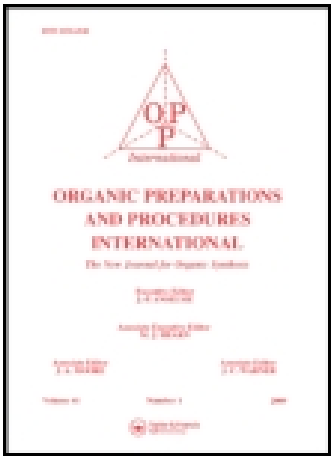

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OPPI BRIEF

An Efficient and Practical Synthesis of Salmeterol

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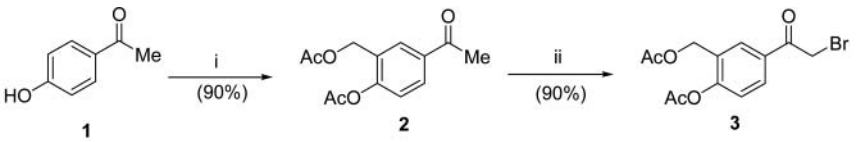
Salmeterol (Serevent® **9**) is a potent, long-acting β2-adrenoreceptor agonist used as a bronchodilator for the prevention of bronchospasm in patients with asthma and chronic obstructive pulmonary disease.[1] Unlike other bronchodilator drugs, salmeterol is much more lipophilic and displays many unusual pharmacological properties.[2] The synthesis of salmeterol was first reported in the patent literature.[3] Ruoho's group described a short and convenient route for the synthesis of salmeterol from salicylaldehyde[4] and enantioselective syntheses of (*R*)- and (*S*)-salmeterol have been developed.[5–7] Although it is claimed that the (*S*)-enantiomer of salmeterol had a higher selectivity for β2 receptors and that it did not trigger certain adverse effects associated with the administration of (±)-or (*R*)-salmeterol,[8] the drug is marketed as a racemate. Due to the length, low yields, high cost and difficulties of previous syntheses on a large scale,[3] an efficient and practical method for the preparation of salmeterol seemed desirable. Herein, we report a convenient route in good overall yields starting from 4-hydroxyacetophenone (**1**) *via* a highly selective bromination of compound **2**. Moreover, the lipophilic amine **6** was obtained in two steps under mild conditions from the reaction of 1,6-dibromohexane with 4-phenylbutanol instead of the three-five steps previous-ly reported in the literature.[9,10]

The starting sequence for the synthesis is outlined in *Scheme 1*. This approach involves the preparation of phenacyl bromide **3** in a three-step sequence from 4-hydrox-



i) 1.Me_2NH, HCHO, H_2O, 10-12 °C, 6h; 2.Ac_2O, toluene, reflux, 4h ii) Br_2, $CHCl_3$, propylene oxide, 0 °C, 2h

Scheme 1

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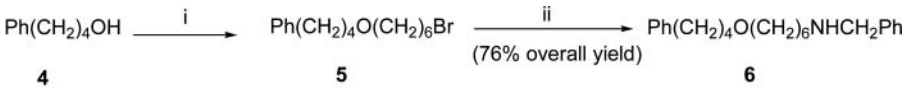
yacetophenone (**1**). Treatment of compound **1** with dimethylamine and formaldehyde followed by addition of acetic anhydride provided compound **2** in high yield (90%). Bromination of **2** was conducted in $CHCl_3$ in the presence of propylene oxide[11] at 0–5 °C in 90% yield.

The preparation of the amine portion is illustrated in *Scheme 2*. Condensation of 4-phenylbutanol (**4**) with 1,6-dibromohexane was carried out in toluene in the presence of

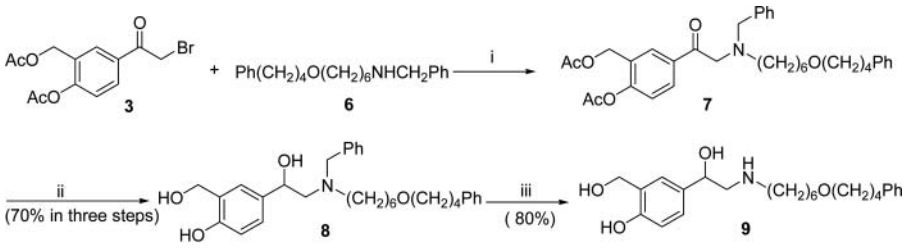


i) 1,6-dibromohexane, KOH, TBAB, $PhCH_3$, r.t. 10h; ii) benzylamine, Et_3N, KI, MeCN, 45 °C, 6h

Scheme 2

KOH. However, the yield of bromoether **5** was relatively low (60%) due to the formation of *bis*-ether by-products, making the purification of the desired bromoether **5** difficult and time-consuming. We found that the yield could be increased to 85% and without the formation of by-product by the addition of 10 mol% of tetra(*n*-butyl)ammonium bromide (TBAB) to the reaction mixture. Furthermore, the reaction was complete within 10 hours instead of the reported 1–3 days.[9,12] After removal of the excess of 1,6-dibromohexane, the crude product was treated directly with benzylamine in triethylamine and potassium iodide at 45°C until the bromoether **5** was consumed as monitored using TLC. Excess of benzylamine was removed by distillation under reduced pressure to leave **6** as a yellowish oil which was purified by conversion to its oxalate salt (≥98% pure by HPLC).

Condensation of **3** with amine **6** in the presence of K_2CO_3 led to aminoketone **7**. The aminoketone was processed to the next step without further purification by dissolution of in ethanol, followed by addition of conc. hydrochloric acid. After compound **7** had been consumed (as shown by TLC analysis), the pH of the reaction mixture was adjusted to 12 with 40% aqueous NaOH and then treated with sodium borohydride to give the compound **8** in 70% overall yield from compound **3**. Catalytic hydrogenolysis of the benzyl group on 10% Pd-C afforded salmeterol **9**, which was recrystallized from ethyl acetate to give a white powder, mp. 75–76°C (80% overall yield from compound **8**). The product was identified by NMR and MS spectrum and also by comparison with a standard sample (*Scheme 3*).



i) K_2CO_3, methyl isobutyl ketone; r.t., 4h ii) 1.conc. HCl, 0-5 °C, 10h 2. $NaBH_4$, r.t., 8h; iii) Pd/C, EtOH, 45 °C, 36h

Scheme 3

In conclusion, we have devised an efficient and convenient route for the synthesis of the anti-asthma drug salmeterol. This method has advantages, such as easily available staring material, simple operation, low cost and high yields.

Experimental Section

Purification of the products was performed using flash column chromatography on silica gel (200∼300 mesh) and light petroleum ether (bp. 60∼90°C). ^{1}H NMR spectra were obtained on a Bruker AM-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. The progress of the reactions was monitored by TLC on silica gel polygram SILG/UV 254 plates. All compounds were identified by comparison with ^{1}H NMR reported in the references cited below. Melting points were measured on Buchi B-540 apparatus and are uncorrected.

2-Acetoxy-5-acetylbenzyl Acetate (2)[13]

To a 500 mL three-neck round bottom flask, 33% aqueous dimethylamine (27.0 g, 220 mmol) and 4-hydroxyacetophenone (15.0g, 110 mmol) were added to a 37% aqueous formaldehyde solution (20.0 g, 220 mmol) at 10-12°C. After stirring for 6.0 h, 10 N sulfuric acid (16 mL) was then added over 30 minutes keeping the temperature below 20°C. After the 4-hydroxy acetophenone was consumed, the pH of the solution was adjusted to 7.5 by addition of 27% aqueous ammonia. The aqueous layer was extracted with toluene (3 × 60 mL), the organic extracts were combined, washed with water, brine and was dried over $MgSO_4$. Evaporation of the filtrate under reduced pressure produced an oily pale-yellowish residue which was used directly in the next step without further purification.

Acetic anhydride (28.0 g, 275 mmol) was added into a solution of the above residue in toluene (200 mL). The reaction mixture was refluxed for 4 h. It was then washed with 10% of sodium carbonate aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 24.7 g (90%) of a pale yellowish oil.[13] ^{1}H NMR ($CDCl_3$): δ 2.09 (s, 3H), 2.35 (s, 3H) 2.61 (s, 3H), 5.12 (s, 2H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.98 (dd, $J = 2.5$, 8.5 Hz, 1H), 8.06 (d, $J = 2.5$ Hz, 1H).

2-Acetoxy-5-(2-bromoacetyl)benzyl Acetate (3)[13]

Propylene oxide (1.20 g) (***CAUTION***: Possible carcinogen) was added to a solution of bromine (3.80 g, 24.0 mmol) in chloroform (10.0 mL) and stirred for 0.5 h. Then this freshly prepared reagent was added to a solution of compound **2** (6.0 g, 24 mmol) in chloroform (12.0 mL) at 0°C. The organic layer was washed with water and brine, then concentrated under reduced pressure to give **3** as a yellowish oil (29.5 g, 90%). ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3 H), 2.36 (s, 3 H), 4.44 (s, 2 H), 5.13 (s, 2 H), 7.26 (d, $J = 8.5$ Hz, 1H), 7.99 (dd, $J = 2.5$, 8.5 Hz, 1H), 8.09 (d, $J = 2.5$ Hz, 1H).^{13}C NMR ($CDCl_3$): δ 20.67, 20.75, 30.41, 60.73, 123.22, 129.12, 130.28, 131.05, 131.77, 153.14, 168.39, 170.35, 189.87.

4-(6-Bromohexyloxy)butylbenzene (5)[4]

To a mixture of 4-phenylbutanol (10.0 g, 67 mmol) and 1,6-dibromohexane (26.0 g, 107 mmol) in toluene (60.0 mL) were added potassium hydroxide (7.50 g, 134 mmol) and tetra- *(n*-butyl)ammonium bromide (2.10 g, 6.7 mmol). After stirring for 10 h at room temperature, the reaction mixture was poured into water (20 mL). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue that was distilled under vacuum to remove the excess 1,6-dibromohexane; the crude yellowish oil (**5**) obtained was used directly in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.36–1.37 (m, 2H), 1.42–1.44 (m, 2H),

1.55–1.62 (m, 4H), 1.67–1.69 (m, 2H), 1.81–1.87 (m, 2H), 2.62 (t. $J = 7.5$ Hz, 2H), 3.37–3.42 (m, 6 H), 7.15–7.18 (m, 3 H), 7.25–7.28 (m, 2 H).

N-Benzyl-6-(4-phenylbutoxy)hexan-1-amine (6)[4]

A mixture of benzylamine (5.0 g, 50 mmol) and triethylamine (8.0 g, 83 mmol) and potassium iodide (346 mg, 2.08 mmol) in acetonitrile (30.0 mL) was stirred at 45 °C for 30 minutes. Then 4-(6-bromohexyloxy)butylbenzene (**5,** 13.0 g, 41.7 mmol) was added drop-wise and then the reaction mixture was stirred until the bromoether **5** was consumed by TLC analysis. The solvent and excess benzylamine were removed under reduced pressure, followed by addition of water and dichloromethane. The organic layer was separated, washed with aqueous potassium carbonate, dried and concentrated to give compound **6** as a yellowish oil. Dissolution of this crude residue in methanol (70.0 mL), followed by the addition of a solution of oxalic acid (3.80 g) in methanol (60.0 mL) gave a solid formed which was collected and dried. This solid was dissolved into the 10 % NaOH aqueous solution and the pH of the solution was adjusted to 7. After removal of solvent, the reaction mixture was extracted with ethyl acetate (3 × 80 mL) and washed with water and brine. The organic phase was concentrated to give **6** (10.7 g, 76% in two steps) as a pale yellowish oil. ^{1}H NMR ($CDCl_3$): δ 1.41–1.58 (m, 4H), 1.62–1.76 (m, 8H), 2.66–2.70 (m, 4H), 3.42–3.48 (m, 4H), 3.83 (s, 2H), 7.22–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 26.02, 27.08, 27.94, 29.27, 29.58, 29.93, 35.59, 49.28, 53.93, 70.52, 70.71, 125.51, 126.68, 127.94, 128.09, 128.19, 128.26, 140.40, 142.33; EIMS *m/z* 339 ($[M]^+$, 8), 91(100), 106(38), 206(28), 190(24), 148(22), 120(20), 65(12).

4-Hydroxy-1-[[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]methyl]-1,3-benzene dimethanol (8)[3]

A solution of compound **6** (16.0 g, 47.2 mmol) in methyl isobutyl ketone (70.0 mL) was added to a solution of **3** (13.0 g, 39.5 mmol) in methyl isobutyl ketone (80.0 mL), followed by addition of potassium carbonate (6.50 g, 47.4 mmol). The reaction mixture was stirred for 4 h at room temperature. Then ethyl acetate (80.0 mL) and water (30.0 mL) were added, the organic phase was separated and concentrated to dryness under reduced pressure. The residue was dissolved in ethanol (100 mL) followed by addition of conc. HCl (20.0 mL) while cooling **in ice bath**. After the reaction mixture had been stirred for 10 h, the pH of the mixture was adjusted to 12 by addition of 40% NaOH solution. Then $NaBH_4$ (2.50 g, 73.5 mmol) was added and stirred for 8 h at room temperature. Then 10 N H_2SO_4 (5.0 mL) was added to adjust the pH to 8. After removal of the solvent, the reaction was extracted with ethyl acetate (3 × 80 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the desired compound **8** (14.0 g, 70%) as a colorless oil. The spectroscopic data of compound 7 and 8 are as follows:

Compound **7**: ^{1}H NMR ($CDCl_3$): δ 1.25–1.28 (m, 3H), 1.50–1.67 (m, 9H), 2.07 (s, 3H), 2.34 (s, 3H), 2.58–2.65 (m, 4H), 3.32–3.41 (m, 6H), 3.72 (s, 1H), 3.80 (s, 1H), 5.07 (s, 2 H), 7.14–7.19 (m, 6H), 7.24–7.34 (m, 7H).

Compound **8**: ^{1}H NMR ($CDCl_3$): δ 1.27–1.32 (m, 4H), 1.49–1.55 (m, 4H), 1.59–1.64 (m, 2H), 1.66–1.69 (m, 2H), 2.41 (m, 1H), 2.50–2.64 (m, 5H), 3.36 (t, $J = 6.5$ Hz, 2H), 3.41 (t, $J = 6.5$ Hz, 2H), 3.86 (d, $J = 13.5$ Hz, 1H), 4.53 (dd, $J = 5.0$, 9.0 Hz, 1H), 4.71 (s, 2 H), 6.76 (d, $J = 8.0$ Hz, 1H), 6.90 (d, $J = 2.0$ Hz, 1H), 7.06 (dd, $J = 7.0$, 13.0 Hz,

1H), 7.16 (t, $J = 7.0$ Hz, 3H), 7.25–7.29 (m, 5H), 7.31–7.35 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 25.95, 26.69, 27.02, 27.94, 29.24, 29.54, 35.63, 53.70, 58.43, 62.06, 63.79, 69.11, 70.64, 70.77, 116.09, 125.16, 125.37, 125.59, 126.65, 127.22, 128.17, 128.32, 128.36, 128.96, 132.78, 138.35, 142.36, 155.43; EIMS *m/z* 487 ([M-H_2O]$^+$, 9), 352 (100), 91 (73), 134 (28), 353 (26) , 112 (10).

4-Hydroxy-1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol (Salmeterol 9) [3]

Compound **8** (7.10 g, 14 mmol) was dissolved in ethanol (60.0 mL) and hydrogenated at 58 psi (0.4MPa) pressure in the presence of 10% Pd-C (600 mg) for 36 h at 45 °C. After removal of the catalyst, the filtrate was concentrated *in vacuo*. The crude solid was recrystallized from EtOAc to give 4.6 g (80%) of salmeterol (**9**) as a white powder, mp. 75-76 °C (lit.[3] 75-77 °C), ^{1}H NMR ($CDCl_3$): δ 1.25-1.30 (m, 4H), 1.43 (t, $J = 7.0$ Hz, 2 H), 1.51 (dd, $J = 6.5$, 13.5 Hz, 2H), 1.58-1.64 (m, 2H), 1.65-1.68 (m, 2H), 3.36 (t, $J = 7.0$ Hz, 2H), 3.40 (t, $J = 6.5$ Hz, 2H), 4.50 (t, $J = 6.5$ Hz, 1H), 4.62 (s, 2H) 4.78 (s, 4H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.89 (s, 1 H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.15 (t, 3H, $J = 7.5$ Hz), 7.25 (q, $J = 6.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 26.01, 27.04, 27.99, 29.30, 29.43, 29.59, 35.68, 49.29, 56.55, 62.98, 70.72, 70.83, 71.42, 116.21, 125.65, 126.11, 126.39, 128.23, 128.37, 133.50, 142.42, 155.63; EIMS *m/z* 397 ([M-H_2O] $^+$,10), 112 (100), 91 (64), 262 (36), 114 (28), 116 (23).

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