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Enantioselective synthesis of bronchodilating agent (*R*)-Salmeterol [#]

P L N Ranganath[ab], T Anil[a] & A Venkat Narsaiah*[ab]

[a] Organic Synthesis Laboratory, Fluoro-Agrochemicals Department,
CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, India

E-mail: vnakkirala@iict.res.in; vnakkirala2001@yahoo.com

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Synthesis of β_2-adrenoreceptor agonist bronchodilator (*R*)-Salmeterol has been described with good yields. The synthesis commenced from commercially available starting materials, 4-hydroxy benzaldehyde and phenylbutanoic acid. The features of the synthetic strategy are Wittig olefination and Sharpless asymmetric dihydroxylation.

Keywords: Enantioselective, amino alcohol, catecholamines, branchospasm, dihydroxylation

Adrenergic agents, Norepinephrine, Epinephrine, Dopamine and (*R*)-Salmeterol (Figure 1), which modulates various processes like rate and force of cardiac retrenchment, restriction, dilation of blood vessels and bronchioles and many[1,2]. The catecholamines, mediates several functions *via* α-(α_1,α_2) and β-(β_1,β_2,β_3)-receptors as mentioned in the super family of *G*-protein coupled receptors (GPCR's)[3,4]. Preferentially, (*R*)-isomer of many adrenergic agents have high affinity to bind over corresponding adrenoreceptors, because, these are biosynthesized in the body from L-tyrosine and thus responsible for their biological activity.

In spite of other bronchodilators, (*R*)-Salmeterol is more potent, long acting, β_2-adrenergic, agonist used in first line for the treatment of pulmonary diseases like bronchospasm, chronic obstructive pulmonary and also resistant to both COMT (catechol-o-methyl transferase) and MAO (mono amino oxidase)[5-7]. Pertaining to its unique properties, attracted the attention of synthetic chemists and lead to its synthesis in different ways[8-20].

Results and Discussion

As part of our regular research program, in synthesis of biologically active natural and synthetic molecules[21-25], herein we report the enantioselective synthesis of bronchodilating agent (*R*)-Salmeterol.

Retro synthetic analysis (Scheme I) reveals that the molecules could be assembled *via* coupling of two important building blocks, in which amine fragment (**9**) could be accessed from commercially available, 4-hydroxybenzaldehyde (**2**) and halo fragment (**12**) could be resulted from phenyl butanoic acid (**10**), on reduction followed by coupling with 1,6-dibromohexane. The pharmacophoric key precursor, chiral α-amino alcohol (**9**) synthesis, started from 4-hydroxy benzaldehyde (**2**), which on phenolic Aldol condensation[26] with formaldehyde in presence of base to give, 4-hydroxy-3 (hydroxymethyl)benzaldehyde (**3**) in excellent yields. Further, acetonide protection (**4**), followed by Wittig olefination with C_1 ylide salt in presence of ^{t}BuOK afforded, 2,2-dimethyl-6-vinyl-4*H*-benzo[d][1,3]dioxine (**5**) as shown in the Scheme II [27-29].

Thus obtained olefin compound **5,** subjected to Sharpless asymmetric dihydroxylation[30,31] with AD-mix-β, to afford the key intermediate, chiral diol **6**, in 94% yield, with 98% *ee*, confirmed by HPLC data (chiracel OD-H). The diol was subjected to selective protection of primary alcohol[32,33] using TsCl and TEA to afford, compound **7** in very good yields. Thus obtained tosyl was converted into azide through nucleophilic substi tution with NaN_3 in DMF to give, compound **8**, and subsequent reduction of azide with Pd/C (10%)[34] under hydrogen atmosphere to give the chiral amino alcohol (**9**) in 88% yield, as shown in the Scheme II.

The second fragment was synthesized from phenyl butanoic acid (**10**), which on reduction with LAH to give 4-phenylbutan-1-ol (**11**) in good yields[35,36]. The obtained primary alcohol on coupling with 1,6-dibromo hexane in presence of K_2CO_3 resulted, {4[(6-bromo hexyl)oxy] butyl} benzene (**12**) in 65% yields. The key fragments **9** and **12** on coupling gives the core compound **13** in 85% yields. Finally, the acetonide

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deprotection was achieved smoothly in presence of acetic acid - water mixture to give the target molecule, (*R*)-Salmeterol (**1**) in excellent yields and selectivity, as shown in the Scheme III.

Experimental Section

All the air and moisture sensitive reactions were carried out under nitrogen atmosphere. Oven-dried glass apparatus were used to perform all the reaction.

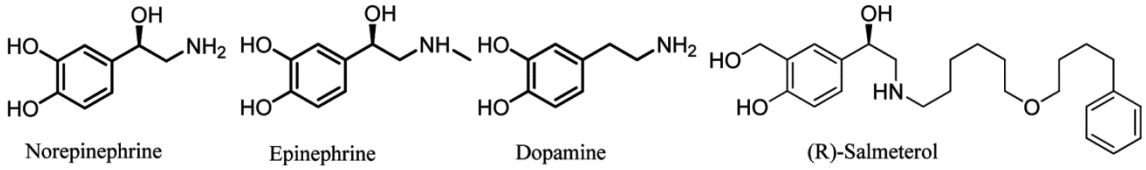
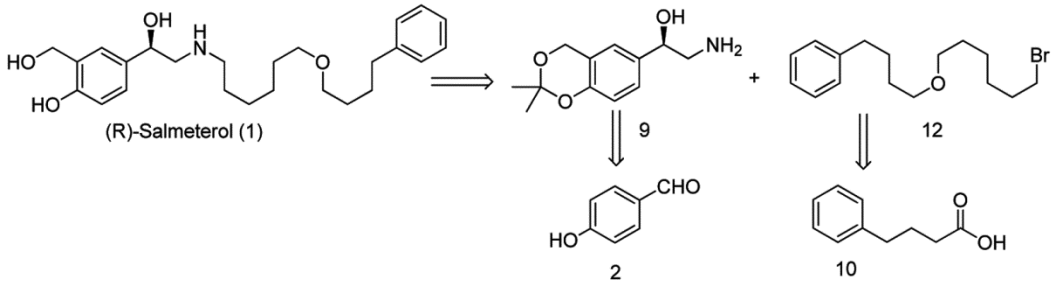
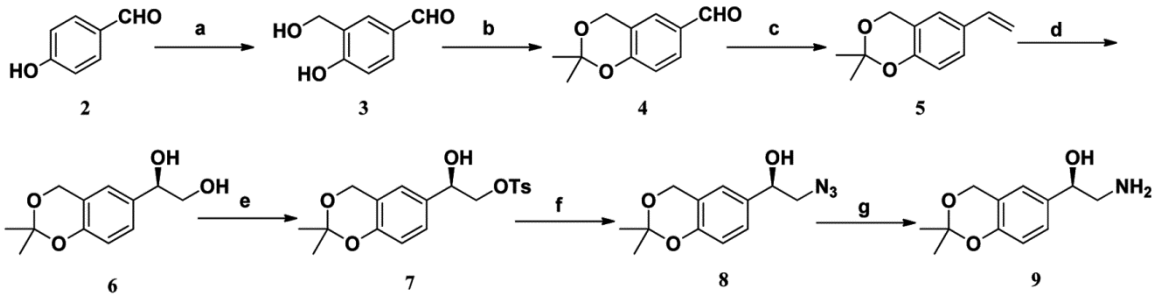


Figure 1

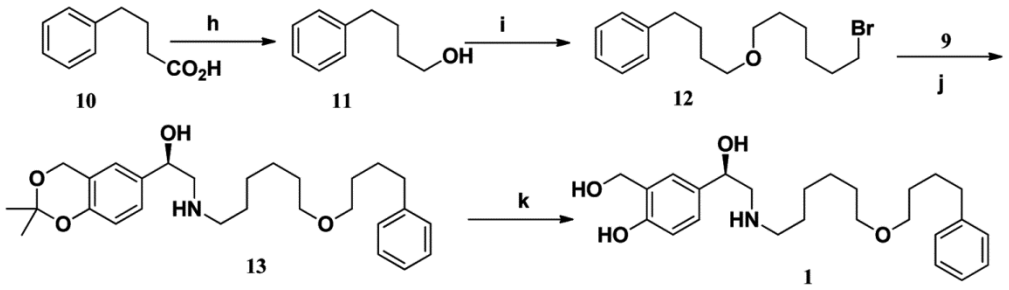


Scheme-I



Reagents and Conditions: (a) HCHO, H_2O, $Na_2B_4O_7$, 1M, NaOH, 40°C, 5d, 83%. (b) 2,2-DMP, Acetone, *p*-TSA, 1 h, 65%. (c) C_1 Wittig, ^{t}BuOK, THF, 0°C, 2 h, 80%. (d) AD-mix-β, ^{t}BuOH:H_2O (1:1), methanesulfonamide, 0°C, 24 h, 94%. (e) TsCl, Bu_2SnO, Et_3N, DCM. 1 h, 79%. (f) NaN_3, DMF, 70°C, 12 h, 92%. (g) Pd/C, H_2, EtOAc, RT, 12 h, 88%.

Scheme II



Reagents and Conditions: (h) LAH, RT, 1 h, 75%. (i) 1,6-dibromhexane, CH_3CN, K_2CO_3, KI, 80°C, 7 h, 65%. (j) CH_3CN, K_2CO_3, KI, 80°C, 24 h, 85%. (k) AcOH-H_2O (2:1), 70°C, 1 h, 88%.

Scheme III

Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz and 500 MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectrophotometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70eV. Optical rotation values were recorded on Horiba sepa300 polarimeter. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

4-Hydroxy-3-(hydroxymethyl)benzaldehyde, 3

To a stirred solution of 4-hydroxy benzaldehyde (10 g, 89.3 mmol), in water (80 mL) was added borax (25 g) and NaOH solution (1M, 60 mL) and stirred for 30 minutes at RT. Then aqueous formaldehyde (40%, 10 mL) was added in one portion. The reaction was stirred at 40°C for 5 days. After completion of the reaction (monitored by TLC) cooled to RT, and mixture was acidified with HCl (3M) upto *p*H 2. Then, extracted with ethyl acetate (3×50 mL). The combined organic portions was washed brine, dried over Na_2SO_4 and concentration under reduced pressure. The crude compound was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (3:7) mixture to gives a pure compound **3** as white solid, in 11.2 g (83%). Mp: 142 - 143°C.; IR (neat): υ 3311, 3217, 2924, 2853, 1784, 1596, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.80 - 7.72 (m, 1H), 7.68 (d, 1H, *J* = 1.9 Hz), 7.60 (d, 1H, *J* = 1.8 Hz), 7.01 (dd, 1H, *J* = 8.3, 3.6 Hz), 4.99 (brs, 1H), 4.87 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 161.1, 132.6, 130.8, 129.6, 122.8, 117.0, 67.6.; HRMS-ESI: *m/z* $[M-H]^+$ Calcd for $C_8H_7O_3$: 151.0475; found: 151.0489.

2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxine-6-carbaldehyde, 4

To a stirred solution of compound **3** (5 g, 32.9 mmol) in dry acetone (50 mL) was added 2,2-DMP (4.4 g, 42.8 mmol) and a cat. amount of pTSA, continued stirring for 1h at RT. After completion of the reaction (monitored by TLC), extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to obtain compound **4** as yellow oil, in 3.90 g (65%). IR (neat): υ 3146, 2924, 2853, 1742, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.71 (d, 1H, *J* = 10.3 Hz), 7.55 (s, 1H), 6.93 (d, 1H, *J* = 8.4 Hz), 4.91 (s, 2H), 1.58 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 156.8, 130.5, 129.5, 126.9, 119.7, 117.7, 100.8, 60.6, 24.8.; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{11}H_{13}O_3$: 193.0872; found: 193.0927.

2,2-Dimethyl-6-vinyl-4*H*-benzo[*d*][1,3]dioxine, 5

To a stirred suspension of compound **4** (2 g, 10.4 mmol) in dry THF (15 mL), was added a solution of C_1 ylide salt (21.1 g, 52.1 mmol, THF) and ^{t}BuOK (5.8 g, 10.4 mmol) at 0°C and continued stirring for 2h at RT. After completion (monitored by TLC), reaction was quenched with cold water, then removed THF under vacuum and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromato graphy using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to give the compound **5** as yellow liquid, in 1.58 g (80%). IR (neat): υ 2991, 2923, 1728, 1614, 1499, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, 1H, *J* = 8.4 Hz), 7.01 (s, 1H), 6.78 (d, 1H, *J* = 8.4 Hz), 6.62 (dd, 1H, *J* =17.3, 10.9 Hz), 5. 59 (d, 1H, *J* = 17.3 Hz), 5.12 (d, 1H, *J* = 10.9 Hz), 4.84 (s, 2H), 1.54 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 136.1, 130.1, 125.9, 122.4, 119.2, 117.1, 111.7, 99.6, 60.8, 24.7.; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{12}H_{15}O_2$: 191.0995; found: 191.1009.

(*R*)-1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl) ethane-1,2-diol, 6

To a stirred mixture of ^{t}BuOH-H_2O (1:1, 63 mL) was added compound **5** (1.2 g, 6.3 mmol), then added AD-mix-*β* (8.8 g) followed by methanesulfonamide (0.6 g) at 0°C and stirred continuously for 24h at same temperature. After the completion of reaction indicated by TLC, sodium sulphite (7.5 g) was added. The suspension was dissolved in cold water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromato graphy using silica gel (60-120 mesh) by eluting with EtOAc-hexane (3:7) mixture to give pure compound **6** as a white solid, in 1.3 g (94%). Mp: 80 - 81°C. Specific rotation: $[\alpha]_D^{25}$ -11 (*c* = 1, $CHCl_3$): IR (neat): υ 3351, 2923, 1731, 1500, 1458, 1142 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.14 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.02 (s, 1H), 6.81 (d, 1H, *J* = 8.43 Hz), 4.84 (s, 2H), 4.77- 4.72 (m, 1H), 3.78 - 3.69 (m, 1H), 3.68 - 3.60 (m, 1H), 1.54 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 132.3, 125.9, 122.4, 119.4, 117.1, 99.6, 74.2, 68.0, 60.8, 24.7, 24.6.; HRMS-ESI: *m/z* $[M-H]^+$ Calcd for $C_{12}H_{15}O_4$: 224.1047; found: 224.1063.

(*R*)-1-(2,2-Dimethyl-4*H*-benzo[d][1,3]dioxin-6-yl) 2-hydroxyethyl-4-methylbenzenesulfonate, 7

To a stirred mixture of **6** (1 g, 4.5 mmol) in dry DCM (10 mL) at 0°C was added Bu_2SnO (0.2 g, 0.9 mmol), TsCl (0.85 g, 4.5 mmol) and Et_3N (0.67 g, 6.7 mmol) and stirring continued for 1h. After completion of the reaction (monitored by TLC), quenched with cold water and extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Thus obtained crude compound **7**, a yellow liquid (1.68 g, 79%), was used for further reaction without purification. Specific rotation: $[\alpha]_D^{25}$ -3.5 (*c* = 1, $CHCl_3$).; IR (neat): υ 3428, 2924, 1725, 1597, 1452, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 2H, *J* = 8.6 Hz), 7.34 (d, 2H, *J* = 8.6 Hz), 7.07 (dd, 1H, *J* = 8.0, 1.8 Hz), 6.95 (d, 1H, *J* = 1.4 Hz), 6.77 (d, 1H, *J* = 8.4 Hz), 4.92 - 4.87 (m, 1H), 4.80 (s, 2H), 4.14 - 4.09 (m, 1H), 4.05 - 3.99 (m, 1H), 2.45 (s, 3H).1.52 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 145.0, 132.6, 130.0, 129.9, 127.9, 126.0, 122.6, 119.6, 117.2, 99.7, 74.2, 71.5, 60.7, 24.8, 24.5, 21.6.; HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{19}H_{22}NaO_6S$: 401.1037; found: 401.1045.

(*R*)-2-Azido-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl) ethanol, 8

To a stirred solution of compound **7** (1 g, 2.6 mmol) in dry DMF (10 mL) was added NaN_3 (0.86 g, 13.2 mmol) and stirred continuously at 70°C for 12 h. After completion of the reaction, confirmed by TLC, extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to afford the compound **8** as colorless liquid, in 0.6 g (92%). Specific rotation: $[\alpha]_D^{25}$ -3.3 (*c* = 1, $CHCl_3$): IR (neat): υ 3428, 2924, 2098, 1725, 1500, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dd, 1H, *J* = 8.4, 1.5 Hz), 7.02 (s, 1H), 6.82 (d, 1H, *J* = 8.3 Hz), 4.85 (s, 2H), 4.84 - 4.76 (m, 1H), 3.52 - 3.37 (m, 2H), 1.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 132.3, 125.8, 122.3, 119.4, 117.3, 99.7, 73.0, 60.8, 58.1 24.7, 24.6.; HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{12}H_{15}N_3$ NaO_3: 272.1011; found: 272.1025.

(*R*)-2-Amino-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl) ethanol, 9

To the compound **8** (0.5 g, 2 mmol) in ethyl acetate (10 mL) was added catalytic amount of Pd/C (10%) and stirred under hydrogen atmosphere at RT, 12h. After completion of the reaction, indicated by TLC, filtered through celite bed. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure, the obtained crude compound **9** as half-white solid, in 0.4 g (88%) and which was used for further reaction without purification. Specific rotation: $[\alpha]_D^{25}$ -2.5 (*c* = 1, $CHCl_3$).; IR (neat): υ 3320, 2957, 2920, 1734, 1462 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ 7.10 (d, 1H, *J* = 8.4 Hz), 7.01 (s, 1H), 6.73 (d, 1H, *J* = 8.2 Hz), 4.88 - 4.82 (m, 1H), 4.80 (s, 2H), 4.45 - 4.37 (m, 2H), 1.77 (s, 2H), 1.45 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 135.8, 125.6, 122.4, 118.9, 115.9, 99.0, 73.1, 60.1, 49.3, 24.5, 24.4.; HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{12}H_{17}NNaO_3$: 246.1104; found: 246.1117.

4-Phenylbutan-1-ol, 11

To a stirred solution of 4-phenylbutyric acid (2 g, 12.2 mmol) in dry THF (20 mL) was added LAH (0.66g, 18.3 mmol) at 0°C and the reaction mixture was stirred for 1h at RT. After completion of the reaction, as indicated by TLC, then quenched with ammonium chloride solution and solvent was removed under reduced pressure. The residue was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to give the pure compound **11** as yellow liquid, in 1.3 g (75%). IR (neat): υ 3745, 3350, 3046, 2850, 1454, 1243 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.23 (m, 2H), 7.21 - 7.12 (m, 3H), 3.63 (t, 2H, *J* = 6.4 Hz), 2.63 (t, 2H, *J* = 7.3 Hz), 1.73 - 1.64 (m, 2H), 1.63 - 1.54 (m, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 128.4, 128.2, 125.9, 125.6, 62.6, 35.5, 32.1, 27.4.; HRMS-ESI: *m/z* $[M-H]^+$ Calcd for $C_{10}H_{13}O$: 149.1044; found: 149.1059.

[4-(6-Bromohexyloxy)butyl] benzene, 12

To a stirred solution of compound **11** (1 g, 6.7 m mol) in dry acetonitrile (20 mL) was added 1,6-di bromohexane (0.54 g, 2.3 mmol) followed by K_2CO_3 (0.1 g, 0.67 mmol) and KI (0.11 g, 0.67 m mol) at RT.

The reaction mixture was stirred for 7h at 80°C. After completion of reaction (confirmed by TLC), the reaction mixture was concentrated and residue was diluted with cold water and extracted with EtOAc (3×20 mL). The combined organic layers, washed with brine, dried over Na_2SO_4 and concentrated. The crude product, purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to afford the compound **12** as yellow liquid, in 1.3 g (65%). IR (neat): υ 3044, 2928, 2843, 1562, 1455, 1169, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.25 (m, 2H), 7.22 - 7.15 (m, 3H), 4.06 (t, 2H, *J* = 6.6 Hz), 3.18 (t, 2H, *J* = 6.9 Hz), 2.65 (t, 2H, *J* = 7.4 Hz), 2.32 (t, 2H, *J* = 7.3 Hz), 2.02 - 1.91 (m, 2H), 1.87 - 1.76 (m, 2H), 1.68 - 1.57 (m, 4H), 1.50 - 1.29 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 128.4, 128.3, 125.9, 64.1, 35.1, 33.6, 33.2, 32.5, 30.0, 28.4, 27.7, 26.5, 24.9.; HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{16}H_{25}BrNaO$: 336.0987; found: 336.0998.

(*R*)-1(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2[6 (4-phenylbutoxy)hexylamino]ethanol, 13

To a stirred mixture of compound **9** (0.3 g, 1.34 m mol) and K_2CO_3 (400 mg, 2.89 mmol) in dry aceto nitrile (10 mL) at r. t., was added compound **12** (0.25 g, 0.8 mmol) and continued stirring for 48h at 80°C. TLC confirms the completion of reaction and then the reaction mixture was concentrated and residue was dissolved in water and extracted with EtOAc (3×10 mL). The combined organic layers, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtained the crude compound **13** as yellow liquid, in 0.5 g (85%). Specific rotation: $[\alpha]_D^{25}$ -11.6 (*c* = 1, $CHCl_3$).; IR (neat): υ 3445, 3052, 2926, 1632, 1380, 1453, 1263, 1213, 1117, 760 cm^{-1}.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.27 (m, 1H), 7.20 - 7.16 (m, 4H), 7.08 (dd, 1H, *J* = 8.4, 2.0 Hz), 6.88 (s, 1H), 6.80 (d, 1H, *J* = 8.4 Hz), 4.88 - 4.84 (m, 1H), 4.83 (s, 2H), 3.66 (t, 4H, *J* = 6.4 Hz), 3.13 - 3.10 (m, 1H), 2.80 - 2.77 (m, 1H), 2.65 (t, 4H, *J* = 7.4 Hz), 1.74 - 1.56 (m, 8H), 1.53 (s, 6H), 1.42 - 1.32 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 142.2, 129.1, 128.3, 128.2, 125.7, 125.5, 121.7, 119.5, 117.2, 99.6, 70.6, 62.7, 60.8, 60.3, 52.1, 50.9, 35.7, 35.6, 32.2, 29.6, 29.3, 28.0, 27.5, 24.7, 24.6.; HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{28}H_{41}NNaO_4$: 478.2933; found: 478.2845.

(*R*)-4-(1-Hydroxy-2-[(6-(4-phenylbutoxy)hexyl) amino)ethyl)-2-(hydroxymethyl)phenol, 1

To a stirred solution of acetic acid (4 mL) and water (2 mL) was added the compound **13** (50 mg, 0.1mmol) and stirred at 70°C for 1h. The completion of reaction was confirmed by TLC. The reaction mixture was neutralized by adding sat. $NaHCO_3$. Then reaction mixture extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, to obtain the crude product, which was recrystalized with ethyl acetate to yield pure product as solid, in 40 mg (88%). Mp: 75 - 76°C [lit,[17] 75 - 76°C]. Specific rotation: $[\alpha]_D^{25}$ -20.1 (*c* = 1, $CHCl_3$), [lit,[11b] $[\alpha]_D^{25}$ -20.6 (*c* = 1, $CHCl_3$).; IR (neat): υ 3443, 3048, 2929, 1627, 1396, 1453, 1396, 1263, 1213, 1113, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 - 7.22 (m, 2H), 7.19 - 7.12 (m, 3H), 6.95 (s, 1H), 6.84 (d, 1H, *J* = 7.4 Hz), 6.67 (d, 1H, *J* = 7.4 Hz), 4.88 - 4.68 (m, 3H), 4.43 (s, 2H), 3.38 (t, 2H, *J* = 6.4 Hz), 3.33 (t, 2H, *J* = 6.4 Hz), 2.91 - 2.79 (m, 2H), 2.59 (t, 4H, *J* = 7.2 Hz), 1.72 - 1.54 (m, 6H), 1.53 - 1.45 (m, 2H), 1.36 - 1.15 (m, 4H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 142.3, 130.9, 128.3, 128.2, 126.7, 126.3, 125.6, 115.8, 70.7, 70.6, 68. 6, 61.0, 54.1, 48.0, 35.6, 29.6, 29.4, 29.2, 27.9, 26.4, 25.8, 25.6, 22.8.; HRMS-ESI: *m/z* $[M+H]^+$ Calcd for $C_{25}H_{38}NO_4$: 416.27954; found: 416.28009.

Conclusions

In summary, we have accomplished the enantio selective synthesis of β_2-agonist, (*R*)-Salmeterol successfully. The synthesis comprises, a simple, facile and inexpensive methodologies, in good yields with an overall yield of 9.5 % in 11 steps. The required chiral center in pharmacophore was fixed using Sharpless asymmetric dihydroxylation protocol.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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