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Improved process for the preparation A Long-acting β2-adrenergic agonist (LABA) Salmeterol and identification, characterization and control of its potential process impurity

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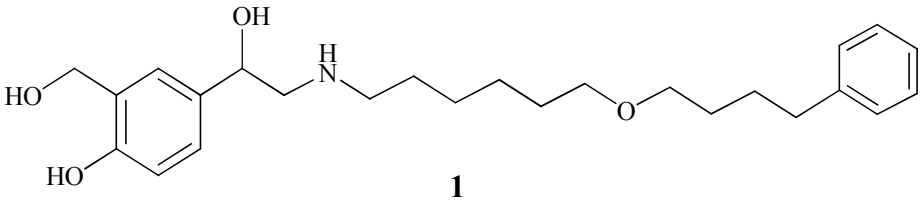
ABSTRACT

*An improved and commercial viable process for the active pharmaceutical ingredient of new Long-acting β2-adrenergic agonist (LABA) Salmeterol has been developed. This improved process includes the isolation of Salmeterol **1** and identification, controlling and synthesis of its potential Diether impurity **2**.*

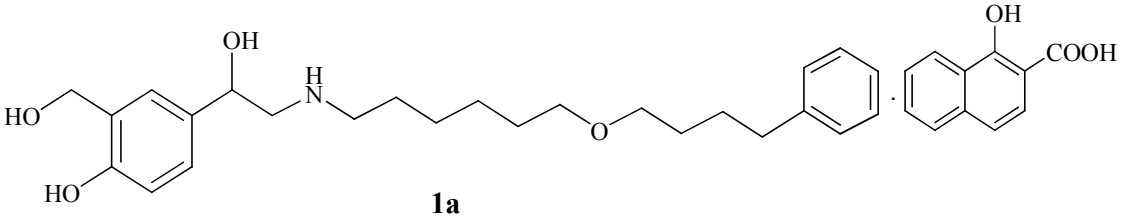
Key words: Salmeterol, Long-acting β2-adrenergic agonists (LABA), Diether impurity, Commercial viable process.

INTRODUCTION

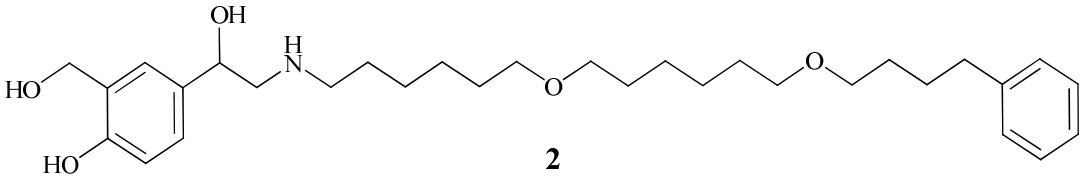
Salmeterol and its pharmaceutically acceptable salts are long-acting-beta-agonists. Salmeterol xinafoate is a selective β2-adrenoreceptor agonist. It is clinically used as a long-acting inhaled bronchodilator for maintenance treatment of asthma and to control nocturnal asthma. Unlike other bronchodilator drugs, Salmeterol is much more lipophilic and displays many unusual pharmacological properties.



1
Salmeterol



1a
Salmeterol xinafoate



2

Back ground and literature search:
There are several process disclosed in the literature for synthesis of Salmeterol xinafoate, but all of them suffer severe disadvantages with respect to quality, especially on higher scale or on commercial manufacturing scale.

The innovator's (GB2140800 and US4992474) discloses several processes [1] for the synthesis of Salmeterol xinafoate, one process comprising the reaction of 2-bromo-l-[4-hydroxy-3-(hydroxymethyl) phenyl] ethanone with N-[6-phenylbutoxy) hexyl] benzenemethanamine in the presence of diisopropylethylarnine in THF, followed by usual work-up and purification. The viscous oil so obtained was subjected to hydrogenation in absolute ethanol over 10% palladium on carbon and 10% platinum on carbon catalysts followed by purification to afford Salmeterol free base as white solid.

Disadvantage of above process is requiring of cumbersome column purifications and usage of expensive 10% platinum on carbon catalysts for preparation of **1**.

In order to avoid the column purifications and to prepare Salmeterol and its pharmaceutically acceptable salts, second generation process [2] (2560/CHE/2008 A) documented in literature by coupling of N-benzyl-6-(4-phenylbutoxy)hexan-1-amine **4** (Free base) and Methyl 2-(benzyloxy)-5-(2-bromoacetyl) benzoate **3** in the presence of diisopropyl ethyl amine in DCM solvent to give Methyl 5-(2-(benzyl(6-(4-phenylbutoxy) hexyl) amino) acetyl)-2-(benzyloxy)benzoate **5** and further it was reduced with Vitride in toluene solvent to give 2-(benzyl (6-(4-phenylbutoxy)hexyl) amino)-1-(4-(benzyloxy)-3-(hydroxy methyl) phenyl) ethanol **6** and then it was debenzylated in the presence of 10% Pd/C with 2 – 4kg/cm^2 hydrogen pressure at 20 – 30°C followed by work up process to give 4-(1-hydroxy-2-(6-(4-phenylbutoxy) hexylamino) ethyl)-2-(hydroxy methyl) phenol (Salmeterol base) as crystalline solid in 45.8% yield.

Disadvantage of above process is low yield of **1** due to work up process in last step with excess volumes of solvent and water.

To prepare Salmeterol and its intermediates, third generation process [3] (WO2012/032546 A2) documented by using **3** and **4** intermediates which are used in 2560/CHE/2008 A. This patent process describes the coupling of N-benzyl-6-(4-phenylbutoxy)hexan-1-amine hydrochloride **4** and Methyl 2-(benzyloxy)-5-(2-bromoacetyl) benzoate **3** in the presence of K_2CO_3 in DMF solvent to give Methyl 5-(2-(benzyl(6-(4-phenylbutoxy) hexyl) amino) acetyl)-2-(benzyloxy)benzoate **5** and further it was reduced with $LiAlH_4$ to give 2-(benzyl(6-(4-phenylbutoxy)hexyl)amino)-1-(4-(benzyloxy)-3-(hydroxy methyl)phenyl)ethanol **6** and then it was debenzylated in the presence of 10% Pd/C with 5 – 6kg/cm^2 hydrogen pressure at 40°C to give 4-(1-hydroxy-2-(6-(4-phenylbutoxy) hexylamino) ethyl)-2-(hydroxy methyl) phenol (Salmeterol base) as oily residue.

The disadvantage of this process is usage of pyrropheric reagent (LiAlH4) and isolation of Salmeterol base **1** as oily residue.

In all the reported synthetic schemes, N-benzyl-6-(4-phenylbutoxy) hexan-1-amine (Free base of **4**) serves as the key intermediate in the synthesis of Salmeterol (GB patent 2140800; US patent US4992474; Tetrahedron Letters, Vol. 35 (50), pages 9375 – 9378, 1994; and Synthetic Communication, Vol. 29 (12a), Pages, 2155 – 2162, 1999) and we are also used this key intermediate.

MATERIALS AND METHODS

Salmeterol **1** is prepared according to procedure as described in WO2012032546A2 and 2560CHE2008 patents. FT-IR spectrums were determined on Thermo model Nicolet-380 as KBr pellet. Melting points were determined on polmon instrument. The mass spectrum was recorded on positive Q1 MS by mass spectrometer and the 1H NMR data was acquired in $CDCl_3$ and DMSO as solvents on an Avance 300 MHz/ Bruker 400MHz spectrometer using TMS as internal standard.

4-(1-hydroxy-2-(6-(4-phenylbutoxy) hexylamino) ethyl)-2-(hydroxy methyl) phenol [Salmeterol 1]:
Taken **4** (200gm, 0.530 mol), DCM (1000ml) and water (600ml) in to round bottom flask and pH adjusted to 8 – 9 with 10% sodium carbonate solution (400ml) and separated the layers after 10 min stirring. Charged **3** (185gm, 0.510mol) in to organic layer and then slowly added Diisopropyl ethyl amine (137.5gm, 1.063mol). After maintained for 4hrs at ambient conditions charged water (600ml) and separated the layers. The organic layer was distilled under vacuum at below 50°C to result a residue. Toluene (1400ml) was charged to residue at 25 – 35°C followed by stirring and cooling to 0 – 5°C. Slowly added a dilute solution of Vitride (70% solution, 614ml) in Toluene (400ml) under nitrogen atmosphere and maintained for 1 hr at same temperature. The reaction mass was quenched by adding reaction mass slowly to an aqueous solution of Sodium potassium tartarate (614gm in 1600ml of water) followed by stirring 1 hr at 25 – 35°C. The reaction mass was filtered and separated the organic and aqueous layer from filtrate. The aqueous layer was extracted with Toluene (400ml) and washed the total organic layer with water (800ml). The organic layer was distilled to result a residue. Charged methanol (1000ml) to residue and followed by added 5% Pd/C (40gm) and stirring under 3 – 4kg/cm^2 for 2hrs at ambient conditions. The reaction mass was filtered and washed with methanol (200ml) and distilled filtrate and isolated product in Methyl tertiary butyl ether (1000ml). The wet compound was dried for 5hrs at 45 – 55°C to afford title compound **1** (155gm, 73.32%); **m.p:** 72 – 75°C.

1H-NMR (400MHz, $CDCl_3$): δ 1.282 – 1.293 (4H, m), 1.410 – 1.545 (3H, m), 1.585 – 1.700 (4H, m), 2.490 – 2.505 (2H, d), 2.529 – 2.639 (4H, m), 3.346 – 3.430 (4H, q), 4.474 – 4.516 (1H, t), 4.591 (3H, brs), 4.659 (2H, s), 6.713 – 6.740 (1H, d), 6.887 (1H, s), 7.011 – 7.038 (1H, d), 7.159 – 7.181 (3H, d), 7.238 – 7.287 (2H, t); **MS:** m/z 416.4 (M+H);

(4-(6-(6-bromohexyloxy) hexyloxy) butyl) benzene [9 (I1)]:
Sodium acetate (78.52gm, 0.1596mol) and Tetra butyl ammonium bromide (82.22gm, 0.2553mol) to (4-(6-bromohexyloxy) butyl) benzene **9** (100gm, 0.3192mol) and then heated to 110 – 120°C for 2hrs. Cooled the reaction mass to 25 – 35°C and charged Cyclohexane (1000ml) and then stirred for 20min. Filtered the reaction mass for removing of unwanted salts and washed with Cyclohexane (2×200ml) and washed the filtrate with water (2×500ml). The organic layer was distilled under vacuum at below 60°C to result a residue **10** and methanol (300ml) was charged to residue and stirred for 10min and then cooled to 0 – 5°C. Charged potassium carbonate (22gm, 0.1596mol) to the reaction mass and stirred for 2 hrs at same conditions. Charged water (500ml) and dichloromethane (500ml) to the reaction mass and stirred for 10min at 25 – 35°C and then separated the layers. The aqueous layer was extracted with dichloromethane (2×300ml) and washed the total organic layer with water (300ml). The organic layer was distilled under vacuum at below 50°C to result a residue **11**. Charged potassium hydroxide (50.30gm, 0.8964mol) and tetra butyl ammonium bromide (1.92gm, 0.0059mol) to solution of **11** and toluene (750ml). Slowly charged 1, 6-Dibromo hexane **8** to the reaction mass for 1hr at 25 – 35°C and maintained for 10hrs. Charged water (500ml) and stirred for 25min and then separated the layers. The aqueous layer was extracted with toluene (2×150ml) and washed the total organic layer with water (300ml). The organic layer was distilled under vacuum at below 70°C to result a residue and followed by high vacuum fractional distillation at vapor temperature at below 115°C to remove excess **8** to afford title compound **9(I1)** (150gm, 73.86%) as a residue.

1H-NMR (400MHz, $CDCl_3$): δ 1.334 – 1.386 (6H, m), 1.405 – 1.493 (2H, m), 1.553 – 1.602 (8H, m), 1.644 – 1.704 (2H, m), 1.829 – 1.899 (2H, q), 2.612 – 2.649 (2H, m), 3.369 – 3.435 (10H, m), 7.154 – 7.189 (3H, m), 7.253 – 7.292 (2H, m); **MS:** m/z 412.3;

N-benzyl-6-(6-(4-phenylbutoxy) hexyloxy) hexan-1-amine hydrochloride [4 (I1)]:
Benzyl amine (130gm, 1.2132mol), potassium carbonate (50gm, 0.3628mol), potassium iodide (1.6gm, 0.0096mol) and N, N-Dimethyl formamide (200ml) taken in to round bottom of flask and stirred for 10min and cooled to 10 – 15°C. A solution of (4-(6-(6-bromohexyloxy) hexyloxy) butyl) benzene **9 (I1)** in N, N-Dimethyl formamide (1200ml) was added slowly for 30min and at 10 – 15°C and then allowed the reaction mass to 25 – 35°C and maintained for 2hrs. Charged water (500ml) in to reaction mass and stirred for 10min and then separated the layers and washed the product oil layer and washed with water (200ml). Taken product oil layer, dichloromethane (700ml) and water (200ml) in to round bottom flask and adjusted pH below 1 with hydrochloric acid (40ml) in water (160ml) solution at 25 – 35°C. Separated the layers and organic layer washed with water (200ml) and distilled the organic layer completely under vacuum at below 50°C and co-distilled with methyl tertiary butyl ether (100ml) to remove dichloromethane solvent traces. Charged ethyl acetate (100ml) and methyl tertiary butyl ether (1500ml) in to reaction mass and heated to 40 – 45°C and maintained for 20min. cooled the reaction mass and stirred for 1hr and then filtered the reaction mass and washed with methyl tertiary butyl ether (50ml). The wet compound was dried for 4hrs at 45 – 50°C to afford title compound **4 (I1)** (57gm, 49.49%).

1H-NMR (400MHz, $CDCl_3$): δ 1.303 – 1.341 (8H, m), 1.493 – 1.708 (10H, m), 1.843 (2H, brs), 2.602 – 2.650 (2H, t), 2.709 – 2.762 (2H, t), 3.303 – 3.427 (8H, m), 4.007 (2H, s), 7.142 – 7.165 (3H, m), 7.188 – 7.292 (2H, t), 7.350 – 7.427 (3H, m), 7.581 – 7.607 (2H, d), 9.872 (1H, brs); **MS:** m/z 440.4 (M+H);

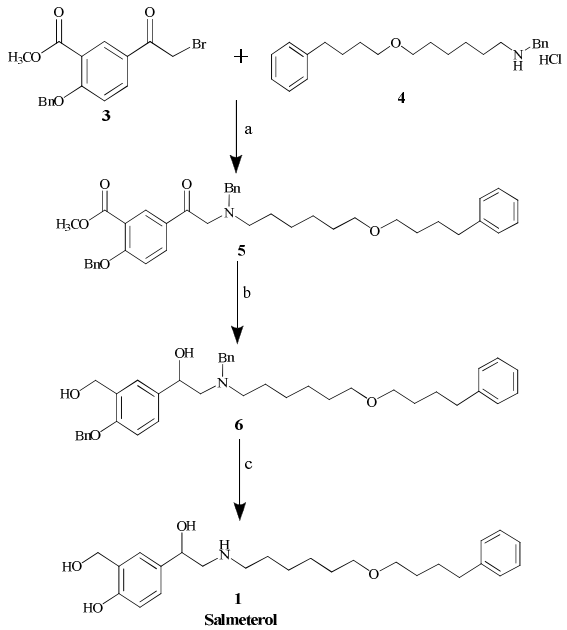
4-(1-hydroxy-2-(6-(6-(4-phenylbutoxy) hexyloxy) hexylamino) ethyl)-2-hydroxymethyl) phenol [2]:
Taken **4 (I1)** (45gm, 0.0948mol), DCM (225ml) and water (135ml) in to round bottom flask and cooled to 5 – 10°C and pH adjusted to 8 – 9 with 10% sodium carbonate solution (100ml) and reaction mass changed to ambient conditions. Separated the layers and extracted the aqueous layer with DCM (45ml) and washed total organic layer with water (45ml). Charged **3** (33.3gm, 0.0916mol) in to organic layer and then slowly added Diisopropyl ethyl amine (33.75gm, 0.176mol). After maintained for 5hrs at ambient conditions charged water (150ml) and stirred for 10 – 15min. Separated the layers and organic layer washed with water (2×100ml). The organic layer was distilled under vacuum at below 50°C to result a residue. Toluene (315ml) was charged to residue at 25 – 35°C followed by stirring and cooling to 0 – 5°C. Slowly added a dilute solution of Vitride (70% solution, 110ml) in Toluene (90ml) under nitrogen atmosphere and maintained for 1 hr at same temperature. The reaction mass was quenched by adding reaction mass slowly to an aqueous solution of Sodium potassium tartarate (110gm in 360ml of water) followed by stirring 1 hr at 25 – 35°C. The reaction mass was filtered and separated the organic and aqueous layer from filtrate. The aqueous layer was extracted with Toluene (90ml) and washed the total organic layer with 20% aqueous sodium chloride solution (180ml), 1% aqueous acetic acid solution (180ml) and 1% aqueous sodium bicarbonate solution (180ml) respectively. The organic layer was distilled under vacuum at below 70°C to result a residue. Charged methanol (225ml) to residue and followed by added 5% Pd/C (9gm) and stirring under 3 – 4kg/cm^2 for 4hrs at 25 – 35°C. The reaction mass was filtered and washed with methanol (45ml) and distilled filtrate under vacuum at below 50°C and then added ethyl acetate (150ml) at ambient conditions. Charged oxalic acid (5.2gm, 0.0577mol) in to the reaction mass and cooled to 0 – 5°C and stirred for 1hr. Filtered the reaction mass and washed with ethyl acetate (25ml). The wet compound was dried for 4hrs at 40 – 50°C to afford title compound **2** (25gm, 43.67%);

1H-NMR (400MHz, $CDCl_3$): δ 1.20 – 1.35 (8H, brs), 1.40 – 1.50 (8H, brs), 1.554 – 1.626 (4H, m), 2.553 – 2.589 (2H, m), 2.895 – 2.931 (3H, m), 3.018 – 3.046 (1H, d), 3.25 – 3.40 (8H, m), 4.487 (2H, s), 4.803 – 4.827 (1H, d), 6.759 – 6.780 (1H, d), 7.041 – 7.061 (1H, d), 7.166 – 7.330 (6H, m); **MS:** m/z 516.4 (M+H).

RESULTS AND DISCUSSION

As part of our research program, we are interested to develop a commercial, cost effective and industrial eco-friendly process for preparation of Salmeterol. Our research work focuses on the design of a commercial viable process and optimizing all parameters of the reactions that are involved in the synthesis of Salmetero1. Based on a literature search designed the synthesis as illustrated in below Scheme – 1.

Scheme – 1

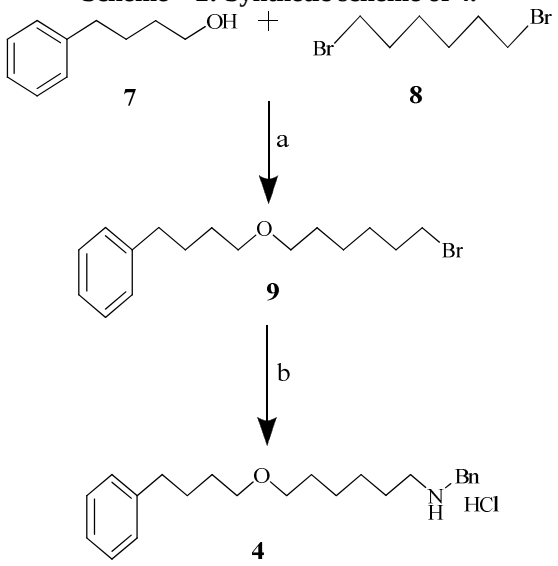


Reagents and conditions: *(a). Na2CO3, DIEA, Dichloromethane at 25 – 35°C; (b). Vitride, Toluene at 0 – 5°C; (c). Pd/C, Methanol, Methyl tertiary butyl ether at 25 – 35°C.*

In order to develop commercial process for Salmeterol **1**, optimized the above route of synthesis each step. The condensation of bromo ester **3** with free base of N-benzyl ether **4** in the presence of diisopropyl ethyl amine in dichloromethane solvent at ambient condition to get dibenzyl keto derivative **5** in good yield and quality. Dibenzyl keto derivative **5** reduced to Dibenzyl alcohol derivative **6** with Vitride in Toluene solvent. Further debenzylation of **6** to get Salmeterol **1** as an off white color solid in 70% yield and 99% HPLC purity. Although a potential impurity **2** formation observed in significant level and it was not eliminated by purification techniques due to structural similarities of **1** and **2**.

We extensively worked on identification of potential impurity **2** and developed a commercial process for Salmeterol **1** by controlling the formation of this impurity. During the optimization study we faced problem with one potential impurity to get ICH quality of the product and its molecular weight identified by LC-MS analysis (516.4 in +ve mode) which is 100 units higher than **1** molecular weight (415.57), Based on this it was suspected that adding of hexyloxy moiety to **1** and the origin could be from N-benzyl ether **4** starting material. Synthetic route of **4** is illustrated in below Scheme – 2.

Scheme – 2: Synthetic scheme of 4.

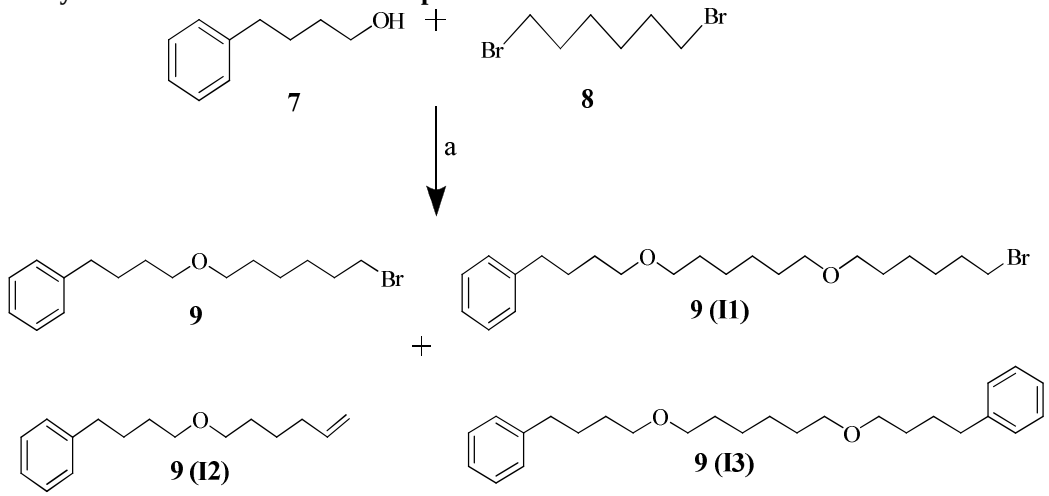


Reagents and conditions: *(a). KOH, TBAB, Toluene at 25 – 35°C; (b). Benzyl amine, K_2CO_3, KI, DMF at 25 – 35°C.*

Identification of new potential impurity 2:

Condensation of 4-Phenyl butan-1-ol **7** and 1, 6-Dibromo hexane **8** in the presence of potassium hydroxide and tetra butyl ammonium bromide in toluene solvent medium to give (4-(6-bromohexyloxy) butyl) benzene **9** and it was purified with high vacuum fractional distillation to remove the unreacted **8** at vapor temperature below 140°C. Further **9** react with benzyl amine in the presence of potassium carbonate and potassium iodide in N, N-Dimethyl formamide solvent medium and followed by hydrochloride salt formation to give **4**. In preparation of **9** below impurities formation are identified and synthesis scheme of identified impurities in **9** are illustrated in below Scheme – 3.

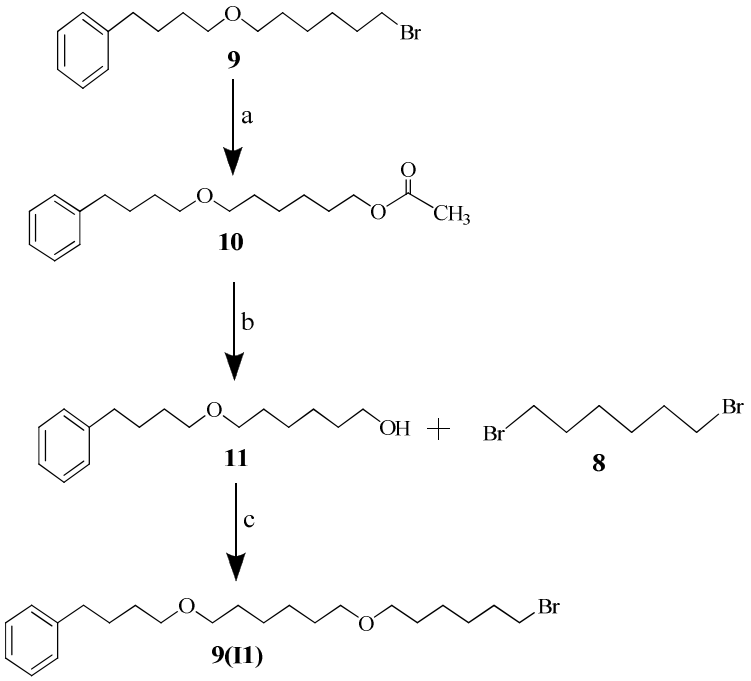
Scheme – 3: Synthetic scheme of identified impurities in 9.



Reagents and conditions: *(a). KOH, Toluene at 25 – 35°C.*

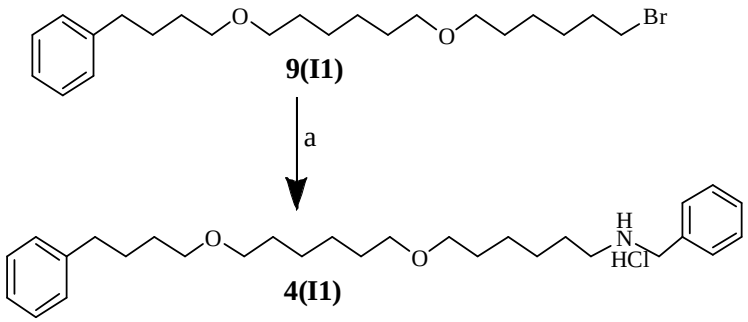
We identified the **9(I1)**, **9(I2**) and **9(I3)** impurities in preparation of **9** and first impurity **9(I1)** is possible to convert further reactions as **9** and last two impurities are not convertible impurities. **9(I1)** impurity was converted as **4(I1)** in preparation of **4** and new potential impurity **2** in preparation of **1** Synthetic path way of **9(I1)** and its convertible impurity in **4** is given in Scheme – 4 and 5 respectively.

Scheme – 4: Synthetic scheme of 9(I1)



Reagents and conditions: *(a). AcoNa, TBAB at 110 – 120°C; (b). K_2CO_3, Methanol at 0 – 5°C; (c). KOH, TBAB, Toluene at 25 – 35°C.*

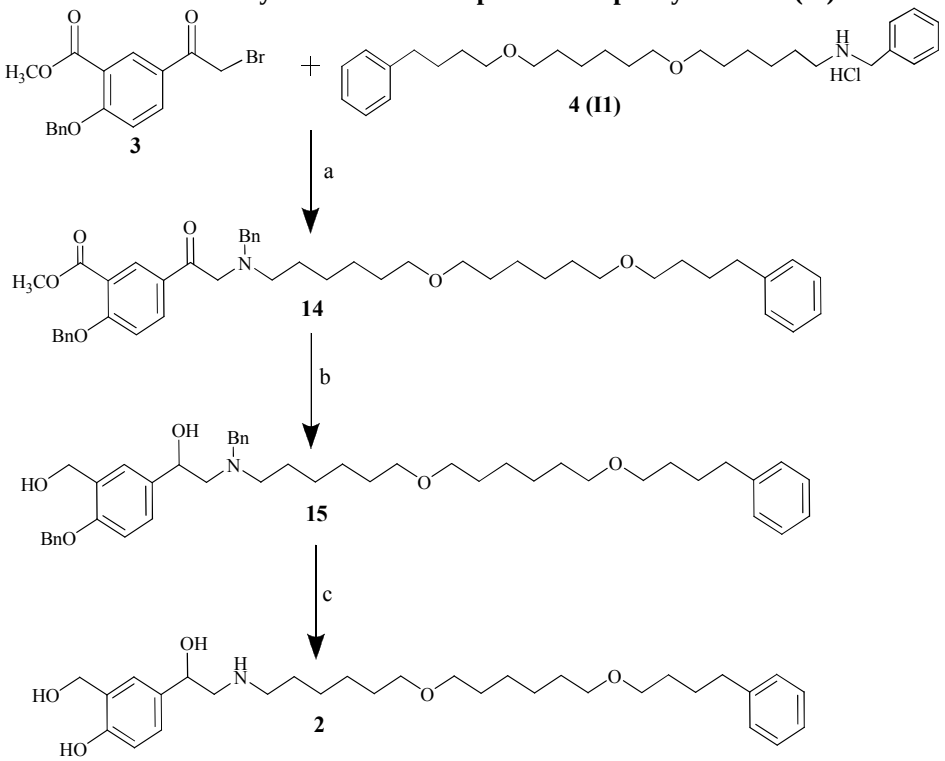
Scheme – 5: Synthetic scheme of 9 (I1) convertible impurities in preparation of 4



Reagents and conditions: *(a). Benzyl amine, K_2CO_3, KI, DMF at 25 – 35°C.*

We here in report a new potential impurity **2** synthetic route in Salmeterol (Scheme – 6) from **4 (I1)** as per same synthetic path way of Salmeterol **1**. Synthetic scheme of **2** is illustrated below in Scheme – 6.

Scheme – 6: Synthetic scheme of potential impurity 2 from 4 (I1).



Reagents and conditions: *(a). Na2CO3, DIEA, Dichloromethane at 25 – 35°C; (b). Vitride, Toluene at 0 – 5°C; (c). Pd/C, Methanol, Methyl tertiary butyl ether at 25 – 35°C.*

We identified the potential impurity **2** was carryover impurity from **9** which was containing **9(I1)** during the optimization study and **9(I1)** impurity was controlled in 9 by passing the solution of **9** in Cyclohexane on silica gel bed. The attempts were summarized in Table – 1.

Table – 1: Experimental study of potential impurity 2 carry over

S. No	9(I1) in 9	4(I1) in 4	2 in 1
1	0.98%	0.93%	0.86%
2	0.88%	0.87%	0.77%
3	0.06%	0.08%	Not detected
4	0.10%	0.09%	Not detected
5	0.06%	0.06%	Not detected

** 9(I1) content in 9 monitored by GC and remaining are monitored by HPLC.*

CONCLUSION

In conclusion, we have developed an improved three step, inexpensive, and industrially scalable protocol for the synthesis of the long-acting-beta-agonist drug Salmeterol xinafoate, which can provide high yields and high quality product in each stage.

We also identified and prepared and characterized a new potential impurity 2 and established its origin and control in the process.

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