMe)	MeOH	4	89	(2*S*)-**4b**
3	(2*S*)-**1**	Ph^- ($LiCuPh_2$)	Et_2O	2	62	(2*S*)-**4c**
4	(2*S*)-**1**	2,6-Me_2PhO^- (2,6-Me_2PhO^-)	Acetone/DMF (1:1)	4	74	(2*S*)-**4d**
5	(2*R*)-**1**	N_3^- (NaN3)	DMF	1	71	(2*R*)-**5a**, (2*S*)-**4a**, (46:54)
6	(2*R*)-**1**	MeO^- (NaOMe)	MeOH	4	93	(2*R*)-**5b**, (2*S*)-**4b** (52:48)
7	(2*R*)-**1**	Ph^- ($LiCuPh_2$)	Et_2O	2	90	(2*R*)-**5c**, (2*S*)-**4c** (45:55)
8	(2*R*)-**1**	2,6-Me_2PhO^- (2,6-Me_2PhO^-)	Acetone/DMF (1:1)	6	76	(2*R*)-**5d**, (2*S*)-**4d**(84:16)
9	(2*S*)-**2**	N_3^- (NaN_3)	DMF	6	88	(2*R*)-**5a**, (2*S*)-**4a**, **6** (8:46:46)
10	(2*S*)-**2**	MeO^- (NaOMe)	MeOH		No rxn	
11	(2*S*)-**2**	CN^-(NaCN)	CH_3CN	6	83	(2*R*)-**5e**, (2*S*)-**4e** (50:50)
12	(2*S*)-**2**	SCN	CH_3CN	6	91	(2*R*)-**5f**, (2*S*)-**4f** (46:54)
13	(2*R*)-**2**	N_3^- (NaN_3)	DMF		No rxn	
14	(2*R*)-**2**	CN^- (NaCN)	CH_3CN		No rxn	

[a] Mole amount was used for the reactions.
[b] Those were isolated yields and not to be optimized.
[c] The ratios were determined by ^1H NMR.

MeOH by De Kimpe and D'hooghe[6] to obtain methoxymethylaziridine (2*S*)-**4b** with retention of configuration at C-2 of the aziridine[7] (entry 2). Reaction with Ph_2CuLi yielded the expected product (2*S*)-**4c** in 62% yield with retention of configuration (entry 3). However, the same reaction of 1-[1′(*R*)-α-methylbenzyl]-(2*R*)-(*p*-toluenesulfonyloxymethyl)aziridine (2*R*)-**1** with sodium azide yielded two different isomers 1-[1′(*R*)-α-methylbenzyl]-(2*R*)- and (2*S*)-azidomethylaziridine (2*R*)-**5a** and (2*S*)-**4a** with the ratio of 46:54 in 71% yield in 1 h in DMF (entry 5). The same reaction with NaOMe in MeOH also yielded (2*R*)- and (2*S*)-methoxymethylaziridine (2*R*)-**5b** and (2*S*)-**4b** with the ratio of 52:48 in 93% yield (entry 6). Reaction with Ph_2CuLi yielded both isomers of (2*R*)- and (2*S*)-benzylaziridine (2*R*)-**5c** and (2*S*)-**4c** with the ratio of 45:55 in 90% yield (entry 7). Therefore, the nucleophilic substitution reactions of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(*p*-toluenesulfonyloxymethyl)aziridine (2*S*)-**1** proceeds by pathway i while 1-[1′(*R*)-α-methylbenzyl]-(2*R*)-(*p*-toluenesulfonyloxymethyl)aziridine (2*R*)-**1** yields two products coming from both pathways i and ii as in Scheme 1. Formation of two products indicates that both electrophilic positions of the substrate 1-[1′(*R*)-α-methylbenzyl]-(2*R*)-(sulfonyloxymethyl)aziridines are almost equally reactive toward the external nucleophile while the electrophilic center in the side chain of the isomer 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(sulfonyloxymethyl)aziridines is much more reactive. We performed minimum energy calculations of both substrates (2*S*)-**1** and (2*R*)-**1** to figure out the configurational difference between two stereoisomers by the density functional model shown in Figures 1 and 2.[8]

The minimum energy conformation of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(sulfonyloxymethyl)aziridines is quite different from that of 1-[1′(*R*)-α-methylbenzyl]-(2*R*)-(sulfonyloxymethyl)aziridines. Especially the reaction site bearing toluenesulfonyloxy leaving group in the isomer 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(sulfonyloxymethyl)aziridines is relatively less hindered while that of the other isomer is more sterically hindered and blocks the reaction site shown in Figure 2. This indicates that two different reaction pathways (i and ii) are available and the direct displacement reaction (i) would be dominant only if the substrate is quite active

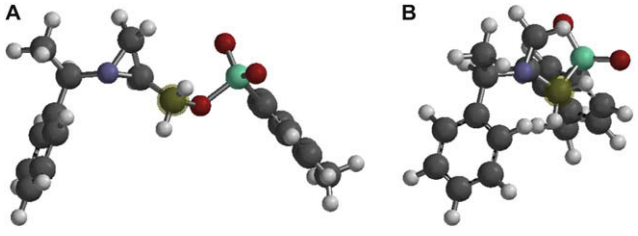


Figure 1. The minimum energy conformer of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-*p*-toluenesulfonyloxymethylaziridine (2*S*)-**1** as its side view (A) and the view (B) in front of the carbon bearing toluenesulfonyloxy group with yellowish circle.

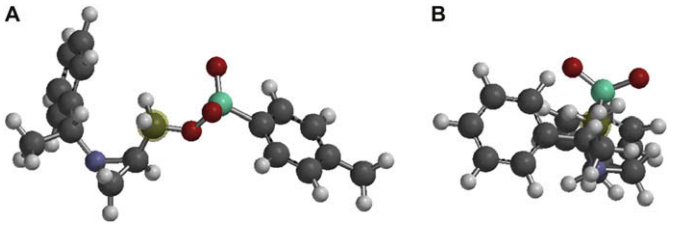
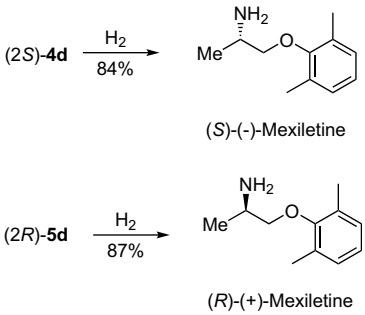


Figure 2. The minimum energy conformer of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-*p*-toluenesulfonyloxymethylaziridine (2*R*)-**1** as its side view (A) and the view (B) in front of the carbon bearing toluenesulfonyloxy group with yellowish circle.

with a good leaving group and also its conformation provides less hindered electrophilic center for the coming nucleophile. Otherwise, ring opening reaction followed by the concomitant ring closure with the displacement of the leaving group by the ring nitrogen as an internal nucleophile can compete with direct displacement to give two reaction products. Examples were documented regarding the aziridine ring opening reaction followed by ring closure with organocupper[9] and alkyllithium[10] reagents. If the substrate has less reactive leaving group, the product by pathway ii would be obtained even if the substrate has less hindered conformation. When we carried out the substitution reaction of (2*S*)-**2** with sodium azide three products were obtained including (2*S*)-azidomethylaziridine (2*S*)-**4a**, (2*R*)-azidomethylaziridine (2*S*)-**4b**, and 2-amino-1,3-diazidopropane (**6**) with the ratio of 8:46:46 in 88% yield (entry 9). Two isomers of aziridine were originated from the reaction pathways i and ii shown in Scheme 1 while the diazido compound (**6**) came from further azide ring opening reaction[11] of the azidomethylaziridine. The reaction of (2*S*)-**2** with a cyanide nucleophile in DMF yielded two isomeric 2-cyanomethylaziridines (2*R*)-**5e** and (2*S*)-**4e** in 83% yield with the same ratio after 6 h of reaction time while no change was observed with sodium methoxide in MeOH (entries 10 and 11). The similar reaction of (2*S*)-**2** with SCN^- proceeded to afford two isomeric 2-thiocyanomethylaziridines (2*R*)-**5f** and (2*S*)-**4f** in 91% yield (entry 12). However, the other isomer 1-[1′(*R*)-α-methylbenzyl]-(2*R*)-(methylsulfonyloxymethyl)aziridine (2*R*)-**2** was inert with all tested nucleophiles including N_3^-, MeO^-, and CN^- (entry 13 and 14). The conformation of the reaction site of this substrate is sterically hindered as observed in (2*R*)-**1** and also methanesulfonate is less active toward nucleophiles compared with toluenesulfonate group.

This substitution reaction is valuable for introducing a new group into the side chain of an aziridine and this method was applied for the preparation of both isomers of mexiletin (Scheme 2). Mexiletine is an orally effective antiarrhythmic,[12] antimyotonic,[13] and analgesic[14] agent in its racemic form and is available for clinical use as the racemate. Mexiletine undergoes stereoselective disposition in human associated with the selective binding of the (*R*)-(−)-mexiletine to a cardiac sodium channel and the higher antiarrhythmic activity of this enantiomer.[15] This isomer was prepared from (2*R*)-1-[1′(*R*)-α-methylbenzyl]-(*p*-toluenesulfonyloxymethyl)aziridine (2*R*)-**1**, which was transformed into 2-(2,6-dimethyphenoxy)methylaziridine upon treatment with 2 equiv of 2,6-dimethylphenol in DMF/acetone (1:1) in the presence of K_2CO_3 under reflux for 4 h. Two diastereomers 2*R*- and 2*S*-(2,6-dimethyphenoxy)methylaziridines (2*R*)-**5f** and (2*S*)-**4f** were obtained with the ratio of 84:16 in 76% yield (entry 8). The major isomer was isolated and converted into (*R*)-(−)-mexiletine upon treatment with H_2 in MeOH in the presence of $Pd(OH)_2$ in 87% yield.[16] The other isomer (*S*)-(−)-mexiletine was also obtained from the direct substitution pathway of 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(*p*-toluenesulfonyloxymethyl)aziridine (2*S*)-**1** by 2,6-dimethylphenol to yield (2*S*)-(2,6-dimethyphenoxy)methylaziridine (2*S*)-**4d** as a single isomer and followed by hydrogenolysis in 63% overall yield.



Scheme 2.

In conclusion, the nucleophilic substitution reactions of 1-[1′(*R*)-α-methylbenzyl]-(2*R*)- and (2*S*)-(sulfonyloxymethyl)aziridines with various nucleophiles including N_3^-, MeO^-, CN^-, SCN^-, and diphenylcuperate yielded substitution products depending on the stereochemistry of substrates, nucleophiles, and the characteristics of the leaving groups. When the reaction site is less sterically hindered for the reactive nucleophiles to approach to the substrate 1-[1′(*R*)-α-methylbenzyl]-(2*S*)-(*p*-toluenesulfonyloxymethyl)aziridines, product is obtained as a single isomer while all the other starting materials afford a mixture of two isomers from two different reaction pathways.

3. Experimental

3.1. General methods

Chiral aziridines are available from Aldrich. All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 s. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230–400 mesh). ^1H NMR and ^{13}C NMR spectra were obtained using a Varian 200 (200 MHz for ^1H and 50.3 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ=7.26) for ^1H NMR and chloroform (δ=77.2) for ^{13}C NMR. Data are reported as: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants are given in hertz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data were reported as follows: $[\alpha]_D^{25}$ (concentration *c*=g/100 mL, solvent). Elemental analyses were performed by the Perkin–Elmer 240 DS elemental analyzer. High resolution mass spectra were recorded on a 4.7 T IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer.

3.2. General procedure for the preparation of (*S*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2*S*)-1 or (*R*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2*R*)-1

Into the solution of (2*S*)- or (2*R*)-hydroxymethylaziridine (450 mg, 2.54 mmol) in CH_2Cl_2 (5 mL) were added DMAP (30 mg, 0.254 mmol) and Et_3N (290 mg, 0.4 mL, 2.80 mmol). The resulting solution was cooled to 0 °C and stirred for 10 min before adding *p*-toluenesulfonylchloride (540 mg, 2.80 mmol). The reaction mixture was stirred for 1 h until all the starting material was consumed.

The mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/*n*-hexane, 1:1) provided products as oil.

*3.2.1. (S)-1-[((R)-1-Phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2S)-**1***[6]

Yield 96%. Liquid. $[\alpha]_D$ +1.0 (*c* 1.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (2H, d, *J*=8 Hz), 7.37–7.21 (7H, m), 3.96 (2H, t, 5.2 Hz), 2.43 (3H, s), 2.50–2.41 (2H, m), 1.90–1.84 (1H, m), 1.54–1.53 (1H, m), 1.41–1.37 (4H, m), 1.39 (3H, d, *J*=6.6 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 144.9, 144.1, 133.1, 129.9, 128.4, 128.0, 127.2, 126.7, 73.0, 69.3, 37.3, 31.4, 23.3, 21.8.

*3.2.2. (R)-1-[((R)-1-Phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2R)-**1***

$[\alpha]_D$ +12.0 (*c* 1.0, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (2H, d, *J*=8.2 Hz), 7.36–7.28 (7H, m), 4.11 (1H, dd, *J*=10.8, 4.8 Hz), 3.82 (1H, dd, *J*=10.6, 7.4 Hz), 2.43 (3H, s), 1.92–1.81 (1H, m), 1.53–1.52 (1H, d, *J*=3.2 Hz), 1.40–1.35 (1H, m), 1.36 (3H, d, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 144.6, 143.8, 133.0, 129.7, 128.1, 127.7, 126.9, 126.5, 72.7, 68.9, 36.9, 31.1, 23.0, 21.4. Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.2; H, 6.39; N, 4.25. Found: C, 65.5; H, 6.69; N, 4.27.

3.3. General procedure for preparation of (*S*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl methanesulfonate (2*S*)-2 or (*R*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl methanesulfonate (2*R*)-2

The same procedure as for the preparation of (*S*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2*S*)-**1** or (*R*)-1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl 4-methylbenzenesulfonate (2*R*)-**1** as described in Section 3.2 except that methanesulfonyl chloride was used instead of *p*-toluenesulfonylchloride.

*3.3.1. (S)-1-[((R)-1-Phenylethyl)aziridin-2-yl]methyl methanesulfonate (2S)-**2***

Yield 87%. Liquid. $[\alpha]_D$ +15.5 (*c* 5.7, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.36–7.28 (5H, m), 4.21 (1H, dd, *J*=11, 4.8 Hz), 3.89 (1H, dd, *J*=11, 7.0 Hz), 2.70 (3H, s), 2.57–2.47 (1H, m), 1.92–1.80 (2H, m), 1.60 (1H, d, *J*=6.4 Hz), 1.42 (3H, d, *J*=6.4 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 143.8, 128.2, 127.2, 126.7, 71.2, 69.3, 37.7, 36.1, 31.7, 22.7. Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.4; H, 6.71; N, 5.49. Found: C, 56.6; H, 6.90; N, 5.48.

*3.3.2. (R)-1-[((R)-1-Phenylethyl)aziridin-2-yl]methyl methanesulfonate (2R)-**2***

Liquid. $[\alpha]_D$ +33.9 (*c* 3.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.26 (5H, m), 4.43–4.35 (1H, dd, *J*=11, 4.4 Hz), 4.01 (1H, dd, *J*=11, 7.8 Hz), 3.06 (3H, s), 2.56–2.46 (1H, q, *J*=6.6 Hz), 2.01–1.90 (1H, m), 1.67 (1H, d, *J*=3.2 Hz), 1.46–1.43 (1H, m), 1.43 (3H, d, *J*=6.6 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 143.7, 128.2, 127.0, 126.5, 72.3, 68.9, 37.5, 37.2, 31.4, 23.0. Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.4; H, 6.71; N, 5.49. Found: C, 56.3; H, 6.58; N, 5.61.

3.4. General procedure for the substitution reactions of 1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl sulfonates (2*S*)-1, (2*R*)-1, (2*S*)-2, and (2*R*)-2

To the solution of any one of the substrates among 1-[((*R*)-1-phenylethyl)aziridin-2-yl]methyl sulfonates (2*S*)-**1**, (2*R*)-**1**, (2*S*)-**2**, and (2*R*)-**2** (0.5 mmol) in a specified solvent (15 mL) under nitrogen at room temperature was added a nucleophile (1.5 mmol). The mixture was stirred under reflux for the specified reaction time until all the starting material was consumed, except for dimethylcuperate at −78 °C and then 0 °C. The reaction was quenched by adding water at room temperature and the mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography provided analytically pure product.

*3.4.1. (2S)-(Azidomethyl)-1-[(R)-1-phenylethyl]aziridine (2S)-**4a***

Liquid. $[\alpha]_D$ +16.5 (*c* 1.7, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.34–7.21 (5H, m), 3.18–3.03 (2H, m), 2.87 (1H, q, *J*=5.4 Hz), 1.87–1.82 (1H, m), 1.67–1.46 (1H, m), 1.44–1.32 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 128.4, 127.2, 126.7, 69.8, 53.5, 37.1, 32.4, 23.2. MS (ES^+) *m*/*z* (rel intensity): 225 [(M+Na), 100], 203 [(M+H), 98]. HRMS (EI) calcd for $C_{11}H_{14}N_4$: 202.1218, found 202.1216.

*3.4.2. (2S)-(Methoxymethyl)-1-[(R)-1-phenylethyl]-aziridine (2S)-**4b***

Liquid. $[\alpha]_D$ +54.5 (*c* 1.0, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.36–7.24 (5H, m), 3.46–3.38 (5H, m), 2.46 (1H, q, *J*=6.2 Hz), 1.79–1.77 (1H, m), 1.58–1.56 (1H, s), 1.49–1.31 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.5, 128.3, 127.0, 126.8, 75.0, 69.8, 59.0, 39.1, 31.2, 23.3. HRMS (EI) calcd for $C_{12}H_{17}NO$: 191.1310, found 191.1305.

*3.4.3. (2S)-Benzyl-1-[(R)-1-phenylethyl]aziridine (2S)-**4c***

Liquid. $[\alpha]_D$ +23.8 (*c* 0.19, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.75–7.06 (10H, m), 3.78 (1H, dd, *J*=10.6, 5.2 Hz), 2.11–2.09 (1H, d, *J*=3 Hz), 1.67–1.43 (2H, m), 1.32–1.27 (3H, m), 1.04–0.96 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.1, 143.8, 128.4, 127.4, 127.1, 127.0, 125.9, 70.1, 49.4, 37.5, 34.0, 23.2. HRMS (EI) calcd for $C_{17}H_{19}N$: 237.1517, found 237.1509.

*3.4.4. (2S)-[(2,6-Dimethylphenoxy)methyl]-1-[(R)-1-phenylethyl]aziridine (2S)-**4d***

Liquid. $[\alpha]_D$ −13.1 (*c* 0.49, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.47–7.28 (5H, m), 6.98–6.92 (3H, m), 3.87 (1H, dd, *J*=5 and 10 Hz), 3.66 (1H, dd, *J*=6 and 10 Hz), 2.67 (1H, q, *J*=6.6 Hz), 2.23 (6H, s), 2.02–1.96 (1H, m), 1.64 (1H, d, *J*=6.2 Hz), 1.55 (3H, d, *J*=6.6 Hz), 1.52–1.50 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 144.4, 130.7, 128.6, 128.2, 126.9, 126.5, 123.6, 73.7, 69.5, 37.8, 32.1, 23.3, 16.1. MS (ES^+) *m*/*z* (rel intensity): 304 [(M+Na), 85]. HRMS (EI) calcd for $C_{19}H_{23}NO$: 281.1780, found 281.1776.

*3.4.5. (2S)-(Thiocyanatomethyl)-1-[(R)-1-phenylethyl]-aziridine (2S)-**4f***

Liquid. $[\alpha]_D$ +29.1 (*c* 0.61, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.31–7.29 (5H, m), 3.01–2.92 (1H, m), 2.79–2.70 (1H, m), 2.46 (1H, q, *J*=6 Hz), 1.94–1.91 (1H, m), 1.78–1.74 (1H, m), 1.68–1.63 (1H, m), 1.38 (3H, d, *J*=6.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 128.6, 127.5, 126.9, 112.3, 69.8, 37.4, 36.9, 34.7, 22.7. MS (ES^+) *m*/*z* (rel intensity): 302 [(M+Na), 100], 282[(M+H), 30]. HRMS (EI) calcd for $C_{12}H_{14}N_2S$: 218.0878, found 218.0887.

*3.4.6. (2R)-(Azidomethyl)-1-[(R)-1-phenylethyl]aziridine (2R)-**5a***

Liquid. $[\alpha]_D$ 19.7 (*c* 4.3, EtOAc). ^1H NMR (200 MHz, $CDCl_3$) δ 7.47–7.32 (5H, m), 3.47–3.38 (1H, dd, *J*=4.2 and 12.9 Hz), 3.20 (1H, dd, *J*=7.6 and 12.9 Hz), 2.57 (1H, q, *J*=6.2 Hz), 1.92–1.82 (1H, sept), 1.68 (1H, d, *J*=2.6 Hz), 1.58 (3H, d, *J*=6.4 Hz), 1.42–1.38 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.4, 128.5, 127.2, 126.9, 69.7, 54.2, 38.7, 31.6, 23.3. MS (ES^+) *m*/*z* (rel intensity): 225 [(M+Na), 100], 203[(M+H), 10]. HRMS (EI) calcd for $C_{11}H_{14}N_4$: 202.1218, found 202.1221.

*3.4.7. (2R)-(Methoxymethyl)-1-[(R)-1-phenylethyl]-aziridine (2R)-**5b***

Liquid. $[\alpha]_D$ −24.6 (*c* 1.0, ethyl acetate). ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.19 (5H, m), 3.44–3.35 (1H, m), 3.28–3.20 (1H, m), 2.50–2.44

(1H, m), 1.87–1.69 (3H, m), 1.59–1.50 (1H, m), 1.42–1.34 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 128.4, 127.2, 126.8, 69.6, 46.5, 39.3, 34.0, 23.1. HRMS (EI) calcd for $C_{12}H_{17}NO$: 191.1310, found 191.1311.

*3.4.8. 2-Benzyl-1-[(R)-1-phenylethyl]aziridine (2R)-**5c**, (2S)-**5c***

Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75–7.06 (10H, m), 3.51–3.43 (1H, m), 2.11–2.09 (1H, d, J=3 Hz), 1.67–1.43 (2H, m), 1.32–1.27 (2H, m), 1.04–1.09 (3H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.4, 141.2, 128.9, 128.3, 128.1, 127.5, 127.1, 125.8, 70.7, 53.5, 32.0, 19.6, 14.1. Anal. Calcd for $C_{17}H_{19}N$: C, 86.3; H, 8.07; N, 5.90. Found: C, 86.1; H, 8.26; N, 5.76.

*3.4.9. (R)-2-[(2,6-Dimethylphenoxy)methyl]-1-[(R)-1-phenylethyl]aziridine (2R)-**5d***

Liquid. $[\alpha]_D$ +54.4 (c 1.2, $CHCl_3$). ^{1}H NMR (200 MHz) δ 7.50–7.41 (5H, m), 7.15–7.03 (3H, m), 3.96–3.89 (2H, m), 2.65 (1H, q, J=2 Hz), 2.46 (6H, s), 2.13 (1H, q, J=3 Hz), 1.77–1.74 (1H, m), 1.66–1.52 (4H, m). ^{13}C NMR (50.3 MHz) δ 155.7, 144.4, 130.8, 128.6, 128.2, 126.7, 123.6, 74.6, 69.5, 38.9, 31.0, 23.2, 16.3. MS (ES^+) m/z (rel intensity): 302 [(M+Na), 100], 282 [(M+H), 50]. MS (ES^+) m/z (rel intensity): 304 [(M+Na), 100]. HRMS (EI) calcd for $C_{19}H_{23}NO$: 281.1780, found 281.1785.

*3.4.10. 2-(R)-[1-((R)-1-Phenylethyl)aziridin-2-yl]acetonitrile (2R)-**5e** and (2S)-**4e** as a mixture*

Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.31 (5H, m), 3.78–3.73 (1H, m), 2.85–2.73 (2H, m), 2.57–2.27 (3H, m), 1.92 (1H, s), 1.73–1.52 (2H, m), 1.43–1.33 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.5, 144.1, 128.8, 128.5, 127.5, 127.4, 126.7, 126.6, 118.7, 117.3, 69.6, 58.3, 58.1, 47.3, 33.4 33.2, 29.6, 29.4, 24.5, 24.3, 23.2, 21.4, 18.4, 18.3. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.4; H, 7.58; N, 15.4. Found: C, 77.3; H, 7.79; N, 15.3.

*3.4.11. 1-[(R)-1-Phenylethyl]-2(S)-(thiocyanatomethyl)aziridine (2S)-**4f***

Liquid. $[\alpha]_D$ +29.1 (c 0.82, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.23 (5H, m), 3.04–2.96 (1H, m), 2.81–2.68 (1H, m), 2.48 (1H, q, J=6.2 Hz), 2.00–1.93 (1H, m), 1.75–1.72 (1H, m), 1.69–1.61(m, 1H), 13.9(d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.8, 128.6, 128.3, 127.6, 126.9, 112.3, 69.9, 37.4, 36.9, 34.7, 22.8. HRMS (EI) calcd for $C_{12}H_{14}N_2S$: 218.0878, found 218.0882.

*3.4.12. 1-[(R)-1-Phenylethyl]-2(R)-(thiocyanatomethyl)aziridine (2R)-**4f***

Liquid. $[\alpha]_D$ +40.8 (c 0.57, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.23 (5H, m), 3.33–3.22 (1H, m), 2.83–2.70 (1H, m), 2.51 (1H, q, J=6.2 Hz), 2.00–1.93 (1H, m), 1.71–1.70 (1H, m), 1.52–1.47 (4H, m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.8, 128.5, 127.3, 126.8, 112.5, 69.4, 38.3, 38.1, 34.5, 23.5. HRMS (EI) calcd for $C_{12}H_{14}N_2S$: 218.0878, found 218.0874.

*3.4.13. (2S)-1,3-Diazido-N-[(R)-1-phenylethyl]propane-2-amine (**6**)*

Liquid. $[\alpha]_D$ +16.3 (c 1.4, ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.21 (5H, m), 4.84–3.93 (1H, m), 3.47–3.18 (m, 4H), 2.64 (q, J=6.2 Hz, 1H), 1.50–1.41 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 128.7, 127.3, 126.5, 55.6, 54.1, 53.1, 51.6, 24.9. HRMS (EI) calcd for $C_{11}H_{15}N_7$: 245.1389, found 245.1383.

3.5. (*S*)-(−)-Mexiletine

To the solution of (2*S*)-**4d** (158 mg, 0.56 mmol) in MeOH (3 mL) was added 5 mg of Pd/C. The reaction mixture was stirred at room temperature with atmospheric pressure of H_2 for 12 h and then the catalyst was filtered. The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane, 1:3) to provide analytically pure product in 84% yield. Liquid. $[\alpha]_D$ +2.9 (c 0.14, $CHCl_3$), lit.:[13] $[\alpha]_D$ +2.5 (c 4.9, $CHCl_3$). Spectral data were in agreement with those of the literature value.

3.6. (*R*)-(+)-Mexiletine

This was prepared in the same manner as (*S*)-(−)-mexiletine starting from (2*R*)-**5d**. Liquid. $[\alpha]_D$ −2.8 (c 0.34, $CHCl_3$), lit.:[13] $[\alpha]_D$ −2.7 (c 4.7, $CHCl_3$). Spectral data were in agreement with those of the literature value.

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