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A convenient synthesis of (*R*)-salmeterol via Rh-catalyzed asymmetric transfer hydrogenation

Juntao Liu [a], Di Zhou [b], Xian Jia [b], Ling Huang [a], Xingshu Li [a,*], Albert S. C. Chan [a]

[a] *School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510006, China*
[b] *School of Pharmaceutical Engineering, ShenYang Pharmaceutical University, Shenyang 110016, China*

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ABSTRACT

(*R*)-Salmeterol was synthesized in eight steps with salicaldehyde as the starting material. The key chiral intermediate, alcohol **5**, was prepared via Rh-catalyzed asymmetric transfer hydrogenation with (*S*,*S*)-PEG-BsDPEN or (*S*,*S*)-TsDPEN ligand and sodium formate as the hydrogen donor under mild conditions.
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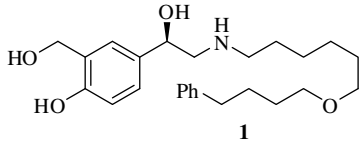
1. Introduction

Salmeterol is a selective long-acting β_2-adrenoreceptor agonist, which is used clinically as an inhaled bronchodilator for the treatment of asthma and chronic bronchitis.[1] It is well established that the (*R*)-enantiomer (Scheme 1) is more active as a β-agonist and has less side effects when compared to the racemate.[2] On the other hand, Sepracor reported that the (*S*)-enantiomer of salmeterol had a higher selectivity for the β_2 receptors.[3]



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Scheme 1. β_2-Adrenoreceptor agonist (*R*)-salmeterol.

Due to their unique property, both (*R*)- and (*S*)-salmeterol have received high interest for pharmacological and clinical studies in recent years. Helquist et al. first reported the synthesis of both enantiomers of salmeterol via the asymmetric borane reduction of an α-bromoketone for the preparation of the key chiral intermediate with chiral oxazaborolidine catalysts (CBS).[4] Procopiou et al. described an enantioselective route to (*S*)-salmeterol, including the enantioselective reduction of an azidoketone intermediate to an azido alcohol mediated by *Pichia angusta*.[5] Goswami et al. prepared (*R*)-salmeterol through a bio-transformation pathway involving *Rhodotorula rubra*.[6] Procopiou et al. outlined a synthetic route of (*R*)-salmeterol **1** by the asymmetric reduction of a phenacyl derivative with (*S*)-phenylglycinol as a chiral auxiliary.[7] These authors also reported a synthetic method for (*R*)-salmeterol **1** from chiral oxazaborolidine (CBS) catalyzed asymmetric borane reduction of an α-aminoketone followed by the potassium trimethylsilanolate induced cleavage of 1,3-oxazolidin-2- and 5-ones.[8] Dixon et al. described a chiral auxiliary induced stereoselective oxy-Michael approach to the synthesis of (*R*)-salmeterol **1**.[9] In recent years, the asymmetric transfer hydrogenation of prochiral ketones has become an important tool in building chiral secondary alcohols which are versatile building blocks in medicinal chemistry. Herein, we report the convenient synthesis of (*R*)-salmeterol **1** via catalytic asymmetric transfer hydrogenation.

2. Results and discussion

The synthetic strategy for chiral salmeterol is illustrated in Scheme 2. The reaction of amine **8** with chiral epoxide **6** produced intermediate **9**. Removal of the protective groups afforded the desired product (*R*)-salmeterol **1**.

As an important intermediate for the synthesis of the chiral epoxide **6**, prochiral α-bromoketone **4** was prepared from salicaldehyde in three steps (Scheme 3). In the presence of aluminum chloride, bromoacetyl bromide reacted with salicaldehyde to give acetophenone derivative **2**.[10] Then the aldehyde group of compound **2** was reduced regioselectively by sodium borohydride in acetic acid to give intermediate **3**.[11] Ketal formation from intermediate **3** with 2,2-dimethoxypropane catalyzed by *p*-toluenesulfonic acid gave the desired prochiral α-bromoketone **4**.

Although chiral secondary alcohols could be obtained through a biotransformative pathway or asymmetric borane reduction, from both an economical and practical viewpoint, it was of high interest to use Ru- or Rh-catalyzed asymmetric transfer hydrogenation[12] to prepare the chiral intermediate bromoalcohol **5,** due to operational simplicity and the ready availability of the reductants.

TsDPEN, a widely used chiral ligand in the catalytic asymmetric transfer hydrogenation of ketones, and PEGBsDPEN, a ligand which behaved well in the HCOONa–H_2O system, were used as chiral

* Corresponding author. Tel.: +86 20 35693517; fax: +86 20 39332673.
E-mail address: xsli219@yahoo.com (X. Li).

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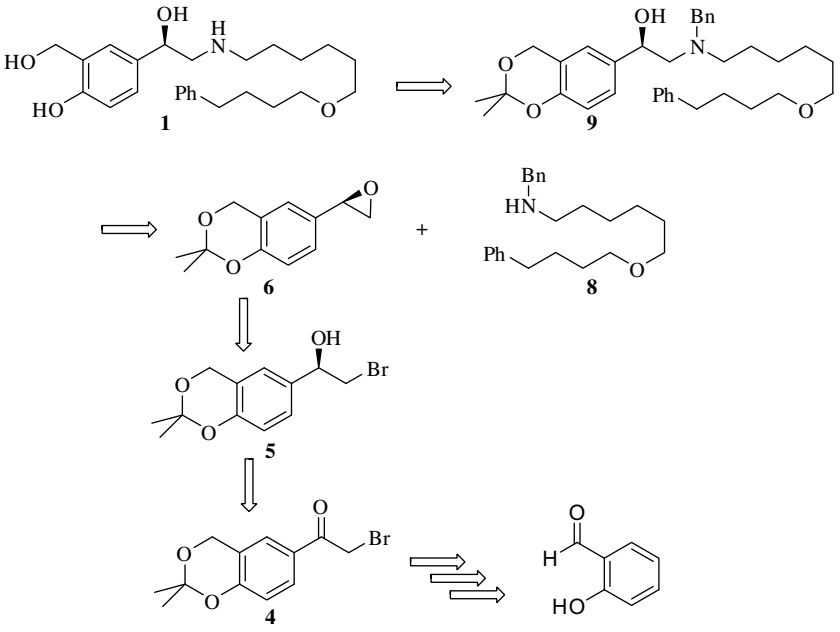
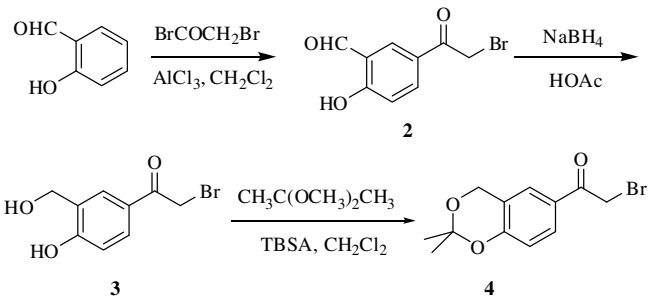
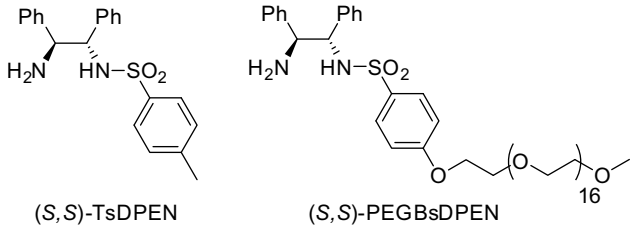


Scheme 2. Retrosynthetic analysis of (*R*)-salmeterol.



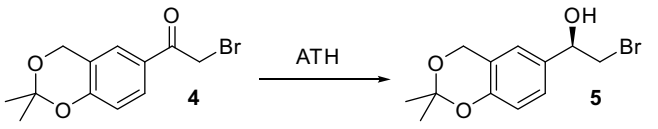
Scheme 3. Synthetic route to prochiral α-bromoketone **4**.



Scheme 4. Chiral ligands for asymmetric transfer hydrogenation.

ligands for the reaction (Scheme 4).[13] Trace product was obtained in HCOOH–Et_3N azeotropic mixture with Ru– or Rh–TsDPEN as catalyst, with a large amount of by-product appearing (Table 1, entries 1 and 2). When sodium formate was used as the hydrogen donor, both Rh- and Ru–TsDPEN catalyzed asymmetric transfer hydrogenation of α-bromoketone **4** in water gave the desired product α-bromoalcohol **5** with good yield and enantioselecivity (89% ee and 92% ee, respectively, Table 1, entries 3 and 4). The use of Rh/(*S*,*S*)-PEGBsDPEN gave better enantioselectivity than that of (*S*,*S*)-TsDPEN under the same reaction conditions (entry 5). When the solvent was changed to PEG–H_2O (9:1, v/v), both catalyst systems provided improved ee values (96% ee and 98% ee, respectively; entries 6 and 8).[14] When the (*R*,*R*)-TsDPEN was chosen as the chiral ligand, the (*S*)-enantiomer was obtained (entry 7).

Table 1
Various conditions for asymmetric transfer hydrogenation of α-bromoketone **4**[a]



Entry	Catalyst	Hydrogen donor and solvent	Yield[b] (%)	ee[c] (%)
1	(*S*,*S*)-TsDPEN/Ru	HCOOH–Et_3N	Trace	—
2	(*S*,*S*)-TsDPEN/Rh	HCOOH–Et_3N	Trace	—
3	(*S*,*S*)-TsDPEN/Ru	HCOONa/H_2O	85	89(*R*)[d]
4	(*S*,*S*)-TsDPEN/Rh	HCOONa/H_2O	88	92(*R*)
5	(*S*,*S*)-PEGBsDPEN/Rh	HCOONa/H_2O	89	93(*R*)
6	(*S*,*S*)-TsDPEN/Rh	HCOONa/PEG–H_2O[e]	92	96(*R*)
7	(*R*,*R*)-TsDPEN/Rh	HCOONa/PEG–H_2O	89	95(*S*)
8	(*S*,*S*)-PEGBsDPEN/Rh	HCOONa/PEG–H_2O	93	98(*R*)

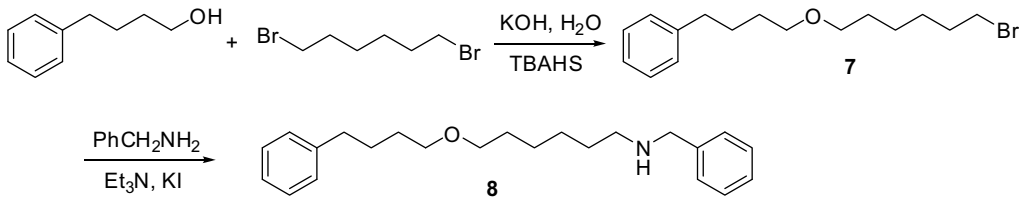
[a] The reaction was carried out at room temperature for 12 h (S/C = 100/1).
[b] Isolated yields were obtained by flash chromatography.
[c] The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configuration was assigned on the basis of the signs of the specific rotation.
[e] PEG/H_2O = 9/1 (v/v).

Attaching a hydrophilic PEG chain onto the structure of the (*S*,*S*)-PEGBsDPEN ligand made the catalyst system able to be recycled for several times in PEG/H_2O (Table 2, entries 1–5).[13] As

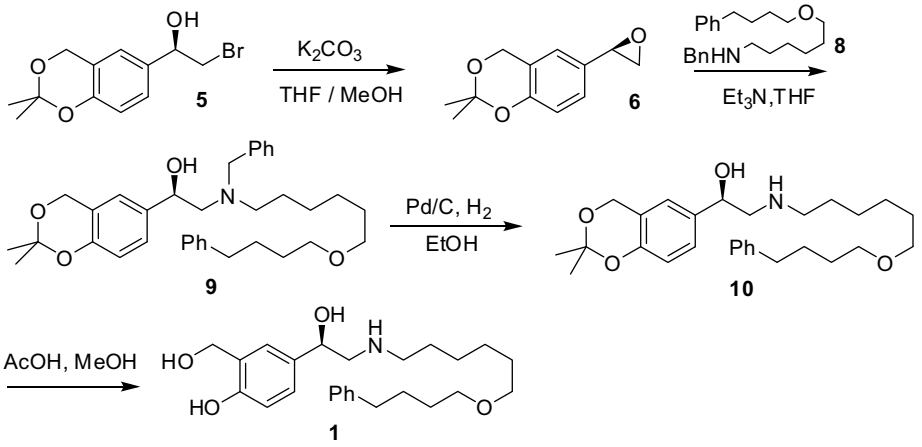
Table 2
Catalyst recycling of asymmetric transfer hydrogenation of α-bromoketone[a]

Entry	Time (h)	Yield[b] (%)	ee[c] (%)
1	12	90	98
2	12	92	97
3	12	90	98
4	18	85	98
5	20	79	97

[a] The reactions were carried out with Rh/(*S*,*S*)–PEG–BsDPEN catalyst (S/C = 100/1) and 5.0 equiv of HCOONa as hydrogen donor at room temperature in PEG–H_2O (9:1, v/v). After each batch, 1 equiv of HCOOH was added to regenerate HCOONa.
[b] Isolated yields were obtained by flash chromatography.
[c] The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column.



Scheme 5. Synthesis of long-chain amine **8**.



Scheme 6. Total synthesis of (*R*)-salmeterol **1**.

summarized in Table 2, the prochiral α-bromoketone gave good yields in the first three runs, and then the catalyst activity decreased slightly; the enantioselectivity was consistent in all the five runs.

The secondary amine **8** was prepared with a modified method according to the literature.[8] 4-Phenylbutanol reacted with 1,6-dibromohexane to give bromoether **7** in the presence of *tetra*-butylammonium hydrogen sulfonate (TBAHS) and potassium hydroxide at room temperature in high yield. Then bromoether **6** was allowed to react with benzylamine in the presence of triethylamine and potassium iodide to yield the long chain secondary amine **8** (Scheme 5).

The α-bromoalcohol **5** could be quantitatively transformed into epoxide **6** in the presence of potassium carbonate in a mixture of THF and MeOH at room temperature. Heating the mixture of epoxide **6** and amine **8** to 120 °C in the presence of triethylamine under neat conditions gave the ring opening product **9**. Removal of the benzyl group by Pd/C catalyzed hydrogenolysis, followed by acidolysis of the ketal protective group with acetic acid afforded (*R*)-salmeterol **1** (Scheme 6).

3. Conclusion

In conclusion, we have outlined a convenient and efficient enantioselective synthetic route to (*R*)-salmeterol **1** using commercially available salicaldehyde as the starting material under mild conditions. During the process from compound **2** to compound **3**, the carbonyl group of the aldehyde was selectively reduced in a $NaBH_4$/AcOH system, while that of the ketone moiety was kept intact. The Rh/(*S*,*S*)-PEGBsDPEN catalyzed asymmetric transfer hydrogenation of prochiral ketone **4** gave bromoalcohol **5** with excellent enantioselectivity (98% ee). The overall yield is 35% from salicaldehyde.

4. Experimental

The NMR spectra were recorded with TMS as the internal standard on a Varian 300 MHz spectrometer. Coupling constants were given in Hertz. Enantiomeric excesses were determined by HPLC with a Chiralcel OD-H column. Optical rotation was determined on a Perkin Elmer 341 polarimeter. MS spectra were recorded on Thermo GC–MS with EI or Agilent LC–MS 6120 with ESI. The reactions were monitored by thin layer chromatography using silica gel coated plates. Elemental analyses were carried out using a CHNS analyzer.

4.1. Preparation of 5-(2-bromoacetyl)-2-hydroxybenzaldehyde 2

To a suspension of aluminium chloride (1.06 g, 8 mmol) in 50 ml of dichloromethane was added slowly bromoacetyl bromide (480 mg, 2.4 mmol) at 10 °C. The temperature of the mixture was brought to 30 °C and the stirring was continued for an hour. To this mixture was added a solution of salicaldehyde (245 mg, 2 mmol) in dichloromethane at 30 °C. The reaction mixture was stirred at 35 °C for 15 h and then was quenched with water at 0 °C. The dichloromethane layer was separated and removal of the solvent afforded a slurry residue. Heptane was added to the slurry and the mixture was stirred for 15 min. The wet cake obtained by filtration was washed with *n*-heptane and dried at 50 °C to a constant weight. White crystals were obtained by recrystallization of the product in a mixture of dichloromethane and *n*-hexane (80% yield). ^{1}H NMR ($CDCl_3$) δ: 11.49 (s, 1H), 9.96 (s, 1H), 8.28 (s, 1H), 8.17 (d, J = 8.8 Hz 1H), 7.09 (d, J = 8.8 Hz 1H), 4.38 (s, 2H); ^{13}C NMR ($CDCl_3$) δ: 196.2, 188.9, 165.6, 137.1, 135.7, 126.8, 120.0, 118.4, 29.9; GC/MS(EI) m/z: 241.9, 243.9 (M^+); Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.90. Found: C, 44.35; H, 2.71.

4.2. Preparation of 2-bromo-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone 3

To a solution of 5-(2-bromoacetyl)-2-hydroxybenzaldehyde (486 mg, 2 mmol) in 10 ml of acetic acid was added sodium borohydride (76 mg, 2 mmol) in three portions at 8–10 °C. The reaction mixture was then brought to room temperature and the stirring was continued for another hour. Water (20 ml) was added, and then the mixture was neutralized with a saturated solution of potassium bicarbonate. The aqueous solution was extracted twice with 20 ml of ethyl acetate. The combined organic phase was washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a crude yellow solid product. Further purification by recrystallization in mixture of dichloromethane and *n*-hexane afforded a white solid product (85% yield). ^{1}H NMR (DMSO-d_6) δ: 8.01 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.77 (s, 2H), 4.52 (s, 2H); ^{13}C NMR (DMSO-d_6) δ: 19.2, 159.5, 129.7, 129.2, 128.5, 125.2, 114.4, 57.7, 33.3; GC/MS (EI, m/z): 243.9 245.9 (M^+); Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 43.97; H, 3.55.

4.3. Preparation of 2-bromo-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl) ethanone 4

To a suspension of 2-bromo-1-(4-hydroxy-3-(hydroxymethyl)-phenyl)ethanone (490 mg, 2 mmol) and *p*-toluenesulfonic acid (1.7 mg, 0.01 mmol) in 10 ml of dichloromethane was added dropwise 2,2-dimethoxypropane (289 mg, 2.2 mmol) in dichloromethane (5 ml). The suspension was stirred vigorously until it became homogeneous. After the reaction was complete, as monitored by TLC, it was washed with saturated sodium bicarbonate solution (10 ml). The organic phase was separated and distilled under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give a yellowish oil (99% yield). ^{1}H NMR ($CDCl_3$) δ: 7.82 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.89 (s, 2H), 4.38 (s, 2H), 1.57 (d, J = 1.6 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 189.9, 156.3, 129.6, 126.5, 126.3, 119.5, 117.7, 100.7, 60.5, 30.6, 24.7; GC/MS (EI, m/z): 283.9, 285.9 (M^+); Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60. Found: C, 50.40; H, 4.46.

4.4. Preparation of (*R*)-2-bromo-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl) ethanol 5

A suspension of η^5-pentamethylcyclopentadienylrhodium dimer (3.0 mg, 0.005 mmol) and (*S,S*)-PEG-BsDPEN (16 mg, 0.012 mmol) in the mixture of PEG-800 (1.8 ml) and H_2O (0.2 ml) was prepared. The mixture was purged with argon and stirred at 40 °C for 1 h. HCOONa (340 mg, 5 mmol) and bromoketone **4** (285 mg, 1 mmol) were added into the preformed catalyst solution. The mixture was stirred at room temperature for 12 h until the reaction was complete. Dichloromethane was added and the organic phase was separated. The combined organic phases were washed with 2 ml of saturated brine and dried with sodium sulfate. The organic solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give a white solid product. The enantiomeric excess was determined by chiral HPLC with a Chiracel OD-H column. (Hex/IPA = 90/10, 220 nm). Retention time: 21.87 min, 24.35 min (major). (93% yield, 98% ee.) $[\alpha]_D^{20} = -29.3$ (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.14 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 4.84 (t, J = 3.6 Hz, 1H), 4.82 (s, 2H), 3.63–3.28 (m, 2H), 2.17 (s, 2H), 1.53 (d, J = 1.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 151.2, 132.2, 125.8, 122.3, 119.5, 117.2, 99.7, 73.4, 60.8, 39.9, 24.7, 24.6; GC/MS (EI, m/z): 286.0, 288.0 (M^+); HRMS Calcd for $C_{14}H_{19}BrO_5$: 345.0343. Found: (ESI, m/z): 345.0307 (M+AcOH)$^+$; Anal. Calcd for $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.27. Found: C, 50.16; H, 5.13.

4.5. Preparation of (*R*)-2,2-dimethyl-6-(oxiran-2-yl)-4*H*-benzo[*d*][1,3]dioxine 6

To a solution of (*R*)-2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)ethanol (287 mg, 1 mmol) in a mixture of THF/MeOH (2.5 ml/2.5 ml) was added potassium carbonate (414 mg, 3 mmol). The mixture was filtered after it was stirred vigorously at room temperature for 2 h. The filtrate was concentrated under reduced pressure and further purification was performed by flash column chromatography on neutral aluminum oxide (petroleum ether/ethyl acetate = 20/1) to give **6** as a yellowish oil (93% yield). $[\alpha]_D^{20} = -39.7$ (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 6.98 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.96 (m, 1H), 4.82 (s, 2H), 3.59 (m, 2H), 1.54 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 150.51, 129.24, 125.67, 123.37, 119.87, 117.55, 99.55, 60.64, 24.63; GC/MS EI m/z: 206.1 (M^+); Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.74; H, 6.70.

4.6. Preparation of 4-(6-bromohexyloxy)butylbenzene 7

To a mixture of 4-phenylbutanol (0.75 g, 5 mmol) and 1,6-dibromohexane (2.42 g, 10 mmol) were added potassium hydroxide (1.12 g, 20 mmol) and *tetra*-butylammonium hydrogen sulfate (0.17 g, 0.5 mmol). After stirring for 20 h at room temperature, the mixture was filtered and the filtrate was dissolved in 10 ml of ether. The resulting solution was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by vacuum distillation to give compound **7** (81% yield). ^{1}H NMR ($CDCl_3$) δ: 7.27–7.22 (m, 2H), 7.18–7.16 (m, 3H), 3.42–3.36 (m, 6H), 2.64–2.60 (m, 2H), 1.86–1.79 (m, 2H), 1.68–1.52 (m, 6H), 1.48–1.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 142.4, 128.3, 128.1, 125.6, 70.6, 70.6, 35.6, 32.7, 32.4, 29.5, 29.3, 27.9, 27.2, 25.3; LC/MS (ESI, m/z): 313.2 (M^+); Anal. Calcd for $C_{16}H_{25}BrO$: C, 61.34; H, 8.04. Found: C, 61.21; H, 7.90.

4.7. Preparation of *N*-benzyl-6-(4-phenylbutoxy)hexan-1-amine 8

To a mixture of benzylamine (0.321 g, 3 mmol) and triethylamine (0.2 g, 2 mmol) was added sodium iodide (0.015 g, 0.1 mmol). The mixture was stirred at 45 °C for 30 min. Then, 4-(6-bromohexyloxy)butylbenzene **7** (0.314 g, 1 mmol) was added drop-wise. The reaction was continued until TLC monitoring showed the disappearance of bromoether **7**. The solvent and excess amines were evaporated under reduced pressure. Water and dichloromethane were added to the crude product for extraction and the organic phase was separated, washed with brine and dried with anhydrous $MgSO_4$. The filtrate was evaporated to dryness to give a yellowish oily product. Further purification by flash column chromatography on silica gel (dichloromethane/methanol = 50/1) gave the desired product (75% yield). ^{1}H NMR ($CDCl_3$) δ: 7.31–7.29 (m, 4H), 7.25–7.15 (m, 6H), 3.78 (s, 2H), 3.42–3.34 (m, 4H), 2.64–2.59 (m, 4H), 1.96 (br, 1H), 1.63–1.53 (m, 8H), 1.35–1.31 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 142.7, 136.6, 129.8, 129.3, 128.9, 128.7, 128.5, 128.2, 125.9, 71.0, 70.9, 62.4, 55.4, 52.9, 48.4, 36.0, 29.9, 29.6, 28.6, 28.3, 27.0, 26.2; LC/MS (ESI m/z): 340.3 (M+H)$^+$; Anal. Calcd for $C_{23}H_{33}NO$: C, 81.37; H, 9.80; N, 4.13. Found: C, 81.24; H, 9.67; N, 4.01.

4.8. Preparation of (*R*)-2-(benzyl(6-(4-phenylbutoxy)hexyl)-amino)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3] dioxin-6-yl)ethanol 9

The mixture of chiral epoxide **6** (206 mg, 1 mmol) and amine **8** (339 mg, 1 mmol) was heated to 120 °C without an added solvent

for 12 h. The residue was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give product **9** as a yellow oil. (83% yield) $[\alpha]_D^{20} = -13.9$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.29–7.25 (m, 5H), 7.22–7.20 (m, 2H), 7.15–7.12 (m, 3H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.85–4.81 (m, 1H), 4.78 (s, 2H), 4.57–4.52 (m, 1H) 3.87 (d, *J* = 13.2 Hz, 1H), 3.48 (d, *J* = 13.2 Hz, 1H), 3.41–3.32(m, 4H), 2.63–2.55 (m, 4H), 2.53–2.42 (m, 2H), 1.62–1.44 (m, 8H), 1.54 (s, 6H), 1.32–1.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ:150.8, 142.7, 138.8, 134.3, 129.2, 128.6, 128.5, 127.5, 126.1, 125.9, 122.4, 119.5, 117.1, 99.7, 71.2, 71.0, 69.5, 62.9, 61.3, 59.0, 54.2, 36.2, 30.1, 29.8, 28.5, 27.6, 27.3, 26.5, 25.3, 25.0; LC/MS (ESI *m*/*z*): 546.4 $(M+H)^+$; HRMS Calcd for $C_{35}H_{47}NO_4$: 545.3500, found: (FAB, *m*/*z*): 545.3488 (M^+); Anal. Calcd for $C_{35}H_{47}NO_4$: C, 77.03; H, 8.68; N, 2.57. Found: C, 76.89; H, 8.54; N, 2.43.

4.9. Preparation of (*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-(6-(4-phenyl butoxy)hexylamino)ethanol 10

To the crude product **9** (545 mg, 1 mmol) in 5 ml of methanol was added 10% Pd/C (54 mg). The solution was placed in a stainless steel reactor which was then charged with hydrogen gas (150 psi). After being stirred for 24 h at room temperature, the reaction mixture was filtered through Celite to remove the catalyst. The filtrate obtained was evaporated to give the product **10** as a yellowish slurry (95% yield). $[\alpha]_D^{20} = -16.5$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.26–7.21 (m, 2H), 7.15–7.13 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.83 (m, 1H), 4.81 (s, 2H), 4.48 (m, 1H), 3.40–3.38 (m, 4H), 3.37 (m, 1H), 2.70 (m, 1H), 2.64–2.59 (m, 4H), 1.66–1.36 (m, 8H), 1.52 (s, 6H), 1.35–1.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ:150.8, 142.6, 128.6, 128.5, 126.0, 125.9, 122.3, 119.6, 117.3, 99.8, 87.9, 71.1, 71.0, 61.2, 54.7, 36.1, 30.1, 29.8, 29.7, 28.4, 27.6, 26.5, 25.2, 25.0; LC/MS (ESI *m*/*z*): 456.4 $(M+H)^+$; Anal. Calcd for $C_{28}H_{41}NO_4$: C, 73.81; H, 9.07; N, 3.07. Found: C, 72.67; H, 8.95; N, 2.95.

4.10. Preparation of (*R*)-salmeterol 1

To a solution of **10** (228 mg, 0.5 mmol) in methanol (2.5 ml) was added acetic acid (2.5 ml). After the mixture was stirred for 48 h at room temperature, saturated potassium carbonate solution was added slowly to basify the mixture. Ethyl acetate (20 ml) was added to extract the product and the solvent was distilled off to give final product **1** (93% yield). $[\alpha]_D^{20} = -18.7$ (*c* 1.06, CH_3OH) [lit.[7a] $[\alpha]_D^{20} = -18.5$ (*c* 0.81, CH_3OH)]; ^1H NMR (CD_3OD) δ: 7.35–7.12 (m, 5H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.68 (m, 1H), 4.65 (s, 2H), 3.42–3.35 (m, 4H), 2.85–2.65 (m, 4H), 2.60 (m, 2H), 1.72–1.48 (m, 8H), 1.39–1.26 (m, 4H); ^{13}C NMR (CD_3OD) δ: 154.5, 142.3, 133.6, 128.1, 128.0, 127.9, 127.1, 125.7, 125.3, 114.5, 71.6, 70.4, 70.3, 59.7, 56.4, 50.2, 35.2, 30.3, 29.2, 28.9, 27.9, 26.7, 25.7; LC/MS (ESI *m*/*z*): 416.3 $(M+H)^+$; Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.26; H, 8.97; N, 3.37. Found: C, 72.13; H, 8.79; N, 3.27.

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