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An Improved Synthetic Process of Two Key Intermediates and Their Application in the Synthesis of Lifitegrast

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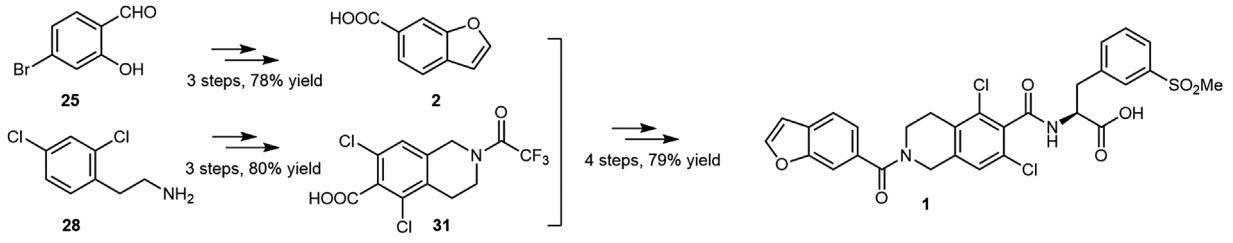

Abstract

Benzofuran-6-carboxylic acid **2** and 2-(*tert*-butoxycarbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid **21** are two key intermediates for the synthesis of lifitegrast (**1**). The present study aimed to obtain lifitegrast from the key intermediates of **2** and 5,7-dichloro-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (**31**), which had the same core structure as **21**. In this study, the synthetic routes of **2** and **31** were explored. **2** and **31** were synthesized from 4-bromo-2-hydroxybenzaldehyde (**25**) and 2-(2,4-dichlorophenyl)ethan-1-amine (**28**), with the yields of 78 and 80%, respectively. The route avoided the harsh reaction conditions of generating **2** in a previous study and could more efficiently achieve the core structure of 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid. Besides, the hydrolysis reaction conditions of preparing lifitegrast were also optimized. In this work, lifitegrast was obtained from **2** and **31** with high purity (>99.9%) and an overall yield of 79%, which was higher than the reported yield of 66%.

Keywords

- lifitegrast
- benzofuran-6-carboxylic acid
- 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid
- improved synthetic process

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Introduction

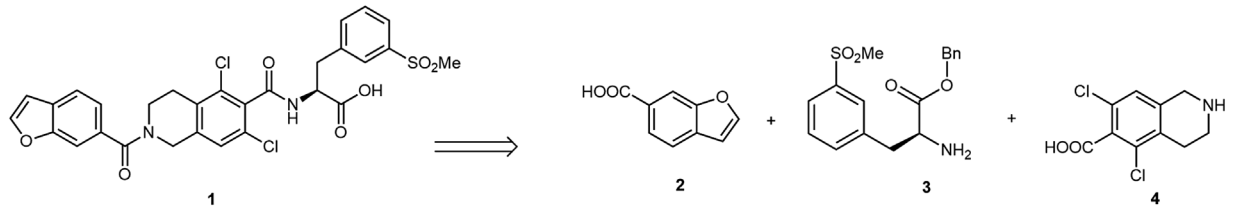
Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a multifactor disease (e.g., low blink rate) characterized by decreased tear secretion or increased tear evaporation while affecting the optical tables and tear glands.[1] DED is classified into aqueous-deficient DED and evaporative dry eye as the major two subtypes. Studies have shown that DED affects approximately 5 to 50% of the global population.[2] With the increase in age, the prevalence of DED is gradually increased, and the incidence of DED in Asian people is higher than that of other people.[3,4]

Lifitegrast is a novel small-molecule integrin antagonist that can competitively block the binding of lymphocyte function-associated antigen-1 and intercellular adhesion molecule-1,[5–11] thus affecting the activation of T cells and the release of cytokines (proteins). It is a new chemical entity developed by Shire Development LLC and approved by the Food and Drug Administration in July 2016 for the treatment of the symptoms and signs of DED. It provides a new option for patients with DED.[12] With the acceleration of the pace of life, a large number of people have the symptom of DED in China, shown in recent survey reports. So, it would be of great interest to develop a more economical route for process development researchers.

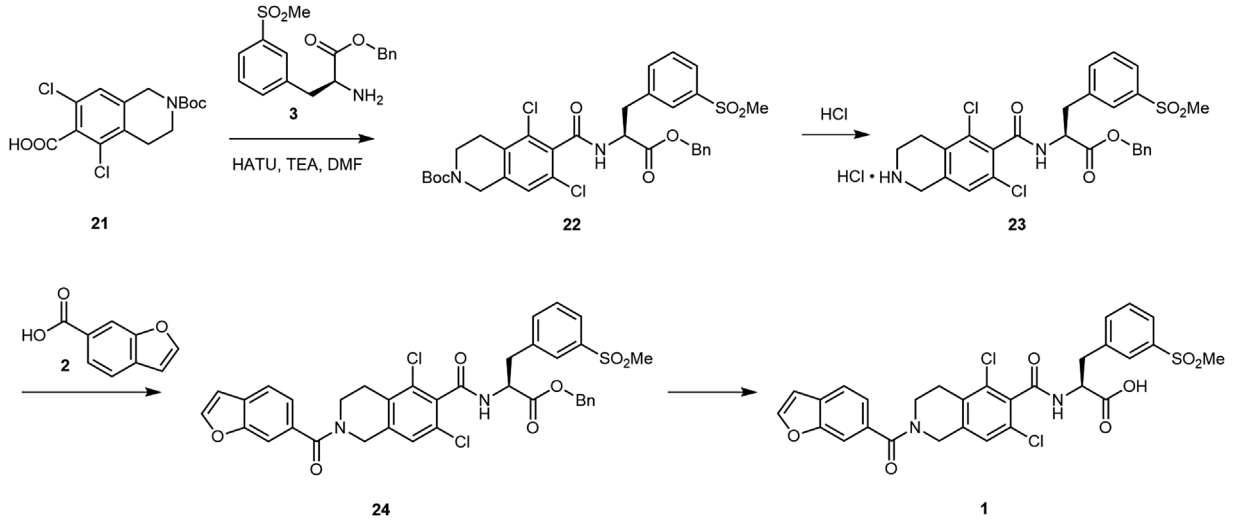
The retrosynthetic analysis for lifitegrast (**1**) is depicted in ►**Scheme 1**, and there were three intermediates, including benzofuran-6-carboxylic acid (**2**), benzyl (*S*)-2-amino-3-(3-(methylsulfonyl)phenyl propanoate (**3**), and 5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (**4**).

A reported method for the synthesis of lifitegrast is illustrated in ►**Scheme 2**, which starts from the amidation reaction of compounds **3** and **21** (Boc-**4**).[13] After removing the Boc group in a HCl solution, the resulting compound **23** is subjected to amidation with **2** to provide **24**, which undergoes ester hydrolyzation to give the target compound **1**. However, there are some challenges in the reported method: (1) the reaction conditions for the preparation of intermediate **2** were harsh and difficult to operate; (2) the yields of intermediate **4** were low and the process is difficult to scale up; and (3) the degradation of lifitegrast occurred in hydrolyzation, so the conditions should be controlled strictly. In this manuscript, we are dedicated to solving the problems mentioned above.

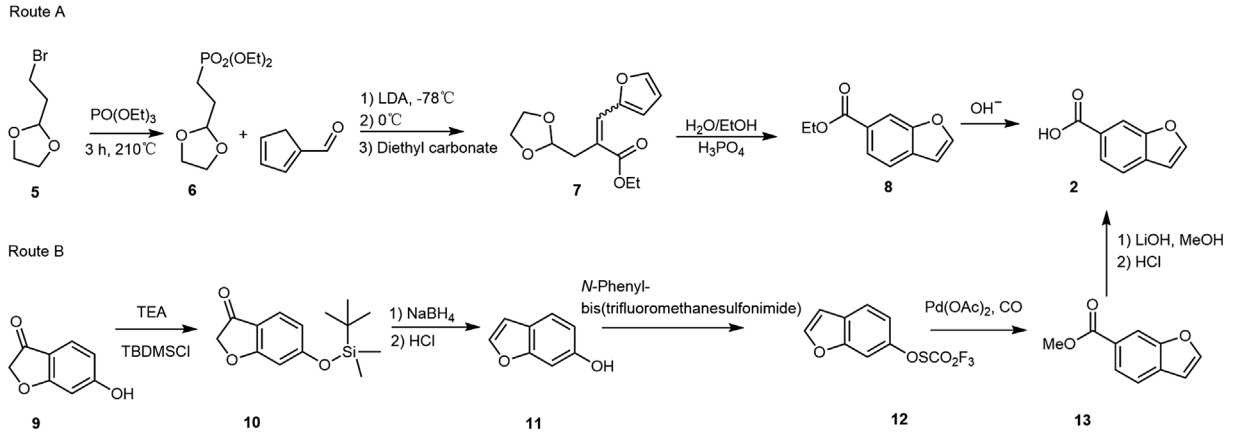
Intermediate **2** can be obtained in two ways (►**Scheme 3**).[13,14] One starts from commercial 2-(2-bromoethyl)-1,3-dioxolane **5**, through a substitution reaction, Wittig olefination reaction, cyclization reaction, and amide hydrolysis reaction to give intermediate **2** (route A, ►**Scheme 3**). However, the reaction time of the route A was too long, and the operation of the reaction was complex. The other way employed the inaccessible and expensive 6-hydroxy-2(3*H*)-benzofuranone **9** as the key material, which was converted to intermediate **2** through five steps, including a substitution reaction, a reduction reaction, dehydration, carbonyl insertion, and an ester



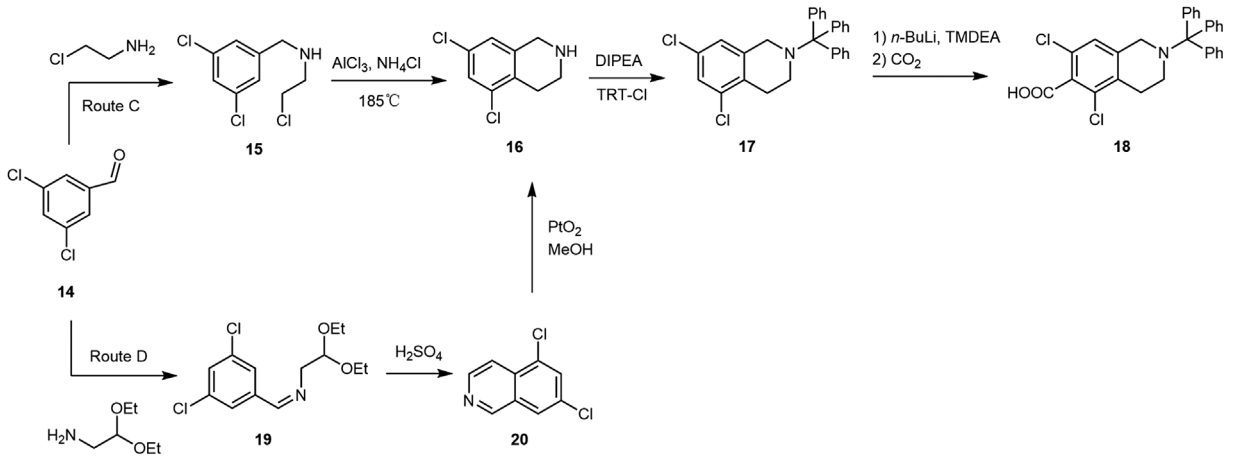
Scheme 1 Retrosynthetic analysis of lifitegrast (**1**).



Scheme 2 Original approach to synthesizing lifitegrast.



Scheme 3 Reported synthesis routes of compound **2**.



Scheme 4 Reported synthesis routes of compound **18**.

hydrolysis reaction (route B, ►**Scheme 3**). Unfortunately, the operation is complicated, and the reaction time is long, while the introduction of carboxyl groups requires palladium acetate in the fourth step, which may have heavy metal palladium residual problem.

Compound **18** was a derivative of intermediate **4**. Zeller et al achieved **18** (Ph_3C-**4**) from two routes (routes C and D, ►**Scheme 4**) using 3,5-dichlorobenzaldehyde (**14**) as a starting material.[13] As for route C, the second step involves cyclization to construct the tetrahydroisoquinoline ring at high temperature in a sealed tube without solvent. This step required a high reaction vessel and had a risk of explosion. In addition, the yield of the first step was only 35%, which severely limited the practicability of the route. Route D also had some insufficiency, including complex operations that are not conducive to actual production. Besides, it would be dangerous to reduce the isoquinoline ring of compound **20** under high-pressure hydrogen (the third step). Route D not only had a low yield but also used expensive catalysts. Thus, it is crucial to explore a method to construct the tetrahydroisoquinoline ring more reasonably and economically.

As for the preparation of lifitegrast, intermediate **3** coupled with compound **21** (Boc-**4**) under HATU and triethylamine in *N*,*N*-dimethylformamide. After removing the Boc group to get compound **23**, it was coupled with compound **2** to get compound **24**, followed by hydrolysis to get the final product compound **1**. During the last step, there were three impurities (►**Fig. 1**; impurity **1**, **2**, and **3**) produced when 2 mol/L sodium hydroxide was used for hydrolysis or hydrogenation with Pd/C to remove benzyl.[6]

In this article, we will focus our effort on solving the synthetic problems given bellow: (1) avoid the harsh reaction conditions of compound **2**; (2) design a more efficient route to synthesize compound **4**; (3) optimization of the hydrolysis condition of compound **1** to improve the final product's purity.

Results and Discussion

Synthesis of Intermediate 2

We designed a novel synthetic route to obtain **2**. First (►**Scheme 5**, route E), compound **25** and bromoacetic acid are coupled to afford **26** through Williamson ether synthesis.

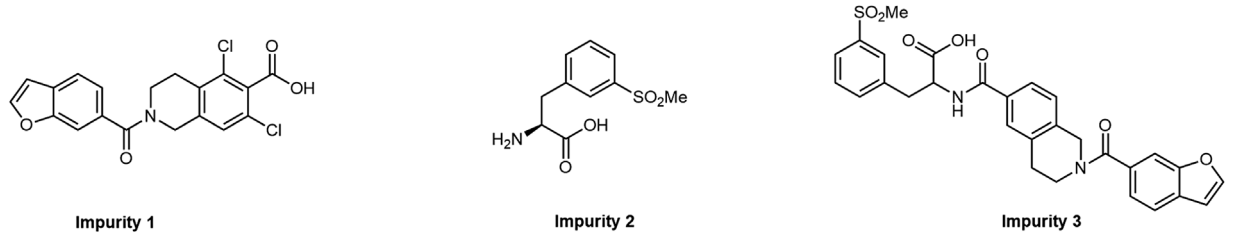
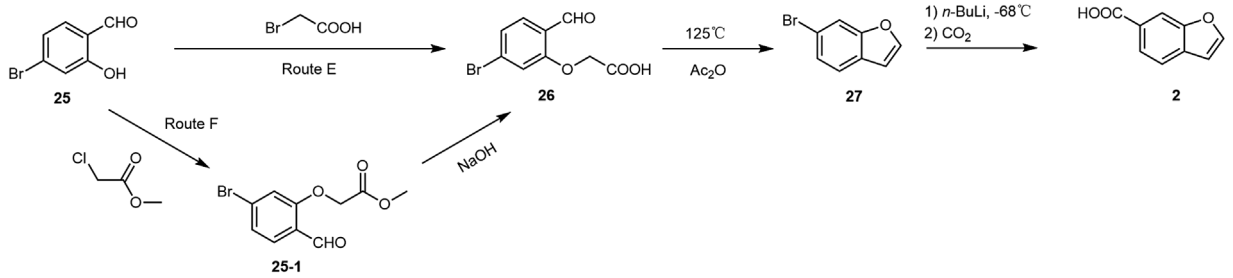
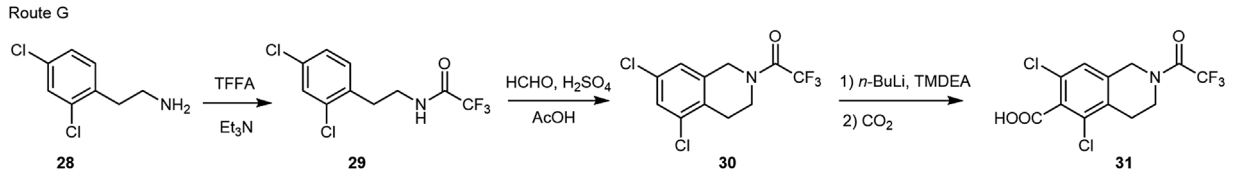


Fig. 1 The structures of three impurities.



Scheme 5 Novel synthesis methods of intermediate **2**.



Scheme 6 Novel synthesis methods of intermediate **31**.

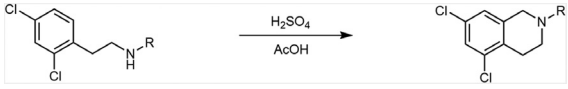
Compound **26** underwent a ring-closure reaction to give 6-bromobenzofuran **27**, which was reacted with CO_2 in the presence of *n*-butyllithium to give the target product. However, **26** was obtained with an unacceptable yield of 30%, despite several attempts to optimize the reaction conditions, and **25**, as a starting material, remained even though the reaction time lasted for 24 hours at 75°C. To solve this problem, **26** was prepared through etherification of **25** with methyl 2-chloroacetate as the initial step to get **25-1** followed by its ester hydrolysis (►**Scheme 5**, route F,). Fortunately, all the efforts were effective, as the yield of **26** was improved, reaching 90%.

Synthesis of Intermediate 31

We aimed to obtain **4** by getting rid of the use of platinum catalysis and acquiring an improved yield. The synthesis route of **31** (CF_3CO-**4**) was designed in this work (►**Scheme 6**). In this route, *N*-(2,4-dichlorophenethyl)-2,2,2-trifluoroacetamide **29** was obtained via a substitution amidation reaction of 2-(2,4-dichlorophenyl)ethan-1-amine **28** and trifluoroacetic anhydride, and converted to 1-(5,7-dichloro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethan-1-one **30** via a Pictet–Spengler reaction with paraformaldehyde in a mixture of sulfuric acid and acetic acid. Then **31** (Tfa-**4**) was synthesized by a reaction of compound **30** with carbon dioxide under *n*-butyl lithium.

The substrates of the Pictet–Spengler reaction were screened (►**Table 1**). When R = H (compound **28**), no satisfactory results were achieved (►**Table 1**, entry 1). When R = *t*-butoxycarbonyl, (a Boc-protecting group), there was also no reaction. Then, some strong electron-withdrawing groups were tried, with acceptable yields (►**Table 1**, entries 3–5). Considering the convenience of removing the protective groups, we finally chose trifluoromethyl as the protective group for the subsequent reaction.[15–17]

Table 1 Substituents screening of the Pictet–Spengler reaction



Entry	R	Yield %
1	H	No reaction
2	*t*-Butoxycarbonyl	No reaction
3	Trifluoroacetyl	98.54%
4	Tosyl	96.24%
5	4-Nitrobenzenesulfonyl	96.90%

Note: Reagents and conditions: reaction substrate (2.67 mmol), paraformaldehyde (10.68 mmol), concentrated sulfuric acid: acetic acid = 3:2 (V:V), 10 mL, 8 hours, r.t.

Table 2 Effect of different ratios of sulfuric acid to acetic acid on the synthesis of compound 30

Entry	$V_{sulfuric\ acid}$: $V_{acetic\ acid}$	Time (h)	Yield of 30 (%)
1	2:1	4.00	81.58
2	3:2	4.00	98.79
3	1:1	9.00	83.49
4	1:2	48.00	No reaction
5	1:4	48.00	No reaction

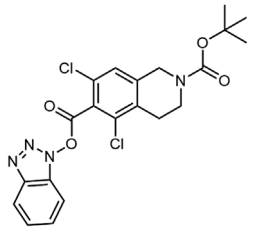


Fig. 2 Structure of intermediate **32**.

The condition of the Pictet–Spengler reaction was further optimized. The ratios of concentrated sulfuric acid to acetic acid (V:V), as well as the reaction time, were screened (►**Table 2**). We found that when the proportion of concentrated sulfuric acid was too low, the reaction time would be prolonged or it would not react (►**Table 2**, entries 4 and 5). When the ratio is too high, the reaction time would be shortened, but the raw material may be decomposed, affecting the yield (►**Table 2**, entry 1). Finally, the volume ratio of 3:2 was selected as the optimal condition (►**Table 2**, entry 2).

Synthesis of Lifitegrast (1)

We noticed that the original synthesis process has a problem to be resolved: compound **32** (►**Fig. 2**), which is a byproduct of the reaction between compound **4** and HATU, is difficult to be converted to amide ester **22** and the yield was only 70%.

Table 4 Reaction condition screening of the hydrolysis with 24

Entry	Reagent	Purity (%)
1	10% Pd/C	87.82
2	NaOH (2 mol/L)	96.37
3	10% Pd/C	87.82
4	LiOH (1 mol/L)	99.45
5	Na_2CO_3 (1 mol/L)	91.22
6	K_2CO_3 (1 mol/L)	100.00
7	Cs_2CO_3 (1 mol/L)	99.27

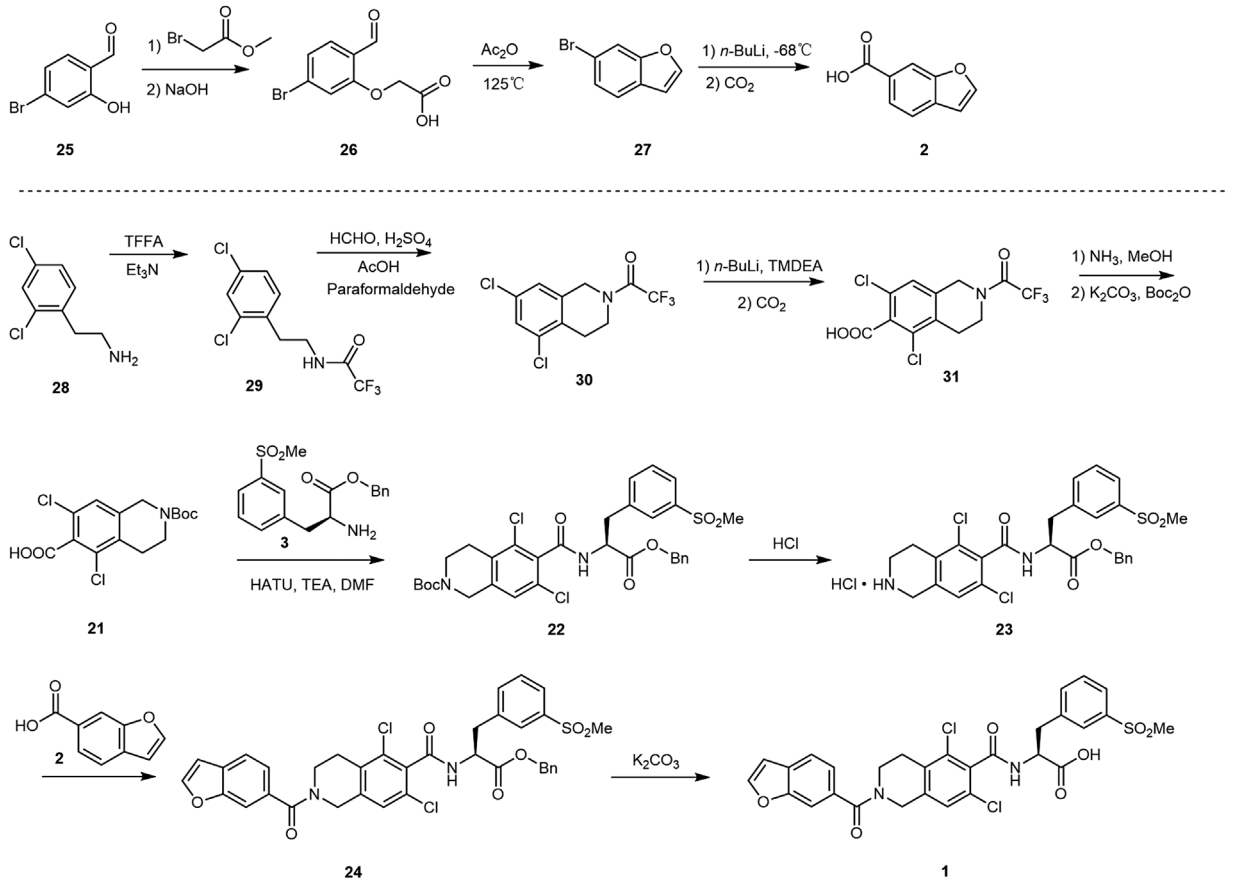
So, we contributed to increasing the yield of **22** and reducing the reaction time.

Condensing reagents, the equiv. amounts of HATU and triethylamine of the reaction were screened. We found the yield of **22** was still lower and the reaction time was longer when the amount of catalyst was increased (►**Table 3**, entries 8 and 9). Using a base is necessary for the reaction to achieve a better yield of **22**. While we tried to change the equiv. of the base, a high yield of **22** (98%) could be provided in a short reaction time with the 5 equiv. base and 1.0 equiv. HATU (►**Table 3**, entry 4). Finally, under the improved reaction conditions, the yield of **22** was improved from 75%[13] to 98%. Meanwhile, the reaction time was reduced to 5 hours.

As for the synthesis of the target product (**1**), the conditions for hydrolysis of benzyl ester derivative **24** were screened (►**Table 4**). In the beginning, Pd/C (►**Table 4**, entry 1) or sodium hydroxide solution (►**Table 4**, entry 2) was tried. Unfortunately, the desired products had a low purity and were contaminated with impurities **1**–**3**, which could not be easily removed by recrystallization. Suffering from the above issues of the economy of Pd/C and the residue of heavy metals, a hydrolysis reaction was chosen to obtain the target product. Subsequently, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, and lithium hydroxide at a concentration of 1 mol/L were screened. Our

Table 3 Reaction condition optimization of intermediate 22

Entry	Base (equiv.)	Catalyst (equiv.)	Time (h)	Yield of 22 (%)
1	Et_3N (2)	HATU (1)	28.00	45.52
2	Et_3N (3)	HATU (1)	20.00	94.19
3	Et_3N (4)	HATU (1)	4.75	97.33
4	Et_3N (5)	HATU (1)	5.00	98.38
5	Et_3N (6)	HATU (1)	4.75	96.42
6	Et_3N (5)	HATU (0.5)	6.00	81.63
7	Et_3N (5)	HATU (0.75)	6.00	94.13
8	Et_3N (5)	HATU (2)	30.00	50.60
9	Et_3N (5)	HATU (3)	30.00	40.81
10	DMAP (1.5)	EDC•HCl (1.1)	10.00	No reaction



Scheme 7 The synthesis route of two key intermediates and lifitegrast.

data showed that the use of K_2CO_3 solution (1 mol/L) was effective and should be selected as the optimal condition for debenzylation. Crude product **1** was purified by recrystallization of isopropanol and *n*-heptane (HPLC: >99.9%) to achieve lifitegrast.

Conclusion

In this work, we have developed a novel and practical method for the synthesis of **2** starting from 4-bromo-2-hydroxybenzaldehyde **25**. The synthesis was accomplished in three steps with a total yield of 78%. In addition, we used 2-(2,4-dichlorophenyl)ethylamine as a raw material to obtain the key intermediate **31** in three steps with a yield of 80%. With an optimized synthetic route in hand, lifitegrast was obtained a total yield of 79% (calculated by compound **21**). The total synthesis route of lifitegrast including the two key intermediates is shown in ►**Scheme 7**.

Experimental

General Procedures

Unless specified otherwise, all starting materials, reagents, and solvents are commercially available (Shanghai Haoyuan Chemexpress Co., Ltd., Shanghai, China; Bidepharmatech Ltd., Shanghai, China). Thin layer chromatography (TLC) on silica gel GF254 was used to monitor the progress of all reactions. Melting points were obtained on a melting point apparatus (WRS-2A, Shanghai INESA Scientific Instruments Co., Ltd., Shanghai, China) and were uncorrected. The electrospray ionization (ESI) mass spectra were collected on a Waters ZQ2000 spectrometer (Waters, United States). Compound purity was determined by high-performance liquid chromatography (HPLC) (Waters e2695 HPLC, 2998 PAD, Waters Corp., Milford, MA, United States). Nuclear magnetic resonance (NMR) spectra were recorded in chloroform-*d* or dimethyl sulfoxide-d_6 on a 400 MHz or 600 MHz Bruker NMR spectrometer (Bruker Bio-Spin, Rheinstetten, Germany) with tetramethylsilane as the internal reference, and all chemical shifts were reported in parts per million (ppm).

The purity of the products was measured by a HPLC-peak area normalization method using a Welch Ultimate XB C18 column (4.6 mm × 250 mm, 5 µm) under the following conditions: mobile phase A (ACN) and phase B (0.05% TFA [v/v] water solution) with gradient elution of 0 to 50 minutes: 80 to 10% B; 50 to 51 minutes: 10 to 80% B; 51 to 60 minutes: 80% B. The flow rate was 1 mL/min; the column temperature was 30° C; and the detection wavelength was 220 nm.

Benzofuran-6-carboxylic Acid (2)

Compound **27** (1.77 g, 8.98 mmol) was suspended in anhydrous tetrahydrofuran (20 mL) and was slowly added

2.5 mol/L *n*-butyl lithium in tetrahydrofuran (7.2 mL, 17.96 mmol) at −68°C under a nitrogen atmosphere. After stirring for 1 hour, benzyl chloroformate (3.06 g, 17.97 mmol) was slowly added at the same temperature, and the reaction mixture was stirred for 2 hours. After completion of the reaction, 40 mL of 2 mol/L NaOH solution was added and stirred at 70°C overnight. Then, the mixture was adjusted with 1 mol/L HCl solution, extracted with ethyl acetate (100 mL), washed with brine (50 mL), and concentrated under reduced pressure. The residue was purified by silica column chromatography (100% petroleum ether) to give compound **2** (1.20 g, yield 82%). mp: 186.8–188.2°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 7.6 Hz 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.32 (dd, J = 11.3, 4.1 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.10 (s, 1H). HPLC: t_R = 10.46 minutes, 96.30% purity. ESI-MS (*m/z*) calcd. for $[M-H]^+$ 161.0317; found 161.03. HR-MS (ESI) calcd. for $[M-H]^-$ 161.0317, found: 161.0232.

5,7-Dichloro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (31)

Compound **30** (11.0 g, 36.90 mmol) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine ([TMEDA], 8.58 g, 73.8 mmol) were suspended in anhydrous tetrahydrofuran (200 mL) and slowly added 2.5 mol/L *n*-butyl lithium in tetrahydrofuran (29.52 mL, 73.80 mmol) at −68°C under a nitrogen atmosphere. After stirring for 2 hours, the excess carbon dioxide gas was slowly bubbled into the reaction solution over 1 hour, and a well-dispersed suspension was formed. The mixture was stirred for an additional 4 hours, then warmed to 0°C over 1 hour after monitoring the completion of the reaction using TLC. Water was added and the mixture was added 2 mol/L HCl solution (100 mL), stirred at room temperature for 2 hours, extracted with ethyl acetate (200 mL), washed with brine, and concentrated under reduced pressure to give **31** as a yellowish solid (10.36 g, yield 82%). mp: 174.6–177.2°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.59 (d, J = 28.9 Hz, 1H), 4.81 (d, J = 17.3 Hz, 2H), 3.87 (dd, J = 9.9, 5.7 Hz, 2H), 2.89 (dd, J = 20.3, 6.0 Hz, 2H). HPLC: t_R = 19.91 minutes, 98.30% purity. ESI-MS (*m/z*): calcd. for $[M+H]^+$ 341.9833; found 341.90. HR-MS (ESI) calcd. for $[M-H]^-$ 339.9833, found: 339.9761.

(*S*)-2-(2-(Benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic Acid (1)

To a methanol (200 mL) solution of **24** (40.0 g, 59.74 mmol) was added 1 mol/L potassium carbonate solution (226.9 mL) and stirred at room temperature. After the reaction, the mixture was extracted with 100 mL of toluene, and added 1 mol/L HCl solution to the aqueous phase under stirring conditions to pH <2, the reaction solution was extracted with ethyl acetate (600 mL). The combined extract was washed with brine (300 mL) and concentrated at reduced pressure to afford a white powder. The white solid was recrystallized with isopropanol/*n*-heptane to obtain **1** (34.0 g, yield 97%) as a white powder. mp: 153.2–155.3°C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.88 (s, 1H), 9.03 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.87 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.71 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 62.8 Hz, 2H), 7.05 (d, J = 1.5 Hz, 1H), 4.87–4.76 (m, 2H), 4.73–4.59 (m, 1H), 3.93–3.56 (m, 2H), 3.30 (dd, J = 14.2, 4.5 Hz, 1H), 3.15 (s, 3H), 3.03 (dd, J = 13.9, 10.6 Hz, 1H), 2.75 (d, J = 16.6 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 172.5, 169.9, 164.0, 154.1, 148.2, 141.1, 139.5, 137.5, 134.9, 132.1, 131.6, 129.7, 129.3, 129.1, 128.8, 128.6, 128.2, 125.7, 125.5, 122.4, 121.9, 110.8, 107.3, 53.3, 59.1, 53.5, 44.1, 36.8, 21.5. HPLC: t_R = 18.80 minutes, 100% purity. ESI-MS (*m/z*): calcd. for $[M+H]^+$ 615.0681; found 614.90. HRMS (ESI) calcd. for $[M+H]^+$ 615.0681; found: 615.0750.

Supporting Information

Full experimental detail, as well as ^{1}H, ^{13}C NMR, HRMS spectra of compound **26, 27, 2, 29, 30, 31, 22, 23, 24**, and **1** can be found via the 'Supporting Information' section of this article's webpage.

Conflict of Interest

None declared.

Reference

1 Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II introduction. Ocul Surf 2017;15(03):269–275
2 Shimazaki J. Definition and diagnosis of dry eye 2006. J Eye 2007; 24:181–184
3 Tsubota K, Yokoi N, Shimazaki J, et al; Asia Dry Eye Society. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. Ocul Surf 2017;15(01):65–76
4 Pflugfelder SC. Anti-inflammatory therapy of dry eye. Ocul Surf 2003;1(01):31–36
5 Du G, Du W, An Y, et al. Design, synthesis, and LFA-1/ICAM-1 antagonist activity evaluation of Lifitegrast analogues. Med Chem Res 2022;31(04):555–579
6 Marlin SD, Springer TA. Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell 1987;51(05):813–819
7 Yusuf-Makagiansar H, Anderson ME, Yakovleva TV, Murray JS, Siahaan TJ. Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a therapeutic approach to inflammation and autoimmune diseases. Med Res Rev 2002;22(02):146–167
8 Semba CP, Swearingen D, Smith VL, et al. Safety and pharmacokinetics of a novel lymphocyte function-associated antigen-1 antagonist ophthalmic solution (SAR 1118) in healthy adults. J Ocul Pharmacol Ther 2011;27(01):99–104
9 Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R. Lifitegrast, a novel integrin antagonist for treatment of Dry eye disease. Ocul Surf 2016;14(02):207–215
10 Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol 2016;10:1083–1094
11 Keating GM. Lifitegrast ophthalmic solution 5%: a review in dry eye disease. Drugs 2017;77(02):201–208
12 Nicolls MR, Gill RG. LFA-1 (CD11a) as a therapeutic target. Am J Transplant 2006;6(01):27–36
13 Zeller JR, Venkatraman S, Brot ECA, Iyer S, Hall M. Lfa-1 inhibitor and polymorph thereof. WO Patent 2014018748, January 2014
14 Flick AC, Ding HX, Leverett CA, Fink SJ, O'Donnell CJ. Synthetic approaches to new drugs approved during 2016. J Med Chem 2018;61(16):7004–7031
15 Xu W, Gong X, Odilov A, et al. Scalable process for making 5, 7-dichlorotetrahydroisoquinoline-6-carboxylic acid using

methylene as the protecting group. Org Process Res Dev 2021;25 (11):2447–2452

16 Stokker GE. ChemInform Abstract: preparation of 1,2,3,4-tetrahydroisoquinolines lacking electron donating groups - an intramolecular cyclization complementary to the Pictet-Spengler reaction. Tetrahedron Lett 1996;37:5453–5456

17 Bojarski AJ, Mokrosz MJ, Minol SC, et al. The influence of substitution at aromatic part of 1,2,3,4-tetrahydroisoquinoline on in vitro and in vivo 5-HT(1A)/5-HT(2A) receptor activities of its 1-adamantoyloaminoalkyl derivatives. Bioorg Med Chem 2002;10 (01):87–95

