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Practical Synthesis of 5,7-Dichlorotetrahydroisoquinoline-6-carboxylic Acid—Key Intermediate of Lifitegrast (Xiidra)

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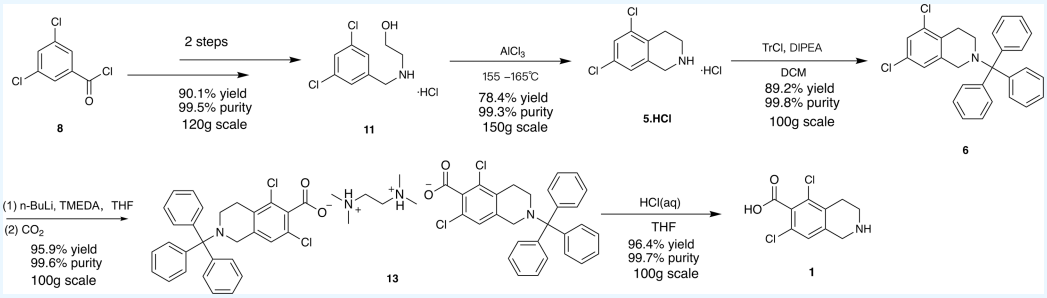

ABSTRACT: In the present study, a practical method for synthesizing the key intermediate 5,7-dichlorotetrahydroisoquinoline-6-carboxylic acid (**1**) of Lifitegrast was proposed. First, an investigation was conducted into the utilization of the impurity and recrystallization method in the synthesis of 5,7-dichlorotetrahydroisoquinoline (**5**·HCl) via Friedel−Crafts cyclization. Through the screening of different protection groups, a previously unreported quaternary ammonium salt (**13**) was isolated with a 95.9% yield and 99.6% purity by simply adjusting the pH during the carboxylation reaction. Subsequently, free state **1** was obtained by controlling the pH to 4−5 with HCl(aq), thereby avoiding the need for a free operation in the synthesis of the API of Lifitegrast. Further, the triphenylmethanol (TrOH) was recycled to triphenylmethyl chloride (TrCl) using $CaCl_2$/HCl(aq) with 93.0% yield and 98.0% purity.

INTRODUCTION

Dry eye disease (DED) is an inflammatory disorder of ocular surfaces leading to severe disability. Over the past several years, only cyclosporine-A emulsions have been added to existing therapy. However, most patients discontinued the use of such therapy due to reported burning sensations in the eye.[1,2] In 2016, the US Food and Drug Administration approved Lifitegrast for the treatment of DED owing to its ability to mitigate T-cell activation and release inflammatory mediators, thereby inhibiting the inflammatory pathways in DED.[3] As the key intermediate of Lifitegrast, a synthesis method for 5,7-dichlorotetrahydroisoquinoline-6-carboxylic acid (**1**) is worthy of investigation (Figure 1).

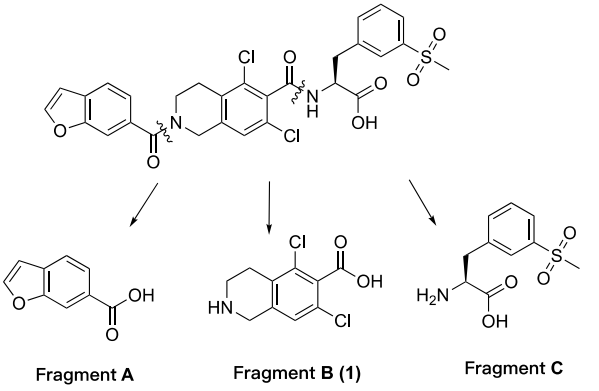

Figure 1. Lifitegrast and key intermediates.

The reported strategies for synthesizing compound **1** were based on the form of hydrochloride salt. Burnier used compounds **2** and **3** as raw materials via reductive amination, Friedel−Crafts, TrCl protection, *n*-BuLi/CO_2 carboxylation and deprotection reactions to obtain **1**·HCl (Scheme 1a).[4,5] However, the overall yield obtained from such route was only 19.6%. At the same time, the raw materials are expensive, and there are no reported relevant work-up procedures. Xu et al. reported obtaining **1**·HCl via using the inexpensive compound **8** as the starting material and methylene as the protecting group,[6,7] but the purity and impurities in each reaction step

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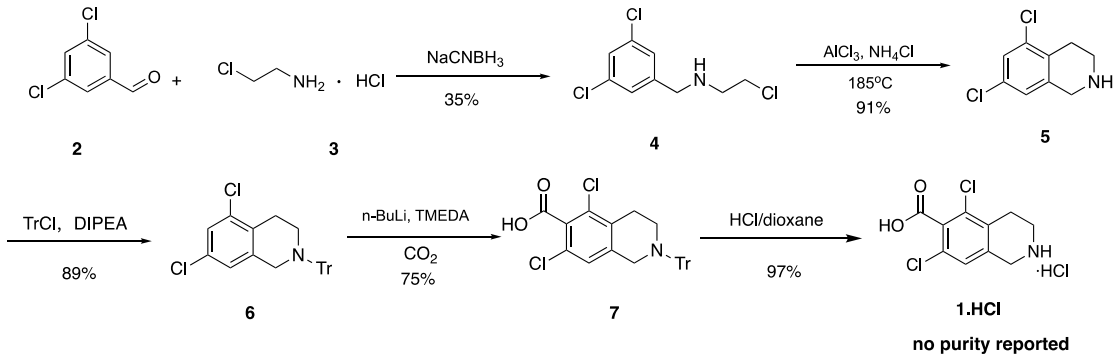
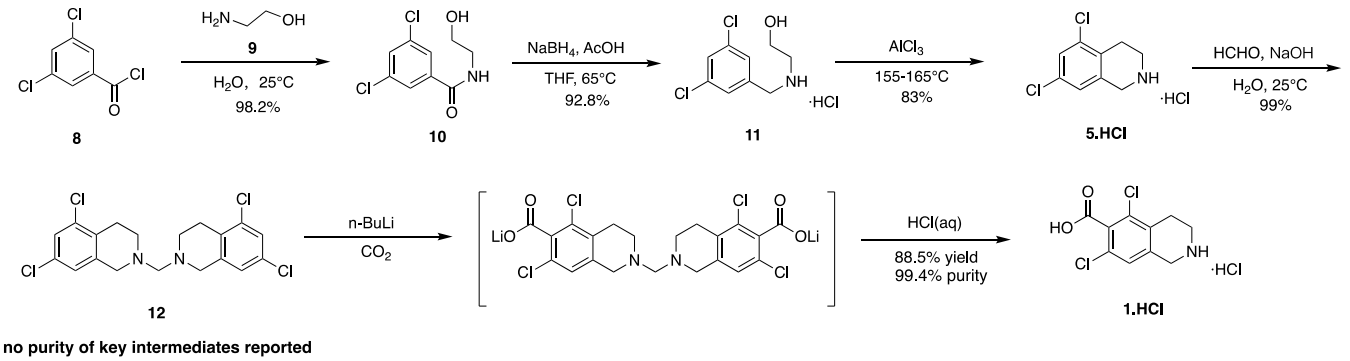
Scheme 1. Synthetic of 5,7-Dichlorotetrahydroisoquinoline-6-carboxylic Acid (1)

a) Burnier's work.



Burnier, J. *et al.* Patent WO2009139817A2, **2009**.

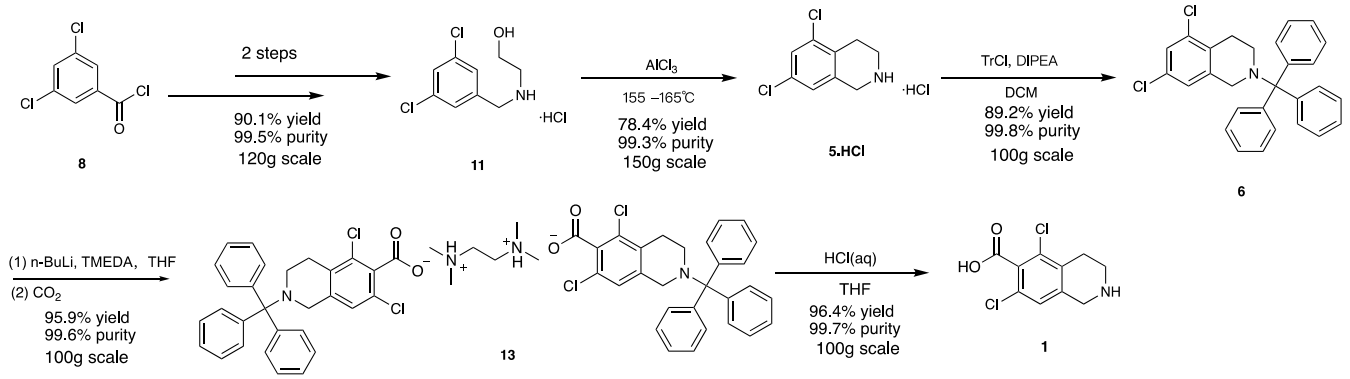
b) Xu's work.



Xu, W. B. *et al. Org. Process Res. Dev.* **2021**, 25, 2447-2452.

c) The present method

Improved process for the synthesis of compound **1**.



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were not reported. In the present study, compounds **8** and **9** were also used as starting materials via substitution, and a reductive reaction was performed to obtain compound **11** with 90.1% yield and 99.5% purity. Meanwhile, the recrystallization condition of **5**·HCl was screened to remove the unexpected aromatization impurity **5a** in the Friedel−Crafts reaction. Subsequently, the different protection methods of secondary amine in the *n*-BuLi/CO_2 carboxylation reaction were investigated. The quaternary ammonium salt (**13**) with 95.9% yield and 99.6% purity was first separated as an intermediate. Finally, compound **1** was obtained with 96.4% yield and 99.7% purity via deprotection by simply controlling the pH. The recovery of TrOH was also accomplished to achieve good atom economy.[8]

RESULTS AND DISCUSSION

Considering the production costs, the commercially available **8** was selected as the raw material, which was used in a substitution reaction to obtain compound **11** with 90.1% yield and 99.5% purity. Xu's research revealed the presence of 6.3% unknown impurities during the synthesis of **5**·HCl through Friedel−Crafts cyclization. The impurity was separated by means of column chromatography and confirmed as an aromatization product of compound **5** (Figure 2). The

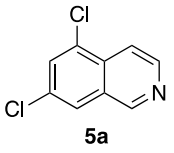


Figure 2. Aromatized impurity **5a** in the Friedel−Crafts cyclization.

impurity **5a** was a result of the metal-catalyzed dehydrogenative aromatization of compound **5** under high temperature. In order to reduce the impurity **5a** in production, the reaction temperature was investigated (Table 1). Since the reaction was performed without solvents and the melting point of compound **11** was 163.4−164.5 °C, once the temperature was reduced to 145−155 °C, no product could be detected (entry 1). After increasing the temperature of the reaction to 165−175 °C, the level of impurity **5a** would increase to 13.6% (entry 3). Therefore, 155−165 °C was selected as the optimal reaction temperature, with the purity of **5**·HCl reaching 93.4% (entry 2). In order to remove the impurity **5a**, different recrystallization systems of crude **5**·HCl were investigated (Table 2). According to the purification method in Xu's research, the impurity **5a** still remained at 3.3% and the yield of

Table 2. Optimization of Recrystallization Solvent for the Friedel−Crafts Cyclization[a]

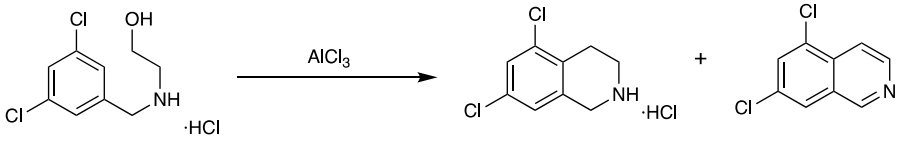
			HPLC (%)[b]	
entry	recrystallization solvent and volume	yield (%)	**5**·HCl	**5a**
1	EtOH/H_2O (5 V/4 V)	31.1	96.5	3.3
2	EtOH (60 V)	21.8	99.2	0.4
3	H_2O (15 V)	48.8	99.4	0.3
4	EtOH/H_2O (10 V/7 V)	32.1	98.0	1.8
5	EtOH/H_2O (10 V/6 V)	41.0	98.4	1.3
6	EtOH/H_2O (10 V/5 V)	47.2	98.9	0.9
7[c]	EtOH/H_2O (10 V/4 V)	78.4	99.3	0.4
8	EtOH/H_2O (10 V/3 V)	60.0	99.0	0.8

[a]Reaction conditions: 10 g scale. [b]Measured by HPLC (area %). [c]Reaction conditions: 150 g scale.

5·HCl was only 31.1% in the system of EtOH/H_2O (5 V/4 V). However, **5**·HCl was obtained with yields of 21.8 and 48.8% while maintaining high purity when using either EtOH or H_2O as a single recrystallization solvent (entries 2 and 3). To increase the yield of **5**·HCl, the different ratios of EtOH/H_2O were screened. The yield and purity of **5**·HCl reached 32.1 and 98.0% by using EtOH/H_2O (10 V/7 V) as solvent (entry 4). The yield and purity changed obviously with the decrease in water (entries 5−8). The results displayed that EtOH/H_2O (10 V/4 V) was the optimal recrystallization system for obtaining the **5**·HCl (entry 5). **5**·HCl had an isolated yield of 78.4% and a purity of 99.3% on a 150 g scale.

To mitigate the impact of the amino group during the carboxylation reaction, the impact of different protective groups on the reaction of compound **5** in the carboxylation reaction was investigated. Boc,[9] Tr,[4,5] and methylene[6,7] were substituted to protect the secondary amine of compound **5** in the carboxylation reaction, in accordance with previous research (Table 3). Using Boc as protecting group, 45.7% unknown impurity was generated in the reaction (entry 1). The impurity was isolated and confirmed to be isomer **16a** of the target product (Figure 3). The oxygen on the carbonyl group was speculated to coordinate with Li first, followed by a Li−H exchange with the benzyl−H to form a five-ring intermediate, which ultimately reacted with CO_2 to produce **16a**[10−12] (Scheme 2).

Table 1. Screening the Temperature for the Friedel−Crafts cyclization[a]



11 **5.HCl** **5a**

		HPLC (%)[b]	
Entry	temperature (°C)	5·HCl	**5a**
1	145−155		
2	155−165	93.4	6.3
3	165−175	85.3	13.6

[a]Reaction conditions: 10 g scale. [b]Measured by HPLC (area %).

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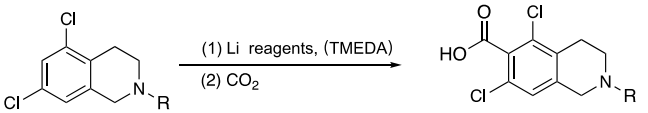
Table 3. Screening the Amino Protecting Groups for the Carboxylation Reaction[a]



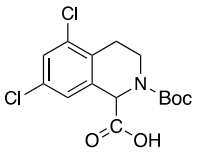
R=Tr (**6**) R=Tr (**7**)

R=-(CH2)- (**12**) R=-(CH2)- (**14**)

R=Boc (**15**) R=Boc (**16**)

						HPLC (%)[d]		
entry	substrate	base (equiv)	TMEDA (equiv)	temperature (°C)	conversion[c] (%)	**7**	**14**	**16**
1	**15**	*n*-BuLi (2.0)	2.0	−60 to −70	89.3			32.9
2	**12**	*n*-BuLi (2.5)	none	−60 to −70	65.9		65.9	
3	**12**	*n*-BuLi (5.0)	none	−60 to −70	93.4		93.4	
4	**6**	*n*-BuLi (2.0)	2.0	−60 to −70	98.9	98.5		
5	**6**	*n*-BuLi (2.0)	none	−60 to −70	80.9	80.4		
6	**6**	*n*-BuLi (2.2)	none	−60 to −70	88.4	87.2		
7	**6**	*n*-BuLi (2.4)	none	−60 to −70	98.2	95.7		
8	**6**	*n*-BuLi (2.0)	2.0	−50 to −60	98.9	94.7		
9[b]	**6**	*n*-BuLi (2.0)	2.0	−70 to −80	88.4	87.2		
10	**6**	LDA (2.0)	none	−60 to −70	34.5	33.9		
11	**6**	LDA (2.0)	none	−40 to −50	84.6	84.0		
12	**6**	LDA (3.0)	none	−40 to −50	92.6	91.5		
13	**6**	LDA (4.0)	none	−40 to −50	93.7	92.6		
14	**6**	LDA (2.0)	none	−20 to −30	54.0	45.5		
15	**6**	LiHMDS (2.0)	none	−40 to −50	3.8	3.8		
16	**6**	LiHMDS (2.0)	none	−20 to −30	25.2	8.3		
17	**6**	LiHMDS (2.0)	none	−10 to 0	2.9	1.0		

[a]Reaction conditions: 10 g scale, reaction time, 1 h. [b]Reaction conditions: 10 g scale, reaction time, 10 h. [c]Conversion determined by HPLC through purity of the reaction mixture. [d]HPLC purity of the reaction mixture.



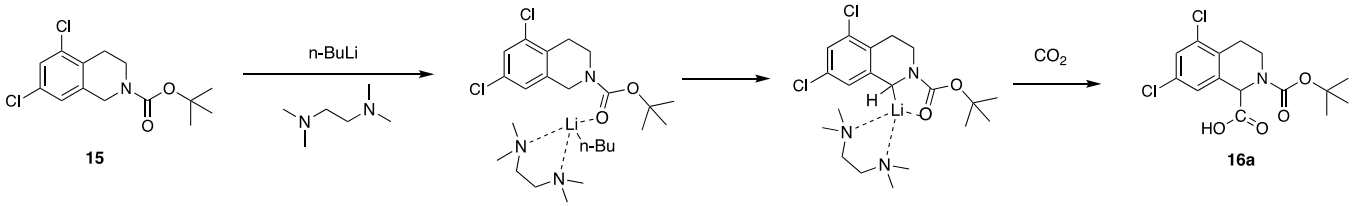
16a

Figure 3. Positional isomeric impurity of compound **16a**.

Next, attempts were made to use methylene and Tr as protecting groups. Compound **12** was maintained at 34.1% by adding 2.5 equiv *n*-BuLi, in accordance with Xu's research (entry 2). Despite increasing *n*-BuLi to 5.0 equiv, 6.7% of compound **12** was still present (entry 3). The use of Tr as a protective group was investigated, and compound **6** could be converted up to 98.9% using 2.0 equiv of *n*-BuLi/TMEDA at a temperature range of −60 to −70 °C (entry 4). However, even with an increased equivalent of *n*-BuLi, compound **6** only converted to 98.2% without TMEDA (entries 5−7). The assumption was that TMEDA could promote depolymerization of *n*-BuLi and increase the activity in the reaction.[13−15] The effect of temperature on the reaction was also investigated. The conversion of compound **6** could decrease to 88.4% at −70 to −80 °C for 10 h, and a small amount of unknown impurities were generated once the temperature increased to −50 to −60 °C (entries 8 and 9). As such, other lithium reagents were investigated, such as LDA and LiHMDS, along with varying the equivalent amount of lithium reagents and temperature in the carboxylation reaction (entries 10−17). Only 3.0 or 4.0 equiv of LDA were found to be effective in the carboxylation reaction, resulting in >90% conversion of compound **6** and >90% purity of compound **7** (entries 12 and 13). Considering the conversion of compound **6**, the first choice was to use 2.0 equiv of *n*-BuLi/TMEDA in the carboxylation reaction.

Since the triphenylmethyl is easily removed under strong acidic conditions,[16] in order to avoid the removal of the

Scheme 2. Formation Process of 16a



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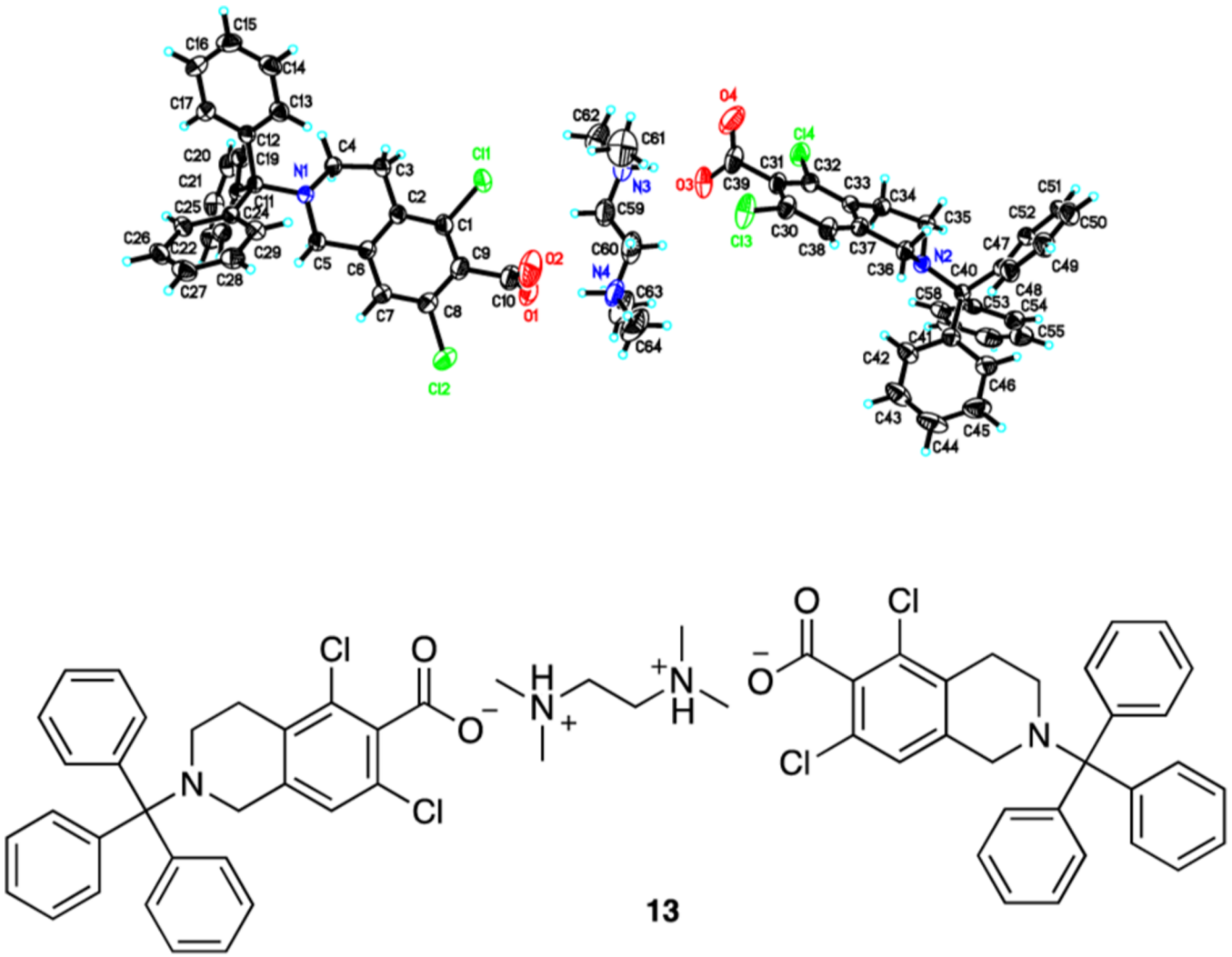

Figure 4. SCXRD and structure of **13**.

protective group in the post-processing, the pH of the reaction system was adjusted to 6−7 when the carboxylation reaction was completed. Product **7** was obtained with a purity of 99.6% through washing with water, concentration, and purification by EA. However, the yield was unexpectedly high, ranging from 104 to 107%. To determine the yield anomaly, single-crystal X-ray diffraction (SCXRD) analysis was conducted on the product obtained from the carboxylation reaction.[17] Notably, the structure was not that of product **7** but rather diammonium salt **13** (Figure 4). Compared with Burnier' work, compound **13** was isolated as a diammonium salt with a yield of 95.9% and purity of 99.6% on a 100 g scale for the first time.

During the synthesis of **1**·HCl, Burnier also did not clarify the details regarding post-processing. To investigate the synthesis process of **1**·HCl, relevant research was conducted to elucidate the step. First, the product was separated via acid−base purification. When compound **13** was completely deprotected under HCl(aq) in THF, compound **1** was washed into the aqueous phase via NaOH(aq). Then, the pH of the separated aqueous phase was adjusted to 6−7, and the solid was obtained by filtration. However, the solid could not be dissolved in DMSO-d_6 during the structure dentification, which is consistent with Xu's research.[6] Once a small amount of TFA-*d* was added, the sample could be dissolved. In view of such findings, the obtained solid was speculated to be compound **1** rather than **1**·HCl. Therefore, a silver nitrate titration experiment was conducted to observe whether the obtained product contained chloride ions at different pH levels (Figure 5). The silver nitrate titration experiment revealed the presence of sediment in the product obtained from the deprotection process at a pH range of 1−3, indicating the presence of chloride ions in the product. On the other hand,

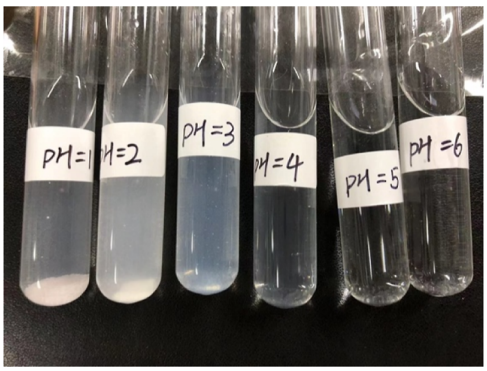

Figure 5. Determination of chloride ions by silver nitrate titration in product **1** at different pH levels.

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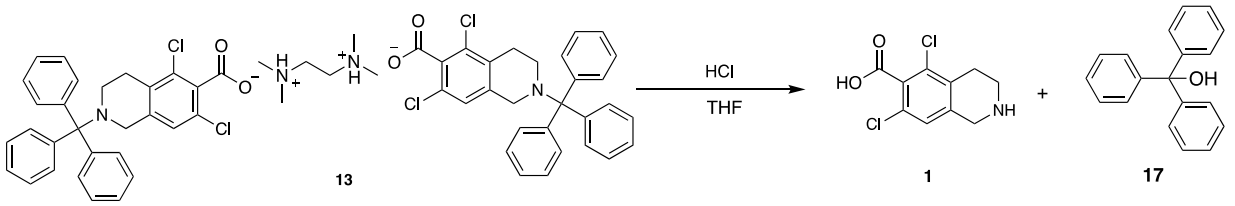
Table 4. Screening of Hydrolysis Reaction Conditions[a]



entry	pH	temperature (°C)	time (h)	yield (%)[b]	HPLC (%)[c]
1	6−7	20−30	1	68.2	98.3
2	5−6	20−30	1	69.3	98.4
3	4−5	20−30	1	76.0	99.3
4	4−5	0−5	1	86.1	99.4
5	4−5	0−5	3	89.8	99.6
6[d]	4−5	0−5	5	96.4	99.7

[a]Reaction conditions: 10 g scale. [b]Isolated yields. [c]Measured by HPLC (area %). [d]Reaction conditions: 100 g scale.

the product obtained from the deprotection process at pH 4−6 showed an opposite phenomenon during the titration experiment. Thus, it was confirmed that the pH of the post-deprotection process had a crucial impact on the form of the resulting product. **1**·HCl and compound **1** could be obtained via adjusting the pH levels to 1 and 4−6 during purification, respectively.

To avoid the dissociation step in the synthesis of Lifitegrast API, the key intermediate **1** was directly obtained. The hydrolysis conditions in the deprotection process were further optimized, as shown in Table 4. Notable yield and purity of compound **1** were obtained at pH 4−5 and 0−5 °C, 5 h (entry 6). The hydrolysis process on a 100 g scale resulted in a yield of 96.4% and purity of 99.7%.

Meanwhile, the recovery of TrOH (**17**) was also completed in the deprotection stage. $CaCl_2$/HCl(aq) was added to the mother liquid of TrOH, the THF layer was separated, and TrCl was obtained with 93.0% yield and 98.0% purity by means of a simple concentration operation.[8] The recycled TrCl could be used to synthesize intermediate **6**, thereby significantly improving the atom economy and avoiding waste emissions.

CONCLUSIONS

In summary, a highly efficient method for the synthesis of 5,7-dichlorotetrahydroisoquinoline-6-carboxylic acid (**1**) with 58.3% overall yield and 99.7% purity was developed and improved. First, an investigation was conducted into the utilization of the impurity and recrystallization method in the synthesis of 5,7-dichlorotetrahydroisoquinoline (**5**·HCl) via Friedel−Crafts cyclization. Second, diammonium salt **13** was isolated for the first time, which greatly improved the yield and purity of the carboxylation reaction. Finally, compound **1** was obtained with 96.4% yield and 99.7% purity by controlling the pH during hydrolysis step, avoiding the dissociation step in the subsequent synthesis of API. Additionally, TrOH recycling was also completed, which improved the atom economy and reduced the production costs.

EXPERIMENTAL SECTION

General procedure: Solvent and reagents obtained from commercial sources were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument with tetramethylsilane as an internal standard. High-resolution mass spectrometry (HRMS) spectra were recorded using a Waters quadrupole time-of-flight (Q-TOF) micromass spectrometer with an electrospray ionization (ESI) source. SCXRD data were recorded on a Bruker D8 Venture. The purity was determined by performing HPLC analysis on a Dionex UItiMate 3000 chromatograph system with a UV detector. The procedures for preparing the diluent for **10** were as follows: NanoChrom chromCore 120 C18 column (150 mm × 4.6 mm, 3 μm) at 30 °C; flow rate, 1 mL/min; UV detector (λ 214 nm); duration, 15 min; A: 0.1% formic acid in water; gradient elution program, time (min)/% 0/95, 10/10, 12/95, and 15/95, B: CH_3CN. The procedures for preparing the diluent for **5**·HCl were as follows: Fortis Diphenyl (150 mm × 4.6 mm, 3 μm) at 40 °C; flow rate, 1 mL/min; UV detector(λ 214 nm); duration, 43 min; A: 0.05% trifluoroacetic acid in water; gradient elution program, time (min)/% 0/90, 30/30, 35/30, 36/90, and 43/90, B: CH_3CN. The procedures for preparing the diluent for **13** and TrCl were as follows: GALAK Phenyl (250 mm × 4.6 mm 5 μm) at 30 °C; flow rate, 1 mL/min; UV detector(λ 214 nm); duration, 60 min; A: 10 mmol/L potassium dihydrogen phosphate in water, H_2O/ACN 95:5, pH, 6.0; gradient elution program, time (min)/% 0/95, 50/20, 55/95, and 60/95, B: CH_3CN/THF = 3:2. The procedures for preparing the diluent for **1** were as follows: Acclaim Mixed-mode WAX-1 (250 mm × 4.6 mm 5 μm) at 30 °C; flow rate, 0.9 mL/min; UV detector (λ 205 nm); duration, 50 min; A: 50 mmol/L potassium dihydrogen phosphate in water, H_2O/ACN 95:5, pH, 6.0; gradient elution program, time (min)/% 0/60, 28/40, 40/60, and 50/60, B: CH_3CN/THF = 4:1. Liquid chromatography/mass spectrometry (LC/MS) was performed on an Agilent LC/MS system consisting of an Agilent 1260 LC system equipped with a single quadruple mass detector and ESI interface (Agilent Technologies).

3,5-Dichloro-*N*-(2-hydroxyethyl) Benzamide (10). Aminoethanol (30.6 g, 0.50 mol) and sodium carbonate (27.8 g, 0.26 mol) were added to water (300.0 mL) in one portion to yield a clear solution, to which 3,5-dichlorobenzoyl chloride (**8**) (100.0 g, 0.48 mol) was added and stirred over a period of 1 h at 25 °C. The granular solid precipitated once chloride **8** was added. Following complete charging, the resulting mixture was stirred at 25 °C for an additional 10 min. The obtained mixture was then stirred for 1 h at a temperature of 75−85 °C to transform the solid particles to powder. The mixture was then cooled to 20 °C, and the resulting solids were filtered, washed with water, and dried at 65 °C. Compound **10**

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was obtained as a white powder solid in 99.0% yield (110.6 g) with an HPLC purity of 98.2%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (t, J = 5.6 Hz, 1H), 7.86 (d, J = 2.1 Hz, 2H), 7.79 (t, J = 2.1 Hz, 1H), 4.76 (t, J = 5.7 Hz, 1H), 3.50 (q, J = 6.0 Hz, 2H), 3.32 (q, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.01, 138.20, 134.68, 130.95, 126.57, 59.92, 42.87. HRMS (ESI-QTOF): m/z calcd for $C_9H_{10}Cl_2NO_2$ [M + H]$^+$ 234.0083; found, 234.0082.

2-[(3,5-Dichlorobenzyl)amino]ethan-1-ol Hydrochloride (11). A suspension of $NaBH_4$ (77.9 g, 2.05 mol) was prepared in THF (720.0 mL). A solution of **10** (120.0 g, 0.51 mol) and AcOH (120.1 g, 2.05 mol) in THF (480.0 mL) was added linearly to the $NaBH_4$ suspension over a period of 1 h at 55 °C. Hydrogen gas was slowly released, and the reaction system was maintained as a well-dispersed suspension during the dropwise addition. The mixture was stirred for an additional 20 h at 65 °C, cooled to 25 °C, and then slowly added to a solution of NaOH (40.8 g, 1.02 mol) in water (360.0 mL) with mechanical stirring over a period of 30 min below 45 °C. The mixture was stirred for another 30 min at 35−45 °C. The resulting phases were separated, and the aqueous layer (bottom) was discarded. Concentrated aqueous hydrochloric acid (50.6 g, 0.51 mol, 36−38% w/w) was dropped into the upper organic layer at 35−45 °C. The mixture was heated to 60−65 °C for 2 h and then cooled to 25 °C, and a solution of NaOH (22.44 g, 0.56 mol) in water (120.0 mL) was added at 25−35 °C. The resulting phases were separated, and the aqueous layer (bottom) was discarded. Aqueous concentrated hydrochloric acid (50.3 g, 0.51 mol, 36%−38% w/w) was dropped into the upper organic layer until the pH reached 3−4. After the majority of the solvent was evaporated under reduced pressure at 40−50 °C, the remaining material was mixed with acetone (240.0 mL) at 55 °C to form a slurry. The mixture was then cooled to 0−5 °C for 30 min, and the resulting solids were separated by filtration and dried in a hot air oven at 65 °C to yield compound **11** in 91.0% yield (119.7 g) with an HPLC purity of 99.5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.66 (s, 2H), 7.74 (d, J = 2.2 Hz, 2H), 7.66 (m, 1H), 5.30 (s, 1H), 4.17 (s, 2H), 3.69 (d, J = 5.9 Hz, 2H), 2.94 (t, J = 5.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 136.55, 134.41, 129.59, 128.84, 56.74, 49.18, 48.94. HRMS (ESI-QTOF): m/z calcd for $C_9H_{12}Cl_2NO$ [M + H]$^+$ 220.0290; found, 220.0287.

5,7-Dichlorotetrahydroisoquinoline Hydrochloride (5·HCl). Hydrochloride **11** (150.0 g, 0.58 mol) was charged into a 1 L three-necked glass flask equipped with a mechanical stirrer and thermometer. After the flask was degassed with nitrogen three times, the temperature was increased to 155−165 °C. Then, $AlCl_3$ (213.9 g, 1.61 mol) was added to the reaction mixture in 20 portions under nitrogen purging over the course of 1 h at a temperature range of 155−165 °C. During the addition of $AlCl_3$, HCl gas was gently released. After the addition was completed, the resulting mixture was stirred at 155−165 °C for 40 h. Then, the mixture was first cooled to 90−100 °C and then directly poured into cold water (900.0 g) over 20 min in a 3 L glass flask equipped with a mechanical stirrer and an ice-water bath at below 40 °C. Then, the mixture was cooled to 5−10 °C, and aqueous hydrochloric acid (57.2 g, 0.58 mol, 36−38% w/w) was dropped in over 10 min at this temperature. After an additional 30 min of stirring, the resulting solid was filtered and washed with water (100.0 g). The wet cake was then added into a mixed solvent of ethanol (1500.0 mL) and water (600.0 mL). After the mixture was heated at 65 °C for 10 min, the solids were completely dissolved. Active carbon (7.5 g) was subsequently added into the reaction mixture and stirred for 1 h at 65 °C. The mixture was filtered, and the filtrate was concentrated at 50−60 °C in a vacuum until around 450.0 g of suspension remained. The suspension was then cooled to 0−10 °C over a period of 1 h with stirring. After another 1 h of stirring at 0−10 °C, the solid was filtered and washed with cold water (100.0 g) to give hydrochloride **5**·HCl as a white solid in 78.4% yield (109.4 g) with an HPLC purity of 99.3%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 2H), 7.58 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 4.24 (s, 2H), 3.37 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 134.44, 134.01, 131.96, 129.84, 127.84, 126.28, 43.64, 23.36. HRMS (ESI-QTOF): m/z calcd for $C_9H_{10}Cl_2N$ [M + H]$^+$ 202.0185; found, 202.0176.

5,7-Dichloroetrahydroisoquinoline-2-triphenylmethyl (6). Compound **5**·HCl (100.0 g, 0.42 mol) and trityl chloride (62.8 g, 0.51 mol) were added to a 3 L three-necked glass flask. DCM (1000.0 mL) was added to the reactor, and the mixture was agitated to form a slurry. The reaction mixture was cooled to 10−15 °C. *N*,*N*-Diisopropylethylamine (135.2 g, 1.05 mmol) was slowly added to the reaction mixture, with the temperature being maintained at 15−25 °C during the addition. Once the addition was complete, the batch was stirred at 15−25 °C for 2 h. The progress of the reaction was determined by analyzing a sample through HPLC. The sample was diluted with acetonitrile and injected into the HPLC system. The analysis indicated that the reaction had reached completion, as less than 1% of the starting material **5**·HCl was observed. Following this, the reaction mixture was diluted with water (500.0 mL). The reaction mixture was stirred for 5 min and then transferred into a separation funnel, wherein the phases were allowed to separate. The DCM layer was washed with water (500.0 mL) and brine (500.0 mL) by stirring for 5 min and then allowing the phases to separate. Subsequently, the DCM layer was concentrated to a residue, which was suspended in EA (1000.0 mL) and stirred for 1 h in a 40 °C water bath. The resulting slurry was cooled to 0 °C for 1 h and then filtered. The filter cake was washed twice with EA and then dried at 65 °C to produce compound **6** as a white powder solid with an HPLC purity of 99.8% in a yield of 89.2% (127.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 6H), 7.35 (t, J = 6.0 Hz, 3H), 7.30 (t, J = 4.4 Hz, 3H), 7.25 (d, J = 2.1 Hz, 1H), 7.25 (t, J = 7.2 Hz, 3H), 6.89 (d, J = 2.1 Hz, 1H), 3.42 (s, 2H), 2.96 (t, J = 3.9 Hz, 2H), 2.59 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.84, 134.84, 131.84, 131.31, 129.19, 127.95, 127.73, 126.50, 126.32, 125.19, 77.09, 50.91, 46.01, 28.06. HRMS (ESI-QTOF): m/z calcd for $C_9H_{10}Cl_2N$ [M − Tr + H]$^+$ 202.0185; found, 202.0183.

Bis (5,7-Dichlorotetrahydroisoquinoline-2-triphenylmethyl-6-carboxylic acid)-tetramethylethylenediamine Salt (13). Compound **6** (100.0 g, 0.23 mol) and anhydrous TMEDA (52.0 g, 0.45 mol) were charged into THF (600.0 mL) at 20−25 °C, and the resulting mixture was degassed three times. Afterward, the solution was cooled to −60 to −70 °C using a liquid nitrogen/acetone bath. Then, a solution of *n*-BuLi in *n*-hexane (282.0 mL, 0.45 mol, 1.6 M) was added gradually over a period of 1 h at a temperature range of −60 to −70 °C. The reaction mixture was stirred for 30 min at the same temperature. An excess of carbon dioxide gas was then slowly introduced into the reaction solution, resulting in the formation of a well-dispersed suspension. The mixture was

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stirred for 1 h and then warmed to a temperature range of −10 to 0 °C. Subsequently, H_2O (400.0 g) was added to the reaction mixture in one portion at −10 to 0 °C to produce a clear solution. The THF layer was concentrated to a residue, which was suspended in EA (500.0 mL) and stirred for 1 h in a 40 °C water bath. The resulting slurry was cooled to 0 °C for 1 h and then filtered. The filter cake was washed twice with EA and then dried with a hot air oven at 50 °C to give compound **13** as a white solid with an HPLC purity of 99.6% in 95.9% yield (236.0 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.7 Hz, 12H), 7.17 (t, J = 9.9 Hz, 12H), 7.05 (t, J = 7.3 Hz, 6H), 6.74 (s, 2H), 3.22 (s, 8H), 2.80 (t, J = 6.0 Hz, 4H), 2.62 (s, 12H), 2.44 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.01, 132.15, 129.90, 129.17, 128.25, 126.73, 126.52, 125.90, 76.98, 53.85, 50.83, 46.32, 44.20, 28.45. HRMS (ESI-QTOF): m/z calcd for $C_{29}H_{23}Cl_2NO_2$ $[M - H]^-$ 486.1106; found, 486.1023.

5,7-Dichlorotetrahydroisoquinoline-6-carboxylic Acid Hydrochloride (1). Compound **13** (100.0 g, 0.09 mmol) and THF (1000.0 mL) were added to a 2 L three-necked glass flask and magnetically stirred to form a well-dispersed suspension. Then, aqueous hydrochloric acid (54.0 g, 0.55 mol, 36−38% w/w) was dropped over a period of 5 min at 20−30 °C. The mixture was stirred for an additional 2 h at this temperature. Subsequently, aqueous sodium hydroxide (38.5 g, 0.96 mol, 10% w/w) was added, the resulting phases were separated, and the THF layer was discarded. Further, the aqueous layer was extracted with THF. Concentrated aqueous hydrochloric acid (41.3 g, 0.01 mol, 36−38% w/w) was dropped into the aqueous layer until the pH reached 4−5, and the solids were precipitated. The precipitated product was filtered, washed with water, and dried in a hot air oven at 65 °C to give compound **1** as a white solid with an HPLC purity of 99.7% in 96.4% yield (43.4 g). ^{1}H NMR (400 MHz, DMSO-d_6/TAF-d): δ 7.75 (s, 1H), 4.55 (s, 2H), 3.70 (t, J = 4.3 Hz, 2H), 3.18 (t, J = 4.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6/TAF-d): δ 165.75, 134.48, 133.80, 130.61, 130.13, 127.75, 126.86, 43.42, 42.90, 23.61. HRMS (ESI-QTOF): m/z calcd for $C_{10}H_9Cl_2NO_2$ $[M + H]^+$ 246.0083; found, 246.0081.

Recovery of TrOH (17) in THF to Synthetize TrCl. In a 2 L three-necked glass flask, a solution of TrOH (100 g, 0.38 mol) with a purity of 99% obtained from deprotection reactions, was added to THF (1000 mL), along with concentrated aqueous hydrochloric acid (100 mL, 36−38% w/w) and $CaCl_2$ (11.1 g, 0.10 mol). The mixture was stirred at 25 °C for 5 h, and the reaction was monitored by HPLC analysis. The results showed that the reaction was complete with less than 3% of TrOH detected. The resulting mixture was found to be two-phase. In addition, the THF layer was isolated and concentrated at 40 °C, resulting in the production of 99.8 g of TrCl, which was obtained as a white solid with a yield of 93.0% and a purity of 98.0%. HRMS (ESI-QTOF): m/z calculated for $C_{19}H_{16}Cl$ $[M + H]^+$ 279.0862; found, 279.0931.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02188.

HPLC spectra for **10**, **11**, **5**·HCl, **6**, **13**, **1**, and TrCl; NMR spectra for **5a**, **16a**, **10**, **11**, **5**·HCl, **6**, **13**, and **1**; MS spectra for **5a**; HRMS spectra for **16a**, **10**, **11**, **5**·HCl, **6**, **13**, **1**, and TrCl; and SCXRD data for **13** (PDF)

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Notes

The authors declare no competing financial interest.

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(17) CCDC 2241848 (**13**) contains the supplementary crystallographic data for this updata.

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