Tetrahedron 69 (2013) 2834–2843

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective synthesis of (−)-(*R*) Silodosin by ultrasound-assisted diastereomeric crystallization

Indrajeet J. Barve [a], Li-Hsun Chen [a], Patrick C.P. Wei [b], Jui-Te Hung [b], Chung-Ming Sun [a,*]

[a] Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan, ROC
[b] Formosa Laboratories, Inc. 36 Hoping Street, Taoyuan 338-42, Taiwan, ROC

ARTICLE INFO

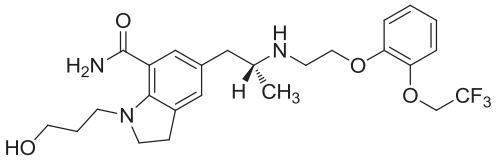
Article history:
Received 2 November 2012
Received in revised form 13 January 2013
Accepted 21 January 2013
Available online 1 February 2013

ABSTRACT

Enantioselective synthesis of clinically approved drug—Silodosin for the treatment of benign prostatic hyperplasia from the commercially available compounds 1-acetyl-5-(2-aminopropyl) indoline-7-carbonitrile **A** and 2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl methanesulfonate **C** is explored. Key step in the synthesis is chiral resolution of intermediate **1**, which was achieved by a simple diastereomeric crystallization using (*S*)-(+)-mandelic acid assisted by ultrasonication. The present synthetic strategy has lesser number of steps and is vastly improved the overall yield in this short route towards target compound—Silodosin.

1. Introduction

Silodosin is a medication for the treatment of problems associated with human prostrate. It is a α_{1a}-adrenoceptor (AR) antagonist that selectively binds to α_{1a}-AR, which is present in the prostate and bladder neck situated at the lower urinary tract.[1,2]



Silodosin

This high selectivity for α_{1a}-AR is due to the inhibition of sympathetic nerve stimulation and relaxation of smooth muscle tone of the lower urinary tract tissues, resulting in reduction of the symptoms of benign prostatic hyperplasia (BPH).[3] Clinical data suggested that Silodosin showed significant improvement in lower urinary tract symptoms associated with BPH, as well as the quality of life.[4–6] There are no reported synthetic methods for Silodosin in the literature and the existing strategy was patented.[7–9]

One of the reported patent synthesis (Scheme 1) started from benzoic acid. After several functional group transformations, racemic amine **I** was obtained. The racemate **I** resolved by diastereomeric crystallization using L-(+)-tartaric acid and the so obtained compound **I** was purified by column chromatography. The coupling of single enantiomer of compound **I** with 2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl methanesulfonate and subsequent deacetylation, partial hydrolysis afforded Silodosin. In another reported patent (Scheme 2), synthesis started from coupling of either **A** and **B** or **A′** and **B′**. After several steps compound **II** obtained, which was resolved by diastereomeric crystallization using (+) mandelic acid at the penultimate step. The cleavage of Boc group at the final step gave Silodosin. The main drawbacks of the reported synthetic routes contain greater number of steps to cause a drastic reduction in the overall yield of the final compound. Hence it is of great interest and challenge to upgrade the current route with an aim to improve reaction efficiency and enhance overall yield in the synthesis.

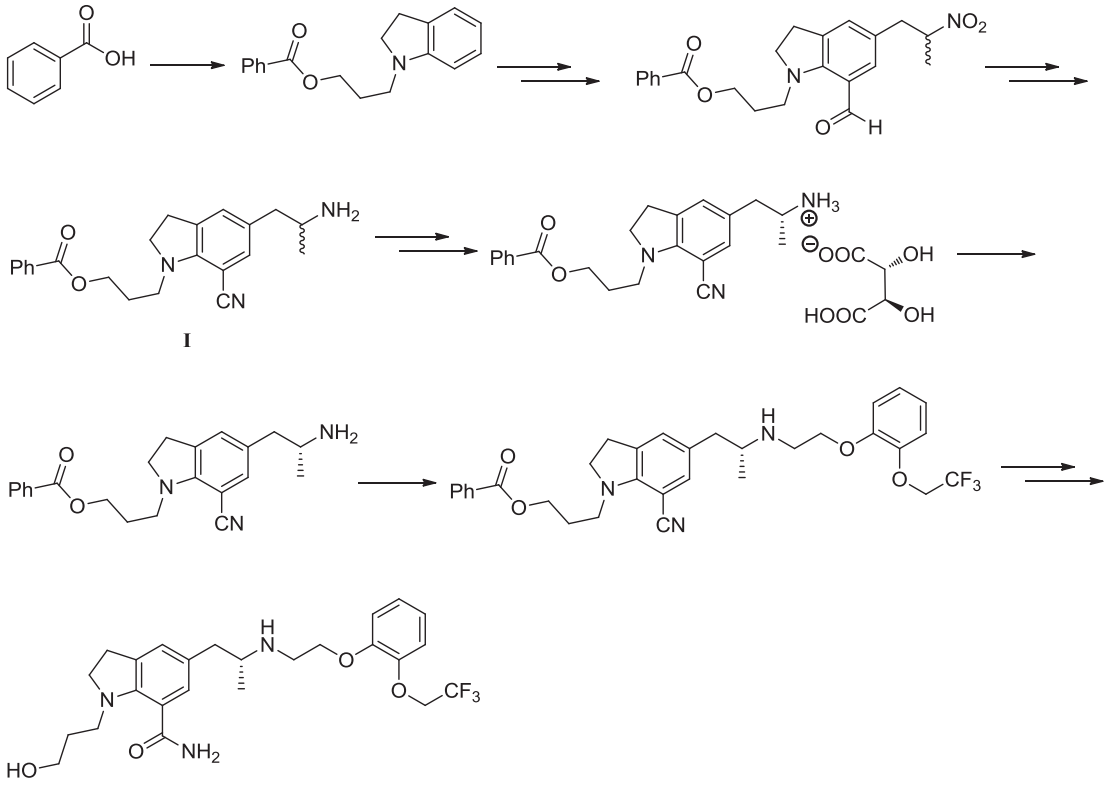
Reterosynthetic analysis for the synthesis of Silodosin is outlined in Scheme 3. It is recognized that the crucial step in the synthesis is the N–C bond formation between 5-(2-aminopropyl)-1-(3-hydroxypropyl) indoline-7-carboxamide **B** and suitably protected β-trifluoromethyl diethyl catechol derivative **C**. From the analysis of patented procedures, we speculated that β-trifluoromethyl diethyl catechol derivative with mesylate as a leaving group would be more facile for nucleophilic substitution. Introduction of the amide and the 3-hydroxy *n*-propyl side chain is predicted by the functional group transformation from the corresponding precursor **3**. It is apparent that the attachment of the catechol moiety can be introduced at any stage in the sequence of proposed reaction scheme. However, during the present route it is planned to use this combination of **A** and **C** in the first coupling step.

2. Results and discussion

Our synthetic endeavour towards Silodosin began with a coupling reaction of commercially available **A** and **C** (Scheme 12).

* Corresponding author. E-mail addresses: cmsun@mail.nctu.edu.tw, chungmingsun@gmail.com (C.-M. Sun).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.01.061



Scheme 1. Reported route for Silodosin.[8]

Condensation of the racemic amine **A** and catechol mesylate **C** in the presence of triethylamine in refluxing ethanol failed to give any desired product **1**. Starting materials **A** and **C** were recovered in this case. An attempt to couple **A** with **C** in the presence of $NaHCO_3$ in refluxing acetonitrile for 36 h, provided compound **1** in only 32% yield along with unreacted starting materials. Refluxing of the reaction for prolonged time (48 h) did not improve the yield. A better protocol for the coupling reaction of compounds **A** and **C** was designed as follows.

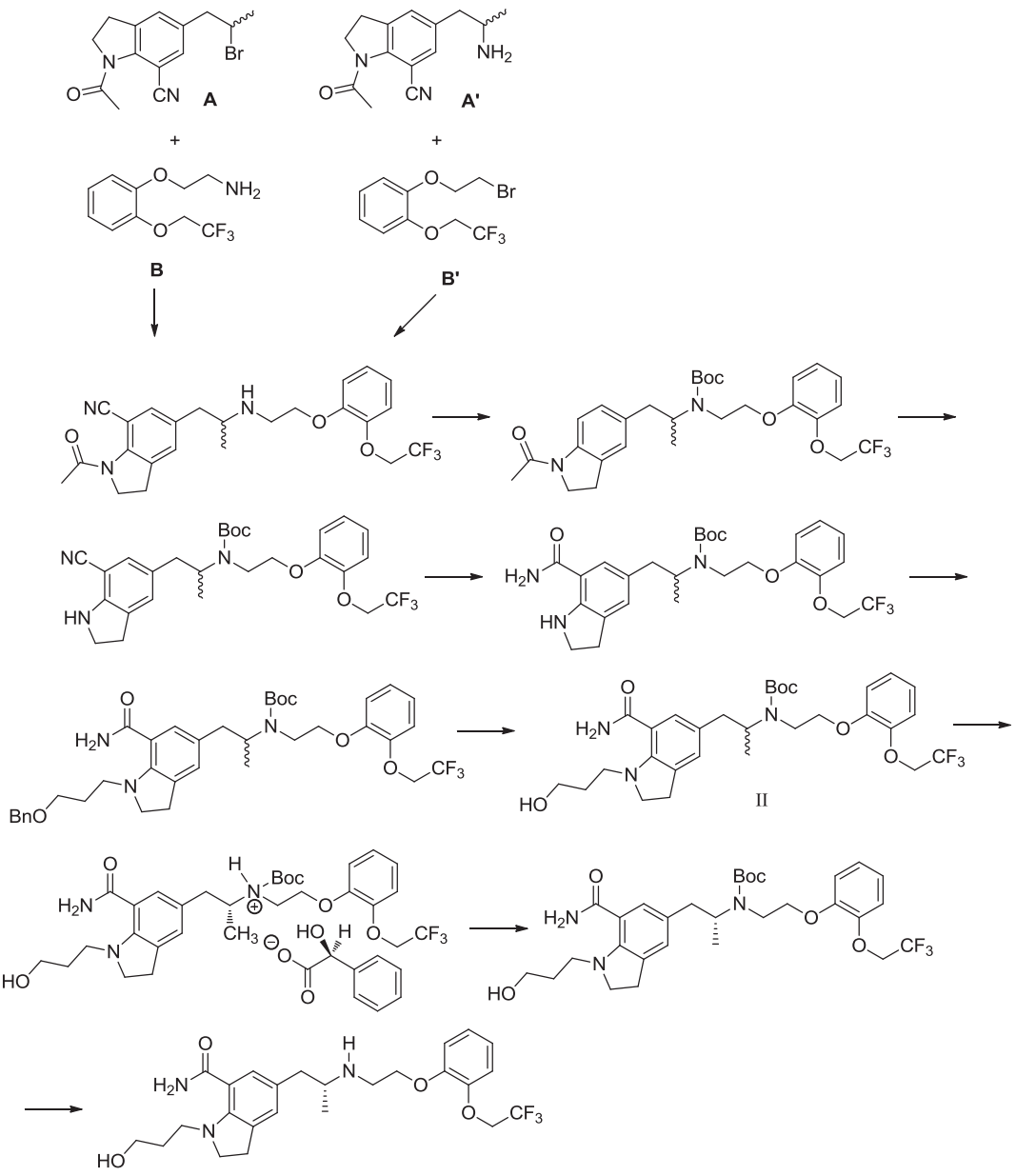
Variety of solvents (polar protic and polar aprotic) with triethylamine and sodium bi carbonate were investigated, but no substantial improvement was observed in terms of isolated yield (Table 1, entries 2–4). A stronger inorganic base is used in order to drive the reaction for completion.

The use of K_2CO_3 in refluxing ethanol or isopropyl alcohol or *tert*-butyl alcohol or acetonitrile for the coupling reaction of compounds **A** and **C** resulted in deacetylated compound **9** (Scheme 5). The deacetylation was observed due to the trace amount of water present in the solvent.

Nevertheless, all efforts in optimizing this step could not improve the yield beyond 58%. Eventually, we found that addition of KI in stoichiometric amount facilitated the coupling reaction to afford the crucial intermediate **1** in 93% yield (Scheme 4).[10] Dry acetonitrile was then used to avoid the formation of deacetylated product **9**. It is likely that mesylate group of **C** was replaced in situ by iodide, which proved to be a better leaving group to deliver **1** in an excellent yield over that of the reported yield (65%) in the patented procedure.[8,9]

Next step was the chiral resolution of the racemic compound **1**, which was achieved by crystallization of the diastereomers by treating **1** with (*S*)-(+) mandelic acid.[11,12] A refluxed solution of **1** and (*S*)-(+) mandelic acid in methanol was allowed to stand at room temperature.

The diastereomeric salt **2** obtained after cooling at room temperature was filtered off and treated with aqueous solution of a base. The extraction of an aqueous layer yielded **3** in very low yield (10%). The incompleteness of the diastereomeric salt **2** formation of **1** and (*S*)-(+) mandelic acid in refluxing methanol was the main reason associated with the yield loss of **3**. Prolong heating (24 h) did not result in the complete transformation of **1** into diastereomeric salt **2**. After cooling of the reaction mixture, (*S*)-(+) mandelic acid with little amount of diastereomeric salt **2** crystallized out to leave most of compound **1** in methanol. Another major problem with this protocol was nature of the diastereomeric salt. The diastereomeric salt **2** was obtained as a sticky solid (Scheme 6). These drawbacks of the refluxing condition for the chiral resolution of **1** made us to search a more efficient technique. Application of ultrasound to crystallization can enhance chiral amplification, resulting in rapid crystallization process and enrichment of the single enantiomer.[13] Accordingly, a solution of racemic compound **1** and (*S*)-(+) mandelic acid in methanol was sonicated for 30 min. The crystallized solid diastereomeric salt was filtered off, and treated with aqueous solution of base. Extraction of aqueous layer afforded **3** in 34% yield (Scheme 12). Threefold increase in the yield during resolution under ultrasound radiation was achieved in the key step. The purity of the single enantiomer **3** was confirmed by chiral HPLC, optical rotation and ^1H NMR. The chiral amplification during crystallization of the diastereomers is due to the influence of ultrasound waves on the physicochemical phenomena of crystallization. The crystallization process composed of two events: nucleation and crystal growth.[14] In the nucleation stage, the dissolved solute molecules start to accumulate into clusters and reach to a critical size to form nuclei. The application of ultrasound energy to crystallization significantly reduces the induction time of nucleation.[15] When ultrasonic energy passes through a solution, it creates the cycle of compression and expansion to produce bubbles. The collapse of the bubbles provides energy, which promotes the rapid cluster formation of diastereomeric salt.[16] In our case, the (*R*,*S*) diastereomeric salt **2** formed had less solubility in methanol, hence it was crystallized out leaving **3′** in the solution (Scheme 7).



Scheme 2. Reported route for Silodosin.[9]

The amino function in **3** was converted to *N*-Boc by treating with di-*tert*-butyl dicarbonate and triethylamine to afford **4** in 90% yield. In the next step, to keep Boc group intact, acidic condition was avoided for the deacetylation of compound **4**.

As the hydrolysis of acetyl group was observed when K_2CO_3 in refluxing solvents was applied for the condensation (Scheme 5), it was speculated that deacetylation of **4** could be smoothly accomplished by same condition. Accordingly, selective N-deacetylation of **4** was achieved by K_2CO_3 in aqueous ethanol to afford **5** in 98% yield. This mild alkaline condition ensured that the *N*-Boc group was remained intact (Scheme 8). Initially, we attempted to introduce the 3-hydroxypropyl side chain in **5** by commercially available benzyl 3-bromopropyl ether.

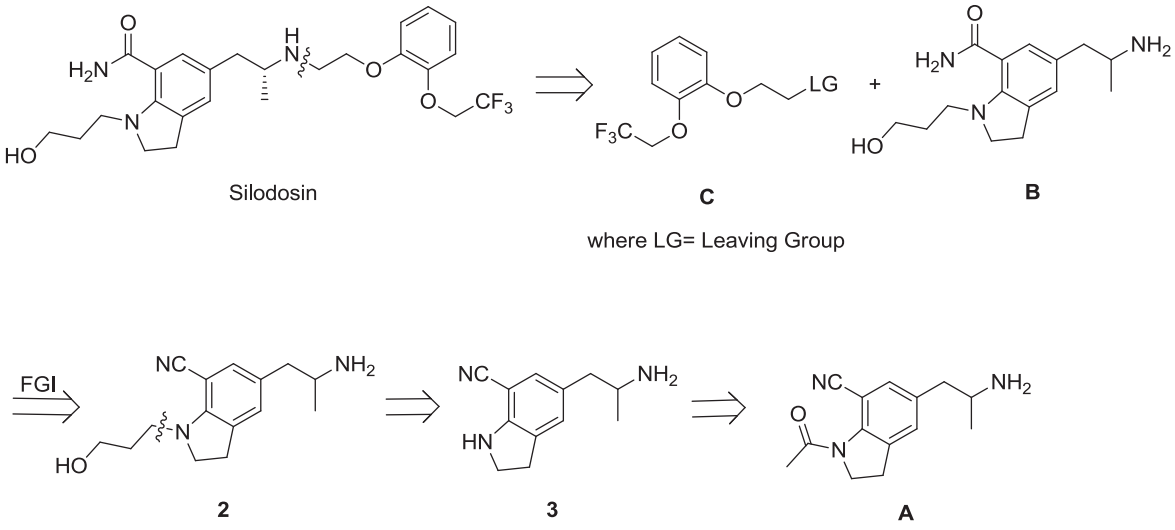
Thus, compound **5** was alkylated with benzyl 3-bromopropyl ether and strong base to afford **6** in 65% yield. The subsequent debenzylation of **6** in the presence of H_2 gas and Pd/C provided **7** in quantitative yield (Scheme 9).

Moving to the next step, deprotection of Boc group of **7** under TFA conditions provided **14** in 67% yield. Formation of side product **10** was detected in 30% yield via dehydration of the 3-hydroxypropyl side chain of **7**, which decreased the yield of **14** (Scheme 10).

In the final step, the partial hydrolysis of nitrile group of **14** was accomplished by a mixture of 30% hydrogen peroxide and NaOH to furnish target compound—Silodosin in 67% yield (Scheme 11).

In short, an attempt for the introduction of 3-hydroxypropyl side chain in **5** using benzyl 3-bromopropyl ether as an alkylating reagent suffered from many drawbacks. Firstly, this approach involved the debenzylation using expensive palladium reagents.[8] Secondly, formation of unwanted byproduct at the penultimate step resulted in significant drop in the yield of Silodosin.

In order to achieve simple, efficient and metal free synthetic sequence, attempts were initiated to search for alternate alkylating reagent. From the literature search it was found that introduction of the 3-hydroxypropyl side chain would be promising if 3-bromopropan-1-ol was used.[17,18] For the sake of ease in handling the reaction steps, it was decided to protect the bare hydroxyl group by *tert*-butyl dicarbonate.



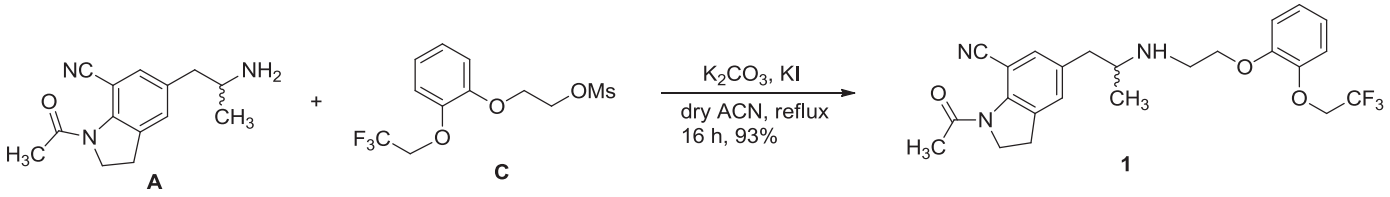
Scheme 3. Retrosynthetic analysis of Silodosin.

Table 1
Optimization of the coupling reaction of compounds **A** and **C**

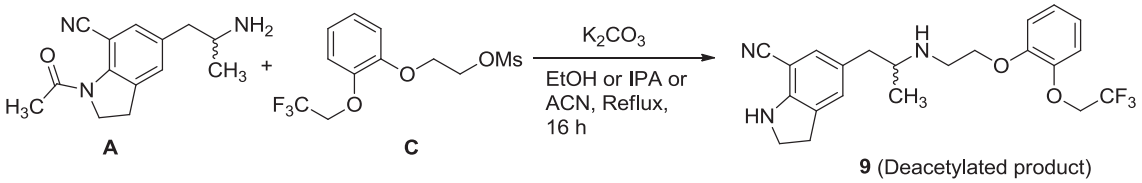
Entry	Base	Additive	Solvent	Time (h)	Yield (%)
1	TEA	—	EtOH	36	No reaction
2	$NaHCO_3$	—	EtOH	36	46
3	$NaHCO_3$	—	IPA	16	42
4	$NaHCO_3$	—	ACN	16	32
5	$NaHCO_3$	KI	DMF	16	46
6	K_2CO_3	—	EtOH	16	44
7	K_2CO_3	—	IPA	16	38
8	K_2CO_3	—	TBA	16	58
9	K_2CO_3	—	ACN	16	52
10	K_2CO_3	KI	ACN	16	93

NMR spectrum, characteristic up-field signals due to *tert*-butyl protons were absent, which indicated removal of both the Boc-groups attached to N and O simultaneously. The product corresponded to **14** was obtained in quantitative yield.

Thus, in this N-alkylation, additional step required for Boc deprotection was escaped, which has greatly contributed to the success of this new synthetic route. Such *N*,*O*-Boc in situ double deprotections are first observed in our study. Consequently, the desired compound **14** was directly isolated in good yield. Final step in this synthesis required partial hydrolysis of nitrile group of **14** into amide, which was achieved by a mixture of 30% hydrogen peroxide and base in methanol to afford Silodosin in an excellent yield.



Scheme 4. Coupling reaction of **A** and **C**.

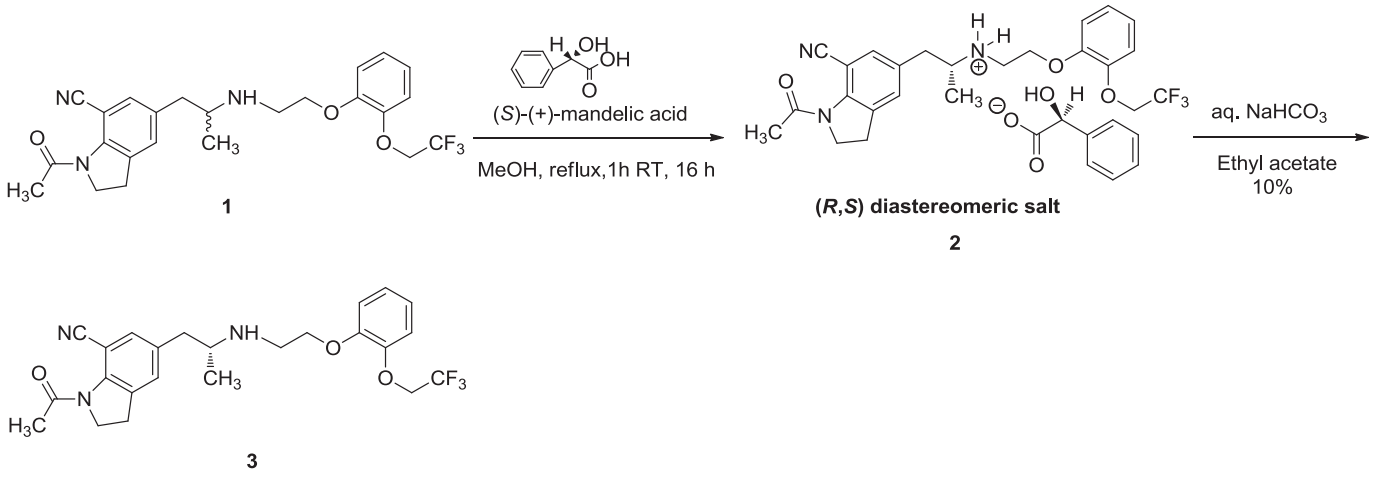


Scheme 5. Coupling reaction of **A** and **C** using K_2CO_3 in polar protic and aprotic solvents.

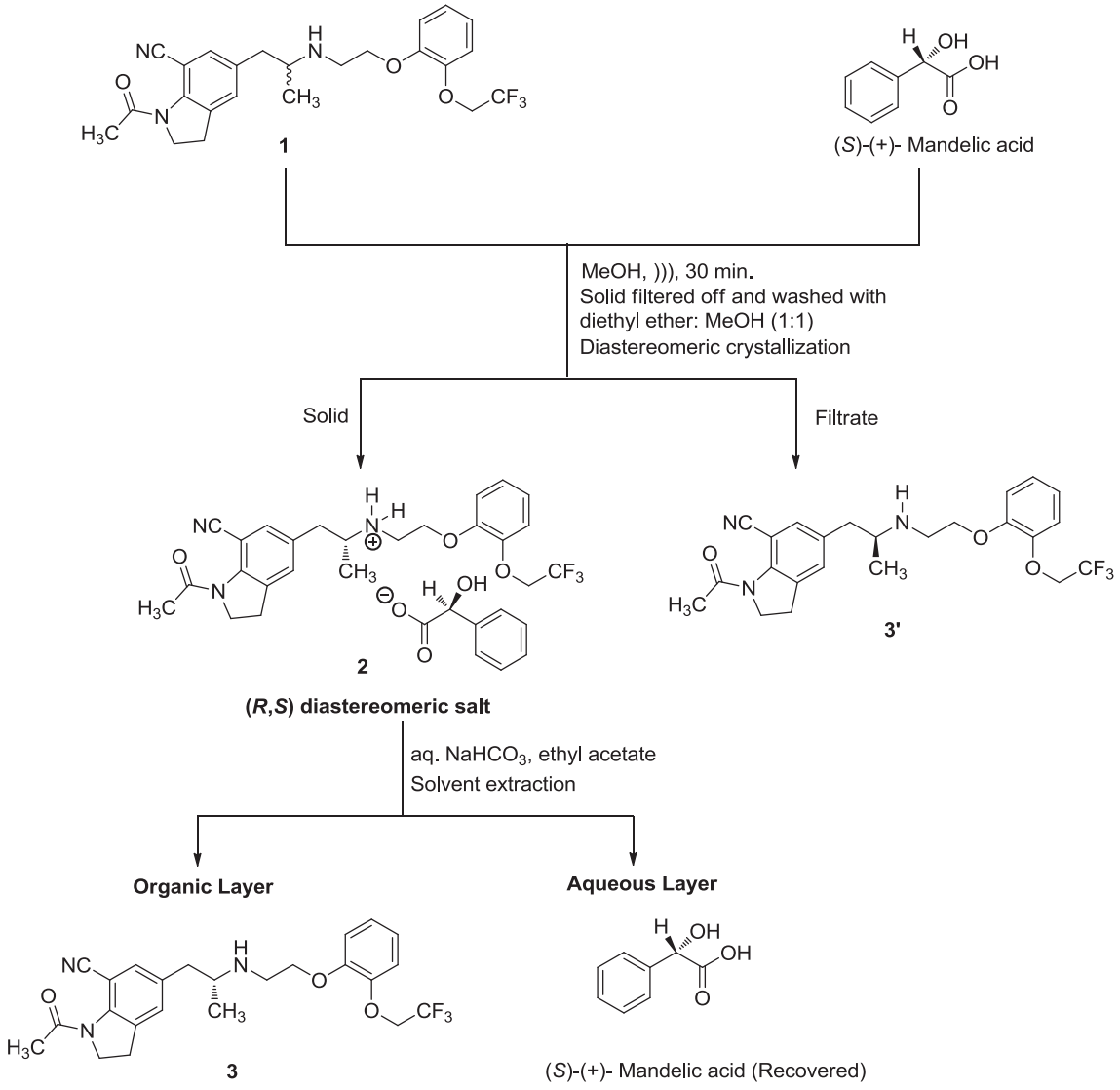
Thus, a new *O*-Boc-protected 3-bromopropan-1-ol **12** was synthesized during the present work for the purpose of introducing 3-hydroxypropyl side chain at the indole nitrogen. Attempted alkylation of compound **5** with 3-bromopropyl *tert*-butyl carbonate **12** in the presence of NaH in dry acetonitrile was the most surprising step in this route (Scheme 12). The expected bis Boc-protected compound **13** due to N-alkylation was not observed. In the ^1H

3. Conclusion

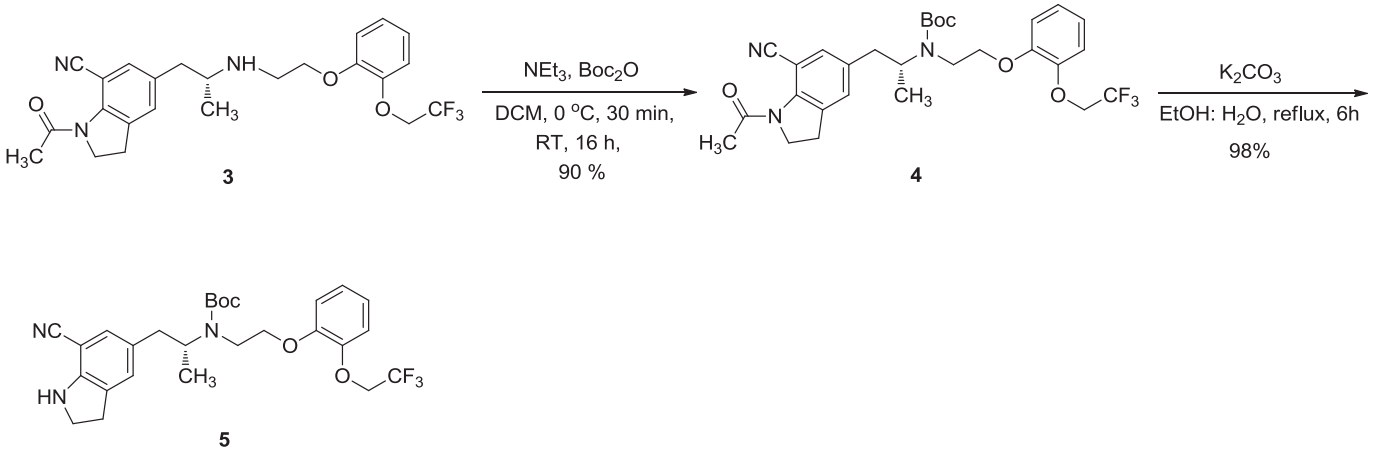
In conclusion, a short and efficient protocol for the synthesis of Silodosin has been accomplished. The title compound was synthesized in enantiomerically pure form in only six steps from commercially available compounds in an overall yield of 15%. The unique feature of this synthetic sequence is the use of simple and



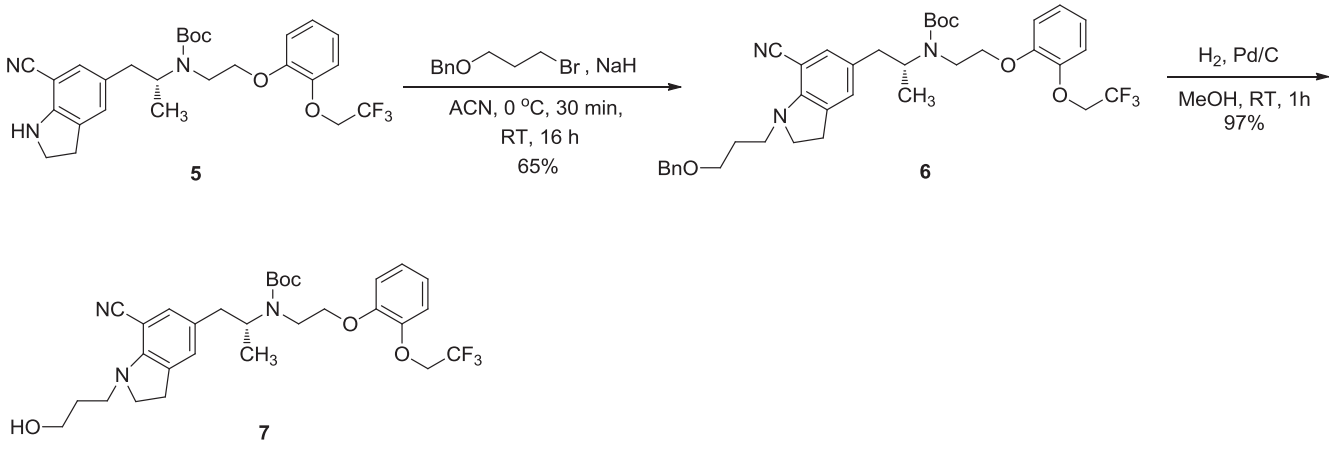
Scheme 6. Chiral resolution of racemic compound **1**.



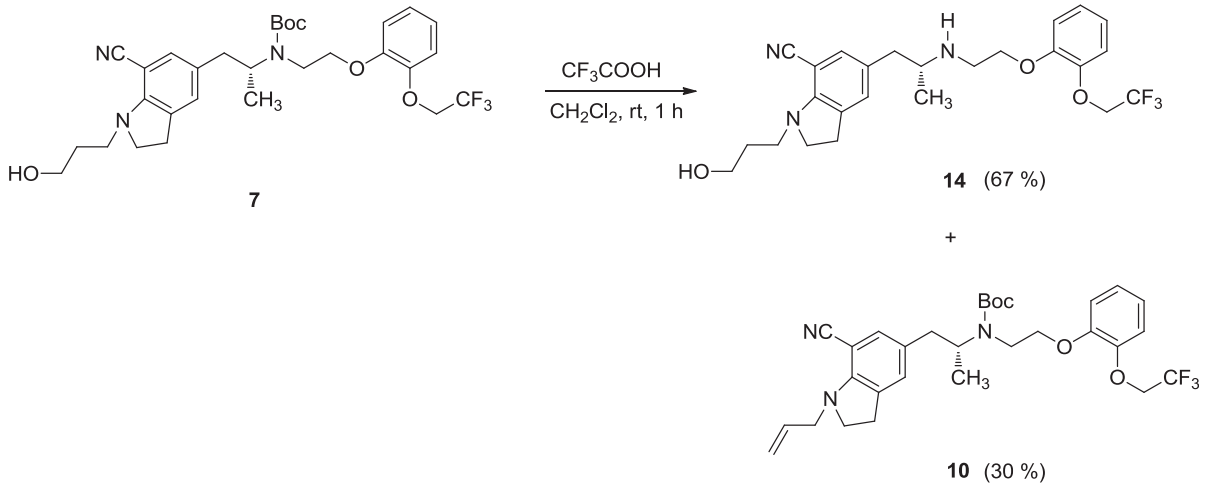
Scheme 7. Resolution of racemic compound **1**.



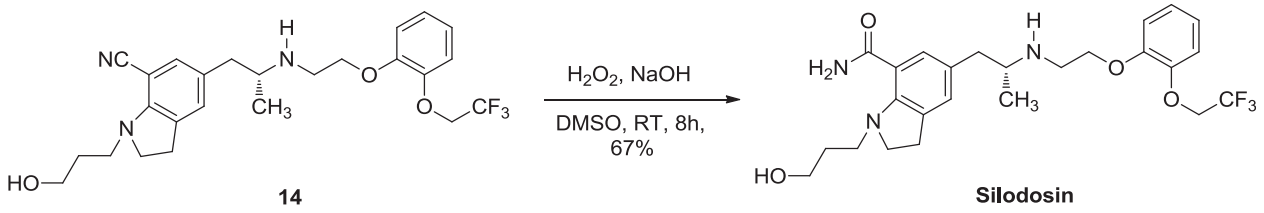
Scheme 8. Boc protection and deacetylation of **3**.



Scheme 9. Alkylation and debenzylation of **5**.



Scheme 10. Deprotection of the Boc group of **7**.



Scheme 11. Partial hydrolysis of nitrile group of **14**.

effective ultrasound radiation to assist diastereomeric crystallization to achieve the chiral resolution of racemic compound **1**.

4. General experimental procedures

4.1. 1-Acetyl-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy) ethyl)amino)propyl)indoline-7-carbonitrile (1)

To a mixture of amine **A** (20 g, 82.7 mmol) and mesylate **C** (20 g, 63.63 mmol) in dry acetonitrile (300 mL) were added K_2CO_3 (26.3 g, 190.9 mmol) and KI (3.16 g, 19.09 mmol), and the reaction mixture was refluxed for 16 h. The solvent was evaporated in vacuo. The residue was diluted with water (500 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (10–15% methanol in dichloromethane) to afford racemic compound **1** (24 g, 93%), which was further subjected for the chiral resolution.

4.2. (*R*)-(−)-1-Acetyl-5-(2-((2-(2-(2,2,2-trifluoroethoxy) phenoxy) ethyl) amino) propyl) indoline-7-carbonitrile (3)

To a stirred solution of **1** (20 g, 43.33 mmol) in methanol (300 mL) was added (*S*)-(+) mandelic acid (6.59 g, 43.3 mmol) and the reaction mixture was sonicated for 30 min. The precipitated solid was filtered, washed with diethyl ether/methanol (100:100 mL) and dried. To a mixture of ethyl acetate (200 mL) and 10% $NaHCO_3$ (200 mL) was added this solid, and the mixture was stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with 10% $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated in vacuo to give **3** (7.8 g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.27 (s, 1H), 7.07–6.87 (m, 4H), 4.33 (q, *J*=8.4 Hz, 2H), 4.13–3.06 (m, 4H), 3.14–2.92 (m, 5H), 2.74 (dd, *J*=13.5, 6.2 Hz, 1H), 2.54 (dd, *J*=6.99, 13.5 Hz, 1H), 2.28 (s, 3H), 1.04 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 149.7, 148.7, 147.4 (d, *J*=11.8 Hz), 141.7, 136.3, 135.9, 132.9, 130.5, 125.7, 124.4, 124.1, 122.4, 121.8, 118.0 (d, *J*=15.0 Hz), 116.7, 114.7 (d, *J*=16.9 Hz), 102.1, 68.9 (d, *J*=17.0 Hz), 68.3, 67.8 (d, *J*=9.7 Hz), 67.1 (d, *J*=13.7 Hz), 54.5, 50.3, 46.3, 42.5, 37.7, 28.7, 23.9, 19.9; MS (EI^+) *m*/*z*: 462.5 $(M+H)^+$; IR (cm^{-1}, neat): 2962, 2931, 2223, 1675; $[\alpha]_D^{25}$ −21.9 (*c* 0.01, MeOH); enantiomeric excess=100% ee.

4.3. (*R*)-*tert*-Butyl(1-(1-acetyl-7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate (4)

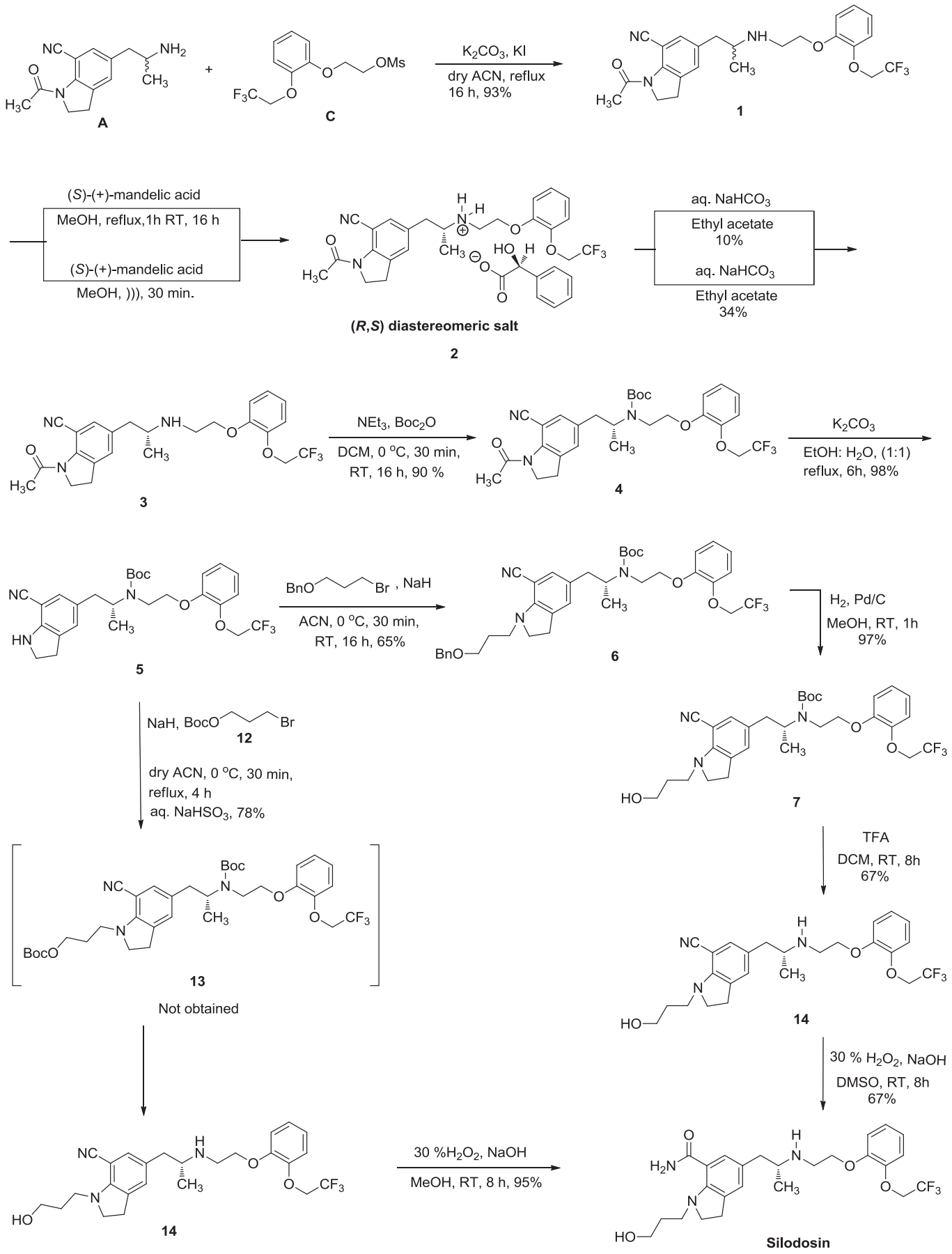
To a stirred solution of **3** (2.7 g, 5.85 mmol) in dichloromethane (50 mL) were added triethylamine (2.44 mL, 17.55 mmol) and di-*tert*-butyl dicarbonate (1.66 g, 7.60 mmol) at 0 °C and the reaction mixture was stirred for 30 min. Further it was stirred at room temperature for 16 h. The solvent was evaporated in vacuo. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (3–5% methanol in dichloromethane) to afford **4** (3.17 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.08 (m, 2H), 7.05–6.79 (m, 4H), 4.34 (q, *J*=8.4 Hz, 2H), 4.08–3.93 (m, 5H), 3.47–3.37 (m, 2H), 3.07–2.82 (m, 3H), 2.65 (dd, *J*=13.8, 6.6 Hz, 1H), 2.25 (s, 3H), 1.40 (s, 9H), 1.24 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 155.8, 155.3, 149.5–147.4 (m), 141.8, 136.5, 135.6, 132.8, 130.3, 125.7, 124.2 (d, *J*=6.2 Hz), 122.0–121.4 (m), 117.9, 117.0, 114.3, 113.8, 102.3 (d, *J*=15.9 Hz), 80.3, 68.2 (d, *J*=12.3 Hz), 67.7 (d, *J*=10.2 Hz), 55.3, 54.7, 50.3, 44.6, 40.5 (d, *J*=42 Hz), 28.8 (d, *J*=6.0 Hz), 24.0, 19.4, 18.6; MS (EI^+) *m*/*z*: 584.2 $(M+Na)^+$; IR (cm^{-1}, neat): 2971, 2931, 2201, 1679; $[\alpha]_D^{25}$ −46.26 (*c* 0.01, MeOH).

4.4. (*R*)-*tert*-Butyl(1-(7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate (5)

To a stirred solution of **4** (3 g, 5.34 mmol) in ethanol/water (50:50 mL) was added K_2CO_3 (14.7 g, 106.8 mmol) and the reaction mixture was refluxed for 6 h. The solvent was evaporated in vacuo. The residue was diluted with water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (5–10% methanol in dichloromethane) to afford **5** (2.76 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 2H), 7.08–6.97 (m, 4H), 4.37 (q, *J*=8.4 Hz, 2H), 4.19–3.98 (m, 3H), 3.66 (t, *J*=8.4 Hz, 2H), 3.53–3.33 (m, 2H), 3.01 (t, *J*=8.5 Hz, 2H), 2.81 (m, 1H), 2.57 (dd, *J*=13.8, 6.6 Hz, 1H), 1.43 (s, 9H), 1.25 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 155.3, 153.5 (d, *J*=13.4 Hz), 149.7–147.4 (m), 131.2, 130.3, 129.7 (d, *J*=13.8 Hz), 124.3, 122.0, 121.8–121.4 (m), 118.2, 117.3, 114.1 (d, *J*=34.5 Hz), 90.5, 80.2, 68.2 (d, *J*=8.3 Hz), 67.7 (d, *J*=8.0 Hz), 67.3, 55.4, 54.7, 47.4, 44.3, 40.5 (d, *J*=39 Hz), 29.4, 28.8, 19.4, 18.6; MS (EI^+) *m*/*z*: 542.2 $(M+Na)^+$; IR (cm^{-1}, neat): 3351, 2973, 2933, 2877, 2213, 1685; $[\alpha]_D^{25}$ −56.2 (*c* 0.01, MeOH).

4.5. (*R*)-*tert*-Butyl(1-(1-(3-(benzyloxy)propyl)-7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy) ethyl)carbamate (6)

To a stirred solution of **5** (2.7 g, 5.19 mmol) in acetonitrile (100 mL) was added NaH (0.24 g, 10.3 mmol) at 0 °C. After stirring for 30 min at the same temperature, benzyl 3-bromopropyl ether (1.0 mL, 5.71 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated in vacuo. The residue was diluted with water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (10–15% ethyl acetate in hexanes) to afford **6** (2.36 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 7.10–6.87 (m, 6H), 4.54 (s, 2H), 4.38 (q, *J*=8.3 Hz, 2H), 4.25–3.84 (m, 3H), 3.76–3.59 (m, 4H), 3.58–3.35 (m, 4H), 2.90 (t, *J*=8.6 Hz, 2H), 2.86–2.66 (m, 1H), 2.55 (dd, *J*=13.8, 6.6 Hz, 1H), 1.99 (p, *J*=6.5 Hz, 2H), 1.45 (s, 9H), 1.26 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 155.3, 151.9, 149.7, 147.3, 138.7, 133.0, 131.7, 129.8, 128.7, 128.0 (d, *J*=10.3 Hz), 125.7, 124.3, 121.8 (d, *J*=31.2 Hz), 121.4, 119.9, 117.4, 114.4, 113.9, 87.9, 80.2, 73.4, 68.7,



Scheme 12. An initially attempted and modified synthetic route for the synthesis of Silodosin.

68.4–67.4 (m), 67.3, 54.5, 53.6, 45.6, 44.1, 40.5, 40.0, 28.8, 28.2, 27.7, 19.4, 18.6; MS (ESI^+) *m/z*: 668.5 $(M+H)^+$; IR (cm^{-1}, neat): 2967, 2931, 2863, 2211, 1683, 1284, 1251, 1162, 1122.

4.6. (*R*)-*tert*-Butyl(1-(7-cyano-1-(3-hydroxypropyl)indolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl) carbamate (7)

To the stirred solution of **6** (2.2 g, 3.29 mmol) in methanol (100 mL) was added 10% Pd/C (1.1 g, 10.3 mmol) and the reaction mixture was stirred at room temperature under H_2 balloon pressure for 1 h. The reaction mixture was filtered over a pad of Celite. The filtrate was concentrated in vacuo to afford **7** (1.52 g, 97%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.04–6.89 (m, 6H), 4.37 (q, *J*=8.3 Hz, 2H), 4.17–3.91 (m, 3H), 3.80 (t, *J*=6.0 Hz, 2H), 3.66 (t, *J*=7.3 Hz, 2H), 3.57 (t, *J*=8.6 Hz, 2H), 3.45 (dd, *J*=23.0, 7.2 Hz, 2H), 2.93 (t, *J*=8.6 Hz, 2H), 2.83–2.70 (m, 1H), 2.55 (dd, *J*=13.9, 6.7 Hz, 1H), 1.92 (p, *J*=7.0 Hz, 2H), 1.44 (s, 9H), 1.25 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 152.1, 149.6, 133.0, 131.6, 130.0, 128.5, 124.3, 121.8 (d, *J*=31.1 Hz), 121.4, 120.2, 117.3, 114.4, 113.9, 88.0, 80.3, 68.3, 67.8 (t, *J*=35.1 Hz), 60.7, 54.4, 53.7, 45.9, 44.4, 40.5, 40.0, 30.8, 28.8, 27.6, 19.4, 18.62; MS (ESI^+) *m/z*: 578.4 $(M+H)^+$; IR (cm^{-1}, neat): 3457–3388, 2971, 2933, 2211, 1677, 1251, 1162.

4.7. 5-(2-((2-(2-(2,2,2-Trifluoroethoxy)phenoxy)ethyl)amino) propyl)indoline-7-carbonitrile (9)

To a mixture of amine **A** (0.46 g, 1.9 mmol) and mesylate **C** (0.5 g, 1.59 mmol) in acetonitrile (50 mL) was added K_2CO_3 (0.65 g, 4.77 mmol) and the reaction mixture was refluxed for 16 h. The solvent was evaporated in vacuo. The residue was diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (10–15% methanol in dichloromethane) to afford compound **9** (0.201 g, 52%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (m, 6H), 4.36 (q, *J*=8.4 Hz, 2H), 4.20–3.98 (m, 2H), 3.64 (t, *J*=8.5 Hz, 2H), 3.16–2.92 (m, 4H), 2.64 (dd, *J*=13.6, 6.3 Hz, 1H), 2.57–2.32 (m, 2H), 1.06 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.14, 149.99, 147.74, 131.23, 130.36, 129.66, 129.24, 124.59, 122.11, 118.57–117.87 (m), 115.37, 114.93, 90.12, 71.34, 69.04, 68.58, 68.11, 67.66, 61.35, 54.73, 47.43, 46.55, 42.87, 29.46, 22.37, 20.19; MS (EI^+) *m/z*: 420.2 $(M+H^+)$; IR (cm^{-1}, neat): 3420–3210, 3037, 2958, 2935, 2875, 2211, 1500, 750.

4.8. (*R*)-1-(3-Hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy) phenoxy)ethyl)amino)propyl)indoline-7-carbonitrile (14)

(*A*) To a stirred solution of **5** (2.5 g, 4.81 mmol) in dry acetonitrile (75 mL) was added NaH (0.57 g, 24.05 mmol) at 0 °C. After stirring for 30 min at the same temperature, 3-bromopropyl *tert*-butyl carbonate **12** (1.38 g, 5.77 mmol) was added and the reaction mixture was refluxed for 4 h. The solvent was evaporated in vacuo. The residue was diluted with water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with satd solution of $NaHSO_3$ (20 g in 100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (8–15% methanol in dichloromethane) to afford **14** (1.78 g, 78%).

(*B*) To a stirred solution of **7** (0.8 g, 1.38 mmol) in dichloromethane (50 mL) was added TFA (0.31 mL, 4.15 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated in vacuo. The residue was neutralized by satd $NaHCO_3$ (100 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (8–15% methanol in dichloromethane) to afford **14** (0.46 g, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.05–6.89 (m, 6H), 4.31 (q, *J*=8.4 Hz, 2H), 4.08 (dt, *J*=6.0, 4.2 Hz, 2H), 3.74 (td, *J*=5.7, 2.7 Hz, 1H), 3.65–3.47 (m, 5H), 3.07–2.85 (m, 6H), 2.63 (dd, *J*=13.6, 6.4 Hz, 1H), 2.45 (dd, *J*=13.6, 7.0 Hz, 1H), 2.07 (m, 1H), 1.82 (m, 1H), 1.05 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 150.0, 147.7, 132.6, 130.3, 130.0, 124.5, 121.9 (d, *J*=16.6 Hz), 118.3 (d, *J*=10.1 Hz), 114.9, 109.9, 90.1, 70.0, 69.2–68.4 (m), 68.1, 67.6, 62.0, 61.5, 54.7, 47.4, 46.6, 42.9, 30.9, 29.4, 20.3 (d, *J*=7.3 Hz); MS (EI^+) *m/z*: 478.3 $(M+H^+)$; IR (cm^{-1}, neat): 3330, 3193, 3073, 2929, 2854, 2360, 2333, 1662; $[\alpha]_D^{25}$ −30.4 (*c* 0.01, MeOH).

4.9. (*R*)-*tert*-Butyl(1-(1-allyl-7-cyanoindolin-5-yl)propan-2-yl)(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)carbamate (10)

Dehydrated compound **10** was formed as a side product as per Scheme 7.

^1H NMR (300 MHz, $CDCl_3$) δ 7.13–6.71 (m, 6H), 5.89 (ddt, *J*=17.2, 10.2, 5.8 Hz, 1H), 5.33–5.06 (m, 2H), 4.37 (q, *J*=8.4 Hz, 2H), 4.25–4.10 (m, 2H), 4.08–3.83 (m, 2H), 3.59–3.46 (m, 2H), 3.46–3.27 (m, 2H), 2.98–2.87 (m, 2H), 2.84 (m, 2H), 2.55 (dd, *J*=13.8, 6.7 Hz, 1H), 1.44 (s, 9H), 1.24 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 154.9, 151.1, 149.3, 146.9, 132.7 (d, *J*=16.5 Hz), 131.3, 129.6, 128.2, 123.9, 117.8, 117.0, 102.3, 88.2, 68.3, 67.9 (d, *J*=10.4 Hz), 67.7, 67.4 (d, *J*=11.0 Hz), 67.2, 66.9, 54.8, 52.6, 50.3, 43.8, 40.1, 39.6, 28.4, 28.3, 27.1, 19.0, 18.2; MS (EI^+) *m/z*: 560.4 $(M+H)^+$ IR (cm^{-1}, neat): 2975, 2933, 2210, 1687, 1502, 1166, 748.

4.10. (*R*)-1-(3-Hydroxypropyl)-5-(2-((2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl)amino)propyl)indoline-7-carboxamide (Silodosin)

(*A*) To a stirred solution of **14** (1.5 g, 3.14 mmol) in methanol was added NaOH (0.16 g, 4.71 mmol) and the reaction mixture was stirred at room temperature for 30 min. To the above reaction mixture was added 30% H_2O_2 (0.11 mL, 4.71 mmol) and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated in vacuo. The reaction mixture was neutralized by 1 N HCl (50 mL) and extracted with ethyl acetate (3×75 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (10–15% methanol in dichloromethane) to afford Silodosin (1.48 g, 95%).

(*B*) To a stirred solution of **14** (1.4 g, 3.13 mmol) in methanol was added NaOH (0.1 g, 4.7 mmol) and the reaction mixture was stirred at room temperature for 30 min. To the above reaction mixture was added 30% H_2O_2 (0.10 mL, 4.7 mmol) and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated in vacuo. The reaction mixture was neutralized by 1 N HCl (40 mL) and extracted with ethyl acetate (3×75 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (10–15% methanol in dichloromethane) to afford Silodosin (0.96 g, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.08–6.82 (m, 5H), 4.27 (q, *J*=8.4 Hz, 2H), 4.08–4.03 (m, 2H), 3.65 (t, *J*=5.6 Hz, 2H), 3.33 (t, *J*=8.4 Hz, 3H), 3.14–2.87 (m, 6H), 2.67 (dd, *J*=13.6, 6.3 Hz, 1H), 2.48 (dd, *J*=13.5, 6.9 Hz, 1H), 1.74–1.70 (m, 2H), 1.04 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 150.2, 149.8, 147.6, 134.2, 130.3, 128.4 (d, *J*=17.1 Hz), 125.7, 124.6, 121.9, 118.6, 118.2, 115.0, 68.9, 68.5, 68.0, 59.7, 54.9, 53.9, 51.1, 46.3, 42.7, 31.3, 28.6, 20.0; MS (EI^+) *m/z*: 496.5 $(M+H)^+$; IR (cm^{-1}, neat): 3355, 3193, 3072, 2929, 2854, 1660. $[\alpha]_D^{25}$ −10.02 (*c* 0.01, MeOH).

Acknowledgements

The authors thank the Formosa Laboratories, Inc. for major financial support. The authors thank the National Science Council of Taiwan for the financial assistance. This work is particularly

supported by 'Center for Bioinformatics Research of Aiming for the Top University Program' of the National Chiao Tung University and Ministry of Education, Taiwan, ROC.

Supplementary data

Analytical data (^{1}H NMR, ^{13}C NMR, LRMS, IR, HPLC) of all intermediates and Silodosin. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.061.

References and notes

1. Shibata, K.; Foglar, R.; Horie, K.; Obika, K.; Sakamoto, A.; Ogawa, S.; Tsujimoto, G. *Mol. Pharmacol.* **1995**, *48*, 250–258.
2. Murata, S.; Taniguchi, T.; Muramatsu, I. *Br. J. Pharmacol.* **1999**, *127*, 19–26.
3. Rossi, M.; Roumeguère, T. *Drug Des. Devel. Ther.* **2010**, *4*, 291–297.
4. Watanabe, M.; Yamanishi, T.; Mizuno, T.; Tatsumiya, K.; Masuda, A.; Honda, M.; Uchiyama, T.; Sakakibara, R.; Yoshida, K. *LUTS* **2010**, *2*, 31–36.
5. Montorsi, F. *Eur. Urol. Suppl.* **2010**, *9*, 491–495.
6. Sountoulides, P.; Dijk, M.; Wijkstra, H.; Rosette, J.; Michel, M. *World J. Urol.* **2010**, *28*, 3–8.
7. Joshi, S.; Bhuta, S.; Talukdar, S.; Sawant, S.; Venkataraman, D.; Pise, A.; Metkar, S.; Chavan, D.; Luthra, P. K. Process for the Preparation of Indoline Derivatives and Their Intermediates Thereof. PCT WO 2011/030356 A2, March 17, 2011.
8. Kitazawa, M.; Ban, M.; Okazaki, K.; Ozawa, M.; Yazaki, T.; Yamagishi, R. 1,5,7-Trisubstituted Indoline Compounds and Salts Thereof. U.S. Patent 5,387,603, February 7, 1995.
9. Gidwani, R. M.; Kolhatkar, M. V. Process for Preparing an Intermediate for Silodosin. PCT WO 2011/124704 A1, October 13, 2011.
10. Maloney, D.; Hecht, S. *Org. Lett.* **2005**, *7*, 4297–4300.
11. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kebeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.
12. Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30–38.
13. Medina, D.; Gedanken, A.; Mastai, Y. *Chem.—Eur. J.* **2011**, *17*, 11139–11142.
14. Sayan, P.; Sargut, S.; Kiran, B. *Ultrason. Sonochem.* **2011**, *18*, 795–800.
15. Amara, N.; Ratsimba, B.; Wilhelm, A.; Delmas, H. *Ultrason. Sonochem.* **2001**, *8*, 265–270.
16. Ruecroft, G.; Hipkiss, D.; Ly, T.; Maxted, N.; Cains, P. W. *Org. Process Res. Dev.* **2005**, *9*, 923–932.
17. Lowdon, I. Manufacture of Rimcazole. PCT WO 2008/040950 A1, April 10, 2008.
18. Jin, H.; Xu, Y.; Shen, Z.; Zou, D.; Wang, D.; Zhang, W.; Fan, X.; Zhou, Q. *Macromolecules* **2010**, *43*, 8468–8478.