Development of a New Process for Tulobuterol Hydrochloride

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Abstract

Tulobuterol is a selective β2-adrenoceptor agonist and has been widely utilized as a therapeutic agent for the treatment of asthma. Synthesis of tulobuterol has achieved many important progresses over the past decades and has gradually become one of the research hotspots in organic chemistry. This study aimed to explore a novel synthesis route to synthesize tulobuterol hydrochloride (**1**), an active ingredient of Chlobamolie Hydrochloride Tablets. In the study, **1** was obtained from the cost-effective, commercially available 2-chloroacetophenone through the key steps including the reactions of bromination, $NaBH_4$ reduction, and amination. Process-related impurities were also investigated. **1** was obtained with excellent purity (99.96%) in 53% overall yield without the need for chromatographic purification. The developed method is green, facile, and cost-effective; thus, it is suitable for the industrial-scale production of **1**.

Keywords
- tulobuterol hydrochloride
- 2-chloroacetophenone
- synthesis process

Introduction

Asthma is a common respiratory disease that causes inflammation in the lungs, and it is usually accompanied by coughing, wheezing, and dyspnea. Tulobuterol is a selective β2-adrenoceptor agonist and was approved in Japan in 1981 for the treatment of asthma.[1] Tulobuterol is commercially available as Chlobamolie Hydrochloride Tablets containing tulobuterol hydrochloride (**1**) as the active ingredient. Chlobamolie Hydrochloride is prescribed to combat lasting dilation of bronchial smooth muscle,[1,2] dyspnea caused by acute or chronic bronchitis, emphysema, and other asthma-related symptoms.[3,4] In addition to the tablet form, tulobuterol can be administered as a topical patch. Amiaid is a patch formulation of tulobuterol, which was developed in 1998.[5] Amiaid is widely used to treat asthma in children because the active ingredient can be easily absorbed through the skin, is fast-acting, and provides long-lasting relief.[6,7]

Over the past decades, many synthetic routes of tulobuterol (**5**) have been reported in the literature (►**Scheme 1**). In 1973, Kato et al disclosed a reductive amination-based approach **5** using 2-chlorophenyl glyoxal as the starting material with an overall yield of 67% yield.[8] Unfortunately, despite the shortness and efficiency of the synthetic route, the starting material is difficult to obtain, thus limiting the widespread application of this strategy. In 1978, Koshinaka et al disclosed a selenium dioxide oxidation and reductive

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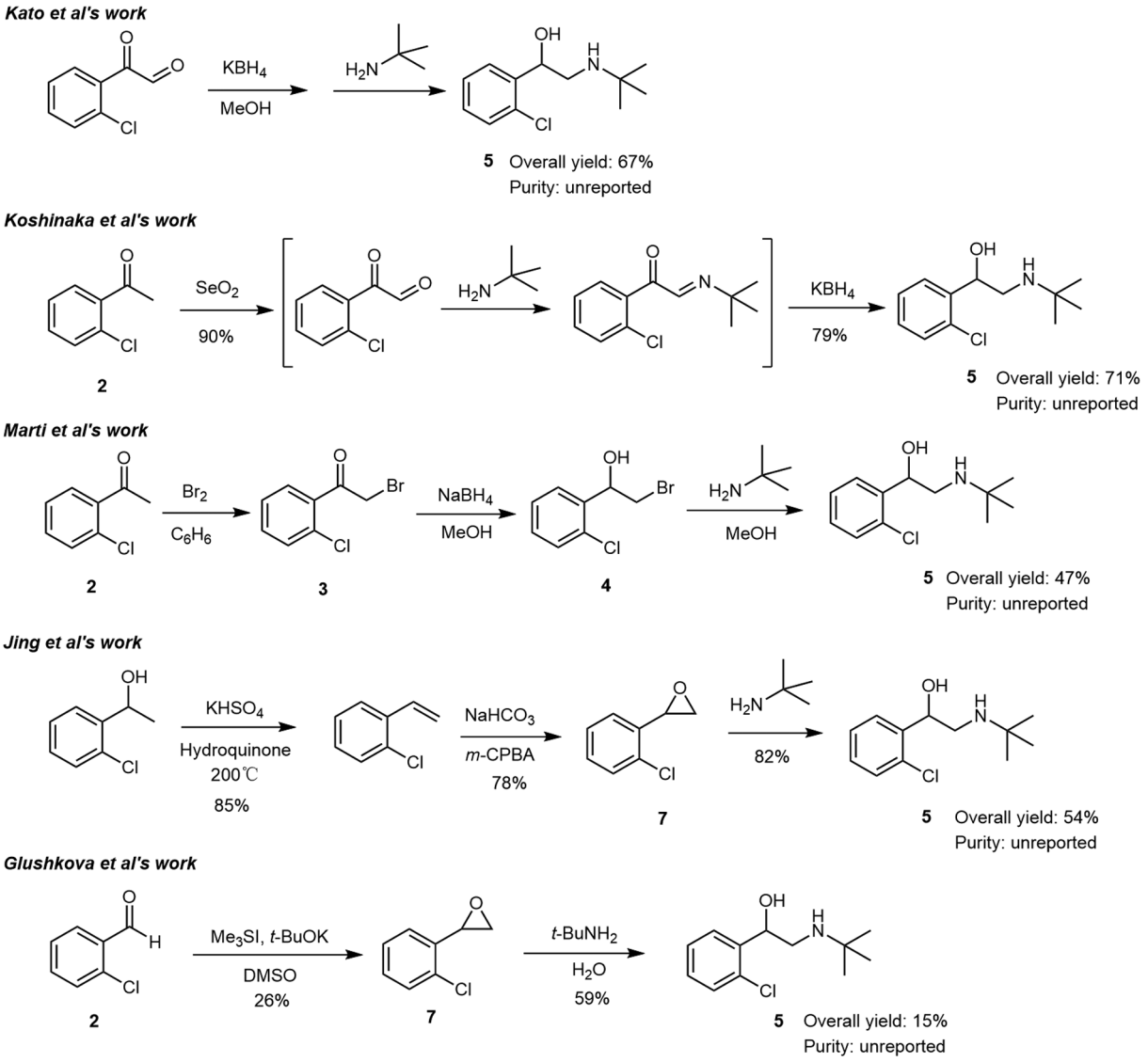
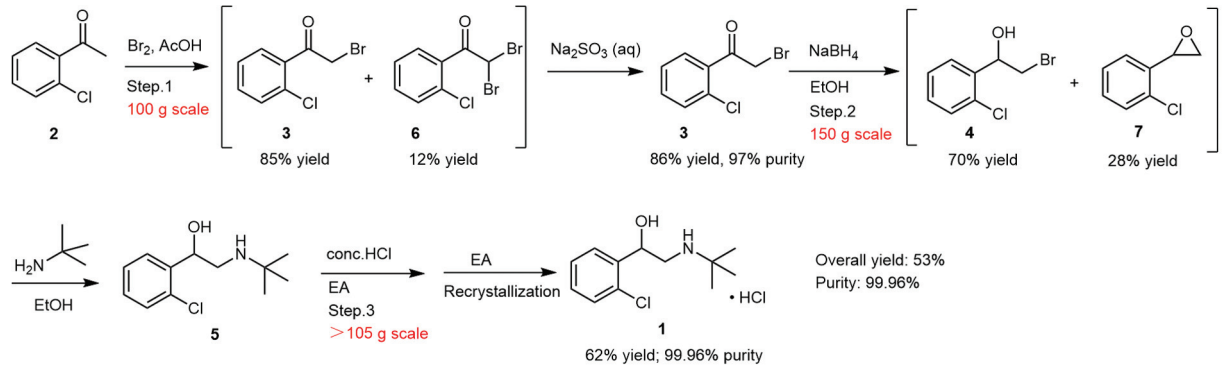


Scheme 1 Synthetic route of tulobuterol in the reported study.

amination approach starting from the commercially available 2-chloroacetophenone (**2**). Their synthesis of **5** was achieved with an overall yield of 71%.[9] While the yield did improve, the catalyst (selenium dioxide) is both expensive and poisonous, again limiting the widespread application of this strategy. In 1984, Marti and Gnehm focused on tulobuterol synthesis starting with common and low-cost materials. Compound **2** was used as the starting material. The key steps included bromination, $NaBH_4$ reduction, and *tert*-butylamine amination. However, the overall yield of compound **5** was only 47%,[10] which was much lower than the reported studies mentioned above. Besides, column chromatography was repeatedly used in the separations, which restricted the application of the methods on an industrial scale. In 2016, Jing et al selected 1-(2-chlorphenyl) ethanol as a raw material to obtain tulobuterol hydrochloride. The key steps included olefination, epoxidation, and amination.[11] The total yield was 54%. However, the enylation reaction required high temperatures for execution and makes the route unattractive for industrial-scale production as suitable high-temperature equipment set-ups are required. In 2020, Glushkova et al disclosed a rapid two-step synthesis of **5** from **2**[12]; unfortunately, the overall yield was only 15%.

Considering the many drawbacks of existing routes to **1**, this study sought a practical synthetic route. The selected synthetic route based on the work by Marti and Gnehm is illustrated in ►**Scheme 2**. Briefly, **2** was reacted with Br_2 to give a mixture of 2-bromo-1-(2-chlorophenyl)-ethan-1-one (**3**) and 2,2-dibromo-1-(2-chlorophenyl)-ethan-1-one (**6**), which could be further transformed to **3** with Na_2SO_3 treatment. Compound **3** was obtained with a total yield of 86% and a purity of 97.6% by using high-performance liquid chromatography (HPLC), and was used to generate tulobuterol (**5**) through reactions of reduction, epoxidation, and amination in one pot. Compound **5** was acidified with hydrogen chloride (HCl) to obtain the target compound (**1**) with a yield of 62% and a purity of 99.9%. The total yield of this route was 53% and the



Scheme 2 Synthetic route of tulobuterol in this work.

purification of the target compound was 99.96%. The method was mild, simple, green, economical, and suitable for adoption on an industrial scale.

Results and Discussion

Optimization of the Bromination Reaction

When 1.5 equiv. of Br_2 was used, the content of by-product **6** was 15.61%, which was consistent with a reported study[13] (►**Table 1**, entry 1). Decreasing the equivalent of Br_2 could reduce the formation of **6**; however, the conversion of raw material **2** was also decreased (►**Table 1**, entries 2–4). When other bromination agents, including NBS, DBH, and HBr/H_2O_2, were assessed, the content of by-product **6** was increased dramatically (►**Table 1**, entries 5–7). Despite our efforts, Br_2 (1.3 equiv.) was selected as the best brominating agent.

To facilitate the conversion of **6** to the desired product **3**, debromination additives were screened when the bromination reaction was finished. Taking guidance from the literature,[14] we first started with $(EtO)_2POH$ (►**Table 1**, entry 8). Our data showed that $(EtO)_2POH$ decreased the content of **6** to 0.58% and pushed the content of **3** to 97.19%. However, the over-reduced by-product **1** was found at a level of 2.21% after a full course of the reaction. Other agents were screened. Na_2HPO_3 and $(EtO)_2POH$ had a similar effect in terms of yield, and both were superior to Na_2HPO_3 (►**Table 1**, entries 8–10). To improve sustainability and avoid phosphorus waste disposal in the environment, cheaper and environment-friendly Na_2SO_3 and its derivatives were selected according to a reported study.[15] Interestingly, Na_2SO_3 was similar to $(EtO)_2POH$ and superior to $NaHS_2O_3$, $Na_2S_2O_5$, $Na_2S_2O_3$, and $Na_2S_2O_4$ in converting **6** to **3** (►**Table 1**, entries 11–15). Compared with Na_2SO_3, K_2SO_3 did not perform better (►**Table 1**, entry 16). Thus, Na_2SO_3 was selected for the next stage of development. We further investigated the effect of equivalents of Na_2SO_3 and temperature on the yield of compound **3** (►**Table 1**, entries 17–22), and found that when the equivalent of Na_2SO_3 was 1.3 and the temperature was 15 to 20°C, **3** could be generated with the maximum yield (►**Table 1**, entry 18). With the optimized reaction conditions in hand, **3** was prepared on a 100 g scale in 86.4% yield and 97.6% HPLC purity.

One-Pot Method to Synthesize 1

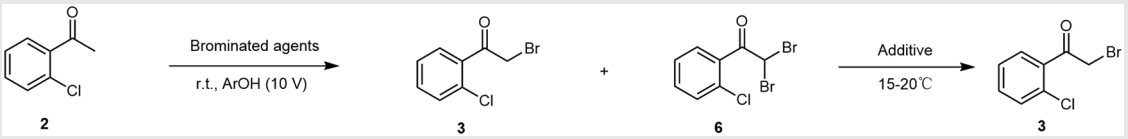
Arakawa et al reported the synthesis of tulobuterol (**5**) from **3** through the successive reaction of reduction and amination.[7] Unfortunately, **7**, as an epoxide impurity, was generated in approximately 28% yield during the reduction step. It is well known that ring opening of **7** can be achieved with the nucleophilic amine to generate β-amino alcohols. Thus, when the reduction reaction was finished, *tert*-butylamine was added directly to convert **7** to the target tulobuterol. After refluxing in EtOH for 6 hours, **5** was obtained smoothly with 92% purity, yet, in parallel with 4% regioisomeric by-product **8**. Notably, a quick conversion of **4** to **7** was also observed in the amination reaction (►**Fig. 1**).

Glushkova et al used HCl/*i*-PrOH to obtain tulobuterol hydrochloride (**1**) in Et_2O. Due to the high toxicity and low boiling point of Et_2O, the application of this approach was restricted in industry. Thus, Et_2O was replaced with ethyl acetate (EA) in the salt-forming reaction. Finally, a crude product of **1** was obtained with 95% purity, alongside 5% isomer **8**. Lastly, the purification of crude **1** through recrystallization was investigated. Unfortunately, due to the high solubility of **1** in MeOH, EtOH, and acetone, we failed to obtain the crystal of **1** from these solvents (►**Table 2**, entries 1–3). Using 3 volumes (V) of *i*-PrOH as the recrystallization solvent, **1** was obtained with a purity of 98.12% and a yield of 79.7% (►**Table 2**, entry 4). Increasing the dosage of *i*-PrOH led to increased purity while reduced yield (►**Table 2**, entries 5–7). We next explored ester solvents for a slurry-based purification to remove isomer impurity **8**, such as butyl acetate, *i*-PrOAc, iso-amyl acetate, and EA (►**Table 2**, entries 8–11). Surprisingly, an excellent purity of 99.96% and a good yield of 85.1% of **1** were obtained by using EA (5 V) as a solvent (►**Table 2**, entry 11). Further adjusting the amount of EA (3 V, or 8 V) decreased the yield or purity of **1** (►**Table 2**, entries 12 and 13). Thus, EA (5 V) was selected as the optimal condition for the purification of **1** in a 105 g scale purification.

Impurity Identification

The impurities related to our synthesis were also analyzed (►**Scheme 3**). By-product **6** was generated from the

Table 1 Optimization of the bromination reaction[a]



Entry	Brominated agents (equiv.)	Additive (equiv.)	HPLC[b]		
			2 (%)	3 (%)	6 (%)
1	Br_2 (1.5)	–	1.03	83.34	15.61
2	Br_2 (1.3)	–	1.86	85.05	12.09
3	Br_2 (1.0)	–	7.30	80.54	10.94
4	Br_2 (0.8)	–	12.52	76.73	8.75
5[c]	NBS (1.5)	–	1.04	79.52	19.04
6[c]	DBH (1.5)	–	0.25	73.88	24.10
7	HBr/H_2O_2 (4.0)	–	1.87	65.03	32.32
8	Br_2 (1.3)	$(EtO)_2POH$ (1.5)	2.21	97.19	0.58
9	Br_2 (1.3)	Na_2HPO_3 (1.5)	1.12	96.79	0.32
10	Br_2 (1.3)	NaH_2PO_2 (1.5)	1.31	63.94	33.36
11	Br_2 (1.3)	Na_2SO_3 (1.5)	2.49	97.02	0.49
12	Br_2 (1.3)	$NaHSO_3$ (1.5)	1.40	96.75	1.21
13	Br_2 (1.3)	$Na_2S_2O_5$ (1.5)	5.26	80.44	9.13
14	Br_2 (1.3)	$Na_2S_2O_3$ (1.5)	2.78	54.83	40.39
15	Br_2 (1.3)	$Na_2S_2O_4$ (1.5)	30.51	39.63	26.67
16	Br_2(1.3)	K_2SO_3 (1.5)	1.35	85.48	13.17
17	Br_2 (1.3)	Na_2SO_3 (1.1)	1.21	96.62	2.07
18	Br_2 (1.3)	Na_2SO_3 (1.3)	1.25	97.61	0.75
19	Br_2 (1.3)	Na_2SO_3 (1.8)	3.87	95.60	0.53
20[d]	Br_2 (1.3)	Na_2SO_3 (1.3)	4.28	95.31	0.35
21[e]	Br_2 (1.3)	Na_2SO_3 (1.3)	1.41	90.82	7.75
22[f]	Br_2 (1.3)	Na_2SO_3 (1.3)	1.12	85.37	13.43

[a]Reaction conditions: **2** (2.0 g, 1.3 mmol, 1.0 equiv.).
[b]Composition of the product was measured by HPLC.
[c]Solvent: dichloromethane (10 V).
[d]Temperature of reduction was 20–25°C.
[e]Temperature of reduction was 10–15°C.
[f]Temperature of reduction was 5–10°C.

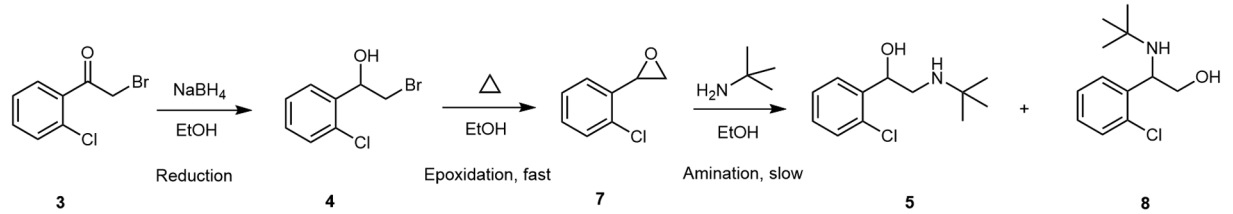
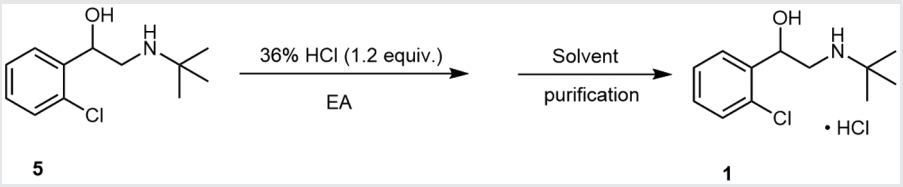


Fig. 1 Investigation of the reaction rate.

bromination reaction (Step 1). By-product **6** and the remaining starting material (**2**) resulted in impurities **9** and **10** after the $NaHB_4$-catalyzed reduction reaction (Step 2). Impurities of **11** and isomer **8** were generated from the ring-opening reaction of **7**. The impurities can be controlled. Compound **6**, **9**, **10**, and **11** could be removed after the synthesis process of crude product **1**. The content of isomer **8** can be controlled to less than 0.05% (HPLC) through a slurry operation at Step 3.

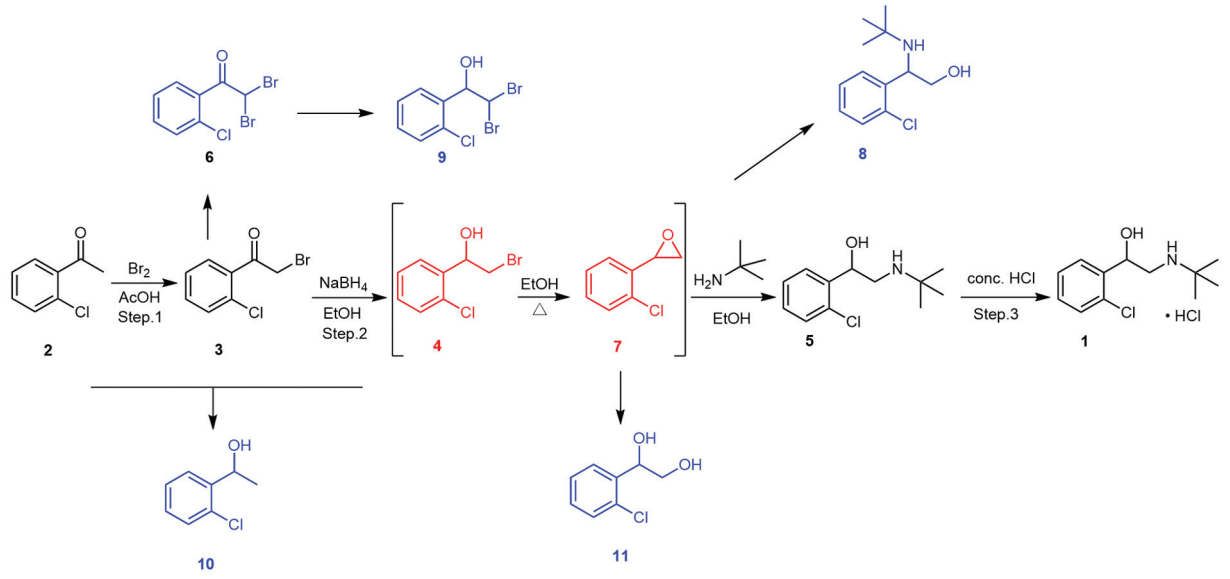
Table 2 Screening of the solvents for purification[a]



5 1

Entry	Solvent	Dosage (V)	HPLC[b]		Yield (%)
			5 (%)	8 (%)	
1	MeOH	3	–	–	–
2	EtOH	3	–	–	–
3	Acetone	3	–	–	–
4	*i*-PrOH	3	98.12	1.88	79.7
5	*i*-PrOH	4	98.53	1.45	68.8
6	*i*-PrOH	6	98.89	0.98	54.3
7	*i*-PrOH	8	99.67	0.33	48.0
8	Butyl acetate	5	97.37	2.63	90.5
9	*i*-PrOAc	5	97.92	2.08	95.5
10	*Iso*-amyl acetate	5	97.55	2.45	85.5
11	EA	5	99.96	0.04	85.1
12	EA	3	99.92	0.08	89.2
13	EA	8	99.99	0.01	63.4

[a]Reaction conditions: **5** (5.0 g, 2.2 mmol, 1.0 equiv.).
[b]Product content was measured by HPLC.



Scheme 3 Impurities generated in the process.

Conclusion

In summary, we have developed an efficient and practical process to synthesize tulobuterol hydrochloride (**1**) using 2-chloroacetophenone (**2**) as the starting material. As a result, the total yield of the target product was 53% and the purity was 99.96%. The highlight of this creative synthetic route was the use of inexpensive and environmentally friendly Na_2SO_3

as the reducing agent to convert process-related impurity **6** into key intermediate **3**. Besides, a one-pot synthesis of tulobuterol (**5**) is developed, instead of stepwise synthesis. Furthermore, EA was selected as an ideal solvent for the purification of **1**. With the optimized purification conditions in hand, isomer **8** was removed by slurry purification to obtain the product with 85% yield and 99.9% purity. This industrially amenable route provided the target product (**1**) in 99.96% purity with an overall yield of 53% from starting material **2**.

Experimental Section

General

All reagents were commercially available and used without further purification unless indicated otherwise. HPLC analysis was conducted on a Dionex UltiMate 3000 HPLC (Dionex, United States) using an Agilent Eclipse plus C18 column (4.6 mm × 250 mm, 5 µm, Agilent, United States). Aqueous sodium octane sulfonate (15 mmol/mL, pH 3.30 ± 0.2)-acetonitrile (90:10, v/v) was used for mobile phase A; acetonitrile was used for mobile phase B. Gradient program was as follows: 0–25 minutes, 15% B; 25–30 minutes, 60% B; 30–31 minutes, 15% B; 31–40 minutes, 15% B. Flow rate = 1.0 mL/min, column temperature = 30°C, and UV detection at 215 nm. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer (Bruker, Germany). Chemical shifts (δ) were given in parts per million and referenced to the residual protonated solvent peak of $CDCl_3$ (δ = 7.26).

Preparation of 2-Chlorophenacyl Bromide (3)

Br_2 (134.4 g, 0.84 mol) was slowly added to a solution of 2-chloroacetophenone (**2**) (100.0 g, 0.65 mol) in acetic acid (1.0 L) over 1 hour. The solution was stirred at room temperature for an additional 8 hours, and then cooled to 10°C. A mixture of Na_2SO_3 (82.0 g, 0.65 mol) in water (400 mL) was then added, and the resulting mixture was stirred at room temperature for additional 2 hours. EA (500 mL) was added for extraction. After stirring for 30 minutes, the organic phase was separated, washed with water (300 mL × 2), dried over Na_2SO_4, and concentrated to give **3** (130.1 g, 86.4% yield based on **2**, HPLC purity 97.6%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.54 (m, 4H), 4.49 (s, 2H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 193.88, 136.09, 132.78, 131.27, 130.58, 130.16, 127.14, 34.64. These values are consistent with those reported in the literature.[10]

Preparation of 1-(2-Chlorophenyl)-2-*tert*-butylaminoethanol (5)

$NaBH_4$ (24.57 g, 0.65 mol) was slowly added to a solution of **3** (150 g, 0.65 mol) in EtOH (1.5 L) at 0°C and stirred the solution for 1.5 hours. Thereafter, *tert*-butylamine (94.8 g, 1.30 mol) was added, and the mixture was refluxed for an additional 6 hours. The progress of the reaction was monitored by HPLC. After the reaction was complete, the reaction solution was cooled to room temperature and filtered. The filtrate was concentrated to dryness, and the resulting residue was dissolved in EA (650 mL) and washed with water (200 mL × 2). The organic phase of **5** was used in the next reaction without further purification.

Preparation of 1-(2-Chlorophenyl)-2-*tert*-butylaminoethanol Hydrochloride (1)

Concentrated HCl (71 mL, 0.78 mol) was added to a solution of **5** in EA (from the previous step). The resulting slurry was stirred at ambient temperature for 1 hour and filtered to obtain crude **1** (107.5 g, 73.2% yield, 95.6% HPLC purity). Crude **1** (105.0 g) was then suspended in EA (525 mL) and stirred at 70°C for 4 hours. Thereafter, the mixture was cooled to room temperature and filtered. The obtained cake was washed with EA (50 mL × 3) and dried at 60°C to afford **1** (89.3 g, 85.0% yield, 99.96% HPLC purity) as a white solid. mp: 160.1–161.5°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J = 3.8 Hz, 4.0 Hz, 1H), 7.33–7.23 (m, 4H), 5.66 (dd, J = 1.1 Hz, 1.2 Hz, 1H), 3.34 (dd, J = 1.4 Hz, 1.0 Hz, 1H), 2.86 (dd, J = 2.0 Hz, 1.8 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 137.96, 131.53, 129.52, 129.32, 127.76, 127.45, 66.44, 57.75, 48.04, 26.15. The values are consistent with those reported in the literature.[9,11,12]

Preparation of 2,2-Dibromo-1-(2-chlorophenyl) Ethenone (6)

Br_2 (4.1 g, 25.9 mmol) was added dropwise at 15 to 20°C to a solution of **2** (1.0 g, 6.5 mmol) in acetic acid (5.0 mL) and the resulting mixture was stirred at ambient temperature for an additional 5 hours. Thereafter, EA (20 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was collected, dried over Na_2SO_4, and concentrated at 55°C to give a residue, which was purified by column chromatography (EA:petroleum ether (PE) = 20:1) to obtain **6** (1.6 g, 81% yield) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.41–7.47 (m, 2H), 7.33–7.37 (m, 1H,), 6.74 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 177.59, 134.08, 133.07, 131.19, 130.89, 130.54, 121.28, 68.78.

Preparation of 2-(2-Chlorophenyl) Oxirane (7)

$NaBH_4$ (0.82 g, 21.6 mmol) was carefully added at 0°C to a solution of **3** (5 g, 21.6 mmol) in ethanol (50 mL). The mixture was stirred at 15 to 20°C for an additional 1 hour, and reaction progress was monitored by thin layer chromatography. When the reaction was complete, the mixture was heated to 35 to 40°C and stirred for 1 hour. The solvent was evaporated in vacuo and the obtained residue was dissolved in EA (50 mL), washed twice with water, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (EA:PE = 30:1) to give **7** (2.3 g, 70% yield, 95.5% purity) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12–7.29 (m, 4H), 4.13 (dd, J = 4.0 Hz, 2.4 Hz, 1H), 3.10 (dd, J = 4.0 Hz, 2.4 Hz, 1H), 2.58 (dd, J = 2.4 Hz, 1.6 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 135.71, 133.39, 129.24, 129.02, 127.17, 125.79, 50.80, 50.13.

Preparation of 2-*tert*-Butylamino-2-(2-chlorophenyl) Ethanol (8)

Compound **8** was separated from the mother liquid of **1**, which was concentrated under vacuum to give a residue. The

residue was purified by silica gel column chromatography (DCM:MeOH = 30:1) to obtain impurity **8** (0.3 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.35 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.26 (m, 1H), 7.19 (m,1H), 4.46 (dd, J = 6.0 Hz, 2.8 Hz, 1H), 3.59 (dd, J = 7.2 Hz, 3.2 Hz, 1H), 3.29 (t, J = 6.8 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 140.47, 132.89, 129.95, 128.52, 128.22, 127.18, 65.29, 55.42, 52.12, 30.14.

Preparation of 2,2-Dibromo-1-(2-chlorophenyl) Ethanol (9)

$NaBH_4$ (0.2 g, 4.8 mmol) was carefully added at 0°C to a solution of intermediate **6** (1.5 g, 4.8 mmol) in ethanol (15 mL). The mixture was stirred at 15 to 20°C for 1 additional hour and concentrated under vacuum to give a residue, which was dissolved in EA/H_2O (15/15 mL). The organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM:MeOH = 100:1) to afford **9** (1.1 g, 78% yield, 96.2% purity) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 1H), 7.34 (m, 3H), 6.08 (d, J = 2.8, 1H), 5.48 (d, J = 4.0 Hz, 1.2 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 136.06, 132.11, 129.97, 129.54, 129.00, 127.12, 75.35, 60.64.

Preparation of 1-(2-Chlorophenyl) Ethanol (10)

Compound **2** (3.85 g, 25.0 mmol) was dissolved in 10 mL methanol. Then, $NaBH_4$ (1.42 g, 37.65 mmol) was added at 0°C and the solution was stirred overnight at room temperature. After completion of the reaction, saturated ammonium chloride solution (10 mL) was added to the mixture. The desired compound was extracted with DCM (10 mL × 3) and the organic layer was evaporated to concentrate. The residue was purified by silica gel column chromatography to obtain **10** (3.10 g, 79% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.25 (m, 1H), 5.36 (d, J = 4.4 Hz, 1H), 5.00–5.06 (m, 1H), 1.31 (d, J = 6.4 Hz, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 144.82, 130.70, 129.40, 128.63, 127.62, 127.18, 64.74, 24.54.

Preparation of 1-(2-Chlorophenyl)-1,2-ethanediol (11)

Compound **7** (1.08 g, 7.0 mmol) was added to 1 M NaOH (10.0 mL) and the mixture was heated at 40°C for 18 hours. The aqueous layer was extracted with DCM (15 mL) and DCM (20 mL × 2) respectively. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under a reduced pressure to give a residue, which was purified by silica gel column chromatography to give **11** (0.46 g, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 7.01–7.19 (m, 3H), 5.12 (d, J = 6.8 Hz, 1H), 4.15 (m, 2H), 3.73 (d, J = 10.4 Hz, 1H), 3.41 (t, J = 8.4 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 137.93, 131.87, 129.37, 128.88, 127.58, 127.12, 71.59, 66.31.

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **1**, **6**, **7**, **8**, **9**, **10**, and **11**, as well as HPLC results for the purities of compounds **3** and **1**, are included in the Supporting Information (►**Figs. S1–S18** [online only]).

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Conflict of Interest

The authors declare no conflict of interest.

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