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**Full Paper**

# A Concise Synthesis of Racemic Lorcaserin

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We report herein the concise synthesis of racemic lorcaserin (±)-**1**, which is an anti-obesity drug. The synthetic route involved the key synthesis of an asymmetrical imide intermediate **11** and its efficient reduction. Imide **11** was synthesized directly by the reaction of nitrile **9** with acid **10**. The reducing system of $NaBH_4$, $AlCl_3$, and trimethylsilyl chloride efficiently fulfilled the reduction of imide **11** to amine **8a**, which could be converted to (±)-**1** via Friedel–Crafts reaction as reported. This route afforded 69 % two-step yield of **8a** from **9** via **11**, and the concise synthesis of (±)-**1** was completed in three steps. This route offers an alternative pathway to the synthesis of (±)-**1** and its analogues.

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## Introduction

Obesity has become one of the most important public health challenges in modern society. As a primary risk factor for type 2 diabetes, obesity is closely associated with the metabolic syndrome and is linked to low-living quality and reduced life-span.[1] Serotonin (5-HT) mediates or regulates a wide variety of behaviours. Its diverse effects are related to the extensive projections of serotonergic neurons of at least 14 different receptor subtypes. Among all those subtypes, current research studies suggest that the role of serotonin in appetite control is largely related to the hypothalamic serotonin 5-$HT_{2C}$ receptor.[2] Lorcaserin (**1**), a highly selective 5-$HT_{2C}$ receptor agonist, has been approved in 2012 by US FDA as the first approved anti-obesity drug since orlistat was approved in 1999. Unlike the earlier non-selective serotonin agonists, lorcaserin is a novel and selective 5-$HT_{2C}$ full agonist with 15–100-fold higher affinity over those of 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors, which mediate the pathogenesis of serotonergic valvulopathy.[3]

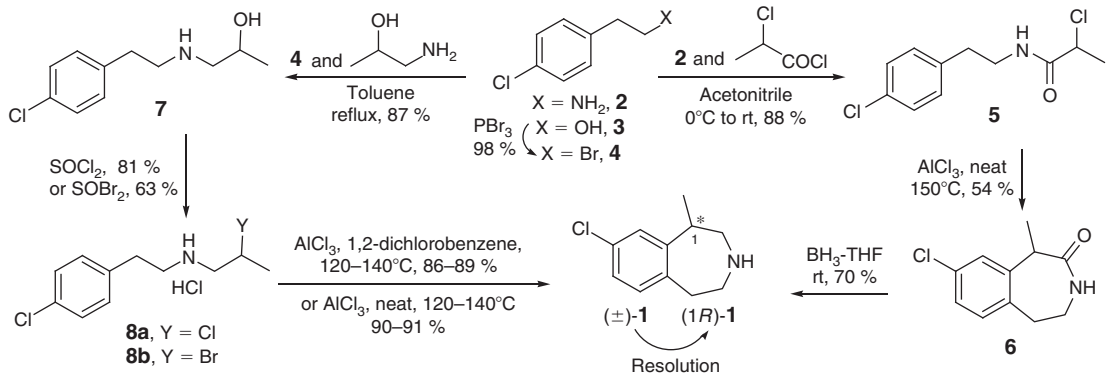
In addition to the Heck coupling approach[4a-c] and olefin Friedel–Crafts reaction[4d] for the synthesis of racemic lorcaserin ((±)-**1**), two major synthetic routes via Friedel–Crafts reaction of (±)-**1** were reported in previous literature[5,6] and outlined in Scheme 1. In one approach,[5] amide compound **5** was obtained by the reaction of 2-chloropropionyl chloride with amine **2**, and then **5** was cyclized into intermediate **6** via Friedel–Crafts reaction catalyzed by 3.0 equiv. of anhydrous $AlCl_3$, and thereafter, reduction of amide **6** into (±)-**1** was accomplished by borane tetrahydrofuran ($BH_3$-THF). In the another synthetic route,[5,6] bromination of alcohol **3** by phosphorous tribromide ($PBr_3$) gave bromide **4**. Alkyl amination of 1-amino-2-propanol by bromide **4** was fulfilled in refluxing toluene to afford alcohol **7**. Chlorination of **7** by thionyl chloride ($SOCl_2$) afforded intermediate chloride **8a**. Alternatively, bromination of alcohol **7** by thionyl bromide ($SOBr_2$) provided intermediate bromide **8b**. Then, (±)-**1** was obtained by Friedel–Crafts reaction of chloride **8a** or bromide **8b** under the catalysis of 1.5 equiv. of anhydrous $AlCl_3$ in 1,2-dichlorobenzene or 5.1 equiv. of anhydrous $AlCl_3$ without solvent. Finally, resolution of (±)-**1** by L-(+)-tartaric acid afforded lorcaserin (**1**). Apart from these processes, there have been synthetic routes to prepare (±)-**1** starting from 4-chlorophenylacetic acid[7] and its esters.[8]

## Results and Discussion

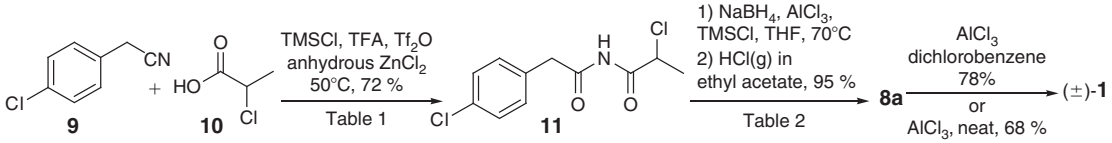
As amine **2**,[5] alcohol **3** [6] or bromide **4**,[6] 4-chlorophenylacetic acid,[7] and its esters[8] used in the previous processes are not primary raw materials and were derived from 4-chlorophenylacetonitrile (**9**), in our synthetic route (Scheme 2), **9** was used as a starting material to synthesize key intermediate asymmetrical imide **11**, and imide **11** was efficiently reduced by $NaBH_4$-Lewis acid reducing system to afford amine **8a**. After that, amine **8a** was transformed into the target compound (±)-**1** by Friedel–Crafts reaction as reported.[5,6] Because this synthetic route avoids unnecessary transformation and total synthesis of (±)-**1** is complete in three steps, it has potential application in the industrial production of lorcaserin (**1**).

### *Synthesis of Asymmetrical Imide **11** by the Reaction of Nitrile **9** and Acid **10***

In our study streamline shown in Scheme 2, asymmetrical imide **11** is the key intermediate. Though cyclic imide is well known for synthesis and application,[9] few available methods[10,11] have been reported for the synthesis of acyclic imide, and only symmetrical imide[10b,10d] or special asymmetrical imide with greatly different acid–nitrile pairs[10b] have been prepared by the reaction of a nitrile with an acid in the presence of Brönsted acid or/and Lewis acid. However, these methods are not suitable for the synthesis of conventional asymmetrical imide, for example, **11** in this work.




**Scheme 1.** Previously reported synthetic routes of racemic lorcaserin ((±)-**1**) and Lorcaserin (**1**).




**Scheme 2.** Synthetic method of racemic lorcaserin (±)-**1** via asymmetrical imide **11** employed in this work.

To synthesize asymmetrical imide **11** by the reaction of nitrile **9** with acid **10**, a series of reaction conditions were explored (Table 1). In our initial trial reaction of nitrile **9** with 2-chloropropionic acid **10**, sulfuric acid, hydrochloric acid, and *p*-toluenesulfonic acid were used to activate the reactivity of **10**, however, only hydrolysis products of carboxylic acid and amide from **9** were isolated (data not shown). Subsequent explorations gave mild yields e.g. at 0°C, the reaction of 1.5 equiv. of **10** with 1.0 equiv. of **9** catalyzed by 1.0 equiv. of trifluoromethanesulfonic anhydride ($Tf_2O$) (Table 1, entry 1) or 1.0 equiv. of $Tf_2O$ in the presence of 1.0 equiv. of trifluroacetic acid (TFA)[10d] (Table 1, entry 2) afforded 33 % or 48 % of the desired product **11**. Using unchanged quantities of **10** and **9**, the reaction catalyzed by 1.0 equiv. of $Tf_2O$ and 2.0 equiv. of TFA (Table 1, entry 3) or 2.0 equiv. of $Tf_2O$ and 1.0 equiv. of TFA (Table 1, entry 4) provided 38 % or 29 % of **11**. It is noted that the increase of TFA (Table 1, entry 3) or $Tf_2O$ to 2.0 equiv. produced more by-products.

Then, anhydrous $ZnCl_2$ was introduced into the reaction. It was observed that the reaction catalyzed by 0.5 equiv. of anhydrous $ZnCl_2$ and 1.0 equiv. of $Tf_2O$ at 0°C and 25°C did not occur (data not shown) and at 50°C (Table 1, entry 5) afforded only 17 % of **11** with non-negligible by-products and a large amount of unreacted **9**. Reducing the amount of $Tf_2O$ to 0.5 equiv. and the addition of 1.5 equiv. of trimethylsilyl chloride (TMSCl) and 0.5 (Table 1, entry 6) or 1.0 (Table 1, entry 7) equiv. of anhydrous $ZnCl_2$ produced 26 % of **11** and considerably lesser amounts of by-products. However, the reaction performed in the absence of $Tf_2O$ did not proceed (Table 1, entry 8), whereas the reaction performed in the absence of anhydrous $ZnCl_2$ depleted **9** and gave a mixture (Table 1, entry 9). It was suggested that $Tf_2O$ accelerated and/or promoted the reaction and also generated more by-product/s. However, TMSCl and anhydrous $ZnCl_2$ reduced the activity of $Tf_2O$ and instigated the production of asymmetrical imide **11** or TMSCl and anhydrous $ZnCl_2$ played a role in inhibiting the generation of by-product/s.

Thereafter, we focussed on the optimization of the ratio of **9** to **10**, TMSCl, anhydrous $ZnCl_2$, TFA, and $Tf_2O$. The reaction catalyzed by 1.0 equiv. of anhydrous $ZnCl_2$, 1.5 equiv. of **10** and TMSCl, and 0.5 equiv. of TFA and $Tf_2O$ with respect to **9** afforded 51 % of **11** (Table 1, entry 10). The reaction catalyzed by 1.5 equiv. of **10** and TMSCl, 1.0 equiv. of anhydrous $ZnCl_2$ and TFA, 0.5 equiv. of $Tf_2O$ produced 48 % of **11** (Table 1, entry 11). The reaction performed with 1.5 equiv. of **10** and TMSCl, and 1.0 equiv. of anhydrous $ZnCl_2$, TFA, and $Tf_2O$ afforded 44 % of **11** (Table 1, entry 12). However, the simultaneous increases of TFA and $Tf_2O$ to 1.0 equiv. and anhydrous $ZnCl_2$ to 1.5 equiv. with 1.5 equiv. of **10** and TMSCl reduced the yield of **11** to 26 % (Table 1, entry 13). It was fortunate that the reaction of **9** in 1.0-g scale and in 2.0-g scale with 1.5 equiv. of **10** in the presence of 1.5 equiv. of TMSCl and TFA, and 1.0 equiv. of anhydrous $ZnCl_2$ and $Tf_2O$ produced good yields (70 % and 73 %, respectively) of the desired product **11** (Table 1, entries 14 and 15). Repeated experiments using the same ratio of **9** to **10**, TMSCl, anhydrous $ZnCl_2$, TFA, and $Tf_2O$ produced the same yields of **11** i.e. 70–75 %. The scale up reaction involving 10.0 g of starting nitrile **9** under the same conditions as entries 14 and 15 (Table 1) achieved 72 % of **11** in 72 h (Table 1, entry 16), suggesting that the reaction in larger scale needed longer reaction times.

Based on entries 14 and 15 (Table 1), some variations were investigated. Using 0.5 equiv. of $Tf_2O$ (Table 1, entry 17), the reaction afforded a reduced yield of **11** to 38 %. Meanwhile, lowering the amount of anhydrous $ZnCl_2$ to 0.5 equiv. afforded 58 % of **11** (Table 1, entry 18). Indeed, reducing the amount of TFA to 1.0 equiv. afforded a lower yield (44 %) of **11** (Table 1, entry 12). These data suggested that the suitable combination of TMSCl, anhydrous $ZnCl_2$, TFA, and $Tf_2O$ was important for the reaction, and the optimal ratios of **9** to **10**, TMSCl, anhydrous $ZnCl_2$, TFA, and $Tf_2O$ were found to be 1.0–1.5, 1.5, 1.0, 1.5, 1.0, respectively, which is the key point for achieving high reaction yields.

It was found that the above solvent-free reaction became a thick mass, thus making stirring difficult at 10–18 h after the reaction started. Considering that efficient stirring could shorten the reaction time and enhance the reaction yield, solvents DCM,

**Table 1. Reaction conditions[A,B] for the preparation of 11 from 9 and 10 (Scheme 2)**

| Entry | T [°C] | Time [h] | TMSCl [equiv.] | $ZnCl_2$ [equiv.][C] | TFA [equiv.] | $Tf_2O$ [equiv.] | Yield [%][D,E] |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 72 | / | / | / | 1.0 | 33 |
| 2 | 0 | 72 | / | / | 1.0 | 1.0 | 48 |
| 3 | 0 | 72 | / | / | 2.0 | 1.0 | 38 |
| 4 | 0 | 72 | / | / | 1.0 | 2.0 | 29 |
| 5 | 50 | 24 | / | 0.5 | / | 1.0 | 17 |
| 6 | 50 | 48 | 1.5 | 0.5 | / | 0.5 | 26 |
| 7 | 50 | 48 | 1.5 | 1.0 | / | 0.5 | 26 |
| 8 | 50 | 48 | 1.5 | 1.0 | / | / | NR |
| 9 | 50 | 48 | 1.5 | / | / | 0.5 | M |
| 10 | 50 | 48 | 1.5 | 1.0 | 0.5 | 0.5 | 51 |
| 11 | 50 | 48 | 1.5 | 1.0 | 1.0 | 0.5 | 48 |
| 12 | 50 | 48 | 1.5 | 1.0 | 1.0 | 1.0 | 44 |
| 13 | 50 | 48 | 1.5 | 1.5 | 1.0 | 1.0 | 26 |
| 14 | 50 | 48 | 1.5 | 1.0 | 1.5 | 1.0 | 70 |
| 15 | 50 | 48 | 1.5 | 1.0 | 1.5 | 1.0 | 73 |
| 16 | 50 | 72 | 1.5 | 1.0 | 1.5 | 1.0 | 72 |
| 17 | 50 | 48 | 1.5 | 1.0 | 1.5 | 0.5 | 38 |
| 18 | 50 | 48 | 1.5 | 0.5 | 1.5 | 1.0 | 58 |
| 19 | 50 | 24 | 1.5 | 1.0 | 1.5 | 1.0 | 29 |

[A]Optimization reactions (1.0 equiv. of **9** and 1.5 equiv. of **10**) were performed in 1.0-g scale of **9** except for reactions in entries 12, 15, and 17 that were performed in 2.0-g scale of **9**, and in entry 16 that were performed in 10.0-g scale of **9**. The progress of the reaction was monitored by TLC.
[B]'/' means without the substance.
[C]$ZnCl_2$ is anhydrous $ZnCl_2$.
[D]Isolated yield of **11**.
[E]NR means no reaction and M means a mixture.

toluene, and THF were successively selected as reaction solvents. However, the reaction performed in DCM or in THF did not proceed, and the reaction performed in toluene did not work well and gave a mixture (data not shown). Therefore, the neat reaction is the only choice in the current stage. Moreover, using low temperatures (0°C or 25°C) was not good for the reaction, whereas the reactions performed at 70°C became complicated (data not shown) under the same reaction conditions as entries 14 and 15 (Table 1). These results indicated that elevated temperatures facilitated the formation of undesired impurities. Furthermore, it was observed that the reaction performed for 24 h (Table 1, entry 19), when compared with that performed for 48 h, dramatically reduced the yield of **11** to 29 % under the same reaction conditions as entries 14 and 15 (Table 1). This result demonstrated that maintaining the heating condition at 50°C was necessary for the completion of the reaction even though the stirring was not efficient. On the other hand, substitution of anhydrous $ZnCl_2$ with anhydrous $FeCl_2$, anhydrous $FeCl_3$, or anhydrous $AlCl_3$ led to no reaction by $FeCl_2$ and anhydrous $AlCl_3$ (data not shown) or the desired product **11** by $FeCl_3$ even though **9** was consumed completely (data not shown). It was concluded that there is currently no sign of improving the reaction by other Lewis acids rather than anhydrous $ZnCl_2$.

It is worth noting that purification of **11** was based on the solubility difference, whereby the desired product **11** displays a relatively better solubility in acetonitrile and DCM than the by-products including symmetrical imide 2-(4-chlorophenyl)-*N*-(2-(4-chlorophenyl)acetyl)acetamide (**12**) (Supplementary Material). Generally, a large scale (e.g. starting from 10.0 g of **9**) of dry crude products, prepared according to entries 14 and 15 (Table 1), was extracted at 40°C by acetonitrile or DCM, and then crystallization of soluble materials from petroleum/ethyl acetate provided pure asymmetrical imide **11** in 70–73 % yield.

In this work, TFA and $Tf_2O$ could independently or together catalyze this type reaction; however, they did not work very well for asymmetrical imide **11**. Even though the concerted or step-by-step mechanism of this reaction and the roles of $Tf_2O$, TFA, $ZnCl_2$, and TMSCl in this reaction are unclear, the suitable combination of $Tf_2O$, TFA, $ZnCl_2$, and TMSCl with two starting materials of nitrile **9** and acid **10** is the key for achieving higher yields of asymmetrical imide **11**. This observation suggests that using the required optimal ratio is good for producing asymmetrical imide **11** in the competition between the formation of symmetrical and asymmetrical imides.

### *Reduction of Asymmetrical Imide **11** to Amine **8a***

After completion of the synthesis of imide intermediate **11**, the reduction of **11** to **8a** was the next key step. First, the reducing system[12] of $NaBH_4$ in the presence of TMSCl was selected to reduce imide **11** to amine **8a**; however, no amine product **8a** was detected even though 10.0 equiv. of $NaBH_4$ and 20.0 equiv. of TMSCl were used (Table 2, entry 1). Then, we introduced metallic Lewis acid (LA) to the reducing system and five different ratios of $NaBH_4$ or $KBH_4$ and anhydrous reagents of $AlCl_3$, $ZnCl_2$ or $MgCl_2$[13] were explored (Table 2, entries 2–6). However, no detectable product **8a** was obtained up to 5.0 equiv. of $NaBH_4$ with 4.0 equiv. of anhydrous $AlCl_3$ (Table 2, entry 7).

Subsequently, TMSCl was introduced into the reduction. Addition of 0.5 or 1.5 equiv. of TMSCl to 6.0 equiv. of $NaBH_4$ and 4.0 equiv. of anhydrous $AlCl_3$ afforded 58 % or 57 % of amine product **8a** (Table 2, entries 8 and 9). Although the increase of TMSCl from 0.5 to 1.5 equiv. did not affect the yield of **8a**, it was improved to 67 % when 4.0 equiv. of TMSCl was used (Table 2, entry 10). In contrast, reducing the amount of anhydrous $AlCl_3$ from 4.0 to 3.0 equiv. made the reduction much less efficient (Table 2, entry 11) though 6.0 equiv. of $NaBH_4$ and 4.0 equiv. of TMSCl were used.

**Table 2. Reaction conditions[A,B] for the reduction of imide 11 into amine 8a**

| Entry | Equivalents | | | Temperature [°C][E] | Time [h] | Yield [%][F] |
|---|---|---|---|---|---|---|
| | $MBH_4$[C] | LA[D] | TMSCl | | | |
| 1 | 10 | – | 20 | 70 | 38 | 0 |
| 2 | 4 | 2 | – | 70 | 12 | 0 |
| 3 | 2.5 | 2.5 | – | 95 | 24 | 0 |
| 4 | 3 | 2 | – | 95 | 24 | 0 |
| 5 | 4 | 2 | – | 95 | 24 | 0 |
| 6 | 6 | 3 | – | 95 | 24 | 0 |
| 7 | 5 | 4 | – | 70 | 24 | <10 |
| 8 | 6 | 4 | 0.5 | 70 | 24 | 58 |
| 9 | 6 | 4 | 1.5 | 70 | 24 | 57 |
| 10 | 6 | 4 | 4 | 70 | 24 | 67 |
| 11 | 6 | 3 | 4 | 70 | 24 | 15 |
| 12 | 6 | 4 | 5.5 | 70 | 24 | 95 |
| 13 | 6 | 4 | 5.5 | 70 | 24 | 96 |
| 14 | 4 | 4 | 5.5 | 70 | 24 | 58 |
| 15 | 6 | 2 | 5.5 | 70 | 24 | 31 |

[A]All optimization reactions were performed with the same scale of starting material **11** (0.5 g) except for reaction in entry 13 (10.0 g).
[B]Reactions in entries 3–6 were performed in THF/toluene (1 : 1), whereas the remaining reactions were performed in THF.
[C]In entries 3, 4, and 6, $MBH_4$ refers to $KBH_4$, whereas in the remaining entries, $MBH_4$ refers to $NaBH_4$.
[D]In entries 3 and 4, $MgCl_2$ was used as LA; in entries 5 and 6, $ZnCl_2$ was used as LA; and in the remaining entries, $AlCl_3$ was used as LA.
[E]Bath temperature.
[F]Isolated yield of salt **8a**.

Interestingly, the reduction yield of **8a** was dramatically increased to 95 % when 5.5 equiv. of TMSCl, 6.0 equiv. of $NaBH_4$, and 4.0 equiv. of $AlCl_3$ with respect to **11** were used (Table 2, entry 12). Compared with the above experiment, it was found that reducing the amount of $NaBH_4$ from 6.0 to 4.0 equiv. sharply decreased the yield of **8a** to 58 % (Table 2, entry 14), and using 2.0 rather than 4.0 equiv. of anhydrous $AlCl_3$ produced only 31 % of **8a** (Table 2, entry 15). These experimental results indicated that the ratio of **11**, $NaBH_4$, anhydrous $AlCl_3$, and TMSCl was crucial to the reduction and the optimal ratio was 1 : 6 : 4 : 5.5. Considering two carbonyl moieties of the imide **11**, the applied equiv. (relative to **11**) of reductants were in reasonable range. Under the optimal reaction conditions, the scale-up reduction of 10.0 g of compound **11** generated 95.6 % of salt **8a** (Table 2, entry 13).

### *Cyclization of Amine **8a** into (±)-**1** by Friedel–Crafts Reaction*

According to the reported procedure,[5,6] the corresponding hydrochloride salt of **8a** proceeded to the intramolecular cyclization by the Friedel–Crafts reaction using 1.5 equiv. of $AlCl_3$ as the catalyst at 130°C in 1,2-dichlorobenzene and finally, ~78 % of (±)-**1** was provided (**Procedure A**, see Experimental). Alternatively, the intramolecular Friedel–Crafts reaction of **8a** was carried out in solvent-free conditions;[5] however, instead of using more than 5 equiv. of anhydrous $AlCl_3$ as reported,[5] the reaction was catalyzed by only 1.5 equiv. of anhydrous $AlCl_3$ at 130°C for 5 h to afford 68 % of (±)-**1** (**Procedure B**, see Experimental). Identical $^1$H NMR spectra and HPLC results (Supplementary Material) of (±)-**1** were obtained to those reported.[5,6]

## Conclusions

In summary, a concise synthetic route of racemic lorcaserin (±)-**1** via an imide intermediate **11** has been developed by starting from cheap and primary raw materials. In this approach, asymmetrical essential skeleton imide **11** was obtained by the relatively mild reaction of primary raw nitrile **9** with acid **10**, which could be a general process to prepare asymmetrical imide. Subsequently, highly efficient reduction of imide **11** to amine **8a** was accomplished by $NaBH_4/AlCl_3$/TMSCl reducing system. After the cyclization of **8a** proceeded by $AlCl_3$, (±)-**1** was afforded as reported.[5,6] Accordingly, the route afforded 69 % two-step yield of **8a** from **9** via **11**, and the total synthesis of (±)-**1** from **9** via **11** by this route was fulfilled in three steps (Scheme 2). As starting from the reaction of primary raw nitrile **9** with acid **10** avoided unnecessary transformations and made the synthesis of (±)-**1** more concise and efficient, this route (Scheme 2) should be attractive in cost and practicability and has potential for large-scale industrial synthesis.

## Experimental

Commercially available materials and solvents were purchased from Alfa Aesar, Energy Chemical, JiaXing Assent Chemical Co. or Xilong Chemical Co. Anhydrous DCM was treated with $CaH_2$ and distilled, anhydrous THF was refluxed with Na and benzophenone and distilled under nitrogen. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV-400 spectrometer at 400 and 100 MHz, respectively, in [D6]DMSO and $CD_3OD$. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to the solvent, and coupling constants ($J$) are expressed in Hertz (Hz). High-resolution electrospray ionization mass spectrometry (ESI MS; in the positive ion or negative ion acquisition mode) analysis was performed on an Applied Biosystems Q-STAR Elite ESI-LC-MS/MS mass spectrometer. HPLC analysis was performed on a Sunfire C18 column (4.6 × 250 mm, 5 µm) eluted by 88 % methanol with 12 % 0.02 M solution (pH 8.0) of potassium hydrogen phosphate at a rate of 0.8 mL $min^{-1}$ and detected at 220 nm. Melting points (uncorrected) were measured using an YRT-3 melting point apparatus (Shanghai, China).

### *4-Chloro-N-(2-chloro-1-oxopropyl)-benzeneacetamide (**11**) and 2-(4-Chlorophenyl)-N-(2-(4- chlorophenyl)acetyl) acetamide (**12**) Obtained by the Reaction of Nitrile **9** and Acid **10***

In a typical synthesis, 8.5 mL 2-chloropropionic acid **10** (98.7 mmol, 1.5 equiv.), 12.5 mL TMSCl (98.6 mmol, 1.5 equiv.), 9.0 g anhydrous $ZnCl_2$ (66.0 mmol, 1.0 equiv.), 7.5 mL TFA (100.0 mmol, 1.52 equiv.), 11.0 mL $Tf_2O$ (66.0 mmol, 1.0 equiv.), and 10.0 g 4-chlorophenylacetonitrile **9** (66.0 mmol) were added sequentially at 0°C. The reaction was stirred at 0°C for 1 h and at room temperature (rt) for additional 1 h before heating to 50°C (bath temperature). After reacting at 50°C for 72 h, the reaction mixture was treated with 100 mL deionized water and 100 mL petroleum ether and stirred at room temperature for 3 h. The resulting precipitate was filtered and equilibrated with ethyl acetate and sat. sol. $NaHCO_3$, and the organic phase was separated and washed with sat. sol. $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. The reaction mixture was then filtered, evaporated, dried under vacuum, and the dried solid was extracted with 100 mL acetonitrile at 40°C, and the undissolved solids of **12** and other by-product/s were filtered. The filtrate was evaporated and the solid was re-crystallized

from ethyl acetate and petroleum ether to afford desired product **11** as a white powder (12.4 g, 72.2 %), mp 131−133°C. $\delta_H$ ([D6]DMSO, 400 MHz) 11.15 (1H, br s), 7.38 (2H, d, *J* 8.4), 7.27 (2H, d, *J* 8.5), 4.85 (1H, q, *J* 6.7), 3.89 (2H, s), 1.55 (3H, d, *J* 6.7). $\delta_C$ ($CD_3OD$, 101 MHz) 173.4, 171.3, 134.1, 132.3, 131.8 (2C), 129.6 (2C), 54.9, 43.8, 20.8. HRMS *m*/*z* 282.0059 $[M + Na]^+$; cacld for $C_{11}H_{11}Cl_2NNaO_2$ 282.0065. Pure **12** as a white solid was obtained by silica gel column chromatography eluted by DCM, mp 208.9–211.9°C. $\delta_H$ ([D6]DMSO, 400 MHz) 11.03 (1H, br s), 7.36 (4H, d, *J* 8.4), 7.26 (4H, d, *J* 8.5), 3.83 (4H, s). HRMS *m*/*z* 344.0216 $[M + Na]^+$; cacld for $C_{16}H_{13}Cl_2NNaO_2$ 344.0221.

### *Synthesis of Hydrochloride Salt of 2-(4-Chlorophenyl)-N-ethyl-N-2-propylchloride (**8a**)*

Typically, 8.7 g $NaBH_4$ (230.7 mmol, 6.0 equiv.) was suspended in 150 mL anhydrous THF under a nitrogen atmosphere and in an ice bath, and 20.5 g $AlCl_3$ (153.8 mmol, 4.0 equiv.) was added to the reaction mixture in three batches. After the mixture was stirred at room temperature for 1 h to yield a white sticky solid, 10.0 g compound **11** (38.4 mmol) in 100 mL THF and then 26.5 mL TMSCl (209.0 mmol, 5.5 equiv.) were added sequentially to the reaction mixture. After the addition, the reaction mixture was heated to 70°C (bath temperature) and stirred for 1 day, and the reaction was carefully quenched with water (50 mL) in an ice bath after cooling to room temperature. The mixture pH was adjusted to 14 by 30 % NaOH solution, and the reaction mixture was stirred for ~30 min then extracted with DCM (2 × 150 mL). The organic layer was washed with 150 mL sat. sol. $NaHCO_3$ and 100 mL sat. brine, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure to give a pale yellow liquid. In an ice bath, the resulting liquid was dissolved in 100 mL ethyl acetate before hydrogen chloride gas was passed through the solution and stirred for ~30 min to produce 9.9 g hydrochloride salt of **8a** as a white solid (96 % yield). $\delta_H$ ([D6]DMSO, 400 MHz) 9.07 (2H, br), 7.41 (2H, d, *J* 8.4), 7.30 (2H, d, *J* 8.4), 4.56–4.46 (1H, m), 3.40 (1H, m), 3.29–3.22 (1H, m), 3.21–3.13 (2H, m), 3.03–2.93 (2H, m), 1.53 (3H, d, *J* 6.6).

### *Synthesis of (±)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine ((±)-**1**) from **8a** by Intramolecular Friedel–Crafts Reaction*[5,6]

In **Procedure A**, the mixture of 3.0 g hydrochloride salt of **8a** (11.2 mmol), 2.2 g anhydrous $AlCl_3$ (16.8 mmol), and 20.0 mL 1,2-dichlorobenzene was stirred at 130°C for 16 h; or in **Procedure B** (neat), the mixture of 3.0 g hydrochloride salt of **8a** (11.2 mmol) and 2.2 g anhydrous $AlCl_3$ (16.8 mmol) was stirred at 130°C for 5 h. After cooling to room temperature, the reaction was quenched by slow addition of 5.0 mL deionized water in an ice bath and then 50 mL 2.0 N HCl and 30 mL (**Procedure A**) or 50 mL (**Procedure B**) ethyl acetate was added and stirred for 1 h. The aqueous layer was separated and the pH was adjusted to 14 by 30 % NaOH solution before extraction with 150 mL DCM. The organic layer was washed with 100 mL sat. sol. $NaHCO_3$ and 100 mL sat. brine, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure to give a yellow liquid (78.2 % yield by **Procedure A** or 68.6 % yield by **Procedure B**). Free base of (±)-**1**: $\delta_H$ ([D6]DMSO, 400 MHz) 7.18–7.10 (3H, m), 3.06–2.97 (1H, m), 2.89–2.68 (5H, m), 2.58 (1H, dd, *J* 13.1, 7.2), 1.23 (3H, d, *J* 7.3). Free base of (±)-**1** was dissolved in ethyl acetate saturated with hydrogen chloride and stirred for 1 h at 0°C, and the precipitated solid was collected by filtration and dried at 30°C under vacuum to provide hydrochloride salt of (±)-**1**. $\delta_H$ ([D6]DMSO, 400 MHz) 9.69 (1H, br s), 9.28 (1H, br s), 7.28–7.18 (3H, m), 3.46 (1H, d, *J* 7.0), 3.30 (1H, dd, *J* 13.2, 7.5), 3.21 (2H, d, *J* 13.4), 3.02 (1H dd, *J* 15.7, 7.0), 2.89 (2H, m), 1.34 (3H, d, *J* 7.3). The $^1$H NMR spectra and HPLC results (Supplementary Material) of (±)-**1** were identical to those reported.[5,6]

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