A New Solvent System (Cyclopentyl Methyl Ether−Water) in Process Development of Darifenacin HBr

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S Supporting Information

ABSTRACT: Darifenacin is a potent and competitive M_3 selective receptor antagonist (M_3SRA), and its hydrobromide salt (**1**) is the active ingredient of pharmaceutical formulations for oral treatment of urinary incontinence. The present work demonstrates an efficient, commercial manufacturing process for darifenacin hydrobromide (**1**).

■ INTRODUCTION

Darifenacin (originally developed by Pfizer, trade name Enablex in USA and Canada, Emselex in Europe) is an effective medication used for treatment of overactive bladder (OAB) symptoms.[1] OAB is a common condition symptomized by urinary urgency, with or without urge in continence, usually with frequency and nocturia that notably affects the lives of millions of people.[2] Human bladder tissue contains M_2 (80%) and M_3 (20%) muscarinic receptors, and the latter act as the primary mediator of detrusor contraction in response to cholinergic activation.[3,4] So muscarinic receptor antagonists are the current treatment of choice for OAB.[5] As different subtypes of muscarinic receptors are widely distributed in the human body to play key physiological roles, a very selective M_3 receptor antagonist is in high demand in the market for OAB medication. Darifenacin is a potent and competitive M_3 selective receptor antagonist (M_3SRA) that has been shown to have high affinity and selectivity (59-fold higher) for the M_3 receptor, with low selectivity for the other muscarinic receptor subtypes.[6] Its hydrobromide salt (**1**) (Figure 1) is the active ingredient of pharmaceutical formulations. The efficacy, tolerability and safety of darifenacin in the treatment of OAB are well established.
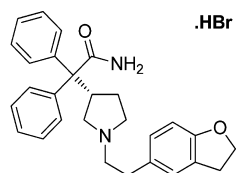
Darifenacin HBr (1)

Figure 1.

The commercial process[7] of darifenacin mainly uses the N-alkyation of chiral intermediate free base (**2**) or tartrate salt (**3**) with halide (**4**) as depicted in Scheme 1. Usually, the tartrate salt (**3**) is made free by neutralization using bases like NaHCO₃/NaOH etc. followed by the reaction of the free base (**2**) with the halide (**4**) with base in various solvents under elevated temperature to afford darifenacin free base, which is further converted to darifenacin hydrobromide (**1**) using 48% hydrobromic acid.

An alternate route is also reported for the manufacturing of darifenacin (Scheme 2) by Novartis patent.[7a] Condensation of acid (**7**) with (S)-2,2-diphenyl-2-(3-pyrrolidinyl)acetonitrile hydrobromide (**6**) in the presence of carbonylimidazole (CDI) in ethyl acetate furnishes the corresponding amide **8**, which is further reduced in the presence of sodium borohydride and BF_3−THF complex to produce darifenacin cyano derivative **9**. The cyano group of **9** on controlled hydrolysis by treatment with potassium hydroxide at 50−60 °C provides darifenacin (**5**).

Some of the impurities (Figure 2) associated with the more common process (Scheme 1) can be easily removed during the salt formation and isolation process whereas a few of them need special care/repeated purifications to get rid of up to undetectable percentage.

Impurities **10** (styrene derivative) and **11** (alcohol) originating from the halide **4** form in varying quantities during the process are easy to remove at the salt formation stage as they do not contain any nitrogen atom in their skeleton. A trace amount of impurity **9** originating from the chiral amino intermediate **2** [**6** as impurity in **2**] and impurity **14** can be removed during final purification of the salt. In case a trace amount of impurity **13** (acid) is formed during the process, this will be easily removed during the aqueous work up (at basic pH). The new impurity (**12**, isolated from the mother liquor; structure was confirmed by comparison of isolated sample and authentic sample prepared by alternative synthesis), which forms in a small quantity during the salt formation, can be controlled by ensuring almost complete removal of HBr and controlling the temperature during final purification.

One of the most critical impurities, **15** (dimer impurity) (Figure 3), recently disclosed in WO 2011/D70419,[7b] forms in significant quantity (3−5%) under almost all conditions and gets extracted into organic solvents even though being a quaternary salt. While this impurity can be partly removed during the HBr salt formation, its complete removal to fit the

Scheme 1

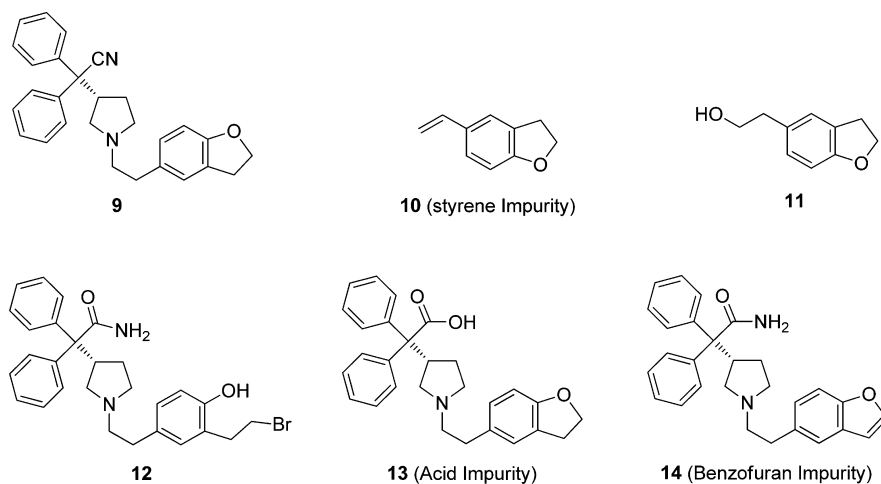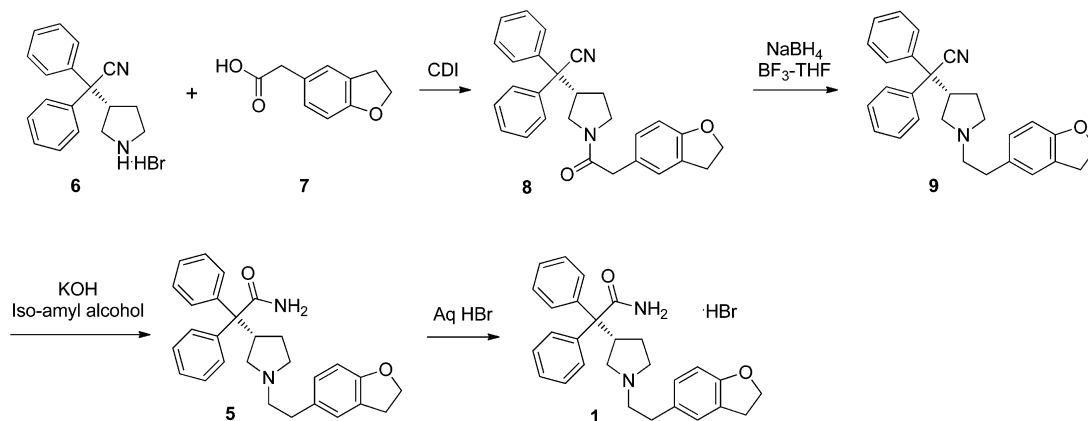[Free Base (**2**) or L-Tartrate salt (**3**)]
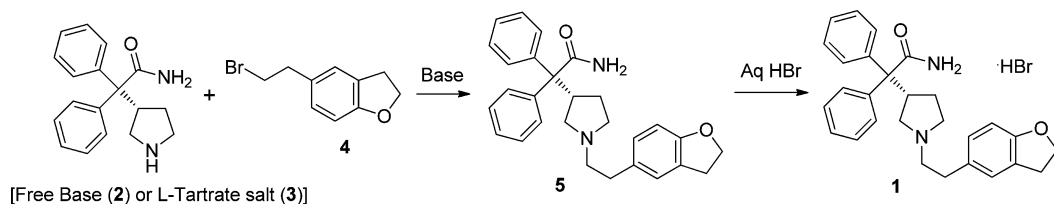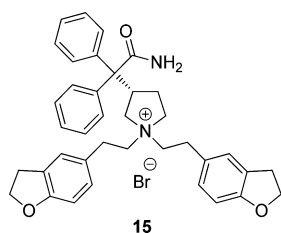
Scheme 2

Figure 2.

Figure 3.

final API into the ICH acceptance criteria[8] seems to be quite tedious as repeated purification is required.

During our group's continuous efforts to develop improved processes for generic drugs, we decided to work on darifenacin HBr (**1**), which has a potential market value. Herein we are reporting an efficient commercial process for darifenacin hydrobromide (**1**).

■ RESULTS AND DISCUSSION

A route to the critical chiral intermediate **2/3** was developed (similar to that reported in US patent 0144354[7d]) using slightly modified conditions (Scheme 3). For the transformation of **20** to **2**, we figured out that the stepwise removal of Boc protection of **20** followed by hydrolysis of the −CN group of compound **6** to CONH$_2$ was preferable in comparison to the one-step procedure (Boc deprotection and hydrolysis) as it offered easy access to remove the unreacted starting material **19** (used in excess in the coupling step) by acid−base work-up after the Boc deprotection before the hydrolysis step; if not removed at this stage, the unreacted diphenyl acetonitrile (**19**) would also undergo hydrolysis to give amide and would be difficult to remove thereafter.

Another interesting observation was the physical nature of free amino intermediate **2**. US patent 0199494[7c] reported this free base (**2**) as a foamy solid, and more recently US patent
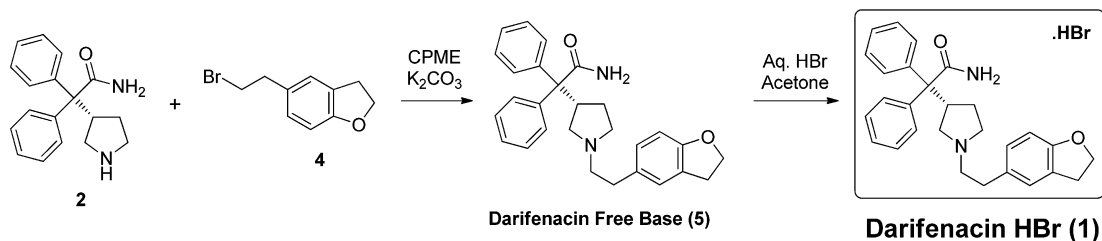
Scheme 3
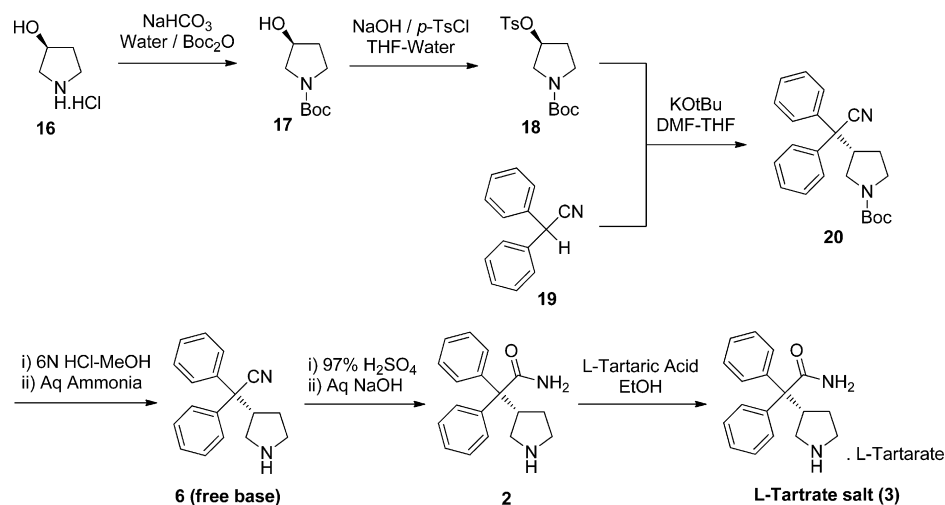
Scheme 4
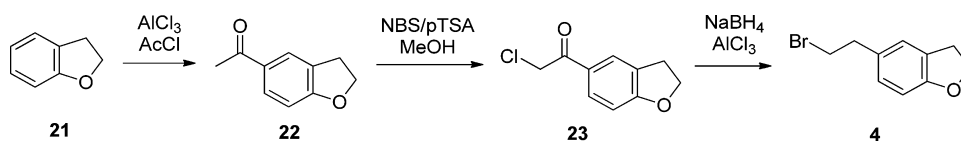
Scheme 5

0144354[7d] reported **2** as an oily residue. We observed that the free base (**2**) can be obtained as nice filterable solid by recrystallization. Alternatively, the tartrate salt **3** is commercially available at a reasonable price.

As shown in Scheme 4, an efficient route was developed for the bromo compound **4**[7h] starting from dihydrobenzofuran (**21**), which on acetylation under Friedel−Crafts (FC) conditions gave the 4-substituted acetyl derivative (**22**) as a sole product. Side chain bromination using *N*-bromosuccinamide (NBS)/*p*-toluenesulfonic acid (*p*-TSA),[9] followed by reduction of the carbonyl group using NaBH$_4$/AlCl$_3$ and subsequent crystallization of the crude bromo compound afforded the desired bromo derivative (**4**) in high yield and purity. Also, this intermediate can be easily sourced from various commercial suppliers.

Towards the final step of the manufacturing process, our initial efforts were based on the reported procedure of alkylation of the free base (prepared by neutralizing the tartrate salt **3** and extracting the free base **2** into dichloromethane (DCM)/ethyl acetate/toluene) with halide (**4**) under basic conditions using K$_2$CO$_3$ in various solvents like acetonitrile/THF/toluene etc. (Scheme 5). After the reaction went to completion, the solvent (acetonitrile/THF) was removed and the free base of the product (along with all the impurities) was extracted into DCM or ethyl acetate. Solvent removal and salt

formation using aqueous HBr in acetone afforded the target compound darifenacin HBr in >98% purity. Subsequently, the N-alkylation reaction was examined by using directly the tartrate salt **3** via in situ release of the free base under the reaction conditions instead of isolation of the crude free base (**2**). This way, we could cut down the additional step of neutralizing the salt and isolating the free base **2** to be used in the alkylation reaction. Although, under most of the conditions, product formation was observed along with a varied percentage of the impurities, one consistent problem we faced was the inconsistent results in in-process monitoring by HPLC as, throughout the whole reaction, the contents were never in a solution phase (reaction mixture was a suspension), thus making the sampling difficult and inconsistent. Use of water in variable percentages along with these solvents solved this problem to some extent but affected the reaction profile with respect to formation of impurities.

At this stage, we decided to investigate the utility of the environment as well as user-friendly solvent and whether the previous solvent mixture like toluene/THF/acetonitrile used in the N-alkylation step could be replaced. A new emerging etherial solvent, cyclopentyl methyl ether (CPME),[10] has distinct advantages over the classical ethers [diethyl ether, diisopropyl ether and methylbutyl ether (MTBE), tetrahydrofuran (THF), dioxane, Me-THF)] with respect to polarity,
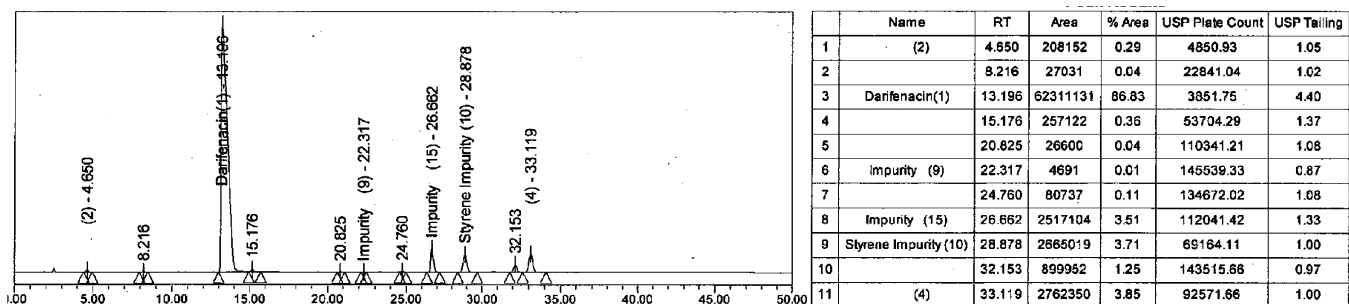
	Name	RT	Area	% Area	USP Plate Count	USP Tailing
1	(2)	4.650	208152	0.29	4850.93	1.05
2		8.216	27031	0.04	22841.04	1.02
3	Darifenacin(1)	13.196	62311131	86.83	3851.75	4.40
4		15.176	257122	0.36	53704.29	1.37
5		20.825	26600	0.04	110341.21	1.08
6	Impurity (9)	22.317	4691	0.01	145539.33	0.87
7		24.760	80737	0.11	134672.02	1.08
8	Impurity (15)	26.662	2517104	3.51	112041.42	1.33
9	Styrene Impurity (10)	28.878	2665019	3.71	69164.11	1.00
10		32.153	899952	1.25	143515.66	0.97
11	(4)	33.119	2762350	3.85	92571.66	1.00

Figure 4. HPLC chromatogram during reaction monitoring (in-process sample).

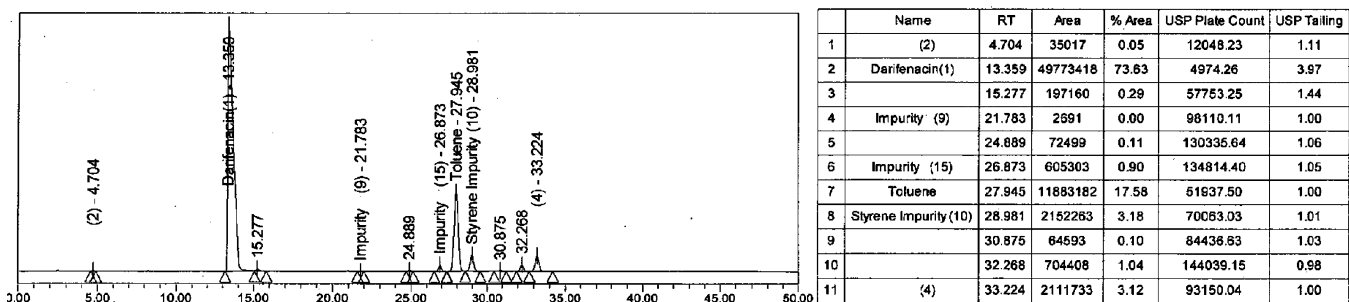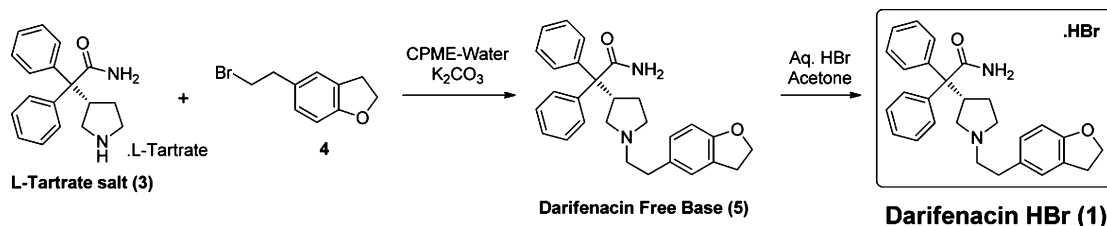|	Name	RT	Area	% Area	USP Plate Count	USP Tailing
1	(2)	4.704	35017	0.05	12048.23	1.11
2	Darifenacin(1)	13.359	49773418	73.63	4974.26	3.97
3		15.277	197160	0.29	57753.25	1.44
4	Impurity (9)	21.783	2691	0.00	98110.11	1.00
5		24.889	72499	0.11	130335.64	1.06
6	Impurity (15)	26.873	605303	0.90	134814.40	1.05
7	Toluene	27.945	11883182	17.58	61937.50	1.00
8	Styrene Impurity (10)	28.981	2152263	3.18	70063.03	1.01
9		30.875	64593	0.10	84436.63	1.03
10		32.268	704408	1.04	144039.15	0.98
11	(4)	33.224	2111733	3.12	93150.04	1.00

Figure 5. HPLC chromatogram after CPME work-up.

Scheme 6

higher boiling point, higher resistance to acid/bases, low volatility and minimal solubility in water. CPME, even though somewhat costlier in comparison, owing to its high recovery percentage could serve as a great replacement for ethers as well as acetonitrile, as demonstrated by its recent uses in the pharmaceutical industry.[10] CPME was chosen for this alkylation step also because of the fact that it would serve as reaction solvent as well as extraction solvent and would avoid the need of solvent removal as in the case of THF or acetonitrile before extracting the free base into solvents like DCM or ethyl acetate.

When the reaction was tried in CPME using the free base **2** and a little excess of bromide (**4**) with K_2CO_3 at elevated temperature (Scheme 5), as usual the reaction proceeded smoothly (<0.5% of starting material **2** was observed in the in-process monitoring by HPLC) and product formation was observed along with impurities. The critical dimer impurity (impurity **15**) was observed in the range of 3−5% by HPLC with RT 26.66 min as shown in Figure 4. The styrene impurity (**10**) which is observed in 3.71% by HPLC (area %) would be actually <1.3% as the response factor (RF) of this impurity is ~3.23.

After the reaction was completed, the heating was stopped for work-up, and we observed some sticky mass on the wall of the reaction flask which remained on the walls even after dilution with CPME and transferring the contents into separating funnel. When this sticky mass was analyzed by

HPLC, we were happy to find out that dimer impurity (**15**) was the major component of the sticky material left in the reaction flask with a small percentage of the product. This was an important observation as it led us to a process wherein we could remove a majority of a critical process impurity (**15**) without taking it forward through the isolation process. Indeed, when the crude free base (CPME layer after aqueous work-up) was analyzed, we were happy to note that the percentage of the dimeric impurity (**15**) was reduced as seen by HPLC (Figure 5).

So, by using CPME the issue of solvent removal before work-up/extraction was eliminated and also the majority of impurity **15** was removed during initial work-up, which remains in solution in CPME at higher temperature but becomes sticky at room temperature and hence left behind in the reactor.

Finally, the direct use of tartrate salt **3** in the CPME−water system was investigated (Scheme 6), and, to our satisfaction, the reaction proceeded nicely with good product formation. The earlier problem of in-process monitoring due to inconsistent sampling was also resolved due to the fact that all the contents of the reaction mass remained in the solution stage throughout the reaction period.

After the reaction was completed, the majority of impurity **15** was removed (as sticky mass) by cooling the reaction mixture to room temperature and diluting the reaction mixture with CPME and water followed by filtration of the reaction mixture

(RM) on a Celite bed. Separation of the layers and CPME removal afforded the free base with <1.0% dimer impurity (**15**), which was taken forward for salt formation in acetone using aqueous HBr. The final product isolated from this process was of >99.7% HPLC purity and devoid of all impurities with NMT 0.1%. This process is currently being used on plant scale for the manufacturing of darifenacin HBr (**1**).

■ CONCLUSION

In conclusion, we have developed an efficient scalable process for manufacturing darifenacin HBr (**1**) using a new solvent system CPME−water in the final step of the process. Our process has distinct advantages like the use of L-tartrate salt of (**3**) instead of free base (**2**), easy sampling during monitoring (everything in solution), CPME used as reaction solvent as well as extraction solvent and efficient removal of dimeric impurity (**15**) before work-up.

■ EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400 MR spectrometer in CDCl$_3$ and DMSO-d_6, and mass spectra were determined on an API-2000LCMS mass spectrometer, Applied Biosystems. Elemental analysis was done in a VarioEL III instrument.

Preparation of 1-(2,3-Dihydrobenzofuran-5-yl)-ethanone (22). To a suspension of anhydrous AlCl$_3$ (233.1 g, 1.74 mol) in dichloromethane (DCM) (1.0 L) under nitrogen atmosphere was added 2,3-dihydrobenzofuran (200 g, 1.7 mol), and the mixture was stirred for 30 min at 0−5 °C. Acetyl chloride (156.8 g, 2.0 mol) was added into the reaction mixture at the same temperature slowly, and stirring was continued for 30 min. After complete conversion of the starting material (monitored by TLC), the reaction mass was poured into chilled dilute HCl (350 mL of concentrated HCl in 2.0 L of demineralized (DM) water) and stirred for 1 h at 25−30 °C. The reaction mixture was extracted with DCM (1.0 L × 2), and the combined DCM layer was evaporated under reduced pressure to obtain a yellow solid. The solid was redissolved in cyclohexane (1.2 L) under reflux, and the mixture was cooled to 10−15 °C slowly and stirred for 3 h. The reaction mixture was filtered to yield compound **22** (230 g, 85%) as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.85 (s, 1H), 7.8 (d, 1H, J = 8.4 Hz), 6.8 (d, 1H, J = 8.4 Hz), 4.7 (t, 2H, J = 8.7 Hz), 3.2 (t, 2H, J = 8.7), 2.5 (s, 3H). ESI-mass: calcd for C$_{10}$H$_{10}$O$_2$ (M$^+$)/z 162.19; found (M + H)/z 163.0, (M + Na)/z 185.1.

Preparation of 2-Bromo-1-(2,3-dihydrobenzofuran-5-yl)ethanone (23). To a solution of **22** (100 g, 0.62 mol) in methanol (500 mL) was added p-TSA·H$_2$O (58.6 g, 0.31 mol), and the mixture was stirred for 30 min at 0−5 °C. Then N-bromosuccinimide (109.7 g, 0.62 mol) was added into the reaction mixture and stirred for 6 h at 0−5 °C. After complete conversion of the starting material (checked by TLC), the reaction was quenched by the addition of 10% aqueous sodium carbonate solution (500 mL) at 15−20 °C and the reaction mass was stirred for 30 min. The reaction mixture was extracted with ethyl acetate (250 mL × 2), and the combined ethyl acetate layer was washed with 10% aqueous sodium carbonate solution (500 mL) followed by DM water (500 mL). The ethyl acetate layer was evaporated under reduced pressure, and the residue was crystallized from a mixture of ethyl acetate and

cyclohexane (1:9, 500 mL) to obtain **23** (100 g, 68%) as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.9 (s, 1H), 7.8 (d, 1H, J = 8.4 Hz), 6.8 (d, 1H, J = 8.4 Hz), 4.7 (t, 2H, J = 8.8 Hz), 4.4 (s, 2H), 3.3 (t, 2H, J = 8.8 Hz). ESI-mass: calcd for C$_{10}$H$_9$BrO$_2$ (M$^+$)/z 241.0; found (M$^+$)/z 241.09, (M + Na)/z 264.9.

Preparation of 5-(2-Bromoethyl)-2,3-dihydrobenzo-furan (4). To a solution of **23** (100 g, 0.41 mol) in THF (500 mL) under nitrogen atmosphere was added NaBH$_4$ (70.6 g, 1.86 mol) in portions, and the mixture was stirred for 1 h at 5−10 °C. Anhydrous AlCl$_3$ (138.2 g, 1.0 mol) was then added into the reaction mixture in portions, and the reaction mixture was heated to 45−50 °C for 4 h. After complete conversion of the starting material, the reaction mixture was poured into chilled dilute HCl (100 mL of concentrated HCl in 400 mL of DM water) and stirred for 30 min at 25−30 °C. THF was distilled out under reduced pressure, and the reaction mixture was extracted with toluene (500 mL × 2). The combined toluene layer was washed with 10% aqueous sodium carbonate solution (500 mL) followed by DM water (500 mL) and evaporated to obtain a residue. The residue was redissolved in methanol (300 mL) and cooled to 5−10 °C, DM water (250 mL) was added and stirring was continued for another 1 h. The reaction mixture was filtered to obtain compound **4** (70 g, 74%) as a white solid. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.0 (s, 1H), 6.9 (d, 1H, J = 8.0 Hz), 6.7 (d, 1H, J = 8.0 Hz), 4.6 (t, 2H, J = 8.7 Hz), 3.6 (t, 2H, J = 7.7 Hz), 3.2 (t, 2H, J = 8.7 Hz), 3.1 (t, 2H, J = 7.7 Hz). ESI-mass: calcd for C$_{10}$H$_{11}$BrO (M$^+$)/z 227.10; found (M$^+$)/z 227.0.

Preparation of (S)-tert-Butyl 3-hydroxypyrrolidine-1-carboxylate (17). To a solution of 3-(S)-hydroxypyrrolidine hydrochloride (**16**) (250 g, 2.02 mol) in water (1.25 L) were added sodium bicarbonate (373.72 g, 4.45 mol) and Boc anhydride (485.51 g, 2.22 mol) at 25−30 °C respectively with 30 min interval, and the reaction mixture was stirred for 10 h. After complete consumption of the starting material, the reaction mixture was diluted with water (625 mL) and ethyl acetate (1.25 L). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (625 mL). The combined organic layer was washed with water and evaporated under reduced pressure at below 50 °C to obtain **17** (360 g, 95%) as a light yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 4.4 (m, 1H), 3.5−3.3 (m, 4H), 2.1−1.9 (m, 2H), 1.5 (s, 9H). ESI-mass: calcd for C$_9$H$_{17}$NO$_3$ (M$^+$)/z 187.24; found (M + H)/z 188.0, (M + Na)/z 210.0.

Preparation of (S)-tert-Butyl 3-(tosyloxy)pyrrolidine-1-carboxylate (18). To a cold solution of **17** (350 g, 1.87 mol) in THF (1.75 L) at 10−15 °C were added sodium hydroxide (186.92 g, 4.67 mol, in 186.92 mL of water) and p-toluenesulfonyl chloride (463.28 g, 2.43 mol) respectively with 30 min interval. The reaction mixture was then warmed to 25−30 °C and stirred for 12 h. After complete consumption of the starting material, THF was distilled out under reduced pressure at below 45 °C and the residue was diluted with water followed by extracted with ethyl acetate (1.05 L × 2). The combined ethyl acetate layer was washed with 1.5 L of aqueous 3% sodium hydrogen sulfate solution followed by water (1.5 L). The ethyl acetate layer was then distilled out under reduced pressure at below 50 °C to obtain **18** (620 g, 97%) as a light yellow viscous liquid. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.8 (d, 2H, J = 8.12 Hz), 7.4 (d, 2H, J = 7.92 Hz), 5.0 (m, 1H), 3.4 (m, 4H), 2.5 (s, 3H), 2.0 (m, 2H), 1.4 (s, 9H). ESI-mass: calcd for C$_{16}$H$_{23}$NO$_5$S (M$^+$)/z 341.43; found (M + H)/z 342.0.

Preparation of (S)-2,2-Diphenyl-2-(pyrrolidin-3-yl)-acetonitrile (6). To a cold solution of diphenyl acetonitrile (19) (124.52 g, 0.644 mol) in a mixture of THF (500 mL) and DMF (500 mL) at 0−5 °C under nitrogen atmosphere was added potassium *tert*-butoxide (101.22 g, 0.90 mol) in portions, and the mixture was stirred for 1 h. A solution of 18 (200 g, 0.59 mol) dissolved in a mixture of THF (100 mL) and DMF (100 mL)) was added into the reaction mixture, and the reaction mixture was heated to 50−55 °C for 2 h under nitrogen atmosphere. After complete conversion, THF was distilled out under reduced pressure at below 50 °C and the residue was cooled to 25−30 °C. The residue was then diluted with water (2.0 L) and extracted with ethyl acetate (1 L × 2). The combined organic layer was washed with a 3% aqueous solution of sodium hydrogen sulfate (1.0 L) followed by water (1 L). The ethyl acetate layer was distilled out under reduced pressure at below 50 °C to yield 20 (213 g) as a light brown viscous oil.

To a solution of the above residue in methanol (600 mL) at 20−25 °C was added concentrated HCl (185 mL), and the reaction mixture was warmed to 25−30 °C and stirred for 7 h. After complete conversion of the starting material, methanol was removed under reduced pressure at below 50 °C and a trace amount was removed by codistilling with toluene (400 mL). The residue was diluted with water (1.0 L) and toluene (1.0 L), cooled to 25−30 °C and extracted with toluene (500 mL). The pH of the aqueous layer was adjusted to 9−10 by using sodium bicarbonate (110 g, 1.05 mol). The reaction mixture was extracted with ethyl acetate (1.0 L × 2). The combined ethyl acetate layer was evaporated under reduced pressure to obtain 6 (145 g, 95%) as a yellow colored viscous oil. ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.5 (m, 4H), 7.3 (m, 4H), 7.2 (m, 2H), 3.3 (m, 1H), 3.1 (m, 1H), 3.0−2.9 (m, 3H), 2.0 (m, 1H), 1.7 (m, 1H). ESI-mass: calcd for C$_{18}$H$_{18}$N$_2$ (M$^+$)/z 262.36; found (M + H)/z 263.0.

Preparation of (S)-2, 2-Diphenyl-2-(pyrrolidin-3-yl)-acetamide (2). To a cold solution of sulfuric acid (376 mL, 90%) at 10−15 °C was added compound 6 (135 g, 0.514 mol) slowly, and the reaction mixture was heated to 85−90 °C for 12 h. After complete consumption of the starting material, the reaction mixture was poured slowly into chilled water (1.0 L) at below 15 °C. The pH of the reaction mixture was then adjusted to 9−10 by adding an aqueous solution of sodium hydroxide slowly. The reaction mixture was then stirred at 25−30 °C for 30 min and extracted with ethyl acetate (1.0 L × 2). The combined ethyl acetate layer was washed with water (1.0 L). The ethyl acetate layer was evaporated under reduced pressure to obtain a solid residue. The compound was recrystallized with ethyl acetate to obtain 2 (110 g, 76%). ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.4−7.3 (m, 10 H), 5.8 (bs, 1H), 5.5 (bs, 1H), 3.5−3.4 (m, 1H), 3.1−3.0 (m, 1H), 3.0 (m, 1H), 2.8−2.7 (m, 2H), 2.0 (m, 1H), 1.7 (m, 1H). ESI-mass: calcd for C$_{18}$H$_{20}$N$_2$O (M$^+$)/z 280.37; found (M + H)/z 281.2, (M + Na)/z 303.0.

Preparation of (S)-2,2-Diphenyl-2-(pyrrolidin-3-yl)-acetamide L-Tartrate (3). To a solution of 2 (100 g, 0.36 mol) in ethanol (1.0 L) was added a solution of L-(+)-tartaric acid (54.6 g, 0.36 mol) in warm ethanol (600.0 mL), and the mixture was stirred for 1 h. The reaction mixture was filtered, and the solid residue was taken in methanol (500 mL) and heated to reflux for 1 h. Reaction mixture was allowed to cool at room temperature and stirred for 3 h. The solid crystals were filtered and dried to obtain 3 (123 g, 80% yield) as colorless crystals. Specific rotation: lit.[11] value [α]$_d^{25}$ +16.3° (c 1.0,

H$_2$O); obtained [α]$_d^{25}$ +16.6° (c 1.0, H$_2$O). ^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.0−7.5 (brs, 4H), 7.4−7.3 (m, 11H), 6.8 (brs, 1H), 3.9 (s, 2H), 3.8−3.7 (m, 1H), 3.40 (m,1H), 3.1 (m, 1H), 2.7−2.6 (m, 1H), 2.5 (m, 1H), 2.1 (m, 1H), 1.4−1.3 (m, 1H). ^{13}C NMR (DMSO-d$_6$, 100 MHz, δ ppm): 174.9, 174.4, 141.2, 140.8, 129.8, 129.6, 127.9, 127.0, 126.9, 72.2, 62.0, 46.1, 43.7, 41.7, 38.8, 26.6.

Synthesis of Darifenacine Hydrobromide (1) from Tartrate Salt (3). Compound 3 (300 g, 0.7 mol) was dissolved in a biphasic mixture of DM water (900 mL) and cyclopentyl methyl ether (1.2 L), and potassium carbonate (404.55 g, 2.93 mol) was added slowly at 25−30 °C and stirred for 30 min. Then compound 4 (185.17, 0.82 mmol) was added into the reaction mixture at 25−30 °C, and the reaction mixture was heated to 70−75 °C for 12 h. After complete consumption of the starting material (monitored by HPLC), the reaction mixture was cooled to 25−30 °C, diluted with CPME (1.2 L) and DM water (900 mL) and stirred for 30 min. The reaction mixture was filtered through a bed of hyflow. The filtrate was separated, and the aqueous layer was extracted with CPME (600 mL). Combined CPME layers were washed with DM water and distilled out to obtain a crude residue. CPME was removed under vacuum; the traces were removed by codistilling with toluene (600 mL) two times. The viscous mass was dissolved in acetone (1.5 L) and cooled to 0−5 °C. Aqueous hydrobromic acid (117.3 mL, 48% in water) was slowly added, and the mixture was stirred for 2 h at 0−5 °C and further for 5 h at room temperature. Acetone was distilled out under reduced pressure, the solid residue was stirred with fresh acetone (2.4 L) for 4 h and the solids were filtered. The wet solid (>99.0% HPLC pure) was redissolved in n-butanol (2.1 L) at reflux temperature and stirred for 3 h at room temperature. The solids were filtered and washed with acetone. The wet solid was dried under vacuum at 50−60 °C to afford darifenacin hydrobromide (1, 265 g, 75%) with >99.7% HPLC purity. ^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.8 (bs, 0.7H), 9.3 (bs, 0.3 H), 7.4−7.3 (m, 10 H), 7.1−7.0 (m, 1H), 7.0−6.7 (m, 2H), 6.7 (m, 1H), 4.5 (m, 2H), 4.0−3.9 (m, 1.3 H), 3.8−3.7 (m, 0.7 H), 3.4−3.3 (m, 2H), 3.1 (m, 2H), 2.9 (m, 1.3 H), 2.8−2.7 (m, 2H), 2.6 (m, 0.7H), 2.4−2.3 (m, 0.7H), 2.2 (m, 1.3H), 1.6 (m, 0.7 H), 1.5 (m, 0.3 H). ^{13}C NMR (DMSO-d$_6$, 100 MHz, δ ppm): 174.4, 174.2, 158.5, 141.2, 140.7, 140.6, 129.7, 129.4, 129.5, 128.3, 128.0, 127.9, 127.5, 127.2, 127.1, 125.4, 125.2, 108.7, 70.8, 62.4, 62.1, 56.1, 55.2, 55.1, 54.7, 53.0, 52.2, 40.0, 40.8, 30.3, 30.1, 29.0, 26.9, 25.6. Calcd for C$_{28}$H$_{30}$N$_2$O$_2$·HBr, (M+)/z: 425.56; found (M + H)/z 427.2, (M + Na)/z 449.3. Anal. Calcd for C$_{28}$H$_{31}$BrN$_2$O$_2$: C, 66.27; H, 6.16; N, 5.52. Found: C, 66.36; H, 6.07; N, 5.68.

Dimeric Impurity (15). *Isolated from the Viscous Mass Left in the Reactor.* ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.4−7.3 (m, 11H), 7.0 (d, 1H, J = 8.0, Hz), 6.9 (s, 1H), 6.7 (d, 1H, J = 8.0 Hz), 6.7 (m, 2H), 6.0 (m, 2H), 4.6−4.4 (m, 6H), 4.1 (m, 1H), 3.9−3.8 (m, 2H), 3.6−3.5 (m, 1H), 3.4 (m, 1H), 3.3−3.0 (m, 7H), 3.0−2.9 (m, 1H), 2.8−2.7 (m, 3H), 2.2−2.1 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, δ ppm): 175.2, 159.5, 159.5, 141.2, 140.6, 129.6, 129.4, 128.8, 128.5, 128.2, 128.1, 128.0, 127.7, 126.7, 126.3, 125.9, 125.3, 109.5, 109.5, 71.4, 71.3, 65.8, 63.3, 62.6, 62.2, 61.6, 42.4, 29.6, 29.6, 29.5, 29.0, 27.0. ESI-mass: calcd for C$_{38}$H$_{41}$BrN$_2$O$_3$ (M$^+$)/z 572.74; found (M$^+$)/z 572.8. Anal. Calcd for C$_{38}$H$_{41}$BrN$_2$O$_3$: C, 69.83; H, 6.32; N, 4.29. Found: C, 68.96; H, 6.12; N, 4.19.

Bromo Phenol Impurity (12). ^{1}H NMR (DMSO-d$_6$, 400 MHz, δ ppm): 9.8 (bs, 1H), 9.5 (bs, 1H), 9.2 (bs, 1H), 7.4−7.3

(m, 10H), 7.0−6.7 (m, 3H), 4.0−3.9 (m, 1H), 3.7 (m, 1H), 3.6 (m, 2H), 3.4−3.3 (m, 1H), 3.1−2.9 (m, 4H), 2.7−2.5 (m, 3H), 2.2 (m, 1H), 2.1 (m, 1H), 1.6−1.5 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, δ ppm): 175.5, 153.6, 141.9, 130.9, 129.1, 129.0, 128.9, 128.6, 128.2, 128.2, 127.8, 127.2, 125.7, 115.9, 62.7, 57.0, 56.0, 43.5, 34.2, 32.2, 30.8, 29.7, 27.9. ESI-mass: calcd for C$_{28}$H$_{31}$BrN$_2$O$_2$ (M$^+$)/z 507.48; found (M + H)/z 508.7.

Benzofuran Impurity (14). ^{1}H NMR (CDCl$_3$, 400 MHz, δ ppm): 7.6 (d, 1H, J = 2.2 Hz), 7.4−7.2 (m, 11H), 7.1 (dd, 1H, J = 8.4, 1.7 Hz), 6.7 (m, 2H), 5.3 (bs, 2H), 3.6 (m, 1H), 3.1 (m, 1H), 3.0−2.9 (m, 6H), 2.7 (m, 1H), 2.3 (m, 1H), 1.9 (m, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz, δ ppm): 175.4, 153.7, 145.3, 143.6, 142.9, 133.2, 129.2, 129.1, 128.3, 127.6, 127.1, 124.9, 120.8, 111.2, 106.3, 63.6, 57.0, 56.9, 53.6, 43.9, 33.5, 28.4. ESI-mass: calcd for C$_{28}$H$_{28}$N$_2$O$_2$ (M$^+$)/z 424.55; found (M + H)/z 425.1, (M + 23)/z = 447.0.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data of selected intermediates and final compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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