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Novel Synthesis of anti-obesity Drug Lorcaserin Hydrochloride

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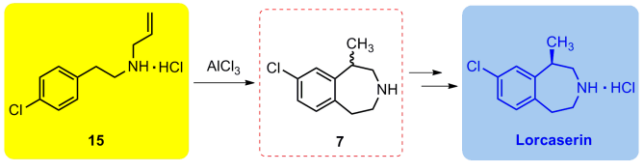


up to 23.1% overall yield
purity > 99.9%
ee > 99.8%

ABSTRACT

A novel synthesis of anti-obesity drug lorcaserin hydrochloride was accomplished in six steps. N-protection of 2-(4-chlorophenyl)ethanamine with di-tert-butyl dicarbonate, N-alkylation with allyl bromide, deprotection, intramolecular Friedel-Crafts alkylation, chiral resolution with L-(+)-tartaric acid and the final salification led to the target molecule lorcaserin hydrochloride in 23.1% overall yield with 99.9% purity and excellent enantioselectivity (>99.8% ee). This convenient and economical procedure is remarkably applicable for scale-up production.

KEYWORADS: Anti-obesity Drug; Lorcaserin Hydrochloride; Synthesis; Scale-up Production

INTRODUCTION

Lorcaserin (Figure 1), a selective serotonin 5-HT_{2C} receptor agonist, is a novel anti-obesity drug approved by the Food and Drug Administration (FDA) on June 27, 2012 for the treatment of obesity.[1]

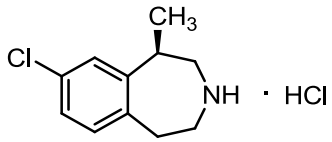
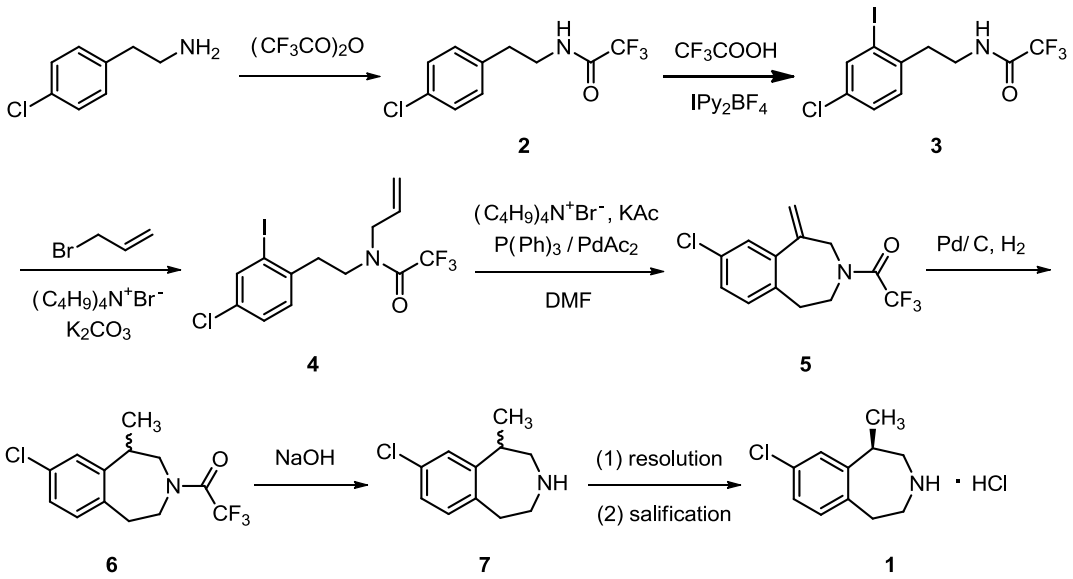


Figure 1. Lorcaserin (**1**).

Several synthetic methods have been reported for the synthesis of lorcaserin. Initially, Smith, Jeffrey et al.[2] disclosed a process for preparation of lorcaserin (Scheme 1), which proceeded in eight-steps, with complicated workups, laborious purification procedures, and used fairly expensive, unstable, environmentally-unfriendly reagents and catalysts, such as Bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) and palladium acetate, resulting in merely 3.7% overall yield. These drawbacks impeded this approach to application for industrial production. Some other methods published in patents[3] also suffered from several drawbacks, such as complicated purification process, low overall yields and the employment of environmentally-unfriendly reagents. All these disadvantages made them unsuitable for industrial-scale production.

Scheme 1. Initial Synthesis of **1**, Lorcaserin



Most of the synthetic endeavors published recently for the synthesis of lorcaserin used 2-(4-chlorophenyl)acetic acid or 2-(4-chlorophenyl)ethanamine as the key starting material. In method 1, condensation of 2-(4-chlorophenyl)acetic acid with isopropyl alcohol amine, reduction of the amide, chlorinated, Friedel-Crafts alkylation, chiral resolution and salification gave lorcaserin hydrochloride via six steps (Scheme 2).[3b] Some issues of method 1 for large-scale synthesis are described below, 1) the use of expensive condensing agent 3,4,5-trimethoxybenzeneboronic acid and reducing agent borane; 2) the dangerous workup steps; 3) large amounts of environmentally-unfriendly acid generated from thionyl chloride and 4) the relatively low 11.6% overall yield.

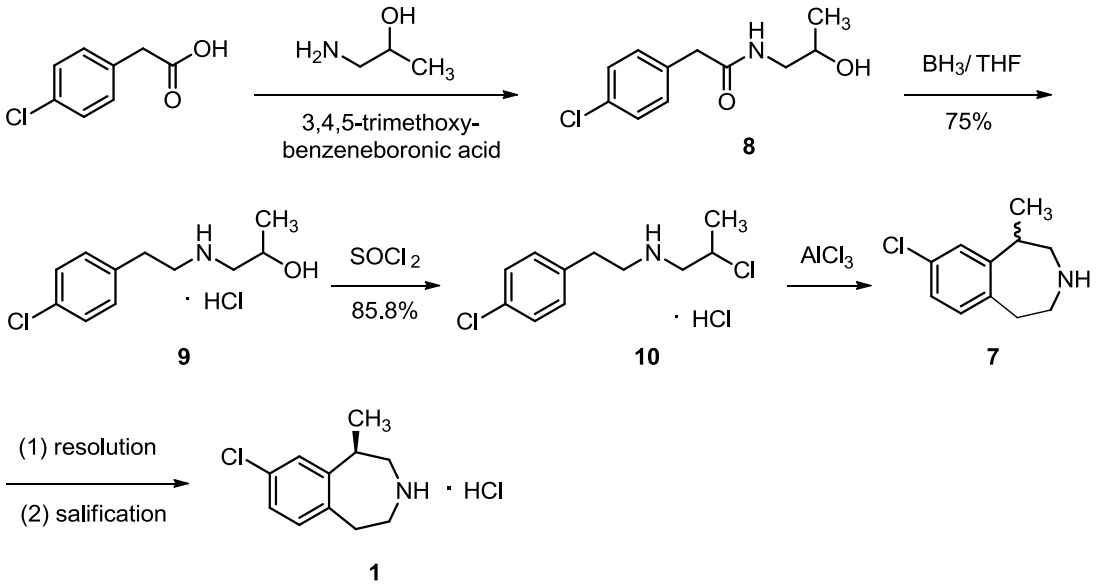
Method 2 was carried out by using 2-(4-chlorophenyl)ethanamine as the starting material. Subsequent reaction with 2-chloropropionyl chloride, Friedel-Crafts alkylation, reduction and chiral resolution led to lorcaserin in 7.2% overall yield (Scheme 2).[3c] Although this route is shorter, the use of toxic and expensive borane is still a problem. Moreover, the Friedel-Crafts

alkylation was conducted in the absence of solvent in high temperature using large amounts of aluminum chloride which led to a complicated workup step and reduced the yield. From a scale-up standpoint, it is also an undesirable method.

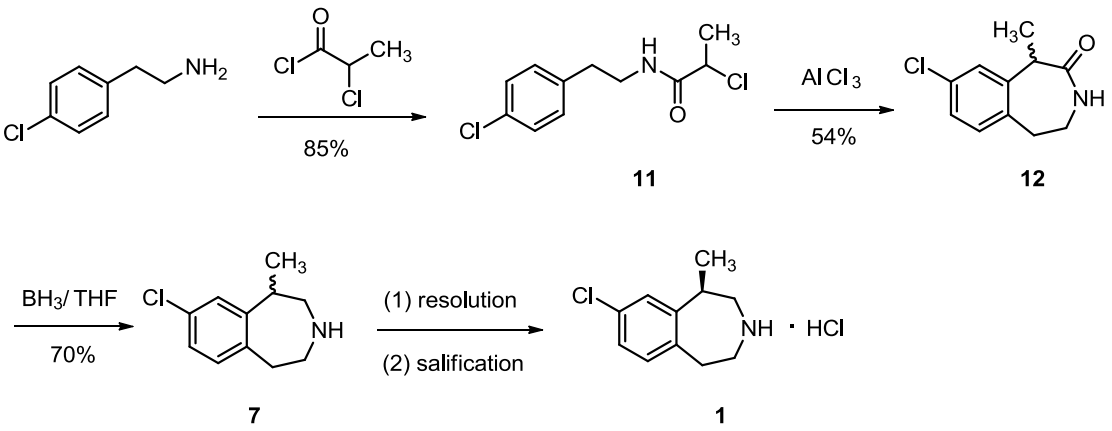
Most notable for us were two asymmetric routes in method 3 and method 4, both avoiding the resolution step by the introduction of chirality in starting material or intermediate (Scheme 2).[4] However, organic catalysts and chiral ligand were charged and the reaction were conducted on millimole scale. And in method 4 the products were purified by flash chromatography,[4b] this isolation approach is a typical technique for research-scale which is not feasible for the pilot plant. Therefore，it is necessary to design a novel method for the preparation of lorcaserin to large-scale production.

Scheme 2. Recent Synthesis of **1,** Lorcaserin

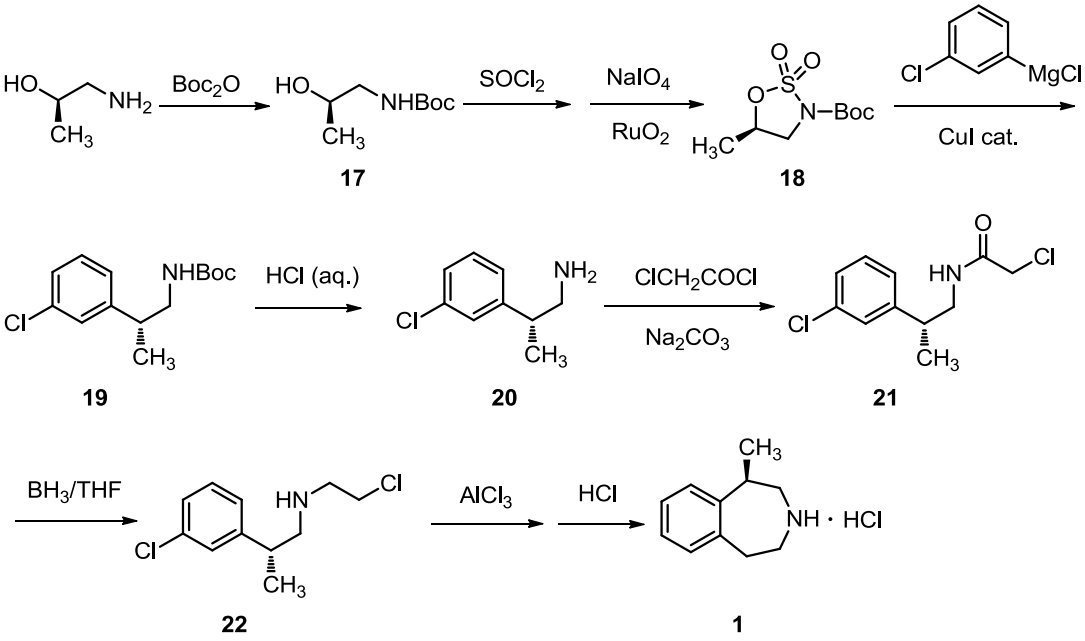
Method 1



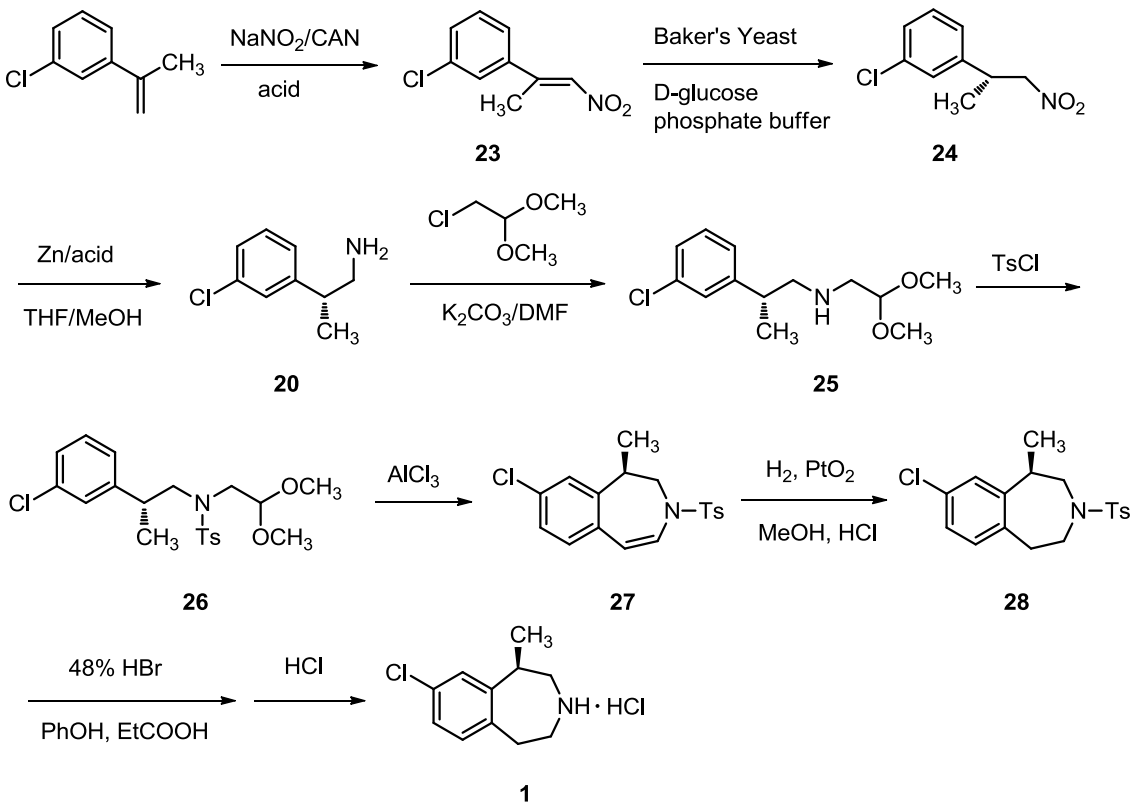
Method 2



Method 3



Method 4



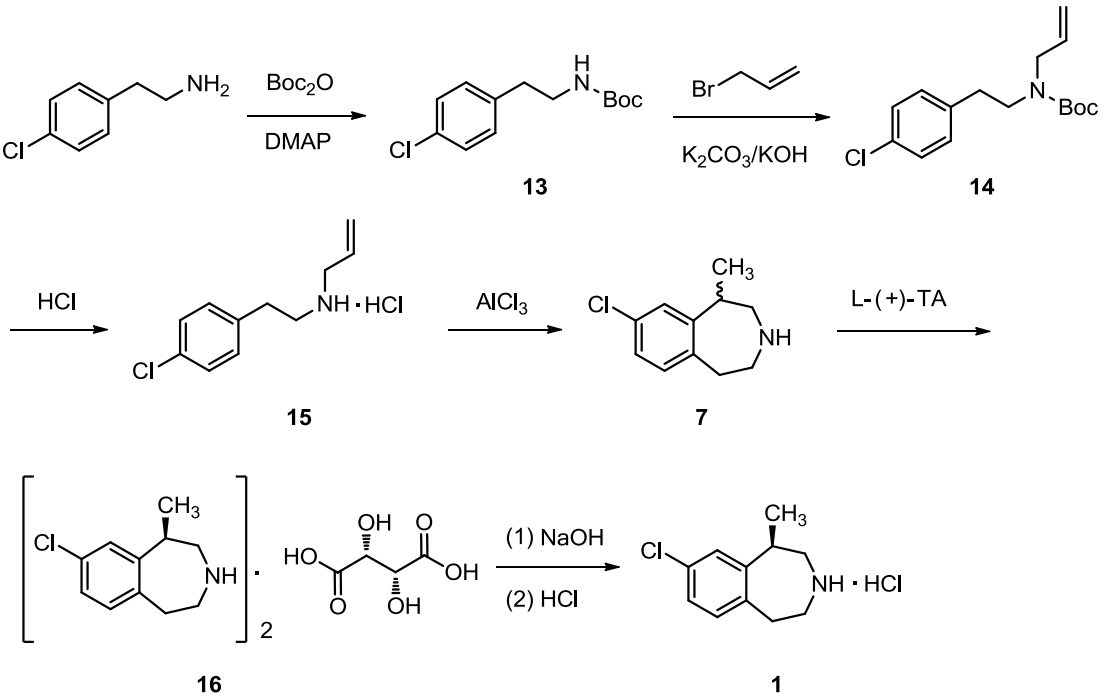
RESULTS AND DISCUSSION

Herein we report a scalable and operationally convenient method that does not have the aforementioned disadvantages to the preparation of lorcaserin in a fairly high overall yield, which undergoes *N*-protection of 2-(4-chlorophenyl)ethanamine with di-tert-butyl dicarbonate,[5] *N*-alkylation with allyl bromide,[6] *N*-deprotection with HCl-saturated EtOAc solution, intramolecular Friedel-Crafts alkylation,[7] chiral resolution with L-(+)-tartaric acid[8] and the final salification (Scheme 3). This scale-up synthesis process is a better alternative to patent[9] which needs column chromatography to separate the monoallyl compound and was only conducted on 1 mmol.

The innovation of this synthetic route is to avoid the use of reducing agent such as borane/THF, which not only reduced the cost and simplified the operation, but also improved the yield compared to the routes mentioned before.[10] A key intermediate, *N*-(4-

chlorophenethyl)prop-2-en-1-amine hydrochloride (**15**)[11] was identified in our synthetic route. The racemic form of lorcaserin was obtained conveniently by an intramolecular Friedel-Crafts alkylation of **15** with an excellent yield (92.3%).

Scheme 3. Novel Synthesis of **1**, Lorcaserin

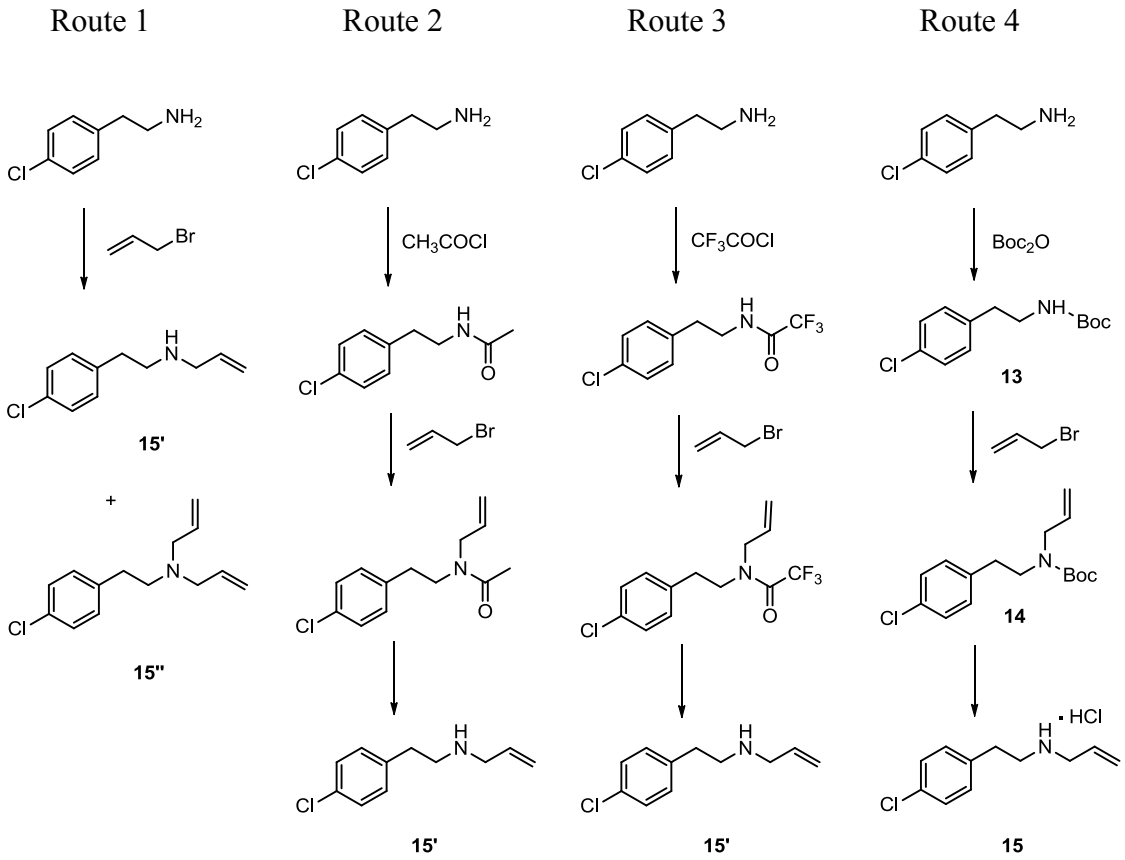


The involvement of this simple intermediate **15** provided several major benefits. First, the application of some expensive or dangerous reducing agents, such as borane/THF, were avoided in the subsequent reaction. Second, the reaction conditions required for the intramolecular Friedel-Crafts alkylation of **15** are found to be milder than those used for intermediate **10** or **11**. In particular, the transformation of **11** into racemic lorcaserin was conducted in a solvent-free system,[12] and required to be in the presence of an excess of aluminum chloride, which lead to complicated workup step and reduce the yield. In contrast, the intramolecular Friedel-Crafts alkylation of **15** can be carried out at 110 ^{o}C in 1,2-dichlorobenzene. Furthermore, the

hydrochloride form of **15** can undergo intramolecular Friedel-Crafts reaction easily, which further simplifies the reaction procedure.

In order to obtain the key intermediate **15** efficiently, a range of experiments were carried out to find the appropriate synthetic routes (Scheme 4).

Scheme 4. Synthetic Routes of the Key Intermediate **15**

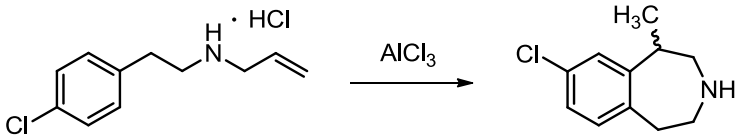


In route 1, *N,N*-diallyl-*N*-(4-chlorophenethyl)prop-2-en-1-amine (**15''**) was the main byproduct which could not be avoided, and column chromatography was needed to purify *N*-allyl-*N*-(4-chlorophenethyl)prop-2-en-1-amine (**15'**). Taking this issue into consideration, we introduced protection groups, such as acetyl[13] and trifluoroacetyl,[14] onto the amino group of 2-(4-chlorophenyl)ethanamine in route 2 and 3. However, it was still difficult to obtain the pure compound **15'** since the acetyl and trifluoroacetyl groups was difficult to be removed completely

in the deprotection step.[6,13] Additionally, different recrystallization systems were tested to get pure compound **15'**, however, none of them could provide satisfactory yield and purity. To solve the above-mentioned problems, route 4 was designed as shown in Scheme 4.

Catalyzed by 4-dimethylaminopyridine, the reaction of 2-(4-chlorophenyl)ethanamine with di-tert-butyl dicarbonate provided **13**. Intermediate **14** could readily be prepared by coupling **13** with allyl bromide in the presence of potassium carbonate, potassium hydroxide and tetrabutyl ammonium bromide. Product **15** was obtained in excellent yield (89.8%) by treating **14** with HCl-saturated EtOAc solution, and could be used in the next reaction directly without purification or transforming into the free base form.

Table 1. Reaction condition optimization of Friedel-Crafts alkylation in the synthesis of racemic lorcaserin



15 **7**

Entry	Subject	Solvent[a] Temperature[a]		Catalyst[a]	Yield (%)[b]
1	**15**	-	80 °C	H_2SO_4	--[c]
2	**15**	$CHCl_3$	80 °C	H_2SO_4	11
3	**15**	Chlorobenzene	120 °C	$AlCl_3$	60
4	**15**	Chlorobenzene	120 °C	H_2SO_4	45
5	**15**	1,2-dichlorobenzene	110 °C	$AlCl_3$	92
6	**15**	1,2-dichlorobenzene	110 °C	H_2SO_4	68

[a]Conditions were typically as follows: the compound **15** was dissolved in the solvents listed in the left at rt, to which were added cyclization agents listed in the right, then the mixture was stirred for 3~6h; or compound **15** was added into Conc.H_2SO_4. [b]Isolated yield. [c] "--" represents that no product is formed.

In order to synthesize racemic lorcaserin (**7**), a variety of cyclization conditions of the Friedel-Crafts alkylation reaction were explored. As illustrated in Table 1, most cyclization conditions furnished **7** in moderate yields. Notably, using the $CHCl_3$/Conc.H_2SO_4 system gave poor results[14] and directly applying Conc.H_2SO_4 failed to initiate the reaction.[15] Thus, $AlCl_3$ was finally employed as the catalytic agent in 1,2-dichlorobenzene to synthesize **7** in high yield (92.3%).

Intermediate **15** and anhydrous $AlCl_3$ were added into a reaction vessel under the protection of nitrogen gas, which was followed by the addition of 1,2-dichlorobenzene. After stirring at 110 ^oC for 3-6h, cooled, the reaction mixture was quenched with ice water. The water layer was washed with hexane and the pH was adjusted to 13 with 50% NaOH aqueous solution, and then extracted with EtOAc. The combined organic layer was washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product could be purified in the following resolution step.

The last step, chiral resolution with L-(+)-tartaric acid and salification led to the target molecule lorcaserin hydrochloride. First, L-(+)-tartaric acid aqueous solution was added into a solution of **7** in acetone at 50 ^oC. After stirring for 3h at this temperature, additional acetone was introduced, the mixture was cooled to 5~10 ^oC and stirred for another 5h. The precipitate was filtered and dried under vacuum to yield a crude product of lorcaserin tartrate(**16**), which was followed by a further recrystallization from the mixed solvent of acetone and water to afford **16** in 33.2% yield with 99.9% purity and >99.8% ee. Furthermore, **16** was transformed into its free base form followed by converting to its hydrochloride (**1**) through the addition of HCl-saturated EtOAc solution.

CONCLUSION

In summary, a safe, efficient, and scalable process for the synthesis of lorcaserin hydrochloride was developed. This new six-step process enabled the production of the desired product starting from readily available and inexpensive 2-(4-chlorophenyl)ethanamine with an overall yield of 23.1%, which is at least twice as much as others. To the best of our knowledge, compared to the reported procedures, this approach was the most efficient, economical and convenient route to synthesize lorcaserin in a large scale.

EXPERIMENTAL SECTION

General Methods. All chemicals and solvents were either purchased or purified by standard techniques and used without any further purification. TLC was carried out using Yantai thin layer chromatography silica gel plates. Melting points were recorded on an RY-1 melting point apparatus and were uncorrected. MS spectra were acquired on Agilent 1100 series LC/MSD Tarp (SL). The ^{1}HNMR and ^{13}C NMR spectra were recorded on a BRUKER AV-300 or AV-500 NMR spectrometer using TMS as the internal standard. Product purities were determined by HPLC conducted on an Shimadzu LC-15C system using a reverse-phase C18 column, and MeCN-H_2O was used as the mobile phase.

***tert*-Butyl 4-chlorophenethylcarbamate (13).**

To a solution of 2-(4-chlorophenyl)ethanamine (1.50 kg, 9.64 mol) in CH_2Cl_2 (5 L) were added a solution of di-tert-butyl dicarbonate (2.30 kg, 10.54 mol) in CH_2Cl_2 (5 L) and catalytic amount of DMAP at 0 ^{o}C. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the mixture was poured into water (10 L) and extracted with dichloromethane. The organic layer was washed successively with water (5 L) and brine (5 L×

2), dried overnight with anhydrous Na_2SO_4, filtered, concentrated and dried under vacuum to afford white solid product **13** (2.35 kg, 95.5%). Mp: 61-63°C (Mp: 61.5-62.5 °C)[4].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29-7.24 (m, 2H), 7.15-7.08 (m, 2H), 3.33 (t, *J* = 6.5 Hz, 2H), 2.76 (t, *J* = 7.0 Hz, 2H), 1.43 (s, 9H).

MS (ESI, 70 eV): m/ z = 278.1 $[M+Na]^+$.

***tert*-Butyl allyl(4-chlorophenethyl)carbamate (14).**

To a solution of tert-butyl 4-chlorophenethylcarbamate (2.35 kg, 9.19 mol) in toluene (10 L) were added K_2CO_3 (1.59 kg, 11.50mol), KOH (0.69 kg, 12.30 mol), allyl bromide (1.59 kg, 13.14 mol) and tetrabutyl ammonium bromide (0.15 kg, 0.47 mol) at room temperature. The reaction mixture was stirred at 80 °C for 5h, then cooled to room temperature. The pH of the solution was adjusted to 4~5 by addition of 15% aqueous hydrochloric acid, the toluene layer was then separated, and the water layer was extracted with toluene (5 L). The combined organic layer was washed successively with water (10 L) and brine (8 L × 2), dried overnight with anhydrous Na_2SO_4, filtered and concentrated to afford **14** (2.62 kg, 96.3%) as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 5.75-5.70 (m, 1H), 5.13-5.07 (m, 2H), 3.76-3.67 (m, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 1.44 (s, 9H).

MS (ESI, 70 eV): m/ z = 318.1 $[M+Na]^+$.

***N*-(4-chlorophenethyl)prop-2-en-1-amine hydrochloride (15).**

To a stirred solution of **14** (2.62 kg, 8.86 mol) in EtOAc (1L) was added HCl-saturated EtOAc solution slowly until pH=2 and stirred at room temperature until completion of the reaction (by TLC). The precipitate was filtered, washed with EtOAc (1 L) and dried under vacuum to give **15** (1.85 kg, 89.8%) as white crystal. Mp: 196-198 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.40 (bs, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.00-8.86 (m, 1H), 5.49-5.37 (m, 2H), 3.57 (d, *J* = 6.6 Hz, 2H), 3.10-3.05 (m, 2H), 3.00-2.90 (m, 2H).

MS (ESI, 70 eV): m/ z = 196.1 $[M+H]^+$.

8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (7).

To a stirred solution of **15** (1.85 kg, 7.97 mol) in 1,2-dichlorobenzene (8 L) under the protection of nitrogen was added anhydrous $AlCl_3$ (1.59 kg, 11.92 mol). The reaction mixture was then heated and stirred at 110 ^{o}C for 4h. Upon completion of the reaction (by TLC), the reaction mixture was cooled to room temperature and quenched with ice water (10 L) slowly. The water layer was washed with hexane (5L) and the pH was adjusted to 13 with 50% NaOH aqueous solution,and then extracted with EtOAc (5 L×3). The combined organic layer was washed with brine (10 L×2), dried with anhydrous Na_2SO_4, filtered and concentrated to afford crude product **7** (1.44 kg, 92.3%) as yellow oil. The crude product was used in the following reaction without purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 3.10-2.84 (m, 6H), 2.71 (dd, *J* = 13.3, 7.6 Hz, 1H), 1.32 (d, *J* = 7.2 Hz, 3H).

MS (ESI, 70 eV): m/ z = 196.0 $[M+H]^+$.

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine tartrate (16).

To a solution of **7** (1.44 kg, 7.36 mol) in acetone (9 L) was added a solution of L-(+)-tartaric acid (0.28 kg, 1.86 mol) in water (900 mL) under stirring at 50 ^{o}C. The reaction was maintained at this temperature for 3h. Additional acetone (1 L) was introduced and stirred for another 5h after cooling to 5~10 ^{o}C. The precipitate was filtered and dried under vacuum to furnish the crude product of **16** as white crystal. The product of lorcaserin tartrate was then recrystallized

from an acetone-water solution (3:1, v/v; 5 L) to give the pure product lorcaserin tartrate as white crystal (0.66 kg, 33.2%). HPLC purity: 99.9%, Chiral Purity: 99.9%.

HPLC for **16** (t_R= 9.0 min) purity 99.9%: 5 μm C-18 250 mm × 4.6 mm, flow rate = 1 mL/min, 35°C, gradient elution from 20:88 A/B for 30 min to 75:25 A/B over 30 min; A = acetonitrile; B = phosphoric acid in water (pH = 6.0); UV λ = 220 nm.

Chiral HPLC for **16** (t_R= 20.3 min) purity 99.9%: 5 μm AD-RH 250 mm × 4.6 mm, flow rate = 1 mL/min, 35°C, isocratic A/B/C = 92:8:0.1; A = n-hexane; B = isopropanol; C = diethylamine; UV λ =220 nm.

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepinehydrochloride(1)

To a solution of **16** (0.66 kg, 2.44 mol) in water (3 L) was added 20% K_2CO_3 aqueous solution. The pH was adjusted to 8~9 and extracted with cyclohexane (5 L×2). The combined organic layer was washed with brine (5 L×2), dried with anhydrous Na_2SO_4, filtered and concentrated to afford lorcaserin as yellow oil. To a stirred solution of lorcaserin free base in anhydrous ethanol (500 mL) was added HCl-saturated EtOAc solution slowly until pH = 2 and stirred for another 5h at room temperature. The reaction solution was concentrated and then stirred for 1h in methyl tert-butyl ether (2 L) at room temperature. The precipitate was filtered, washed with methyl tert-butyl ether (200 mL) and dried under vacuum to give lorcaserin hydrochloride (**1**) (0.52 kg, 91.2%). HPLC purity: 99.9%, Chiral Purity: 99.9%. Mp: 198-199 ^oC.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.61 (bs, 2H), 7.28-7.21 (m, 3H), 3.54-3.44 (m, 1H), 3.33-3.18 (m, 3H), 3.01 (dd, J = 15.7, 7.1 Hz, 1H), 2.91-2.83 (m, 2H), 1.34 (d, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.4, 138.1, 131.5, 126.4, 126.0, 114.5, 50.1, 44.5, 34.1, 30.8, 17.5.

MS (ESI, 70 eV): m/ z = 196.1 $[M+H]^+$.

HPLC for **1** (t_R= 9.0 min) purity 99.9%: Intersil ODS-3 5 μm C-18 250 mm × 4.6 mm, flow rate = 1 mL/min, 35°C, gradient elution from 20:88 A/B for 30 min to 75:25 A/B over 30 min; A = acetonitrile; B = phosphoric acid in water (pH = 6.0); UV λ = 220 nm.

Chiral HPLC for **1** (t_R= 21.6 min) purity 99.9%: Daicel AD-RH 5 μm 250 mm × 4.6 mm, flow rate = 1 mL/min, 35°C, isocratic A/B/C = 92:8:0.1; A = n-hexane; B = isopropanol; C = diethylamine; UV λ =220 nm.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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