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Asymmetric Synthesis of a TRPV1 Antagonist via *tert*-Butanesulfinamide-Directed Reductive Amination with a Chromanone

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Supporting Information

ABSTRACT: An expedient asymmetric synthesis of TRPV1 antagonist **1** has been developed and demonstrated on multikilogram scale. The enabling route to **1** is detailed herein and characterized by the following key transformations: an aldol-cyclodehydration sequence to install the chromanone, and an auxiliary-mediated diastereoselective reductive amination.

INTRODUCTION

Transient receptor potential vanilloid-1 (TRPV1) has been identified as an important biological receptor for the reduction of nociceptive pain and has stimulated the development of innovative medicines from pharmaceutical companies over the past decade.[1,2] In order to facilitate further examination of **1**[3] as a lead candidate (Figure 1), an expedient and efficient synthesis was required.

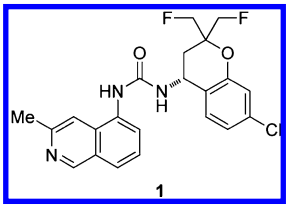


Figure 1. TRPV1 antagonist.

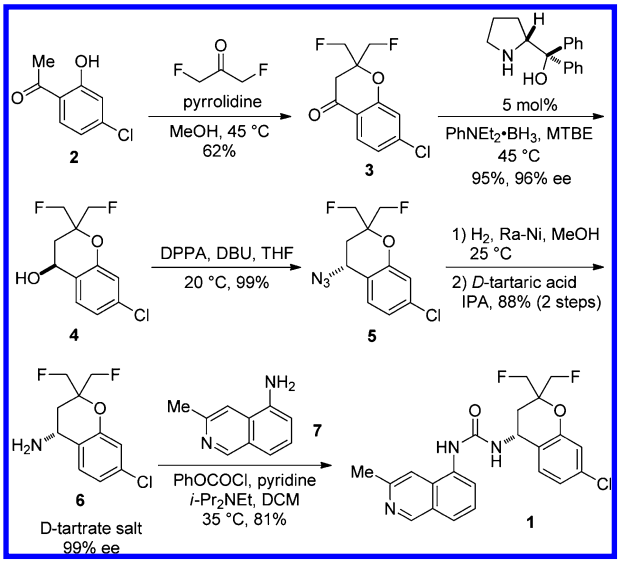
RESULTS AND DISCUSSION

The first generation route commenced with commercially available 4′-chloro-2′-hydroxy acetophenone (**2**), which was condensed with 1,3-difluoroacetone (DFA) to generate chromanone **3**.[4] Corey-Itsuno reduction[5a,b] of **3** afforded the alcohol **4** in excellent yield with high enantioselectivity (95%, 96% ee). Conversion of **4** to azide **5** with DPPA was followed by reduction to the amine using Ra−Ni. Formation of the D-tartaric acid salt **6** further enriched the optical and chemical purity to >99%.[6] The synthesis of **1** culminated in a phenyl chloroformate-mediated coupling between **6** and 3-methyl-isoquinolin-5-amine (**7**).

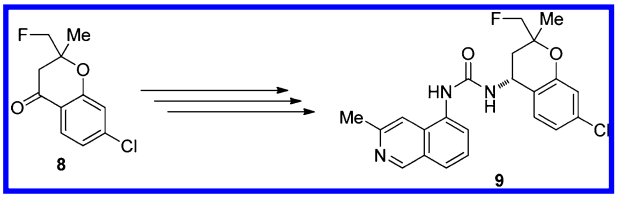
While the first generation route provided a reliable means to access **1** on small scale, there were several underlying issues that limited the scalability of this approach. Of primary concern was the fact that the condensation of 4′-chloro-2′-hydroxy acetophenone with 1,3-difluoroacetone was accompanied by formation of monofluoro impurity **8** (Scheme 2). Despite crystallization of **6** and **1**, monofluoro impurities were not rejected by the process, leading to contaminant **9** at the 3−4% level in isolated **1**. In addition, azide intermediate **5** was found to be highly energetic, making scale-up less than ideal from a safety perspective.[7]

The pyrrolidine promoted aldol-cyclodehydration of **2** to **3** was re-examined to determine the origin of monofluoro impurity **8**. After ruling out the presence of 1-fluoroacetone

Scheme 1. First Generation Synthesis



Scheme 2. Fate of Mono-Fluoro Impurity in API



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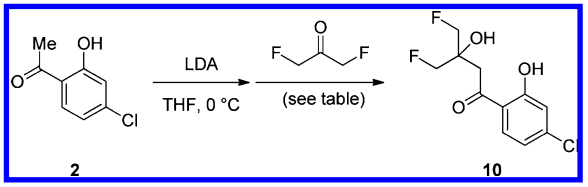
in the 1,3-difluoroacetone, it was concluded that **8** was generated under the reaction conditions. Unfortunately, an extensive solvent, temperature, stoichiometry, and additive screen of the one-pot condensation/cyclization did not establish conditions to effect this transformation without formation of **8** in appreciable quantities.

An alternative, stepwise approach to **3** via **10** was proposed with the aim of reducing the amount of monofluoro impurity **8** formed in the sequence. To that end, a temperature screen was conducted to identify conditions which could efficiently provide β-hydroxy ketone **10** (Table 1).[8] The application of non-

Table 1. Aldol Reaction Survey

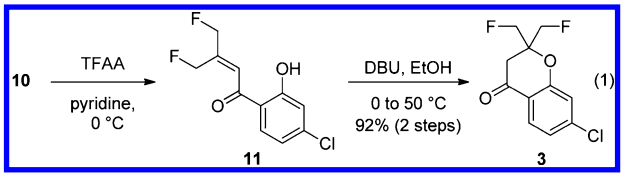


entry	temp (°C)[a]	yield (%)	ratio **2**:**10** (by HPLC)	total unknown impurities (%)[b]
1	−15	53	28:72	39.0
2	−45	80	4:96	12.4
3	−50	84	3:97	11.3
4	−60	ND[c]	5:95	5.5

[a]The temperature at which DFA was charged to the enolate of **2**. [b]Refers to sum total peak area percent by HPLC of compounds not corresponding to **2** or **10**. [c]Not determined.

cryogenic conditions was accompanied by lower yields, recovery of **2**, and impurity formation (entry 1). A notable temperature effect was apparent with this reaction; higher yields and a decrease in total impurities were observed at lower temperatures (entries 2−4).

Dehydration of **10** using TFAA and pyridine to give **11** could be achieved in quantitative yield (eq 1). The enone was then



elaborated to **3** in excellent yield by treatment with DBU in ethanol. Further investigation revealed that isolation of the somewhat unstable enone **11** was not necessary. Simple addition of EtOH and DBU to the reaction solution containing **11** led to chromanone **3** upon heating to 50 °C in 92% yield, for the two steps.[9] Importantly, formation of monofluoro impurity **8** through this sequence was limited to <0.3%.

Reductive Amination Route. As noted earlier, removal of azide **5** from the synthetic route was also of primary interest.[7] An alternative approach for asymmetric installation of the benzylic amine, via Ellman auxiliary-directed diastereoselective imine reduction,[10,11] appeared promising on the basis of literature precedent with structurally similar substrates (eq 2).[12]

Subjection of **3** to the standard conditions[11] for imine formation revealed that after 24 h more than 10% of **3** remained (Table 2, entry 1). A report on an efficient tetralone to sulfinyl ketimine transformation led us to try a 1:1 THF/EtOH cosolvent system, but the rate of conversion was slower (entry 2).[12b] In an attempt to drive the sulfinyl ketimine

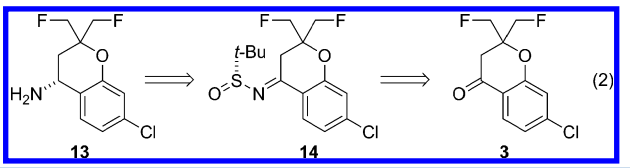
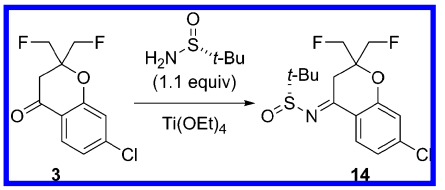


Table 2. Sulfinylimine Formation Optimization



entry	solvent	conc (M)	temp (°C)	$Ti(OEt)_4$ (equiv)	6 h (% **3**)[a]	24 h (% **3**)[a]
1	THF	0.50	70	2.0	23.5	10.4
2	THF/EtOH	0.50	70	2.0	86.4	69.0
3	toluene	0.50	100	2.0	5.2	3.7
4	2-MeTHF	0.50	80	2.0	10.6	3.3
5	2-MeTHF	1.0	80	2.0	12.5	4.6
6	2-MeTHF	0.50	80	3.0	ND[b]	3.5
7	2-MeTHF	0.50	80	4.0	7.8	2.3

[a]Refers to the peak area percent of **3** by HPLC. [b]Not determined.

formation, the reaction was conducted in toluene at elevated temperature: an improvement in reaction rate was indeed observed at 100 °C; however, significant degradation of the product was observed by HPLC analysis (entry 3). Switching the solvent to 2-MeTHF at 80 °C showed a similar rate enhancement, and the level of degradation was low compared to that observed in toluene: only 3.3% of **3** remained after 24 h (entry 4). The reaction rate was unaffected by a 2-fold increase in reaction concentration (entry 5 vs entry 4). An increase in equivalents of $Ti(OEt)_4$ produced only a modest improvement in reaction rate and conversion (entries 4, 6, and 7).

Direct reduction of the imine, without isolation, yielded promising results.[10] Exposure of the crude imine to $NaBH_4$ at −50 °C and warming of the solution to −10 °C afforded **15** in 88.6% de (Table 3, entry 1). A negligible decrease in diastereoselectivity was observed in the reaction that was carried out entirely at −10 °C (entry 2), suggesting a selective reaction to be feasible at noncryogenic temperatures. Increasing the $Ti(OEt)_4$ charge from 2 to 3 equiv caused a measurable increase in the diastereoselectivity of the reduction (entry 3). A decrease in reaction concentration lowered the selectivity of the reduction (entry 4 vs entry 3). While literature precedent cited[12a] the presence of 2% water in the reduction of isolated ketimine to be beneficial to the stereoselectivity, the introduction of water into the one-pot reaction produced the opposite effect (entry 5). The amount of ethanol present in the imine reduction was critical for the best results. Azeotropic removal of the EtOH led to lower diastereoselectivity and a relatively slow reduction (entry 6). Moreover, addition of EtOH (1 equiv) to the reaction solution also lowered selectivity (entry 7). As such, the single equivalent of EtOH generated in the formation of the sulfinyl imine appeared to be optimal for the one-pot stereoselective reduction of **14**.

With the ideal conditions for sulfinyl imine formation and reduction identified, the one-pot procedure was implemented on scale (5.0 kg) to provide **15** in 80% yield and 92% de (eq 3). Exposure of **15** to acidic methanolic conditions, in MTBE,

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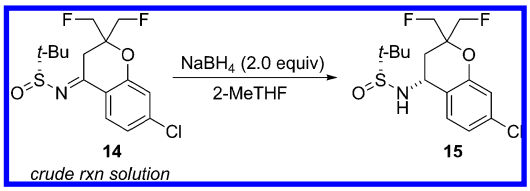
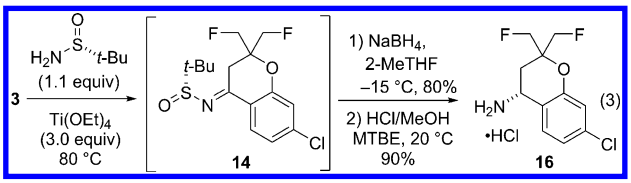
Table 3. Diastereoselectivity of the Reduction of 14 as a Function of Reaction Conditions



entry	conc. (M)	temp. (°C)	$Ti(OEt)_4$ (equiv)[a]	additive	de (%)[c]
1	0.25	−50 to −10	2.0	n/a	88.6
2	0.25	−10	2.0	n/a	87.4
3	0.25	−10	3.0	n/a	91.4
4	0.13	−10	3.0	n/a	89.5
5	0.25	−10	3.0	H_2O (2%)[b]	74.5
6	0.25	−10	3.0	−EtOH	65.9
7	0.25	−10	3.0	+EtOH (1 equiv)	85.0

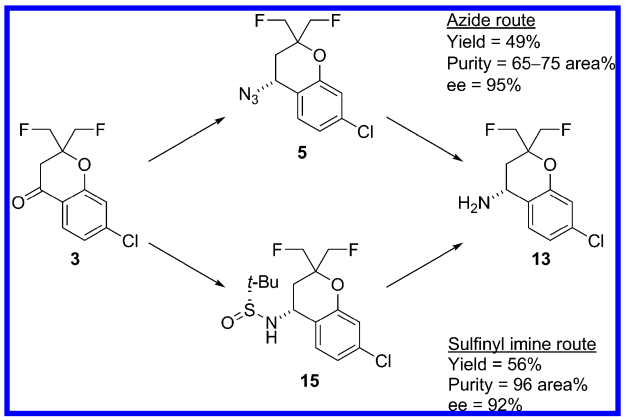
[a]The amount of titanium(IV) ethoxide employed in the formation of sulfinyl imine **14**. [b]Indicates the amount of water charged on a weight basis, relative to the quantity of 2-MeTHF present. [c]Measured by HPLC.



resulted in cleavage of the chiral auxiliary and concomitant precipitation of HCl salt **16** from the solution, in 90% yield.

The quality and downstream performance of chromanamine **13** depended on its mode of preparation (Scheme 3). The

Scheme 3. Purity of Freebase 13, Comparison by Approach

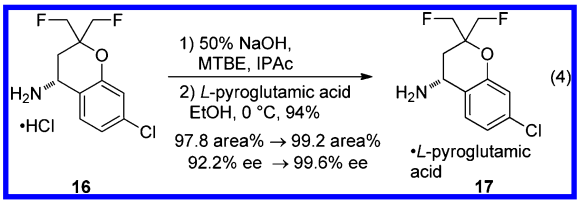


relatively higher purity of **13** that was generated from sulfinyl imine can be attributed to the inherently cleaner reaction profile and the crystalline intermediate (**16**). The azide chemistry generally provided crude **13** in approximately 65−75 area% and 95% ee; isolation of the 1:1 D-tartrate salt of **13** (CH_3CN solvate) improved the purity to 99.5 area% and 99.2% ee.

The sulfinyl imine route afforded material with 96 area% purity, much higher than the azide route, albeit with lower enantiomeric purity (92% ee). Interestingly, preparation of D-tartrate salt of **13** from the sulfinyl imine route, under identical conditions, did not improve the enantiopurity. Inspection of the X-ray powder pattern (PXRD) of the isolated crystals showed that a new, more stable,[13] nonsolvated crystal form had been formed. The nonsolvated form showed diminished rejection of the unwanted isomer relative to that observed with the CH_3CN solvate. Surprisingly, chromanamine **13** obtained from the azide route repeatedly yielded the D-tartrate salt as the CH_3CN solvate even when seeded with the nonsolvated crystal form, and excellent enantiomer rejection was maintained.

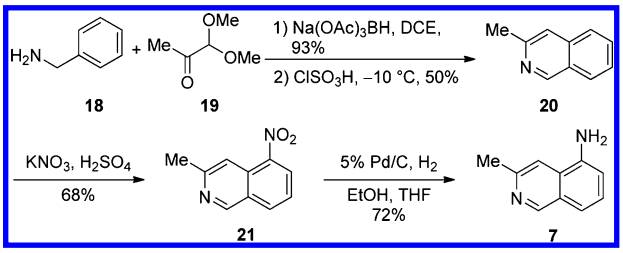
These unusual observations were difficult to rationalize, but it appears that the thermodynamics of the solid form stability was a function of the impurity profile. The significantly less pure matrix of material from the azide sequence seems to favor formation of the acetonitrile solvate over the nonsolvated form.

The benefits of the sulfinyl imine route merited an exploration of an improved salt isolation, without the inherent complexities of the D-tartrate salt. A series of chiral acids was examined and it was found that the L-pyroglutamic acid salt offered the required rejection of the undesired enantiomer of **13** (eq 4, 99.6% ee). Only a single polymorph of **17** was observed during the development and scale-up of this crystallization.



The synthesis of the coupling partner for **17** is illustrated in Scheme 4. Methylisoquinoline **20** was commercially available,

Scheme 4. Synthetic Route to 7



however not in sufficient quantities to support a multikilogram campaign. A lab-scale procedure was developed that featured a reductive amination of **19** with benzylamine that proceeded in 93% yield.[14] Exposure of the reductive amination product to neat chlorosulfonic acid, according to the method of Kido,[15,16] gave **20** in 50% yield. This 2-step preparation of **20** was amenable to scale-up to 5 kg at an external vendor.

Nitration[17] of **20** gave **21** in 68% yield, along with 4.8% of a regioisomer after isolation (91.2:8.8 ratio in the crude reaction mixture).[18] Purification of **21** by crystallization afforded variable results at this stage. After reduction of both **21** and **22** with 5% Pd/C in EtOH/THF, the desired amine **7** was isolated by crystallization and contained less than 0.05% of the regioisomer.

The coupling to produce **1** was achieved in 80% yield by activation of the 3-methylisoquinolin-5-amine (**7**) with phenyl chloroformate followed by addition to a mixture of pyroglutamate salt **17** and Hünig's base (eq 5).

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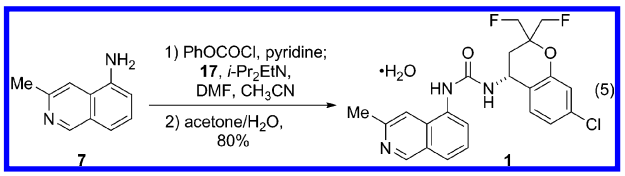
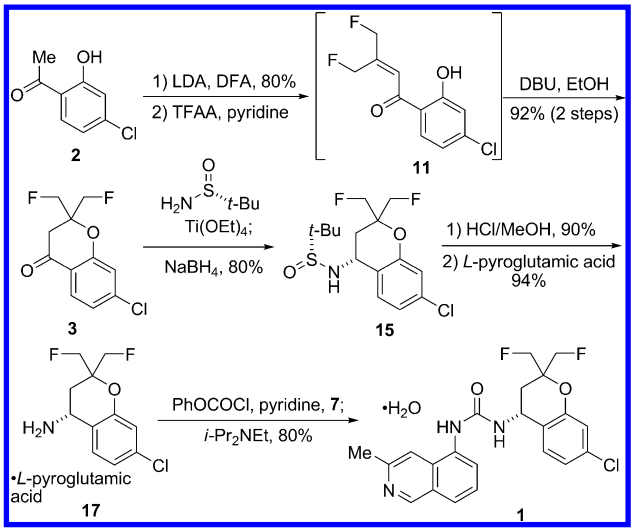


The final product **1** could be isolated directly from the reaction mixture by the addition of water. The levels of **7** remaining after the first isolation were variable. Thus, a recrystallization from acetone/water was developed to reject remaining **7**. Indeed, even when **7** was spiked to the crude mixture at 16 mol%, the level of **7** in isolated **1** was reduced to 3 ppm. The crystallization also delivered reproducible form and particle size.

CONCLUSIONS AND SUMMARY

In summary, a multikilogram enabling route to a novel TRPV1 antagonist has been developed (Scheme 5). The second generation route solved two key issues present in the initial synthesis. The level of the monofluoro impurity **9** was decreased from 4% to 0.2% and the energetic azide intermediate was eliminated from the chemical sequence. The chemistry has been demonstrated on multikilogram scale with a pilot plant campaign yielding 2.6 kg **1** (>99.9% ee).

Scheme 5. Pilot-Plant Campaign to 1



EXPERIMENTAL SECTION

HPLC data were collected using an Agilent 1100 or 1200 series HPLC. Chromatographic conditions are reported as part of the experimental descriptions below. Retention times are uncorrected. Assay yields were obtained by HPLC using pure compounds as standards. Isolated yields refer to yields corrected for purity on the basis of HPLC assays using purified standards.

1-(4-Chloro-2-hydroxyphenyl)-4-fluoro-3-(fluoromethyl)-3-hydroxybutan-1-one (10). A vessel was charged with THF (48.7 kg), diisopropylamine (5.2 kg, 51.7 mol, 2.1 equiv), and then cooled to 0 °C. Butyl lithium (14.3 kg, 51.7 mol, 2.1 equiv) was added over 40 min at <10 °C. After 15 min, a solution of 4′-chloro-2′-hydroxy acetophenone (**2**) (4.2 kg, 24.6 mol) in THF (3.6 kg) was added over 25 min at <10 °C. After 15 min at 0 °C, the solution was then cooled to −50 °C. 1,3-Difluoroacetone (2.78 kg, 29.6 mol, 1.2 equiv) was charged over 35 min at <−50 °C. After 10 min, HPLC analysis[19] indicated 98% conversion of 4-chloro-2-hydroxyacetophenone to **10**. The reaction mixture was warmed to −20 °C and quenched into a 10 w/w% aqueous KH_2PO_4 solution (181 kg). Ethyl acetate (77 kg) was added and the layers were separated. The organic layer was washed sequentially with 10 w/w% aqueous KH_2PO_4 (91 kg), then 20 w/w% aqueous NaCl (60 kg). The organic layer was concentrated under reduced pressure to ∼55 L. Ethyl acetate (50 kg) was charged and the mixture was distilled to ∼35 L. Pyridine (25 kg) was then added and the distillation was continued until the volume was ∼23 L. HPLC analysis of the pyridine solution indicated that the solution was 23.9 w/w% **10** and 88.5 area% (Assay = 5.46 kg **10**, 84% yield). Characterization of the isolated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 8.7, 2.1 Hz, 1H), 4.58 (d, J = 2.1 Hz, 2H), 4.46 (d, J = 2.1 Hz, 2H), 3.90 (s, 1H), 3.34 (t, J = 1.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.94, 162.88, 143.07, 131.02, 119.85, 118.61, 117.92, 84.86 (d, J = 3.9 Hz), 83.11 (d, J = 3.9 Hz), 72.69 (t, J = 18.1 Hz), 38.42 (t, J = 3.6 Hz); IR (KBr) 3484, 2965, 1635, 1565, 1019 cm^{-1}. HPLC ret time: 8.41 min. Anal. Calcd for $C_{11}H_{11}ClF_2O_3$: C, 49.92; H, 4.19; N, 0.0. Found: C, 49.87; H, 4.14; N, 0.1.

7-Chloro-2,2-bis(fluoromethyl)-chroman-4-one (3). A vessel was charged with a solution of **10** (22.8 kg of a 23.9 w/w % solution in pyridine, 20.4 mol) and pyridine (24.3 kg). The solution was cooled to 0 °C and trifluoroacetic anhydride (5.7 kg, 27.8 mol, 1.35 equiv) was added over 1.25 h at <5 °C. After 45 min, HPLC analysis[19] indicated 99.4% conversion of **10** to **11**. Ethanol (33 kg) and DBU (9.2 kg, 61.8 mol, 3 equiv) were added sequentially over 15 min at <5 °C. The reaction mixture was warmed to 50 °C. After 8 h, HPLC analysis indicated 97.8% conversion of **11** to **3**. The reaction mixture was concentrated under reduced pressure to ∼60 L to remove the bulk of the ethanol, then MTBE (60 kg) and a solution of 2 N aqueous HCl (66 kg) were added. The organic layer was separated and washed with 2 M aqueous NaOH (60 kg) followed by a 10 w/w% solution of aqueous KH_2PO_4 (60 kg). The organic layer was concentrated under reduced pressure to ∼26 L, then 2-MeTHF (54 kg) was added and distillation followed to achieve a volume of ∼40 L. 2-MeTHF (53 kg) was added and the product-containing organic layer was concentrated under reduced pressure to ∼26 L. HPLC analysis indicated 4.37 kg of **3** in the 2-MeTHF solution (87% yield). Characterization of the isolated product: ^{1}H NMR (400 MHz, DMSO) δ 7.72 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.4, 2.0 Hz, 1H), 4.75 (d, J = 3.5 Hz, 2H), 4.64 (d, J = 3.5 Hz, 2H), 3.02 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.49, 158.62, 142.24, 127.56, 122.50, 118.26, 118.06, 82.80 (d, J = 4.7 Hz), 81.02 (d, J = 4.7 Hz), 80.64 (t, J = 18.4 Hz), 38.15 (t, J = 3.2 Hz); IR (KBr) 3081, 1702, 1602, 1570, 1422, 1033 cm^{-1}. HPLC ret time: 10.51 min. Anal. Calcd for $C_{11}H_9ClF_2O_2$: C, 53.57; H, 3.68; N, 0.0. Found: C, 53.98; H, 3.36; N, <0.05; mp 59−61 °C.

***(R)*-*N*-((*R*)-7-Chloro-2,2-bis(fluoro-methyl)chroman-4-yl)-2-methylpropane-2-sulfinamide (15).** A vessel was charged with a solution of **3** (29.5 kg, 14.8 w/w% solution in 2-MeTHF), (*R*)-(+)-2-methyl-2-propanesulfinamide (2.4 kg, 19.8 mol, 1.1 equiv), 2-MeTHF (6 kg) and $Ti(OEt)_4$ (12.4 kg, 54.4 mol, 3.0 equiv). The reaction solution was warmed to 80 °C. After 20 h, HPLC analysis[20] indicated 5.4% remaining **3**. This solution was charged to a suspension of $NaBH_4$ (1.4 kg,

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37 mol, 2.0 equiv) and THF (30 kg) over 60 min at <−10 °C. After 18 h, HPLC analysis indicated consumption of the sulfinyl ketimine intermediate. The reaction mixture was then warmed to 2 °C and diluted with 2-MeTHF (64 kg). The reaction was quenched with the cautious addition of a 14.1 w/w % aqueous solution of sodium glycolate/glycolic acid (145 kg, 15 equiv relative to substrate and prepared by the addition of NaOH (0.8 equiv relative to the glycolic acid) to a 15 w/w% aqueous solution of glycolic acid; final pH measured to be 4.7) over 40 min at <10 °C. The mixture was warmed to 20 °C and aged with mixing for 12 h. The resulting layers were separated. The organic layer was then mixed with an aqueous sodium glycolate/glycolic acid solution (73 kg) for 1 h. The resulting layers were separated. The organic layer was mixed with water (55 kg) for 30 min and then allowed to stand for 15 min. The resulting layers were separated. The organic layer was agitated with a 10 w/w% aqueous solution of NaCl (55 kg) for 30 min and allowed to settle for 30 min. The resulting layers were separated and the organic layer distilled to ∼40 L and codistilled with 2-MeTHF (100 kg). This solution was then passed through a polishing filter and distillation was continued to reach ∼60 L. A continuous distillation was performed with MTBE (150 kg) which gave the desired product **15** (4.99 kg, 79.5% yield of the desired product diastereomer, 90.7% de, 84.0 area%) as a 7.5 w/w% solution in MTBE. Characterization of the isolated product: NMR (600 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.3, 1.0 Hz, 1H), 6.97 (dd, J = 8.3, 2.1 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 4.65−4.4 (m, 5H), 3.41 (d, J = 5.8 Hz, 1H), 2.27 (dt, J = 14.3, 5.8, 1.5 Hz, 1H), 2.14 (ddd, J = 14.3, 7.8, 2.1 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 135.1, 130.2, 122.2, 120.7, 117.7, 82.8 (dd, J = 131.7, 3.8), 81.65 (dd, J = 131.7, 3.8), 76.7 (t, J = 18.9), 56.1, 47.6, 30.8 (t, J = 2.7), 22.6; IR 3179, 2966, 1604, 1026 cm^{-1}. HPLC ret time: 12.36 min. HRMS (ES+) calcd for $C_{15}H_{20}ClF_2NO_2S$, 351.08713, Found 352.09484 [M+H]; mp 120−122 °C $[\alpha]_D^{23}$ = −12.75° ($CHCl_3$, 1.073 g/100 mL).

(*R*)-7-Chloro-2,2-bis(fluoromethyl)-chroman-4-aminium Chloride (16). A vessel was charged with MeOH (45 kg) and then acetyl chloride (24.5 kg) was charged over 1 h at <10 °C (*Caution: Exothermic reaction*). After 30 min, this solution (28.3 mol, 1.5 equiv of HCl) was added to the sulfinamide **15** (4.99 kg, 14.2 mol, 1.0 equiv) in MTBE (44 kg) at 20 °C. After 7 h, HPLC analysis[20] indicated complete consumption of sulfinamide **15**. The reaction mixture was filtered and the cake was washed with MTBE (34 kg, pre-cooled to 0 °C) to provide **16** as a tan, crystalline solid (4.14 kg, 93% yield, 98.5 area%, 92.2% ee). ^{1}H NMR (400 MHz, DMSO) δ 9.10 (bs, 3H), 7.76 (dd, J = 8.4, 0.4 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 4.73−4.51 (m, 5H), 2.54 (dd, J = 13.7, 6.2 Hz, 1H), 2.06 (ddd, J = 14.4, 12.0, 3.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 152.6, 133.4, 128.3, 120.8, 117.7, 116.4, 83.5 (d, J = 173.8, 5.7), 81.3 (d, J = 173.8, 5.7), 77.0 (t, J = 17.8), 41.6, 27.1; IR 2964, 2884, 2017, 1608 cm^{-1}. HPLC ret time: 7.54 min. HRMS (ES+) calcd for $C_{11}H_{12}ClF_2NOS$, 247.05755, Found 248.06516 [M+H]; mp 206−208 °C; $[\alpha]_D^{23}$ = −9.85° (MeOH, 1.089 g/100 mL).

(*R*)-7-Chloro-2,2-bis(fluoromethyl)-chroman-4-amine (*S*)-5-oxopyrrolidine-2-carboxylate (17). A vessel was charged with **16** (4.1 kg salt (3.32 kg freebase), 14.4 mol, 92.2% ee, 98.5 area%), MTBE (30.6 kg), and water (41.5 kg). A 50 w/w% aqueous solution of NaOH (2.3 kg, 4 equiv) was charged to the reactor at 20 °C. Upon dissolution, the mixture was filtered through a polypropylene filter, and the filtrate was transferred to a separatory funnel. The lower layer was removed, and the organic layer was washed with a 25 w/w% aqueous solution of NaCl (20 kg × 2). The organic layer was then passed through an 8 in. Cuno filter housing with a Zeta Carbon Filter 53SP and rinsed with MTBE (2 × 8 kg). The combined filtrate was concentrated under reduced pressure to ∼5 volumes (20 L), and then codistilled with isopropyl acetate (∼70 kg) until the water content was determined to be <0.5 w/w% by Karl Fischer analysis. The solution was then filtered. A separate vessel was charged with L-pyroglutamic acid (2.0 kg) and ethanol (28 kg, 200 proof). To the freebase solution was charged ethanol (20.0 kg) and a portion of the L-pyroglutamic acid solution in ethanol (1.23 kg, 5% of the total solution needed, 0.05 equiv). To the clear solution was charged **17** (20.0 g, 0.1% seed load). The remainder of the L-pyroglutamic acid solution (26.0 kg, to make ∼1.05 equiv) was added to the thin slurry over 4 h. The slurry was then cooled to 0 °C and the supernatant was analyzed by HPLC to confirm appropriate level of **13**. The product was isolated by filtration and washed with ethanol (2 × 12 kg). The crystallization provided **17** as a beige solid (4.58 kg, 94% yield, 64.3 w/w% 13, 99.2 area%, 99.6% ee, 0.35 area% desfluoro impurity). ^{1}H NMR (400 MHz, DMSO) δ 7.80 (s, 1H), 7.55 (dd, J = 8.3, 0.8 Hz, 1H), 7.00 (dd, J = 8.3, 2.1 Hz, 1H), 6.89 (d, J = 2.1 Hz, 1H), 4.73−4.45 (m, 4H), 4.05−3.95 (m, 2H), 2.35−2.15 (m, 2H), 2.13−2.06 (m, 2H), 1.99−1.89 (m, 1H), 1.77 (ddd, J = 15.8, 8.0, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 176.85, 174.95, 152.91, 132.31, 129.00, 124.45, 120.75, 116.12, 83.8 (dd, J = 174.3, 5.2 Hz), 81.8 (dd, J = 174.3, 5.9 Hz), 77.53 (t, J = 17.9 Hz), 55.53, 41.84, 30.97 (t, J = 2.9 Hz), 29.30, 24.86; IR 3280, 2781, 2204, 1671, 1634, 1543 cm^{-1}. HPLC ret time: 11.13 min. Anal. Calcd for $C_{16}H_{19}ClF_2N_2O_4$: C, 51.00; H, 5.08; N, 7.43. Found: C, 51.04; H, 5.01; N, 7.33; mp 167−169 °C; $[\alpha]_D^{23}$ = −20.98° (50/50 H_2O/Acetonitrile, 1.17 g/100 mL).

3-Methylisoquinoline (20). A vessel was charged with benzylamine (25.5 mL, 233 mmol, 1.0 equiv), 1,1-dimethoxypropan-2-one (27.6 mL, 233 mmol 1.0 equiv), and DCE (819 mL). Sodium triacetoxyborohydride (69.2 g, 327 mmol, 1.40 equiv) was then added in one portion and the reaction was aged overnight. GC analysis[21] showed complete conversion and the reaction was diluted with a 2.5 w/w% aqueous solution of $NaHCO_3$ (700 mL) The resulting biphasic mixture was mixed for 30 min. The organic layer was discarded and the aqueous layer was basified by the addition of a 1 M NaOH aqueous solution to a pH of ∼14. The aqueous layer was then extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with a 10 w/w% aqueous solution of KH_2PO_4 to reach a pH of ∼7−8, and then washed with a 5 w/w% aqueous solution of NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give *N*-benzyl-1,1-dimethoxypropan-2-amine as a yellow oil (93% yield). A vessel was charged with chlorosulfonic acid (48.0 mL, 717 mmol). *N*-Benzyl-1,1-dimethoxypropan-2-amine (15 g, 71.7 mmol) was then added at <20 °C. Upon complete addition the internal temperature of the reaction adjusted to 100 °C and held for 10 min. The reaction was then quenched onto ice and MTBE was added. The organic layer was discarded and the aqueous layer was cooled and basified by the addition of a 50 w/w% aqueous solution of NaOH to reach pH ∼14. CH_2Cl_2 (200 mL) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL) and the combined organic layers were washed with brine,

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dried over $MgSO_4$, and filtered. Concentration of the organic layer under reduced pressure provided **20** as a tan solid (5.1 g, 100 w/w%, 50% yield). The NMR spectrum of the title compound was consistent with literature precedent.[22]

3-Methyl-5-nitroisoquinoline (21). A vessel was charged with sulfuric acid (44 L) and the internal temperature was adjusted to 0 °C. **20** (4.4 kg, 30.8 mol, 1.0 equiv) was charged to the acid solution. Potassium nitrate (3.42 kg, 34.2 mol, 1.1 equiv) was added in 4 equal portions at <5 °C. The reaction mixture was warmed to room temperature and after 90 min HPLC analysis[23] indicated the reaction to be complete (0.02 area% starting material remaining). Water (66 kg) was added to the mixture at 0 °C. Two-thirds of the contents of the round-bottom flask was transferred to a separatory funnel and held while the remaining contents were processed: an aqueous 50% w/w solution of NaOH (23.2 kg) was added to the vessel at <60 °C, bringing the pH to ≥12. Water (30 kg) was added and the internal temperature was adjusted to 50 °C. The mixture was agitated for 1 h. The solids were filtered and washed with water (20 kg). This crystallization/filtration procedure was repeated two more times on the remaining reaction mixture to give **21** as a tan solid (5.36 kg, 85.9 w/w%, 89 area%, 79.6% yield). This crude product and MeOH (36.4 kg) were then charged to a vessel. The internal temperature was then adjusted to 45 °C. The methanol solution was then filtered through a Cuno housing fitted with a Zeta Carbon Filter 53SP. Water (45 kg) was added to the filtrate in over 1 h and the resulting solids were filtered and rinsed with MeOH/water (20 kg, 1:1 v/v) to give **21** as an off-white solid (4.21 kg, 98 w/w%, 95 area%, 73% yield). The NMR spectrum of the title compound was consistent with literature precedent.[17]

3-Methylisoquinolin-5-amine (7). A vessel was charged with **21** (4.21 kg, 22.4 mol), and 5% Pd/C Johnson Matthey A102023−5 (178 g catalyst, lot contains 52.6% water. Catalyst/substrate ratio: 2 w/w% on a dry catalyst basis). The reactor was purged with nitrogen and a mixture of EtOH (50 kg) and THF (56.5 kg) was added. The reactor was purged with nitrogen followed by hydrogen and pressurized with hydrogen to 30 psig. The mixture was vigorously agitated at 25 °C and 30 psig hydrogen for 4 h, after which time the reaction was complete.[24] The contents of the reactor were filtered through a Cuno filter housing containing a 12 in. polyamide diatomaceous earth filter and two back-up 2 μm nylon inline filters. Approximately half (63 kg) of the filtrate was added to a vessel and concentrated under reduced pressure to ∼11 L. Methanol (20 kg) was added and concentration to ∼11 L was repeated. Methanol (50 kg) was charged and the slurry was warmed to 40 °C to achieve complete dissolution of the solids. The methanolic solution of **7** was filtered through a polypropylene carbon filter and the filtrate was concentrated to 11 L. The second half of the filtrate was processed in the same manner and then combined with the first portion of the filtrate. The combined filtrates were concentrated to ∼31 L. A continuous distillation was performed using EtOAc (153 kg) and the solution temperature was adjusted to 50 °C and held at that temperature for 30 min to achieve full dissolution of the solids. The solution was cooled to 0 °C over 90 min. The resulting slurry was filtered and the wetcake was washed with chilled ethyl acetate (18 kg) and dried to give **7** as an off-white solid (2.34 kg, 101.2 w/w%, 100 area%, 67% yield). The NMR spectrum of the title compound was consistent with literature precedent.[17]

(*R*)-1-(7-Chloro-2,2-bis(fluoromethyl)-chroman-4-yl)-3-(3-methylisoquinolin-5-yl)urea Hydrate (1). A vessel was charged with **7** (1.2 kg, 7.59 mol, 1.0 equiv), pyridine (0.322 kg, 4.07 mol, 0.5 equiv), DMF (20.2 kg), and acetonitrile (10.0 kg). A solution of phenyl chloroformate (1.422 kg, 9.08 mol, 1.2 equiv) in acetonitrile (4.7 kg) was added to the reactor over ∼3 h at 25 °C. The reaction was allowed to proceed overnight (16 h) at room temperature. An in-process sample indicated 0.17 area% of **7** remained. L-Pyroglutamate salt **17** (2.86 kg, 7.59 mol, 1.0 equiv) was then charged to the slurry, followed by diisopropylethylamine (3.1 kg, 24.8 mol, 3.2 equiv). Analysis by HPLC[24] indicated 0.1 area % activated intermediate remaining. The reaction was diluted with acetonitrile (10 kg). To the product-containing solution was charged water (16 kg), followed by seeds of **1**. Water (74 kg) was then charged over 6 h to the slurry. The slurry was assayed for product in solution; a product concentration of 0.06 w/w% **1** was observed in the supernatant. The slurry was then filtered, washed with 50 v/v% acetonitrile/water (16 kg), and dried to provide **1** as a beige solid (2.99 kg, 89.2% yield, 97.8 w/w%, 99.4 area%). A vessel was charged with **1** and acetone (38 kg, 15 mL/g **1**) to yield a solution, which was then filtered through a Cuno R53SP carbon pad. The pad was then washed with acetone (7 kg). To the product-containing solution was charged water (8 kg). To the solution was charged seeds of **1** and then water (60 kg) was added over 4 h. The resulting slurry was sampled to check product in solution (0.04 w/w% **1** in solution). The slurry was filtered and washed with 50 v/v% acetone/water (2 × 15 kg) to provide **1** as an off-white solid (2.735 kg, 90% yield, 101.3% w/w, 99.4 area%, >99.9% ee). ^{1}H NMR (400 MHz, DMSO) δ 9.18 (s, 1H), 8.66 (s, 1H), 8.26 (dd, J = 7.7, 1.0 Hz, 1H), 7.74 (d, J = 0.6 Hz, 1H), 7.71 (dd, J = 8.1. 1.1 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.38 (dd, J = 8.3, 0.9 Hz, 1H), 7.06 (dd, J = 8.3, 2.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H), 5.11−4.99 (m, 1H), 4.73 (dd, J = 8.8, 1.5 Hz, 2H), 4.60 (dd, J = 8.8, 1.5 Hz, 2H), 2.66 (s, 3H), 2.37 (dd, J = 13.7, 6.0 Hz, 1H), 2.02 (ddd, J = 13.6, 10.6, 2.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 154.6, 152.8, 151.5, 150.3, 133.1, 132.1, 128.6, 127.9, 126.4, 125.9, 122.3, 121.1, 120.6, 119.3, 116.0, 111.5, 83.5 (d, J = 151.4, 5.1), 81.8 (d, J = 151, 5.6 Hz), 77.5 (t, J = 17.7 Hz), 41.1, 29.4 (t, J = 3.4 Hz), 24.4; IR 3289, 3063, 1082, 1566, 1233 cm^{-1}. HPLC ret time: 14.78 min. HRMS (ES+) calcd for $C_{22}H_{20}N_3O_2F_2Cl$, 431.12854 [M+H]. IR: 1681.8, 1564.1, 1232.0, 756.7; mp 144−146 °C; $[\alpha]_D^{23}$ = +1.17°(MeOH, 0.9 g/100 mL).

■ ASSOCIATED CONTENT

Supporting Information

Spectral information for some compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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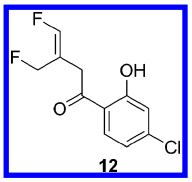

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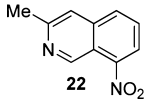
(18) Regiosomer level based on HPLC area%. By inspection of the crude NMR, the regioisomer was tentatively identified as **22**.



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(19) HPLC method: Halo-C18 (0.46 × 150 mm, 2.7 μm); 35 °C, 1.0 mL/min; 90/10 to 10/90 0.1% aqueous $HClO_4$/acetonitrile over 10 min, hold 6 min.

(20) HPLC method: Zorbax Eclipse XDB-C18 (0.46 × 150 mm, 5.0 μm); 35 °C, 1.0 mL/min; 90/10 to 10/90 0.1% aqueous $HClO_4$/acetonitrile over 15 min, hold 5 min.

(21) GC method: Performed on an Agilent 6890 Series GC using an HP-5 5% Phenyl Methyl Siloxane column (30.0 m × 320 μm × 0.25 μm). Method information: Injection temp = 250 °C, Column start temp = 50 °C, method parameters: 50 to 200 °C at 10 °C/min, then hold at 200 °C for 10 min.

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(24) HPLC method: Zorbax Eclipse SB (0.46 × 150 mm, 3.5 μm); 30 °C, 1.0 mL/min; 95/5 to 10/90 0.1% aqueous $HClO_4$/acetonitrile over 25 min, hold 5 min.