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Facile and practical synthesis of a cannabinoid-1 antagonist via regio- and stereoselective ring-opening of an aziridinium ion

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ABSTRACT

A scalable synthetic strategy of a chiral, trisubstituted imidazolidinone (**1**), a novel cannabinoid-1 antagonist, starting from a commercially available mandelic acid (**5**) is described. The key step involves a regio- and stereoselective ring-opening of an aziridinium ion by an aniline nucleophile (**3**). A mechanistic study revealed the insight into rate amplification at a lower temperature for vicinal diamine **12** formation via a aziridinium ion **14**. Although most intermediates are not isolable by crystallization due to their intrinsic physical properties (oil or foamy solid), the reported synthesis furnished pure **1** without any chromatography purification throughout the entire synthesis. Employing green chemistry principles, this novel synthesis appears to be highly efficient for the manufacturing of multi-kilogram quantities of an optically-pure active pharmaceutical ingredient.

1. Introduction

Imidazolidinone **1** is a structurally novel cannabinoid-1 antagonist,[1a] as compared to two leading analogs: Rimonabant[1b] and Taranabant.[1c] It penetrates the blood–brain barrier and is orally active with potential to treat obesity and diabetes. To assess its efficacy and safety in human, we needed to develop a commercially viable route for the manufacturing of this active pharmaceutical ingredient for clinical trials. Our strategy for the synthesis of **1** is outlined in Scheme 1, which involves an attempt to assemble the target molecule by the condensation of vicinal diamine **2** with a 'carbonyl' surrogate. To establish the stereogenic center of **2**, we considered ring-opening of a chiral, quaternary aziridinium ion **4** with aniline **3** in a regio- and stereoselective manner. Aziridinium salt **4** can be synthesized from a commercially available mandelic acid **5** and sulfonyl acid **6** via a β-amino alcohol scaffold.

2. Results and discussion

2.1. Synthesis of β-amino alcohol

Our synthesis of a β-amino alcohol (**10**) that led to the desired aziridinium salt (**4**) is described in Scheme 2. (*S*)-3-Trifluoromethylmandelic acid **5** was converted to (*S*)-*O*-acetylmandelic acid **7** according to a modified literature procedure.[2] Treating **5** with 1.5 equiv of acetyl chloride in toluene at ambient temperature cleanly furnished **7** in quantitative yield. Traces of acetyl chloride were removed under reduced pressure until the chloride content was determined to be less than 1 wt % as measured by a classical titration of **7** against a 0.1 N silver nitrate solution. This quality control was essential to minimize the formation of an undesired acetamide from **8** with acetyl chloride in the subsequent step. As a result, chromatography purification was avoided. To set up the formation of a quaternary aziridinium salt a few steps later, sulfonyl acid **6**[3] was converted to secondary amine **8** in two steps by first coupling with 4-methoxybenzyl amine followed by selective amide reduction with BH_3-THF. The resulting amine **8** was isolated as a hydrochloric salt in 67% yield. Suppressing racemization during the amide formation involving mandelic acid **7** and amine **8** hydrochloric salt turned out to be a challenging task. Employing a variety of coupling reagents, such as DMTMM,[4] CDMT,[5] and IBCF,[6] that had demonstrated to be effective in our lab in controlling

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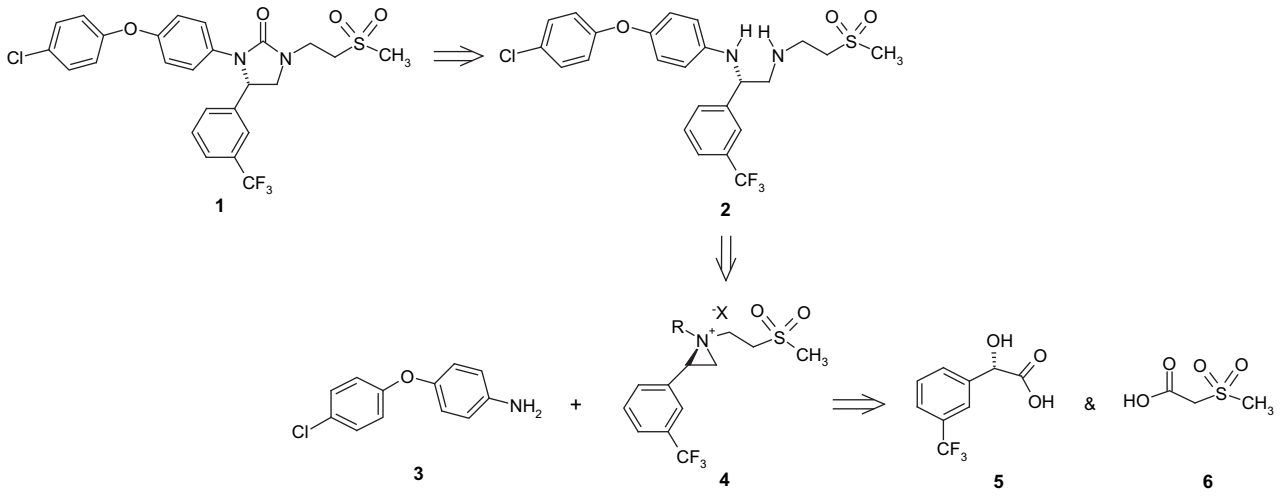
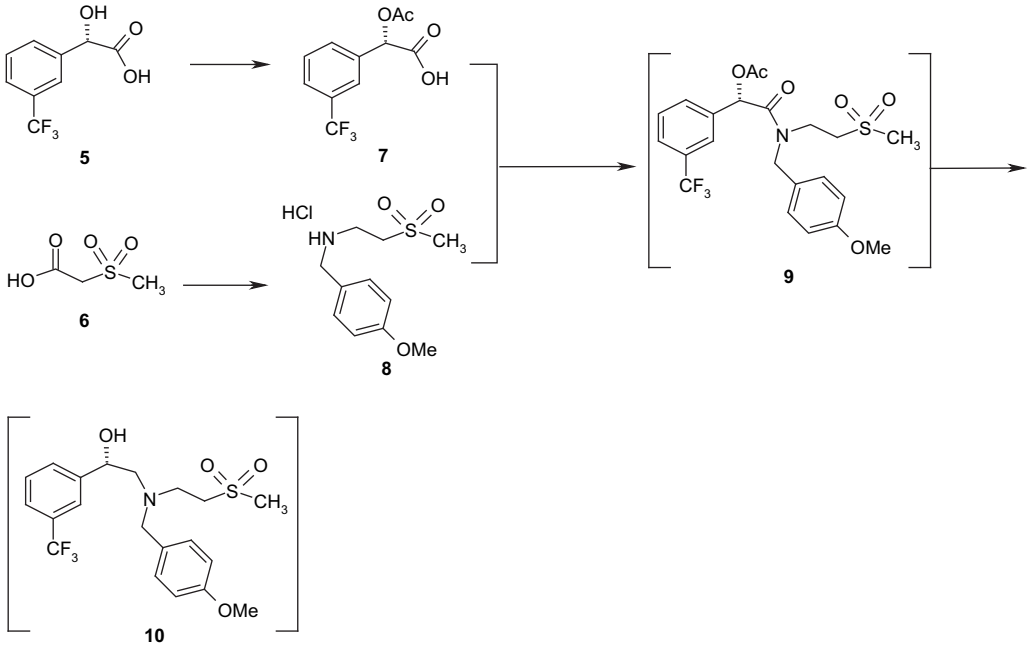


Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Synthesis of chiral β-amino alcohol **10**.

racemization for amide syntheses, we observed significant racemization in the range of 8–30% (Table 1, entries 1–5). DMTMM was found to be more effective when used at lower temperature. High vulnerability to racemization was presumably caused by the enhanced acidity of the benzylic α-CH proton for the respective activated ester, such as **11a** (Fig. 1), formed in situ. Alternatively, acid-catalyzed formation of benzylic cation could also contribute to the racemization. Based on our previous studies to suppress racemization, we observed that increasing the rate of coupling reaction between an 'activated ester' and an amine reduces racemization.[6] We noticed that a potential equilibrium between salt **8** and free base **8a** in the system could diminish the availability of **8a**, which is responsible for the attack to the activated ester **11a**. A lower concentration of **8a** at any given time could ultimately contribute to a slower coupling rate and higher racemization. This hypothesis led us to replace HCl salt **8** with free base **8a** for the amide synthesis employing DMTMM and did minimize racemization from 8 to 1.5% (Fig. 2). Free base **8a** can be generated either through neutralization-extraction procedure or in situ with Cs_2CO_3 in the presence of small amounts of water (see Section 4).

Table 1
Degree of racemization for amide formation involving **7**, **8**, and NMM

Entry	Coupling Reagent	Solvent	Temperature, °C	%Racemization
1	IBCF[a]	EtOAc	25	16
2	CDMT[b]	EtOAc	25	16
3	DMTMM[c]	toluene	25	30
4	DMTMM	toluene	0	13
5	DMTMM	EtOAc	−20	8

[a] IBCF: isobutyl chloroformate.
[b] CDMT: 2-chloro-4,6-dimethoxytriazine.
[c] DMTMM: 4-(4,6-dimethoxy-1,3,5-triazine-2-yl)-4-methyl-morpholinium chloride.

Amide **9** obtained from DMTMM-activated coupling of **7** and **8a** was carried forward to next step without purification or isolation. Treating amide **9** with BH_3-THF selectively reduced the amide and

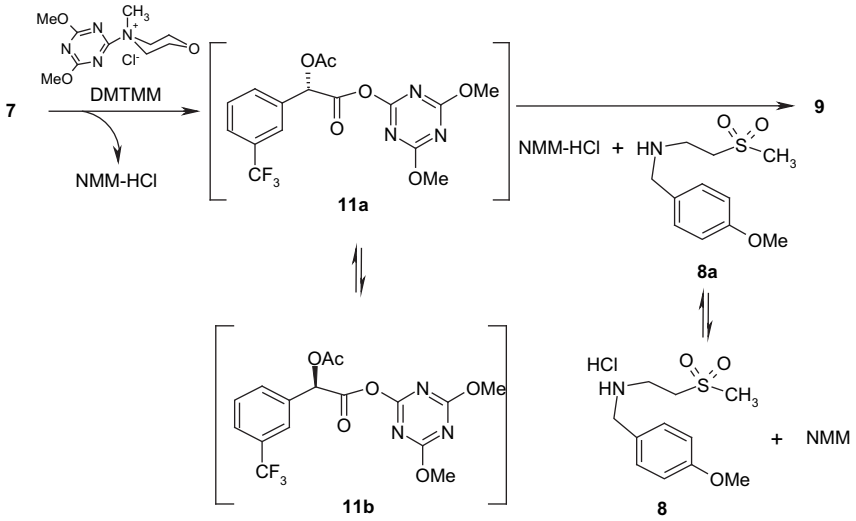


Figure 1. Cause and control of racemization.

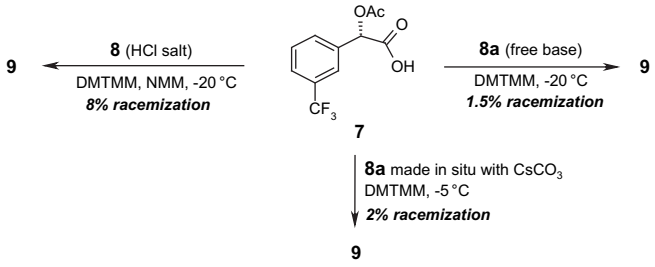


Figure 2. Effect of the amine form on degree of racemization.

acetate groups without reducing the sulfone or causing racemization.[7] The purity of alcohol **10** obtained after aqueous sodium hydroxide work up was acceptable to be used for the next step without further purification.

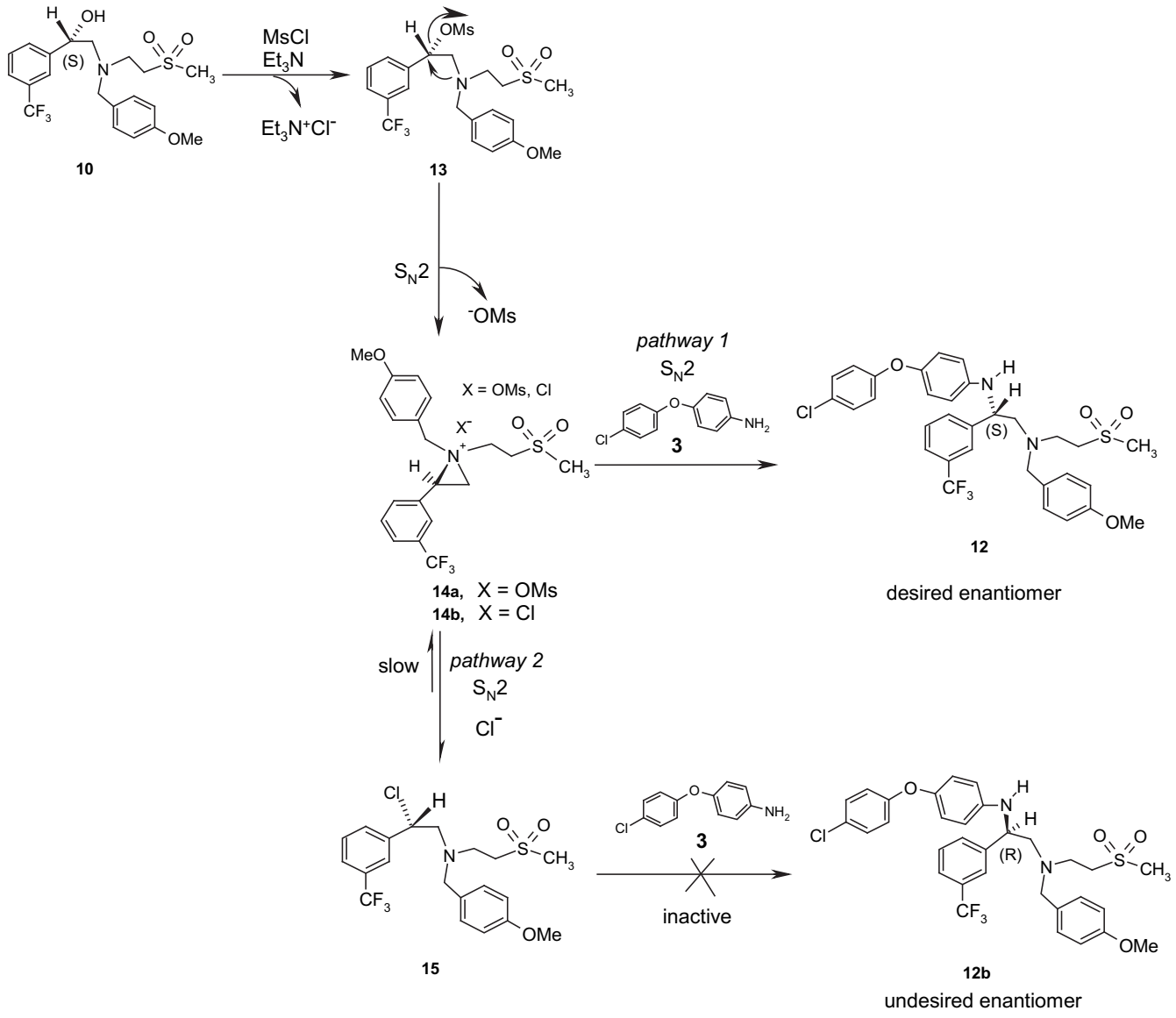
2.2. Regio-and stereoselective opening of aziridinium ion

Syntheses of vicinal diamines (such as **12**, Scheme 3) through aziridinium ions (such as **14**) have been well-studied.[8] Typically, an aziridinium ion can be prepared by treating a β-amino alcohol with mesyl chloride in the presence of Et_3N. Regio-selectivity for the opening of an aziridinium ion to produce a vicinal diamine is dependent on the type of nucleophile and the nature of the aziridinium ion.[9] It has been reported that nucleophilic attacks on phenyl aziridinium ions at the more-hindered benzylic site by aliphatic amines can be accomplished in high yields.[9a,9c,10] Substitutions of aziridinium ions with *aniline* nucleophiles have also been reported.[11] Herein, we disclose our own observations and insights into this type of reaction. Although stable aziridinium salts have been isolated,[9a] our attempts to isolate aziridinium salt **14** after treating β-amino alcohol **10** with mesyl chloride (MsCl) in the presence of Et_3N were unsuccessful. Therefore, a one-pot approach to synthesize vicinal diamine **12** directly was investigated. We observed a temperature effect on the rate of **12** formation (Fig. 3). Treating alcohol **10** with MsCl at rt for 16 h and adding aniline **3** to the resulting intermediate, vicinal diamine **12** was generated with high regio- and stereo-selectivity (98:2 er) in 80% after 5 days. Under these conditions, diamine **12** was the only regio-isomer that we observed according to ^{1}H NMR analyses of the crude product. Interestingly, when the same mesylation was carried out at 0 °C for 30 min, followed by the addition of **3**, the desired **12** was produced in >95% within 16 h. The facts that formation of **12** had been faster at a lower temperature suggested that these two reaction protocols must follow distinct pathways. This prompted a more detailed analysis of these reactions.

As revealed by our ^{1}H NMR studies in toluene-d_8, a detectable intermediate formed rapidly in 0.5 h when **10** was treated with MsCl at 0 °C (Fig. 4, NMR-B). The identity of this intermediate was postulated to be aziridinium salt **14** based on a reported instability and short lifetime of a benzylic mesylate.[12] Over a period of 24 h at rt, aziridinium salt **12** converted to another intermediate exclusively (Fig. 4, NMR-D), which was isolated and fully characterized as β-chloro amine **15** (NMR, and elemental analyses). Chloride attack of aziridinium salt **12** was selective for the benzylic over the unsubstituted position, leading to benzylic chloride **15**, which was supported by similarities in ^{13}C and ^{1}H NMR chemical shifts of C_6H_5CHCl between pure **15** (59.0 and 4.91 ppm, respectively, in $CDCl_3$) and an analogous molecule reported by Sharpless.[11b] Based on these outcomes, a plausible mechanism to explain the kinetic difference is shown in Scheme 3. If aziridinium salt **14** is exposed to aniline **3** shortly after its formation, diamine **12** can be generated by a S_N2 reaction via pathway 1. In the absence of **3**, β-chloro amine **15** is obtained via pathway 2, and is relatively unreactive to the subsequent addition of **3**. Regeneration of aziridinium ion **14** from **15** took place slowly over a period of 5 days via intra-molecular S_N2 reaction. Ions **14** reacted with **3** to furnish diamine **12** exclusively, which also supported the absolute configuration assignment of **15** since nucleophilic substitutions with double inversion of the configuration can only contribute to the stereochemistry outcome of **12**. It is worth mentioning that (1) β-chloro amine **15** was generated through the opening of aziridinium ion **14** with chloride, instead of through the replacement of the mesylate;[11,13] (2) **15** (a benzyl chloride) was inert toward nucleophilic attack by aniline **3**; and (3) a regio-selective and stereo-specific nucleophilic opening of aziridinium ion **14** by **3** is accountable for the chiral vicinal diamine **12** synthesis.

2.3. Completion of the total synthesis

Our initial approach to remove *p*-methoxybenzyl group from **12** (Scheme 4) with neat TFA resulted in an quantitative conversion to diamine **16** as TFA salt. From a large-scale preparation prospect, employing large excess of volatile TFA (bp 72 °C) is unsafe and ecologically-unfriendly. An alternative and greener process was developed for the deprotection utilizing stoichiometric amounts of methanesulfonic acid (b. p. 167 °C/10 mm) at elevated temperature (100 °C) in toluene. Diamine **16**, obtained after base work up, was treated with *p*-nitrobenzoic acid and furnished a crystalline salt **17**



Scheme 3. Plausible pathway for the formation of chiral vicinal diamine **12**.

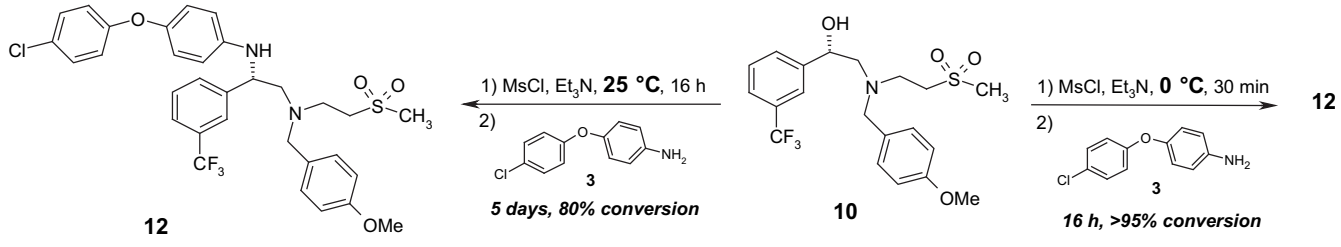


Figure 3. Impact of temperature on the rate of vicinal diamine **12** formation.

with high chemical purity (HPLC assay 98.1%). It is worth mentioning that salt **17** is the only crystalline intermediate of this synthetic route starting from mandelic acid **5**. The rest of the intermediates once generated were used for the next step without further purification or isolation. As a result, the varieties and amounts of solvents used were significantly minimized, which follows the principles of green chemistry. This telescoped approach achieved an overall yield of 34% from **5** to **17** (6 steps), which demonstrated the effectiveness of our synthetic strategy. To assemble the final trisubstituted imidazolidinone **1**, salt **17** was first converted to free base **16** with aqueous NaOH and then reacted with triphosgene. The condensation from **16** took 15 min at rt and provided **1** in quantitative yield. However, triphosgene is not an acceptable choice for manufacturing purpose due to its toxicity. Therefore, a safer alternative using carbonyl diimidazole as the 'carbonyl' surrogate was developed, affording **1** as a crystalline solid in good yield (67%) with high purity (HPLC assay 99%). The enantiomeric ratio of **1** was determined to be 96:4 (S:R) according to

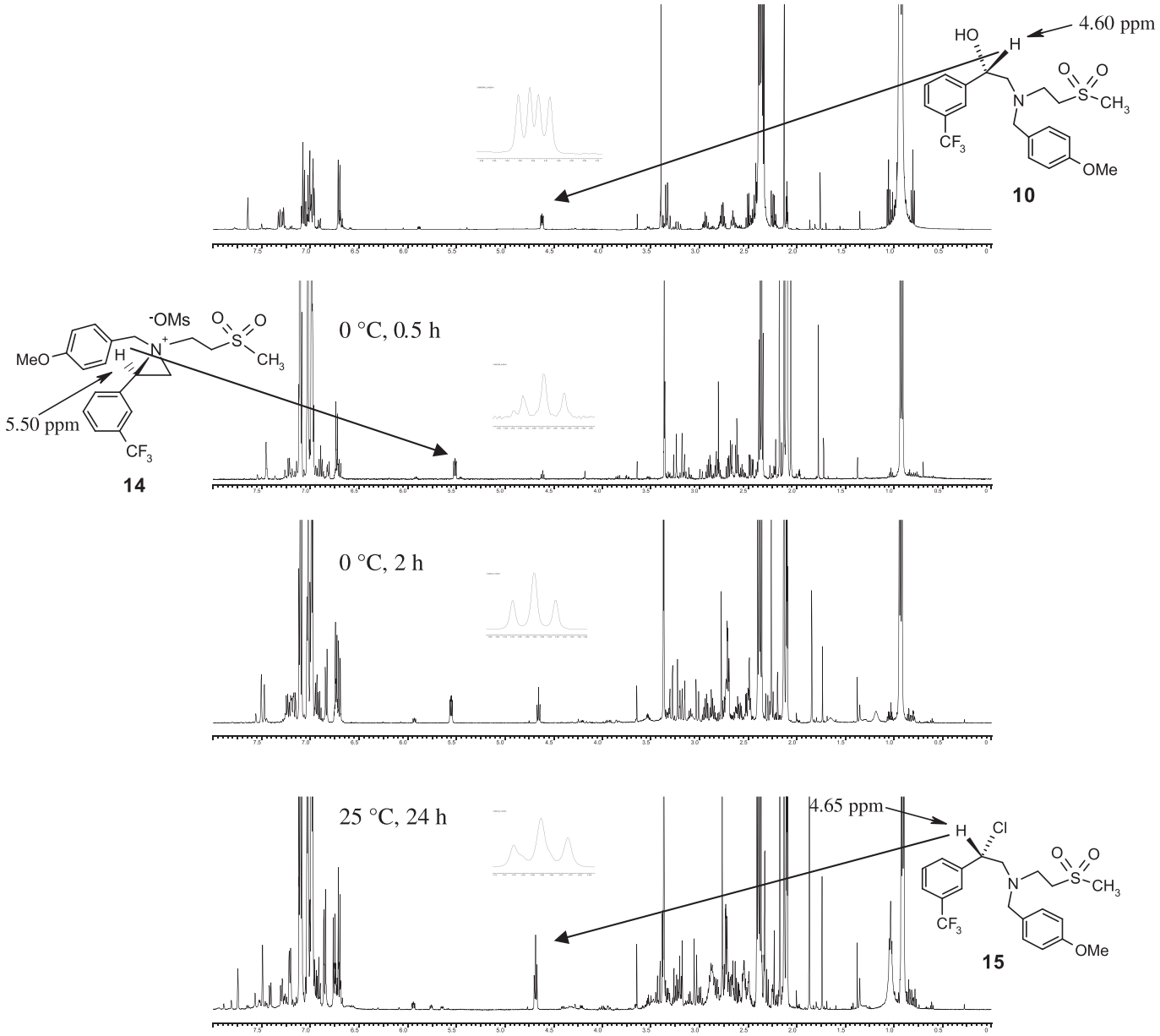


Figure 4. Conversion of β-amino alcohol **10** to β-chloro amine **15** in toluene-d_8 as monitored by ^{1}H NMR.

a chiral HPLC analysis. The undesired (*R*)-enantiomer of **1** was generated during mandelic acid **5** and amide **9** syntheses, with about 2% from each individual steps. The possible conglomerate nature[14] of compound **1** contributed to the isolation of high enantiomeric purity **1** (HPLC 99.8:0.2 er) by a simple recrystallization from ethanol.

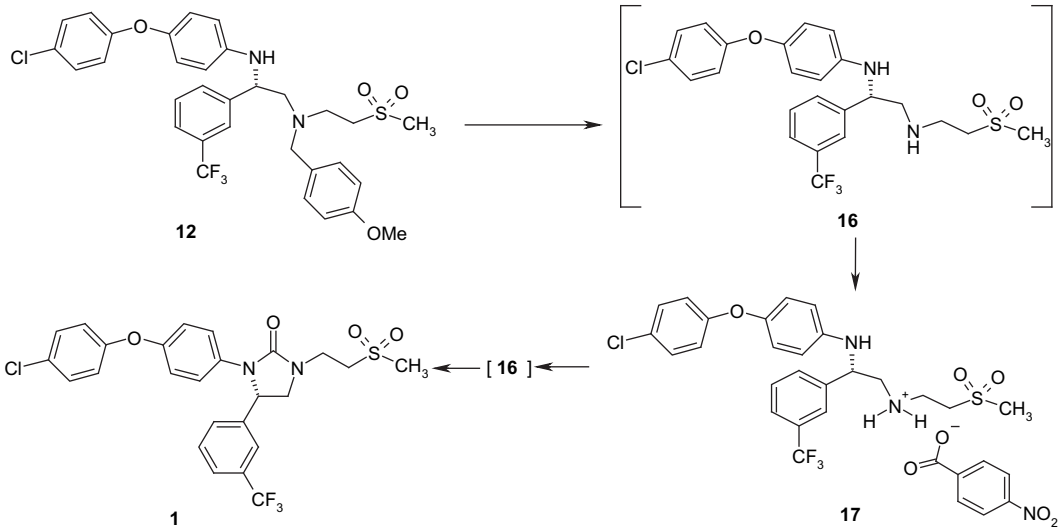
3. Conclusion

In conclusion, starting from a commercially available mandelic acid **5**, a scalable synthetic strategy leading to a chiral trisubstituted imidazolidinone (**1**), a novel cannabinoid-1 antagonist, is described. The key step involves a regio- and stereoselective ring-opening of an aziridinium ion by an aniline nucleophile affording vicinal diamine **12**. A mechanistic study suggested two plausible pathways that are accountable for the kinetic difference of vicinal diamine formation under two different conditions. Although most intermediates are not isolable by crystallization due to their intrinsic physical properties (oil or foamy solid), the reported synthesis furnished pure **1** without any chromatography purification throughout the entire synthesis. As a result, conventional approaches to purify or isolate intermediates using solvent systems were significantly circumvented. This green and novel synthesis appeared to be highly effective for the manufacturing of multi-kilograms of a chemically- and optically-pure pharmaceutical ingredient for clinical trials.

4. Experimental section

4.1. General

All solvents and reagents were purchased from commercial sources and used without further purification. NMR spectra were recorded on either 400 or 500 MHz spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard. HPLC analyses were performed on a Waters, Varian, or Rainin HPLC System connected to a PDA UV detector over 210–400 nm or a UV detector at 254 nm.



Scheme 4. End-game synthesis.

4.2. (*S*)-2-Acetoxy-2-(3-(trifluoromethyl)phenyl)acetic acid (7)

To a 4-L, three-necked, round bottom flask was charged (*S*)-3-(trifluoromethyl)-mandelic acid (**5**) (120 g, 0.55 mol, 98:2 er), toluene (960 mL), and acetyl chloride (66 g, 0.84 mol). The mixture was stirred at rt for 16 h. The mixture was distilled at 40–45 °C under vacuum until the acetyl chloride content was determined to be <1 wt % as measured by titration with 0.1 N $AgNO_3$ solution. The residue was diluted with toluene to a final volume of 400 mL to obtain **7** as a solution, which was used for the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.54 (m, 1H), 7.40 (m, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 5.89 (s, 1H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.2, 134.1, 131.4, 130.9, 129.4, 126.2, 124.3, 123.9, 73.3, 20.5. HRMS calcd for $C_{11}H_9F_3O_4$ $[M-H]^-$ 261.0375, found 261.0367.

4.3. (2-Methanesulfonyl)-*N*-(4-methoxy-benzyl)-acetamide

To a 100-L, three-necked reactor was charged sulfonyl acid **6** (1.22 kg, 8.83 mol), THF (36 L), and 4-methoxybenzyl amine (1.21 kg, 8.83 mol). To the slurry, was added 2-chloro-4,6-dimethoxy-[1,3,5]triazine (1.7 kg, 9.71 mol), followed by *N*-methylmorpholine (1.1 kg, 9.71 mol) over a period of 30 min. The mixture was stirred at rt for an additional 2 h. To the cloudy solution, 1 N NaOH (36.6 L) was added over a period of 1 h and stirred for an additional 1 h. The mixture was evaporated under vacuum to remove most of THF until a suspension was obtained. Any solids were collected by filtration, rinsed with water (4×5 L), and dried at 50 °C under vacuum for 16 h to give the title compound as a white solid (2.09 kg, 92%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (t, J=5.7 Hz, 1H), 7.21 (d, J=8.5 Hz, 2H), 6.89 (d, J=8.5 Hz, 2H), 4.26 (d, J=5.7 Hz, 2H), 4.10 (s, 2H), 3.73 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 158.3, 130.3, 128.6, 113.7, 59.4, 54.9, 41.8, 41.4. HRMS calcd for $C_{11}H_{15}NO_4S$ $[M+H]^+$ 258.0800, found 258.0811.

4.4. (2-Methanesulfonyl-ethyl)-(4-methoxy-benzyl)-amine (8)

To a 5-L, three-necked, round bottom flask was charged (2-methanesulfonyl)-*N*-(4-methoxy-benzyl)-acetamide (100 g, 388 mmol) and THF (330 mL). A solution of 1 N BH_3-THF (777 mL, 777 mmol) was added over a period of 1 h. After the addition, the mixture was allowed to warm to 50 °C and stirred for an additional 7 h. The mixture was cooled to rt and stirred for 16 h. Methanol (95 mL) was added and stirred for 5 min. A solution of 4 N HCl in dioxane was added over a period of 45 min and stirred for an additional 3 h. To the mixture, THF (1 L) was added. Any solids were collected by filtration, rinsed with THF (2×500 mL), and dried at 50 °C under vacuum for 16 h to obtain **8** (79.3 g, 73%) as a white solid: HPLC assay 99%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (br s, 1H), 7.53 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 4.11 (t, J=5.0 Hz, 2H), 3.77 (s, 3H), 3.68 (m, 2H), 3.29 (m, 2H), 3.11 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 131.6, 123.5, 113.9, 55.1, 49.5, 49.2, 40.7, 39.4. HRMS calcd for $C_{11}H_{17}NO_3S$ $[M+H]^+$ 244.1007, found 244.0988.

4.5. (*S*)-2-((4-Methoxybenzyl)(2-(methylsulfonyl)-ethyl)amino)-2-oxo-1-(3-(trifluoromethyl)phenyl) ethyl acetate (9)

To a 4-L, three-necked, round bottom flask was charged **8** (100 g, 0.36 mol), THF (1.2 L), water (63 g), and cesium carbonate (70 g, 0.22 mol). The mixture was stirred at rt for 1.5 h. To the resulting mixture, a solution of **7** (0.38 mol) in toluene (400 mL), prepared from the previously step, was added. The mixture was stirred at rt for 30 min. In portions, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM, 109 g, 0.39 mol) was added. The mixture was stirred at −5.0 °C for 16 h. To the mixture was added 8% aqueous citric acid (800 mL) and THF was evaporated at 45 °C under vacuum. Toluene (730 mL) was added to the residue and the aqueous layer was separated. The organic layer was washed with 8% aqueous citric acid (1×500 mL), 5% aqueous $NaHCO_3$ (1×500 mL), water (1×500 mL), and 15% aqueous NaCl (1×500 mL). The organic phase was evaporated at 45 °C under vacuum until the water content was determined to be <0.15% as measured by Karl Fisher titration. The resulting solution of **9** in toluene was used for the next step without further purification: chiral HPLC assay 96:4 er (2% from racemization, 2% from **5**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J=7.9 Hz, 1H), 7.53 (m, 2H), 7.45 (t, J=7.9 Hz, 1H), 6.98 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.5 Hz, 2H), 6.18 (s, 1H), 4.55 (d, J=16.4 Hz, 1H), 4.37 (d, J=16.1 Hz, 1H), 3.72 (s, 3H), 3.68 (m, 1H), 3.66 (m, 1H), 3.19 (m, 1H), 3.06 (m, 1H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 168.3, 159.6, 134.5, 131.8, 131.4, 129.6, 128.3, 126.6, 126.3, 125.3, 123.6, 114.5, 72.7, 55.2, 51.8, 51.5, 41.4, 41.1, 20.6. HRMS calcd for $C_{22}H_{24}F_3NO_6S$ $[M+H]^+$ 487.1355, found 487.1362. Chiral Technologies Chiralpak™ AD, 5 μm 250 mm×4.6 mm, flow rate=1 mL/min, 20 °C, isocratic, hexane–isopropanol=75:25, UV 230 nm: (*S*)-enantiomer, t_R= 9.6 min; (*R*)-enantiomer, t_R=12.1 min.

4.6. (*S*)-2-((4-Methoxybenzyl)(2-(methylsulfonyl)ethyl)-amino)-1-(3-(trifluoromethyl)phenyl)ethanol (10)

To a 1-L, three-necked, round bottom flask was charged a solution of **9** (42 g, 86.4 mmol) in toluene (234 mL). A solution of 1 N BH_3-THF (216 mL, 216 mmol) was added over a period of 1 h, maintaining the batch temperature below 22 °C. After the addition, the mixture was stirred at ambient temperature for an additional 20 h. The mixture was cooled to 10 °C and treated with 3 N NaOH (130 mL) over a period of 1 h (Note: the first 8 mL of 3 N NaOH addition caused significant foaming and should be added very slowly). The mixture was allowed to warm to 50 °C over a period of 40 min and stirred for an additional 1 h. The mixture was cooled to rt and extracted with toluene (35 mL). The organic phase was separated, washed with 25% NaCl (3×130 mL), and evaporated at 35–38 °C under vacuum until a final volume of 230 mL was reached. The resulting solution of **10** in toluene was used for the next step without further purification: HPLC assay 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.55–7.41 (m, 3H), 7.23 (d, *J*=9.6 Hz, 2H), 6.88 (d, *J*=9.6 Hz, 2H), 4.75 (dd, *J*=10.0, 3.2 Hz, 1H), 3.89 (br s, 1H), 3.82 (s, 3H), 3.81 (d, *J*=12.9 Hz, 1H), 3.58 (d, *J*=13.0 Hz, 1H), 3.25 (m, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 3.05 (m, 1H), 2.85 (s, 3H), 2.73 (dd, *J*=12.8, 3.2 Hz, 1H), 2.60 (dd, *J*=12.8, 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 143.0, 130.7, 130.4, 129.3, 129.2, 128.8, 124.3, 124.2, 122.7, 114.1, 69.9, 62.7, 58.6, 55.3, 52.3, 47.6, 41.7. HRMS calcd for $C_{20}H_{24}F_3NO_4S$ $[M+H]^+$ 432.1456, found 432.1442. HPLC for **9** (t_R=8.7 min), **10** (t_R=6.8 min): Waters Symmetry C_{18} 5 μm 150 mm×3.9 mm, flow rate=1.0 mL/min, 25 °C, gradient elution from 90:10 A:B to 20:80 A:B over 7 min then held for an additional 3 min; *A*=0.1% TFA in water; *B*=0.1% TFA in CH_3CN.

4.7. (*S*)-N^1-(4-(4-Chlorophenoxy)phenyl)-N^2-(4-methoxybenzyl)-N^2-(2-(methylsulfonyl)ethyl)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diamine (12)

To a 2-L, three-necked, round bottom flask was charged a solution of **10** (72 g, 108 mmol) in toluene (83 mL) and toluene (280 mL). The solution was cooled to 0 °C and Et_3N (27.4 g, 271 mmol) was added. Methanesulfonyl chloride (14.9 g, 130 mmol) was charged over a period of 20 min. After the addition, the mixture was stirred at 0 °C for an additional 30 min. A solution of **3** (26 g, 118 mol) in toluene (230 mL) was added. The mixture was allowed to warm to ambient temperature over a period of 1 h and stirred for an additional 16 h. Water (75 mL) and saturated NaCl (100 mL) were added. The organic layer was separated and washed sequentially with a mixture of 20% citric acid (100 mL) and saturated NaCl (100 mL), a mixture of water (100 mL) and saturated NaCl (75 mL), saturated $NaHCO_3$ (150 mL), and a mixture of water (100 mL) and saturated NaCl (75 mL). The resulting solution of **12** in toluene was used for the next step without further purification: HPLC assay 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.57 (d, *J*=7.6 Hz, 1H), 7.52 (d, *J*=7.6 Hz, 1H), 7.45 (t, *J*=7.8 Hz, 1H), 7.37–7.15 (m, 4H), 6.87–6.80 (m, 4H), 7.77 (d, *J*=8.8 Hz, 2H), 6.43 (d, *J*=9.1 Hz, 2H), 5.09 (br s, 1H), 4.27 (d, *J*=4.1, Hz, 1H), 4.25 (d, *J*=4.4, Hz, 1H), 3.79 (s, 3H), 3.23 (m, 1H), 3.11 (m, 2H), 3.04 (m, 1H), 2.80 (s, 3H), 2.79–2.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 156.5, 150.7, 139.0, 138.1, 132.4, 131.1, 130.8, 129.8, 129.5, 127.7, 125.7, 124.4, 123.7, 121.8, 120.4, 119.1, 117.6, 114.8, 58.5, 57.4, 57.2, 55.3, 49.5, 47.2, 41.7. HRMS calcd for $C_{32}H_{32}ClF_3N_2O_4S$ $[M+H]^+$ 633.1802, found 633.1793. HPLC for **10** (t_R=6.2 min), **3** (t_R=6.0 min), **12** (t_R=11.4 min): Waters Symmetry C_{18} 5 μm 150 mm×4.6 mm, flow rate=1.0 mL/min, 25 °C, gradient elution from 90:10 A:B to 5:95 A:B over 10 min then held for an additional 6 min; *A*=0.1% formic acid in water; *B*=0.1% formic acid in CH_3CN.

4.8. [(*S*)-2-Chloro-2-(3-trifluoromethyl-phenyl)-ethyl]-(2-methanesulfonyl-ethyl)-(4-methoxy-benzyl)-amine (15)

A 100-mL, four-necked, round bottom flask equipped with a mechanical stirrer, and a thermocouple was charged **10** (4.31 g, 10.0 mmol), isopropyl acetate (27 mL), and triethylamine (2.53 g, 25.0 mmol). The solution was cooled to −5 °C and methanesulfonyl chloride (1.37 g, 12.0 mmol) was added, maintaining the batch temperature below −5 °C. After the addition, the mixture was stirred at 0 °C for an additional 30 min, allowed to warm to 22 °C, and stirred for an additional 16 h. The mixture was quenched with water (9.0 mL). The organic phase was separated, washed with water (9 mL), and evaporated at 38 °C under vacuum to dryness to obtain crude **15** (4.08 g) as a light yellow oil. Crude **15** (1.5 g) was purified by column chromatography (silica gel, 40% ethyl acetate in heptanes) to afford **15** (1.16 g) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.47 (m, 4H), 7.10 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.91 (t, *J*=7.3 Hz, 1H), 3.84 (s, 3H), 3.70 (d, *J*=13.1 Hz, 1H), 3.58 (d, *J*=13.1 Hz, 1H), 3.17–3.08 (m, 6H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 141.0, 131.0, 130.9, 130.2, 129.2, 129.1, 125.3, 124.4, 123.8, 114.0, 62.8, 59.6, 59.0, 55.3, 52.7, 48.8, 41.8. Anal. Calcd for $C_{20}H_{23}ClF_3NO_3S$: C, 53.31; H, 5.15; Cl, 7.88; N, 3.11; S, 7.13. Found: C, 53.40; H, 5.28; Cl, 7.93; N, 2.95; S, 7.10. HPLC for **15** (t_R=9.01 min): Waters Symmetry C18 5 μm 150 mm×3.9 mm, flow rate=1 mL/min, 22 °C, UV 230 nm, gradient elution from 10:90 *A*:*B* to 80:20 *A*:*B* over 7 min, held for 3 min; *A*=0.1% TFA in acetonitrile; *B*=0.1% TFA in water.

4.9. (*S*)-N^1-(4-(4-Chlorophenoxy)phenyl)-N^2-(2-(methanesulfonyl)ethyl)-1-(3-(trifluoromethyl) phenyl)ethane-1,2-diamine *p*-nitrobenzoate (17)

To a 2-L, three-necked, round bottom flask was charged a solution of **12** (68 g, 108 mmol) in toluene (600 mL) and methanesulfonic acid (125 g, 1.3 mol). The mixture was allowed to warm to 100 °C and stirred for an additional 2 h. The mixture was cooled to 0 °C and 7 N NaOH (200 mL) was added followed by 25% NaCl (200 mL). The organic layer was separated, washed with 25% NaCl (2×250 mL), and evaporated until the final volume of 210 mL was reached to obtain a solution of **16** in toluene. A solution of *p*-nitrobenzoic acid (18 g, 108 mmol) in isopropanol (180 mL) was then added. The mixture was allowed to warm to 75 °C and stirred for an additional 30 min. Heptanes (975 mL) was added over a period of 20 min, maintaining the batch temperature at 65 °C. The mixture was cooled to 15 °C over a period of 1 h and stirred for an additional 1 h. The solids were collected by filtration and rinsed with 7% ethanol in heptanes (250 mL). The solids were dried under vacuum at 50 °C for 16 h to give **17** (36.6 g, 34% from **5**) as a yellow solid: mp 145–146 °C; HPLC assay 98.1%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, *J*=9.0 Hz, 2H), 8.18 (d, *J*=9.0 Hz, 2H), 7.79 (s, 1H), 7.74 (d, *J*=7.0 Hz, 1H), 7.52–7.64 (m, 2H), 7.32 (d, *J*=9.0 Hz, 2H), 6.83 (d, *J*=9.0 Hz, 2H), 6.79 (d, *J*=9.0 Hz, 2H), 6.59 (d, *J*=9.0 Hz, 2H), 6.23 (br, 1H), 4.62 (t, *J*=6.3 Hz, 1H), 3.28 (t, *J*=6.7 Hz, 2H), 3.04 (t, *J*=6.7 Hz, 2H), 2.97 (s, 3H), 2.82–2.92 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 157.6, 149.8, 145.7, 144.8, 144.7, 137.2, 131.0, 130.6, 129.5, 129.3, 128.9, 125.5, 125.4, 123.7, 123.6, 123.2, 120.9, 118.1, 113.9, 56.3, 55.0, 53.4, 42.2, 41.3. HRMS calcd for $C_{24}H_{24}ClF_3N_2O_3S$ $[M+H]^+$: 513.1227, found 513.1235. HPLC for **16** (t_R=7.2 min), **12** (t_R=11.4 min), *p*-nitrobenzoic acid (t_R=6.2 min): Waters Symmetry C_{18} 5 μm 150 mm×4.6 mm, flow rate=1.0 mL/min, 25 °C, gradient elution from 90:10 A:B to 5:95 A:B over 10 min then held for an additional 6 min; *A*=0.1% formic acid in water; *B*=0.1% formic acid in CH_3CN.

4.10. (*S*)-3-[4-(4-Chloro-phenoxy)-phenyl]-4-(3-trifluoromethyl-phenyl)-1-(2-methanesulfonyl-ethyl)-imidazolidin-2-one (1)

To a 2-L, three-necked, round bottom flask was charged a solution of **17** (65 g, 95.4 mmol), isopropyl acetate (1 L), and 0.5 N NaOH (400 mL). The mixture was stirred for 15 min. The organic layer was separated, washed with water (2×700 mL), and evaporated under vacuum until the final volume of 180 mL was reached. Toluene (600 mL) was added and evaporated under vacuum until the final volume of 180 mL was reached to obtain a solution of **16** in toluene. 1,1′-Carbonyldiimidazole (23.2 g, 143 mmol) was added and the mixture was allowed to warm to 100 °C. The mixture was stirred for an additional 4 h, cooled to rt and diluted with toluene (400 mL). The organic phase was washed sequentially with a mixture of 1 N HCl (400 mL) and 25% NaCl (400 mL), 25% NaCl (400 mL), a mixture of 9% $NaHCO_3$ (300 mL) and 25% NaCl (300 mL), and water (400 mL). The organic phase was evaporated under vacuum until the final volume of 300 mL was reached, treated with active charcoal (Pica Pure HP100, 3 g) for 1 h, and filtered through a pad of Celite (16 g). The organic solution was evaporated until the final volume of 200 mL was reached. The resulting solution was allowed to warm to 60 °C, diluted with heptanes (135 mL), cooled to 20 °C, and stirred for an additional 3 h. To the resulting suspensions, ethanol (30 mL) and heptanes (195 mL) were added, and stirred for an additional 12 h. The solids were collected by filtration, rinsed with a solution of 33% toluene in heptanes (150 mL), a solution of 7% ethanol in heptanes (100 mL), and dried at 50 °C under vacuum for 16 h to obtain **1** (33.3 g, 65%) as an off-white solid: chiral HPLC assay 96:4 er. The following recrystallization was used to improve the optical purity. Crude **1** (33.3 g) was dissolve into EtOH (125 mL) at 50 °C, filtered, cooled to 25 °C and seeded. The batch was stirred at rt for 20 h. The solids were collected by filtration, rinsed with EtOH (33 mL), dried at 50 °C under vacuum for 16 h to afford **1** (23.3 g, 70% yield) as a white solid: mp 89–90 °C; chiral HPLC assay 99.8:0.2 er; HPLC assay 99.5%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.66 (d, 1H, J=5.0 Hz, 1H), 7.63 (d, 1H, J=5.0 Hz, 1H), 7.43 (m, 2H), 7.36 (m, 2H), 6.92 (m, 4H), 5.60 (dd, J=10.0, 5.0 Hz, 1H), 3.99 (t, J=10.0 Hz, 2H), 3.75 (m, 1H), 3.67 (m, 1H), 3.44 (m, 1H), 3.32 (m, 1H), 3.03 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.4, 156.0, 151.4, 142.0, 134.9, 130.6, 130.0, 129.7, 129.4, 126.8, 124.7, 124.1, 123.5, 121.8, 119.6, 119.2, 55.9, 50.9, 50.3, 40.6, 37.6. HRMS calcd for $C_{25}H_{22}ClF_3N_2O_4S$ $[M+H]^+$ 539.1019, found 539.1011. Anal. Calcd for $C_{25}H_{22}ClF_3N_2O_4S$: C, 55.71; H, 4.11; Cl, 6.58; F, 10.57; N, 5.20; S, 5.95. Found: C, 55.76; H, 4.32; Cl, 6.72; F, 10.67; N, 5.00; S, 6.09. Chiral HPLC for (*S*)-enantiomer (t_R=9.4 min), (*R*)-enantiomer (t_R=12.3 min): Chiral Technologies Chiralpak™ IA, 5 μm 250 mm×4.6 mm, flow rate=0.5 mL/min, 25 °C, isocratic, CH_3CN–water=80:20. HPLC for **1** (t_R=10.1 min), **16** (t_R=7.1 min): Waters Symmetry C_{18} 5 μm 150 mm×4.6 mm, flow rate=1.0 mL/min, 25 °C, gradient elution from 90:10 *A*:*B* to 5:95 A:B over 10 min then held for an additional 6 min; *A*=0.1% formic acid in water; *B*=0.1% formic acid in CH_3CN.

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References and notes

1. (a) Liu, H.; He, X.; Phillips, D.; Zhu, X.; Yang, K.; Lau, T.; Wu, B.; Xie, Y.; Nguyen, T.; Wang, X. WO 2008076754; *Chem. Abstr.* **2008**, 771087. (b) Donohue, S. R.; Halldin, C.; Pike, V. W. *Tetrahedron Lett.* **2008**, *49*, 2789–2791; (c) Kim, M.-a.; Kim, J. Y.; Song, K.-S.; Kim, J.; Lee, J. *Tetrahedron* **2007**, *63*, 12845–12852.
2. Basavaish, D.; Krishna, P. R. *Tetrahedron* **1995**, *51*, 2403–2416.
3. Truce, W. E.; Norell, J. R. *J. Am. Chem. Soc.* **1963**, *85*, 3236–3239.
4. Shieh, W.-C.; Chen, Z.; Xue, S.; McKenna, J.; Wang, R.-M.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **2008**, *49*, 5359–5362.
5. (a) Fei, Z.; Wu, Q.; Zhang, F.; Cao, Y.; Liu, C.; Shieh, W.-C.; Xue, S.; McKenna, J.; Prasad, K.; Prashad, M.; Baeschlin, D.; Namoto, K. *J. Org. Chem.* **2008**, *73*, 9016–9021; (b) Garrett, C. E.; Jiang, X.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **2002**, *43*, 4161–4165.
6. Shieh, W.-C.; Carlson, J.; Shore, M. *Tetrahedron Lett.* **1999**, *40*, 7167–7170.
7. Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140.
8. For recent reviews on the synthesis of vicinal diamines through aziridium ions, see: (a) Kurteva, V.; Lyapova, M. *Central Eur. J. Chem.* **2004**, *2*, 686–695; (b) Lucet, D.; Le Gall, T. L.; Mioslowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
9. (a) Song, H. A.; Dadwal, M.; Lee, Y.; Mick, E.; Chong, H.-S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1–4; (b) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183–2186; (c) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304–307.
10. (a) Curthbertson, E. O.; Brien, P.; Towers, T. D. *Synthesis* **2001**, 693–695; (b) Frizzle, M. J.; Caille, S.; Marshall, T. L.; McRae, K.; Nadeau, K.; Guo, G.; Wu, S.; Martinelli, M. J.; Moniz, G. A. *Org. Process Res. Dev.* **2007**, *11*, 215–222; (c) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693–4706.
11. (a) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555–3557; (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435–1437.
12. Bentley, T. W.; Christl, M.; Kemmer, R.; Llewellyn, G.; Oakley, J. E. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2531–2538.
13. Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766–6776.
14. Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463–5465.