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TETRAHEDRON: *ASYMMETRY*

A convenient stereoselective synthesis of (*R*)-(−)-denopamine and (*R*)-(−)-salmeterol

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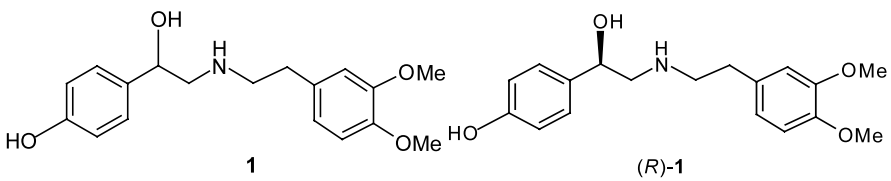
Abstract—β-Adrenoreceptor agonists (*R*)-(−)-denopamine (*R*)-**1** and (*R*)-(−)-salmeterol (*R*)-**2** have been prepared in good overall yield and high enantioselectivity through a biotransformative pathway.

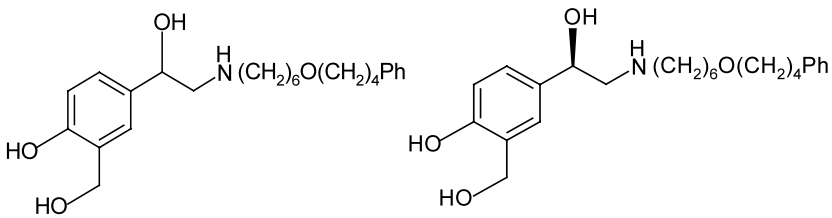
1. Introduction

The importance of enantioselective synthesis in modern organic chemistry means that there is a continuing need for the development of new asymmetric methodologies.[1] Among the numerous methods for asymmetric synthesis, efficient enzyme- or microorganism-catalysed transformation is a preferred tool[2–6] with respect to the chemo-, regio- and enantioselectivity of such transformations and additional environmental aspects. This is particularly true in the pharmaceutical and agrochemical sectors where interest in enantiomerically pure compounds is continuously growing. Yeast-mediated reactions have attracted great interest and play important roles due to the low cost and easy availability of yeast and the versatility of this biocatalyst.

In spite of recent advances[7] in drug specificity, many chiral drugs are marketed as racemates. Thus, denopamine[8] [(±)-α,α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol] (±)-**1** and salmeterol[9] [(±)-1,3-benzenedimethanol-4-hydroxy-α-[((6-(4-phenylbutoxy)hexyl)-amino)methyl] (±)-**2** are two very important β-adrenoreceptor agonists marketed as racemates of which the (*R*)-enantiomer is the active component. Herein, we aim to demonstrate the asymmetric synthesis of the active components of both denopamine **1** and salmeterol **2**.



1 (*R*)-**1**



2 (*R*)-**2**

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2. Results and discussion

2.1. (*R*)-(−)-Denopamine, (*R*)-1

Denopamine **1** is a very important new β_1-receptor agonist, which is effective in the treatment of congestive heart failure. The advantage of denopamine over many of the other drugs possessing positive inotropic activity, is that it can be administered orally. There are only few reported enantioselective syntheses of denopamine and prior to 1991 the maximum enantioselectivity obtained for denopamine was 60%. Corey et al.[10] have reported an enantioselective synthesis of (*R*)-(−)-**1** using CBS-reduction technology[11] to afford the product with 97% e.e. More recently, Gu-Qiang et al.[12] reported another synthesis of (*R*)-**1** through reductive biotransformation of a keto ester. In 1994 Jackson et al.[13] reported another synthesis in which (*R*)-**1** is produced in 68% yield by transformation of an active cyanohydrin. The reported methods however suffer from one or other drawbacks such as high cost involvement, poor yield, poor enantioselectivity or are not attractive for environmental reasons.

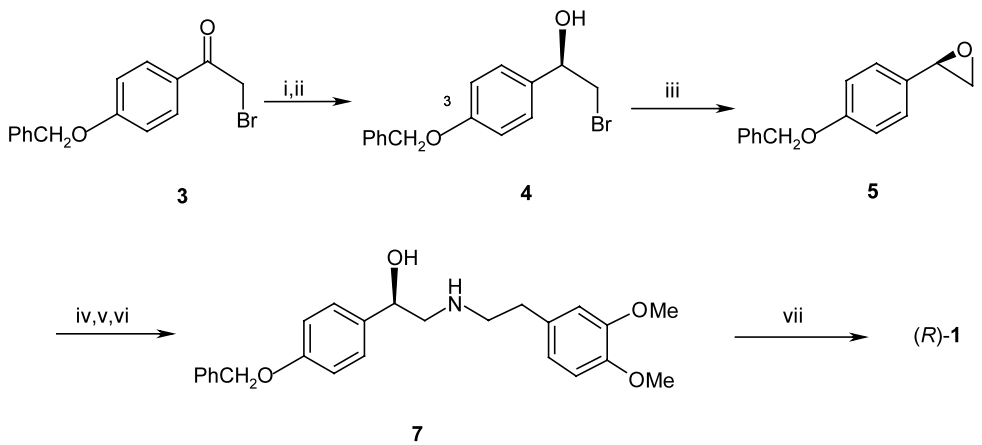
We have recently reported[14] the reduction of a number of ω-bromoacetophenones to the corresponding chiral alcohols with very encouraging yield and enantioselectivity by use of the yeast *Rhodotorula rubra* at room temperature in the presence of an anionic surfactant (the beneficial effect of which was explained earlier). In continuation of this work, and to circumvent some of the drawbacks of the existing methods, attempts were made to prepare (*R*)-**1** from the α-bromoketone **3** using the methodology developed by us, and we now wish to report the synthesis of (*R*)-**1** in promising yield and enantioselectivity.

The synthesis began with the reduction of the bromoketone 4-benzyloxy-ω-bromoacetophenone **3** with *Rhodotorula rubra* (a yeast microbe isolated from local brewery waste) in the presence of sodium lauryl sulfate, an anionic surfactant. The microbial culture of *Rhodotorula rubra* was used after 48 h of growth. The substrate was mixed with the surfactant at a 1:3 in weight-to-weight ratio. The substrate to biocatalyst ratio was maintained at 0.02 and the mixture was shaken at 30°C for 48 h under an argon atmosphere, wherein the product, 2-bromo-1-(4-benzyloxyphenyl)ethanol **4** was obtained in 79–80% yield with enantiomeric excess of 94%, as determined by analysis of its Mosher's[15] ester on a chiralcel OD HPLC column. The product was then purified by chromatography and quantitatively transformed into the corresponding oxetane **5** under basic conditions (K_2CO_3/THF) in 74–75% yield without any loss of enantiomeric purity. Oxetane **5** was then ring opened regioselectively by nucleophilic attack with 3,4-dimethoxyphenethylamine **6** by heating in refluxing *N*,*O*-bis(trimethylsilyl)acetamide in DMSO at 85°C over 35 h to afford 2-(3,4-dimethoxyphenethyl)amino-1-(4-benzyloxyphenyl)ethanol **7** in 70% yield after purification (Scheme 1).

The protected amino alcohol **7** was then deprotected by catalytic hydrogenation in ethanol to afford, after extractive isolation and recrystallization, pure (*R*)-(−)-**1** in 65% yield.

2.2. (*R*)-(−)-Salmeterol, (*R*)-2

Salmeterol (Serevent®) **2** is a potent bronchodilator with long duration of action and has little or no cardiotonic side effects. Most of the reports on the synthesis of salmeterol have been published in patent literature. In 1974, Middlemiss et al.[16] first prepared enantiomerically pure (*R*)-(−)-salbutamol, a derivative of **2**, via resolution of the racemate through fractional crystallization. Zepp[17] and Jackson et al.[13] later prepared enantiomerically pure (*R*)-salbutamol with 61% yield and 79% e.e. through enantioselective hydrocyanation of an aldehyde and reductive amination, respectively. Subsequently, Hett et al.[18] reported the synthesis of both enantiomers of **2** as their hydroxynaphthoic acid salts,



Scheme 1. (i) *Rhodotorula rubra* microbial culture; (ii) sodium lauryl sulfate; (iii) K_2CO_3/THF; (iv) *N*,*O*-bis(trimethylsilyl)-acetamide; (v) DMSO; (vi) 3,4-dimethoxyphenethylamine **6**; (vii) Pd–C/H.

in reasonable yield and 99.9% e.e. using an oxazaborolidine catalyst.

It was of interest to us to see whether our method could be used to synthesize salmeterol in a highly enantioselective way. Thus, a sample of 4-benzyloxy-3-hydroxymethyl-ω-bromoacetophenone **8** was mixed with sodium lauryl sulfate (in a 1:3 weight-to-weight ratio) and added to the microbial culture of *Rhodotorula rubra*. The pH of the reaction mixture was maintained at 7. The mixture was kept under an argon atmosphere and shaken at 200 rpm at 30°C for 48 h. The reaction afforded (*R*)-(−)-2-bromo-1-(4-benzyloxy-3-hydroxymethylphenyl)ethanol **9** in 78–80% yield with 95% e.e. (as determined by the method described above). Enantiomerically pure alcohol **9** was then transformed into the corresponding epoxide **10** without any loss of integrity of the stereogenic centre by heating with potassium carbonate in refluxing THF. Finally this epoxide was reacted with 6-(4-phenylbutoxyhexyl)-1-amine[19] **11** by heating in DMSO in the presence of *N*,*O*-bis(trimethylsilyl)acetamide at 85°C, to afford (*R*)-(−)-2-(4-phenylbutoxyhexyl)amino-1-(4-benzyloxy-3-hydroxymethylphenyl)ethanol **12**. Catalytic hydrogenation of **12** then cleaved the benzyl protecting group to furnish (*R*)-(−)-salmeterol (*R*)-**2** with 96% e.e. in 61% yield (Scheme 2).

An approach was made to synthesize (*R*)-**2** from (*R*)-(−)-2-bromo-1-(6-(1,3-benzdioxan-6-yl)ethanol **14** prepared by microbial reduction of 6-ω-bromacetyl-1,3-benzdioxan **13** with *Rhodotorula rubra* using the above methodology. (*R*)-(−)-2-Bromo-1-(6-(1,3-benzdioxanyl)-ethanol **14** was then transformed into the corresponding epoxide **15** by heating with K_2CO_3 in refluxing tetrahydrofuran. Epoxide **15** was then similarly regioselectively ring opened by nucleophilic attack with 6-(4-phenylbutoxyhexyl)-1-amine **11** to afford 2-(4-phenylbutoxyhexyl)amino-1-(6-(1,3-benzodioxan-6-yl)ethanol **16** in reasonable yield and 94% e.e (Scheme 3).

However, on attempting acid hydrolysis of **16** to cleave the protecting group (deketalization) on the benzene ring, undesired racemisation occurred.[20]

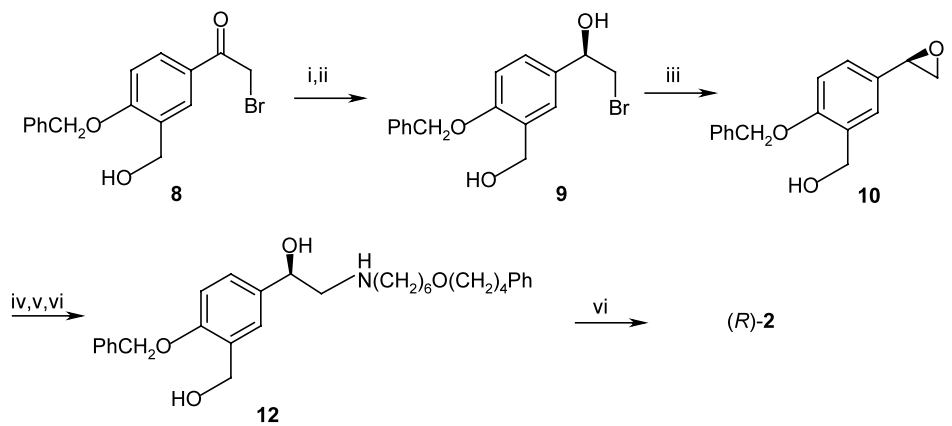
3. Conclusion

In summary, a simple, mild and environmentally friendly biotransformative method has been developed through which (*R*)-(−)-denopamine and (*R*)-(−)-salmeterol can be prepared with high yield and enantioselectivity. The method developed is quite appealing and involves less steps than the other syntheses reported.

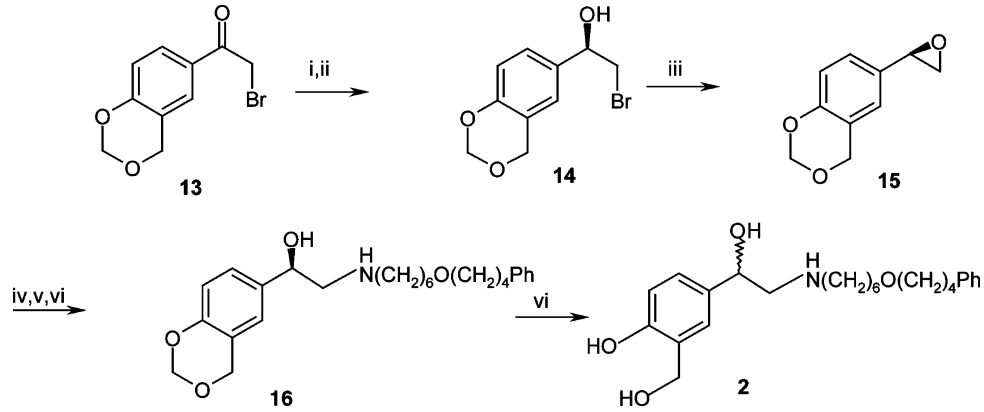
4. Experimental

4.1. Materials and methods

Organic chemicals were purchased from Aldrich unless otherwise indicated. ^{1}H NMR spectra (in $CDCl_3$) were recorded on a Varian T-60 spectrometer and Avance DPX 300 MHz Bruker spectrometer. Chemical shifts were given in parts per million from TMS as internal standard. Enantiomeric excesses were determined by HPLC analysis of the Mosher's esters[15]on a Waters Modular HPLC instrument using a chiralcel OD column (4.6 diameter×250 mm) from Daicel Chemical Company. Optical rotation data were recorded on a Perkin Elmer digital polarimeter model 343. IR spectra were obtained using a Perkin Elmer model 237B spectrometer. Mass spectra were recorded on an AEI Finnigan Mat spectrometer and C,H,N analysis on a Perkin Elmer 2400 instrument. The anaerobic incubations with specific gases in the microbial reactions were carried out in a two necked flat bottomed glass vessel having gas inlet and outlet provision. The gas inlet had its stem elongated with the end immersed in the reaction medium. Both the inlet and outlet tubes were fitted with stop cocks to regulate the flow of gas.



Scheme 2. (i) *Rhodotorula rubra* microbial culture; (ii) sodium lauryl sulfate; (iii) K_2CO_3/THF/reflux; (iv) *N*,*O*-bis(trimethylsilyl)-acetamide; (v) DMSO; (vi) $Ph(CH_2)_4O(CH_2)_6NH_2$ **11**; (vii) Pd–C/H_2.



Scheme 3. (i) *Rhodotorula rubra* microbial culture; (ii) sodium lauryl sulfate; (iii) K_2CO_3/THF/reflux; (iv) *N*,*O*-bis(trimethylsilyl)acetamide; (v) DMSO; (iv) $Ph(CH_2)_4O(CH_2)_6NH_2$ **11**; (vii) HCl/H_2O.

4.2. Preparation of substrates 3, 8 and 13

The brominated derivatives **3**, **8** and **13** were prepared according to the literature report.[21,22]

4.3. Microorganisms, media and culture conditions

The microbial culture of *Rhodotorula rubra* was prepared as per the procedure reported in our earlier communication.[14]

4.4. Whole cell microbial reduction of ω-bromoacetophenones 3, 8 and 13 adsorbed on sodium lauryl sulfate

4.4.1. Preparation of (*R*)-(−)-2-bromo-1-(4-benzyloxyphenyl)ethanol 4 under an argon atmosphere. 4-Benzyloxy-ω-bromo acetophenone **3** (0.3 g, 1 mmol) was first dissolved in acetone and then added to sodium lauryl sulphate (0.9 g) and the mixture was stirred for 10 min. The solvent was removed under reduced pressure and the solid obtained was added to a suspension of the wet microbial cell of *Rhodotorula rubra* (15 g) in water (300 mL), maintaining the pH of the solution at 7. A total of six reaction flasks were taken. Air was driven out of the flasks and argon was added. The flasks were then kept in a shaker at 30°C for 48 h at 200 rpm. The reaction mixtures were extracted in ethyl acetate several times (6×50 mL) and the solvent was dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure. The crude product obtained was then purified by chromatography using 50% petroleum ether–dichloromethane as eluent to afford (*R*)-(−)-2-bromo-1-(4-benzyloxyphenyl)ethanol **4** (0.25 g, 80%); mp 70–73°C; $[\alpha]_D^{25}$: −8.5 (*c* 4, $CHCl_3$), ^{1}H NMR δ: 1.1 (1H, OH, bs), 2.1 (2H, CH_2Br, m), 4.4 (1H, CHOH, d, $J=8$ and 3 Hz), 5 (2H, OCH_2Ph, s), 6.7–7.7 (9H, m, aromat. H); IR (KBr; cm^{-1}): 3330, 2930, 1550, 1250; EIMS *m*/*z*: 306 (M^+), 308. Anal. calcd for $C_{15}H_{15}BrO_2$: C, 58.80; H, 4.90; found: C, 58.65; H, 4.87%.

Similarly, **9** and **14** were prepared.

4.4.2. (*R*)-(−)-2-Bromo-1-(3-hydroxymethyl-4-benzyloxyphenyl)ethanol 9. Isolated yield: 0.24 g (78%); mp: 118°C, $[\alpha]_D^{25}$: −25 (*c* 4, CH_2Cl_2), ^{1}H NMR δ: 2.7 (1H, OH of CH_2OH, bs), 3.5 (1H, OH of CHOH, bs), 3.63 (2H, CH_2Br, m), 4.7 (2H, CH_2OH, s), 4.87 (1H, CHOH, dd, $J=8$ and 4 Hz), 5.1 (2H, OCH_2Ph, s), 6.9–7.4 (8H, aromat. H, m). IR (KBr; cm^{-1}): 3300, 2900, 1500; 1175; EIMS *m*/*z*: 336 (M^+), 338. Anal. calcd for $C_{16}H_{17}BrO_3$: C, 57.14; H, 5.06; found: C, 56.99; H, 4.87%.

4.4.3. (*R*)-(−)-2-Bromo-1-(1,3-benzodioxan-6-yl)ethanol 14. Isolated yield: 0.17 g (69%); mp 67°C; $[\alpha]_D^{25}$: −41 (*c* 1, $CHCl_3$); ^{1}H NMR δ: 1.66 (1H, OH, bs), 2.1 (2H, CH_2Br, m), 4 (1H, CHOH, dd, $J=9$ and 3 Hz), 4.75 (2H, C-CH_2-O, s), 5.1 (2H, O-CH_2-O, s), 6.7 (1H, aromat. 8-H, d, $J=8$ Hz), 7.4 (1H, aromat. 5-H, d, $J=4$ Hz), 7.5 (1H, aromat. 7-H, dd, $J=8$ and 2 Hz); IR (KBr, cm^{-1}): 3330, 2925, 1530, 1135; EIMS *m*/*z*: 258 (M^+), 260. Anal. calcd for $C_{10}H_{11}BrO_2$, C, 46.51; H, 4.26; found: C, 46.44; H, 4.26%.

4.4.4. Preparation of epoxide 5. (*R*)-(−)-2-Bromo-1-(4-benzyloxyphenyl)ethanol **4** (0.225 g, 0.7 mmol) was taken in dry THF (15 mL) and treated with anhydrous potassium carbonate (0.15 g, 1.1 mmol). The mixture was stirred under reflux for 2 h, when the starting materials were shown to be completely consumed by TLC analysis. The mixture was cooled and filtered and the filtrate was concentrated under reduced pressure. Water was added and the mixture extracted with ethyl acetate (3×10 mL). The solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford crude epoxide **5**. The product was purified by passing through a neutral alumina column using 50% dichloromethane in petroleum ether as eluent. Yield of (*R*)-(−)-**5** 0.12 g (74.5%); $[\alpha]_D^{25}=-15.0$ (*c* 1.0, $CHCl_3$), oil; ^{1}H NMR δ: 2.73 (1H, CH_2O-, dd, $J=5.11$ and 2.38 Hz), 3.18 (1H, CH_2O-, dd, $J=5.13$ and 4.09 Hz), 3.81 (1H, CHOH, dd, $J=3.77$ and 2.54 Hz), 5.17 (2H, CH_2OH, s), 6.68–

7.58 (9H, m, aromat H); IR (neat, cm^{-1}) 2950, 1600, 1520, 1295, 755; EIMS m/z: 226 (M^+). Anal. calcd for $C_{15}H_{14}O_2$: C, 79.64, H, 6.19; found: C, 79.62; H, 6.14%.

4.4.5. Benzylated denopamine 7. A mixture of phenethylamine **6** (0.094 mL, 0.48 mmol), anhydrous DMSO (10 mL) and *N*,*O*-bis(trimethylsilyl)acetamide (320 μL) was stirred under nitrogen for 30 min at room temperature. A solution of the (*R*)-epoxide **5** (0.113 g, 0.48 mmol) and anhydrous DMSO (10 mL) was added and the resulting mixture heated at 85°C for 35 h. The mixture was cooled, the solvent distilled off (0.1 mm) and the resulting crude purified by column chromatography over neutral alumina, eluting with hexane–ethyl acetate mixtures. A gummy material was obtained (0.142 g, 70%); $[\alpha]_D^{25} = -34.3$ (*c* 1.00, $CHCl_3$); ^1H NMR δ 1.14 (1H, OH, bs) 2.63–2.88 (6H, $C\underline{H}_2NHC\underline{H}_2C\underline{H}_2$, m), 3.84 (3H, $OC\underline{H}_3$, s), 3.90 (3H, $OC\underline{H}_3$, s), 4.69 (1H, C<u>H</u>OH, dd, $J = 8.23$ and 3.77 Hz), 6.61–7.20 (12H, m, aromat. H); IR (thin film/cm^{-1}) 3280, 2933, 1610, 1454, 1035, 750; EIMS m/z: 407 (M^+). Anal. calcd for $C_{25}H_{29}NO_4$: C, 73.71; H, 7.12; N, 3.44; found: C, 73.68; H, 7.05; N, 3.41%.

4.4.6. (*R*)-(−)-Denopamine (*R*)-1. A mixture of the gummy material obtained above (0.1 g, 0.24 mmol) and 10% Pd–C (0.015 g) was suspended in absolute alcohol and hydrogenated at 50 psi at room temperature for 12 h. The mixture was filtered under vacuum and the catalyst thoroughly washed with ether, ethanol and dichloromethane. Removal of the solvent left a residue which on purification through column chromatography over neutral alumina (E. Merck) yielded (*R*)-(−)-denopamine, (*R*)-**1** (0.051 g, 65%); mp 161°C (lit.[23] 163°C) $[\alpha]_D^{25} = -26.8$ (*c* 1.00, MeOH) [lit.[10] −27.7]; ^1H NMR ($CDCl_3$) 2.52 (1H, O<u>H</u> exchangeable, bs), 2.69 (4H, 2×C<u>H</u>$_2$, m), 2.85 (2H, 1×C<u>H</u>$_2$, m), 3.53 (1H, N<u>H</u> exchangeable, bs), 3.74 (3H, $OC\underline{H}_3$, s) and 3.76 (3H, $OC\underline{H}_3$, s), 4.55 (1H, C<u>H</u>OH, m), 5.24 (1H, O<u>H</u> exchangeable, bs), 6.67 (3H, aromat H, m); 6.82 (1H, aromat. H, d, $J = 1.68$ Hz); 6.85 (1H, aromat. H, d $J = 8.21$); 7.08 (2H, 2×aromat. H, d $J = 8.3$ Hz); IR (KBr, cm^{-1}) 3225, 2980, 1625, 1575, 1515; EIMS m/z 317 (M^+). Anal. calcd for $C_{18}H_{23}NO_4$; C, 68.13; H, 7.25; N, 4.41 found: C, 68.09; H, 7.21; N, 4.40%.

4.4.7. Preparation of epoxide 10. (*R*)-(−)-2-Bromo-1-(4-benzyloxy-3-hydroxymethylphenyl)ethanol **9** (0.22 g, 0.6 mmol) was dissolved in dry THF (15 mL) and the solution was treated with anhydrous potassium carbonate (0.14 g, 0.9 mmol). The mixture was stirred under reflux for 2 h, cooled and filtered. The filtrate was concentrated under reduced pressure, water was added to the residue and the solution was extracted with ethyl acetate (3×20 mL). The solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude epoxide **10**. The product was purified by passing through a silica gel column using 50% dichloromethane in petroleum ether as eluent to afford epoxide **10** as an oil. Yield of (*R*)-(−)-**10** 0.11 g, (67%); $[\alpha]_D^{25} = -19.0$ (*c* 1.00, $CHCl_3$); ^1H NMR δ: 2.76 (1H, $C\underline{H}_2OH$, dd, $J = 5.3$ and 2.4 Hz), 3.15 (1H, $C\underline{H}_2OH$, dd, $J = 5.1$ and 4.2 Hz), 3.85 (1H, C<u>H</u>OH, dd, $J = 3.8$ and 2.6 Hz), 4.22 (2H, $ArC\underline{H}_2OH$, s), 5.24 (2H, $ArC\underline{H}_2OC$, s), 7.10–7.79 (8H, aromat-<u>H</u>, m); IR (thin film/cm^{-1}) 3050, 2950, 1600, 1525, 1355, 755; EIMS m/z 256 (M^+). Anal. calcd for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25; found: C, 74.87; H, 6.05%.

4.4.8. Preparation of benzylated (*R*)-(−)-salmeterol, (*R*)-2. A mixture of amine **11** (0.1 g, 0.4 mmol), anhydrous DMSO (10 mL) and *N*,*O*-bis(trimethylsilyl) acetamide (220 μL) was stirred under nitrogen for 30 min at room temperature. A solution of the epoxide **10** (0.10 g, 0.4 mmol) in anhydrous DMSO (10 mL) was added and the resulting mixture was heated at 85°C for 50 h. The mixture was cooled, the solvent distilled off (0.1 mm) and the resulting crude purified by column chromatography in neutral alumina eluting with hexane–ethyl acetate mixtures. A gummy material was obtained (0.13 g, 66%); $[\alpha]_D^{25} = -25$ (*c* 1.00, $CHCl_3$); ^1H NMR δ: 1.18–1.5 (12H, m), 2.54–2.96 (4H, m), 3.19–3.30 (4H, m), 4.17–5.11 (5H, m), 5.30 (2H, b, exchangable), 6.61–7.20 (13H, m); IR (thin film/cm^{-1}) 3280, 2933, 1610, 1454, 1035, 750; m/z 505 (M^+). Anal. calcd for $C_{32}H_{43}NO_4$: C, 76.03; H, 8.51; N, 2.72; found: C, 75.88; H, 8.39; N, 2.61%.

4.4.9. Preparation of (*R*)-(−)-salmeterol, (*R*)-2. A mixture of the gummy material obtained above (0.12 g, 0.23 mmol) and Pd–C (0.015 g, 15 mol% of **12**) was taken in absolute alcohol and hydrogenated at 50 psi at room temperature for 12 h. The mixture was filtered under vacuum and the catalyst thoroughly washed with ether, ethanol and dichloromethane. Removal of the solvent left a residue, which on purification through column chromatography using neutral alumina (E. Merck) yielded 0.064 g (61%) (*R*)-(−)-salmeterol as an oil; $[\alpha]_D^{25} = -21.5$ (*c* 1.00, MeOH) (lit.[18] $= -22.8$). The enantiomeric excess obtained was 94% based on HPLC data.[15] ^1H NMR δ: 1.18–1.5 (12H, m), 2.54–2.96 (4H, m), 3.19–3.30 (4H, m), 4.17–5.03 (3H, m), 5.30 (2H, b, exchangable), 6.61–7.18 (8H, m); IR (thin film/cm^{-1}) 3300, 2967, 1670, 1610, 1440, 1030, 800; EIMS m/z 415 (M^+). Anal. calcd for $C_{25}H_{37}NO_4$: C, 72.28; H, 8.91; N, 3.37; found: C, 72.12; H, 8.78; N, 3.29%.

Acknowledgements

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