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Process Research and Development of an NK-1 Receptor Antagonist. Enantioselective Trifluoromethyl Addition to a Ketone in the Preparation of a Chiral Isochroman

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Abstract:

CJ-17,493 (4) is a chiral NK-1 receptor antagonist. It was first prepared through a diastereoselective crystallization, then through chiral chromatography of a key intermediate, and ultimately via asymmetric synthesis. Multiple routes for the preparation of a key isochroman were demonstrated, and conditions for improved regioselectivity of a Friedel–Crafts acylation were identified. Cesium fluoride was found to be an acceptable initiator for the generation of a nucleophilic trifluoromethyl anion from CF_3TMS. A cinchonine-derived catalyst was identified for the enantioselective addition of the trifluoromethyl group to the ketone, and it was found that the product of the addition would be converted directly to the isochroman by treatment with *t*-BuOK. A Duff reaction was used for the formylation, and the resulting aldehyde was coupled to amine 5 to afford CJ-17,493 (4).

Introduction

Substance-P (Neurokinin 1 or NK-1) (**1**; Figure 1) is a naturally occurring peptide composed of 11 amino acids in the tachykinin family of peptides. It has been shown to be upregulated in several conditions, such as arthritis, migraine, inflammatory bowel disease, asthma, pain, and depression. As such, NK-1 receptor antagonists are recognized as a new class of potential therapeutic agents for the treatment of these diseases.[1] Recently, aprepitant (**2**)[2] was approved as the first NK-1 receptor antagonist in a new class of antiemetics for control of chemotherapy-induced nausea and vomiting, while maropitant (**3**)[3] was approved as a veterinary medication to prevent and treat acute vomiting in dogs.

CJ-17,493 (**4**; Figure 2) is another NK-1 receptor antagonist which is structurally distinct from aprepitant and maropitant. The drug candidate contains two major fragments: a chiral 2-phenyl-3-amino-substituted piperidine and an isochroman. Structural complexity is added due to the presence of a trifluromethyl-bearing quaternary stereocenter. From a retrosynthetic standpoint, it is clear that the compound can be assembled through coupling of the piperidine fragment (**5**) with a precursor (**6**), either through a reductive amination (X = O) or an alkylation (X = H, halogen).

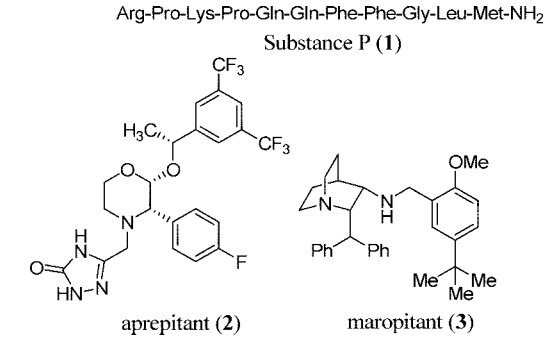

Figure 1

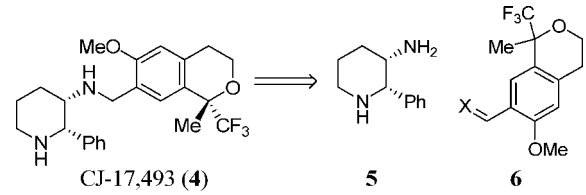

Figure 2

The medicinal chemistry synthesis is depicted in Scheme 1.[4] Anisole derivative **7** was converted to bromo compound **8** in two straightforward steps. Halogen–metal exchange of the bromide was accomplished with *n*-BuLi, followed by a capricious addition to trifluoroacetone. This reaction required cryogenic conditions and was plagued by competitive proton transfer. The alkoxide generated displaced the primary chloride and provided isochroman **9**. Cleavage of the methyl ether was followed by acetylation, to yield acetate **10**, which underwent a surprisingly efficient lipase hydrolysis, providing the desired enantiomer **11** in high yield (45%, 90% of theory) and high ee (94%). The phenol of the undesired enantiomer was removed by extractive workup under basic conditions, while the desired acetate was retained in the organic layer. Hydrolysis of the acetate, followed by alkylation of the phenoxide, provided the methyl ether **12**. A reductive amination approach was pursued for coupling of the piperidine. Thus, formylation of the arene allowed access to aldehyde **13**, which reacted with aminopiperidine **5** to generate the desired target. Overall, this synthetic strategy was reasonable and allowed for the preparation of

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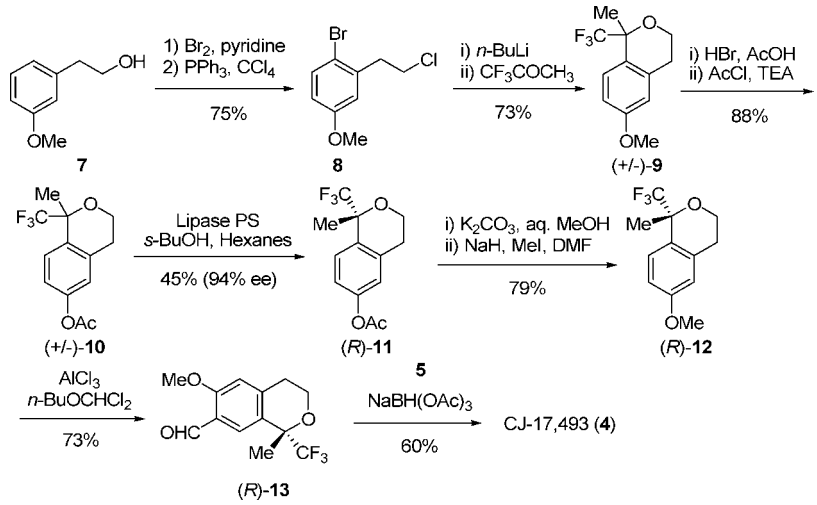
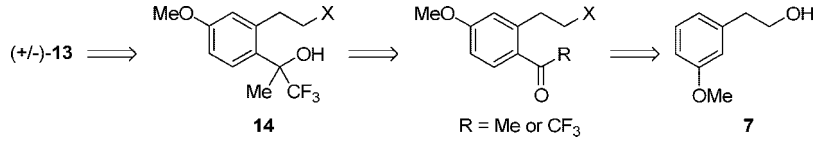
Scheme 1



Scheme 2



several derivatives and access to both enantiomers of the isochroman. However, from a process standpoint, several steps lacked robustness. Condensation of the aryllithium species with trifluoroacetone would be very difficult to scale because of the narrow reaction temperature range. It is also unfortunate that the methyl ether of **9** had to be cleaved and subsequently reinstalled using conditions which must be avoided on a large scale because of safety concerns (NaH in the presence of DMF). Finally, an alternative reagent was desirable for the formylation because of the carcinogenic nature of the dichloromethyl ether selected.

In light of these concerns, an alternative route was sought. Because of the short timelines desired for the preparation of a few kilograms of the product and the availability of a large quantity of enantiomerically pure piperidine **5**, the strategy of coupling **5** with a racemic isochroman and generation of two potentially separable diastereoisomers was adopted. It was known that the enantiomeric purity of product **4** could be enhanced from 94% to >99% *ee* by preparation of the HCl salt. As such, the racemate of aldehyde **13** became the immediate synthetic target. A potential retrosynthesis is depicted in Scheme 2. The isochroman should be generated through an intramolecular alkylation of tertiary alcohol **14**. This approach had a precedent under mild acidic conditions for simple benzylic alcohols[5] and had been demonstrated in Discovery through the alkoxide intermediate. The desired substrate (**14**) would arise either from the addition of MeLi or MeMgX to a trifluoromethyl ketone (R = CF_3) or addition of a trifluoromethyl anion to an acetophenone derivative (R = CH_3). Either intermediate could theoretically be accessed by Friedel–Crafts acylation of anisole **7**.

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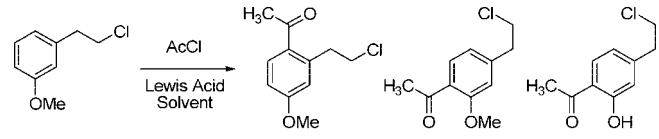
Table 1



entry	Lewis acid (amt, equiv)	solvent	*T*, °C	ratio 17	18	19
1	$AlCl_3$ (2.03)	CH_2Cl_2	−40	1	1	minor
2	$AlCl_3$ (3.38)	CH_2Cl_2	room temp	4	minor	1
3	$AlCl_3$ (3.39)	CH_3NO_2	room temp	1.1	1	0
4	$AlBr_3$ (3.74)	CH_2Cl_2	room temp	11	minor	1
5	$TiCl_4$ (2.17)	CH_2Cl_2	room temp	1	1.3	0

Results and Discussion

It was rapidly found that trifluoroacetylation of anisole derivative **15** (3) under Lewis acid activation could not be achieved using reagents such as TFAA,[6] trifluoroacetyl chloride,[7] 2-trifluoroacetoxypyridine,[8] or 4-(dimethylamino)-1-(trifluoroacetyl)pyridinium trifluoroacetate.[9] Thus, a Friedel–Crafts aromatic electrophilic substitution of **15** with an acetylating agent was pursued.

The first experiments led to surprising results (Table 1). Upon treatment of **15**[10,11] with a slight excess of AcCl in the presence of 2 equiv of $AlCl_3$ at −40 °C, three products (desired **17**, regioisomer **18**, and demethylated regioisomer **19**) were ob-

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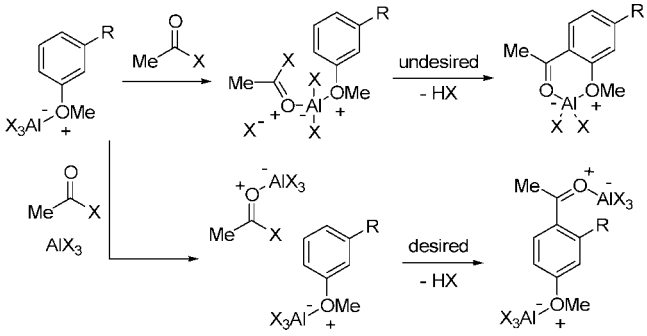
Scheme 3



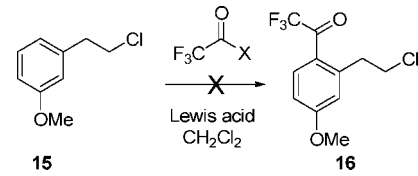
served. Using a larger excess of the Lewis acid at higher temperature (entry 2) increased the ratio of **17**, while the undesired regioisomer was largely demethylated. $TiCl_4$ minimized demethylation but did not improve the selectivity (entry 5), while the use of a polar Lewis basic solvent, such as nitromethane, worsened the ratio (entry 3). Fortunately, using a larger Lewis acid such as $AlBr_3$ maximized the formation of **17** (entry 4).

We speculated that in order to achieve high regioselectivity, it was beneficial to have a bulky Lewis acid coordinate with the aryl ether, which is probably not feasible in a solvent such as nitromethane. This hypothesis would also explain why only the demethylated product of the undesired regioisomer is observed. It is also possible that elevated temperatures and excess Lewis acid might help dissociation of the acylium ion with the Lewis acid and disfavor intramolecular acylation, as shown in Scheme 3.

Having these principles in mind, the optimal conditions were identified (Scheme 4). Arene **15** was added to a 0 °C solution of $AlBr_3$ and AcCl, therefore always assuring a high excess of the Lewis acid. This reaction was dose-controlled, which is also advantageous from a process safety perspective, and provided high regioselectivity (>20:1). Impurity **19** was easily purged in a basic extractive workup.

For the addition of the trifluoromethyl anion to **17**, TBAF-promoted addition of (trifluoromethyl)trimethylsilane to aldehydes and ketones is well precedented.[12] However, elimination of the primary chloride under basic conditions was a concern, and milder conditions to promote the reaction and avoid generation of the styrene were sought. CsF (8 mol %) was identified as a preferred catalyst for the conversion of **17** to **20**. Furthermore, TBAF could be added upon completion of the trifluoromethylation and the resulting tertiary alkoxide underwent nucleophilic displacement of the primary halide, providing the desired isochroman **9** in high overall yield. Unfortunately, while this synthetic sequence is attractive chemically, the physical properties of the intermediates, which were all oils, combined with the very poor stability of acetophenone **17** rendered this route unattractive for scale-up, and a substitute for the primary halide had to be identified.

Performing the acylation directly on **7** was an attractive strategy, since it eliminated the chlorination step and could conceivably provide a functional group more stable toward elimination. The reaction is known to proceed with 3:1



15 **16**

Figure 3

regioselectivity in CS_2, a highly undesirable solvent.[13] Using $AlBr_3$ in conjunction with AcBr, a 10:1 ratio of regioisomers favoring **21** was obtained in high yield (Scheme 5). The synthetic sequence described in Scheme 4 worked equally well on **21**, and the acetate was cleaved using 1 N NaOH. All these operations were carried out in a single reaction and afforded the crystalline diol **22** in 71% overall yield. To complete the synthesis of **9**, several leaving groups were evaluated, and mesylation of the primary alcohol proceeded with concomitant cyclization in near -quantitative yield. Overall, the preparation of racemic **9** was high-yielding and provided a crystalline solid for purification. Because of these attributes, it was implemented on a multikilogram scale.

A second approach was also evaluated (Scheme 6). The route begins from carboxylic acid **23,** which is the precursor to alcohol **7** in the previous route. The Friedel–Crafts acylation proceeded in acceptable yield as a single regioisomer (**24**), potentially from generation of the anhydride followed by intramolecular acylation. Introduction of the trifluoromethyl group to acid **24** could not be accomplished. Esterification afforded the keto ester **25** as a crystalline solid in 91% yield. This substrate proved to be very prone to enolization under basic conditions. In the presence of CsF in DMF, a red color was observed, presumably from the generation of the enolate. Upon addition of CF_3TMS, nucleophilic addition proceeded, although the starting material was never fully consumed. TBAF was introduced to induce cleavage of the silyl ether and lactonization to provide **26** in 54% overall yield.

It had been hoped that conversion of **26** to the hydroxy acid **27** would provide a handle for a classical resolution. While **26** could be hydrolyzed with NaOH, it relactonized upon treatment with a number of chiral amines. Treatment of the sodium carboxylate salt with a chiral amine followed by slow addition of HCl also proved to be unsuccessful. Alternatively, **26** could be reduced to lactol **28** using in situ generated borane, and **9** was obtained by reduction with Et_3SiH under acidic conditions.[14] Since the classical resolution approach failed, this route offered no advantages over that described previously.

A Duff reaction was adopted for the formylation of **9** (Scheme 7). Trifluoroacetic acid was premixed with hexamethylenetetramine (HMTA) for 90 min at 70 °C prior to addition of **9**. Upon completion of the reaction, the resulting imine was hydrolyzed under aqueous acidic conditions, affording aldehyde **13** with 12:1 regioselectivity. In order to achieve high-purity (+/−)-**13** in the penultimate step, the tosyl hydrazone **29** was prepared and provided a highly crystalline intermediate (52% yield from **9** after purification). The hydrazone could be hydrolyzed in 95% yield with $CuCl_2$ in *t*-BuOH/

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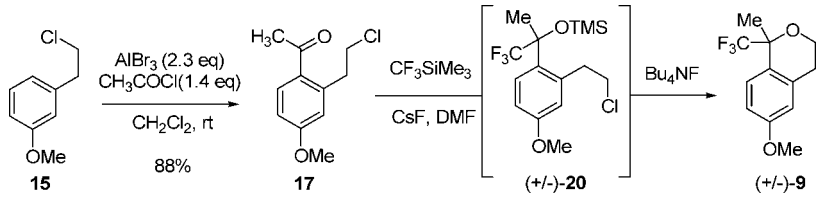
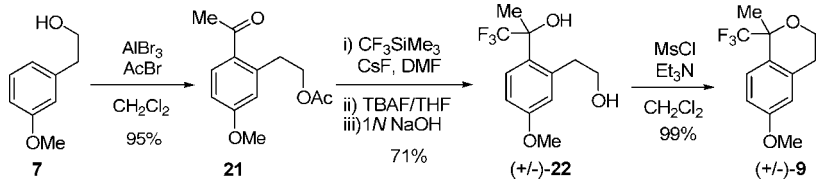
(14) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651.

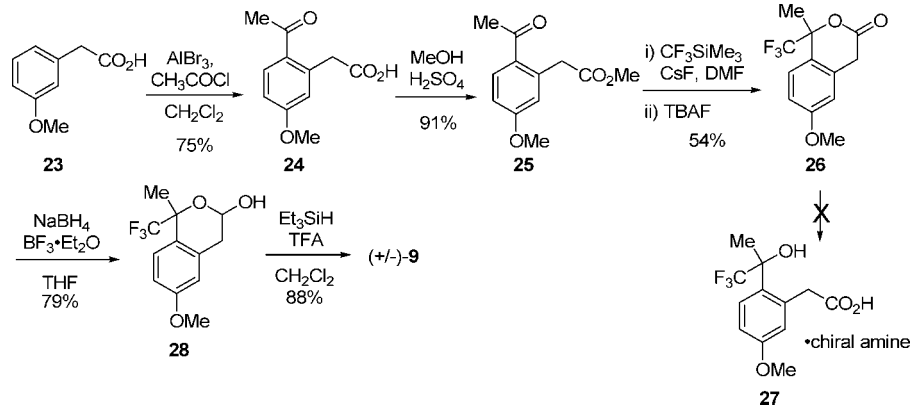
Scheme 4



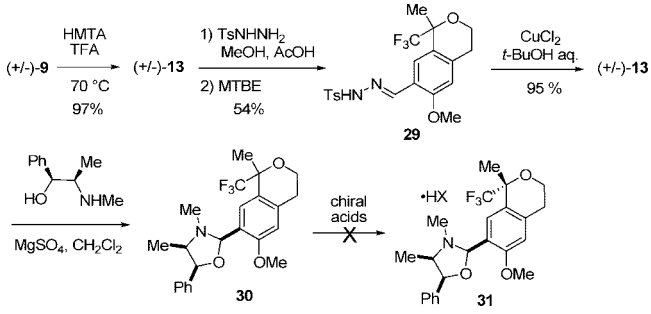
Scheme 5



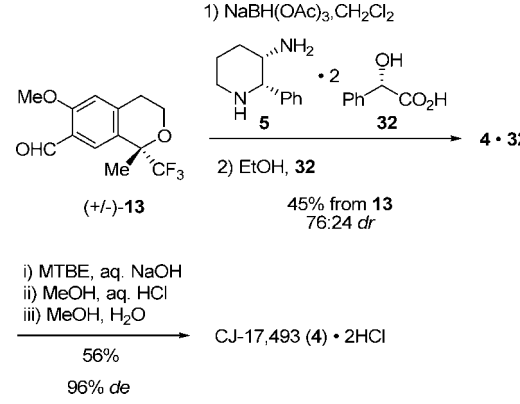
Scheme 6



Scheme 7



Scheme 8



H_2O to provide **13** as a low-melting solid. This method accelerated the rate of hydrolysis to approximately 3 h, as opposed to several days when using $CuSO_4$.[15] On scale, **13** proved to be of sufficient chemical purity to crystallize directly out of heptane after the formylation, which avoided the need for the preparation of the tosyl hydrazone. Attempts to perform a classical resolution through oxazoline **30**[16] met with no success, which meant that a diastereoselective crystallization of the final product would be necessary.

As shown in Scheme 8, racemic **13** was coupled to the resolved dimandelate salt of aminopiperidine (**5**)[17–19] through a reductive amination with sodium triacetoxyborohydride.[20] A basic wash in the workup removed the mandelic and acetic acids, providing a 1:1 mixture of diastereoisomers of **4**. It was known from the work in Discovery Chemistry that a 97:3 mixture of diastereoisomers could be purified through formation of the HCl salt, but this proved to be unsuccessful on the 1:1 mixture. The phase diagram of the HCl salt was generated, and it was determined that any mixture above a 3:1 ratio would be above the eutectic point and should crystallize to high diastereomeric purity.[21] Over a dozen different salts were evaluated

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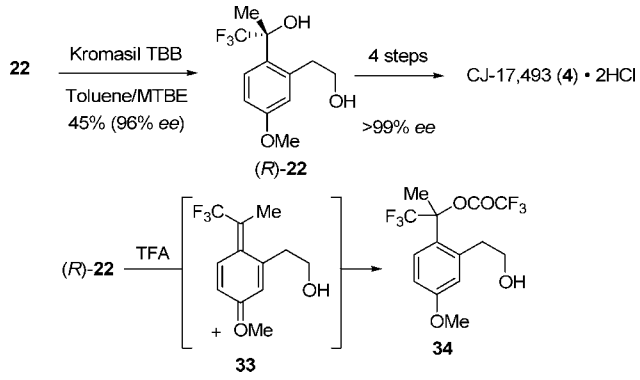
Scheme 9



in a number of solvents to identify a diastereoselective crystallization. It was discovered that (+)-mandelic acid (**32**) reliably provided a 4:1 mixture, while its enantiomer provided little to no enrichment. The crystallization was optimized with EtOH (20 volumes) using 2.0 equiv of the acid to obtain a 4:1 ratio with 45% recovery (representing 36% of the desired diastereomer out of a possible 50% over 2 steps). Another advantage of the mandelate salt was that it provided an excellent purge point of impurities carried through the synthesis, including the products derived from the undesired regioisomer in the Duff reaction.

The completion of the synthesis proved to be operationally simple. The mandelate salt of **4** was filtered and free based in diisopropyl ether with aqueous NaOH. The ether layer was displaced by MeOH, and 2 equiv of aqueous HCl was added. In a final solvent mixture of approximately 3:1 MeOH/H_2O, the dihydrochloride **4**·2HCl) crystallized and was isolated with a dr >98:2. An additional recrystallization provided the final compound in 99% ee, and an excess of 2 kg of the candidate was prepared using this protocol.

While the route described above was acceptable for the first campaign, it clearly lacked efficiency due to intermediacy of racemic **13** taken into the reductive amination. An easy way to lessen the loss of material associated with this approach was to separate the enantiomers of an earlier intermediate. While this could not be achieved through a classical resolution, chiral chromatography appeared to be an attractive option, since many of the intermediates were oils with very high organic solubility (Scheme 9).[22] Diol **22** was rapidly identified as an ideal candidate for simulated moving-bed chromatography,[23] which provided the desired enantiomer (**22**) in 96% ee. One drawback was that, unlike racemic diol **22**, the scalemic product was no longer crystalline. The remainder of the synthesis proceeded as previously described without the need for the mandelate salt formation or recrystallization at the final step. One interesting aspect of this sequence was that it had been demonstrated that (*R*)-**22** could be racemized when treated with a strong acid such as TFA, presumably through the quinone–methide intermediate **33**. Fortunately, this was not the case with the isochroman, which conserved its enantiopurity during the Duff reaction. This observation opened the door for a potential recycle of the undesired enantiomer of the diol.

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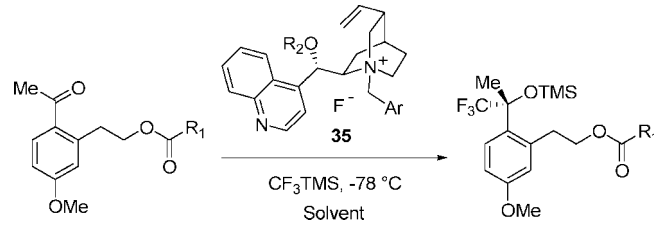
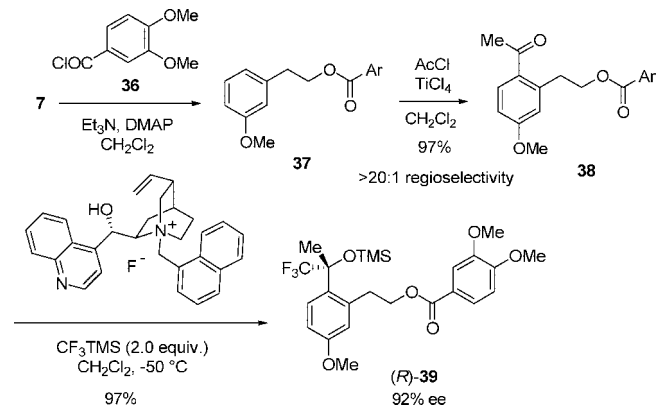
(23) Strube, J.; Haumreisser, S.; Schmidt-Traub, H.; Schulte, M.; Ditz, R. *Org. Process Res. Dev.* **1998**, *2*, 305–319.

Scheme 10



Scheme 11



Ultimately, an enantioselective synthesis of isochroman **9** was wanted to avoid the loss of 50% of a costly intermediate. An attractive approach would be the enantioselective addition of a nucleophilic trifluoromethyl anion to an acetophenone derivative. Much progress has been made in recent years in this area either through the use of chiral auxiliaries[24] or through the use of organocatalysis on a cinchonine-derived framework.[25–27] Since the conditions described in the literature were not appropriate for our original substrate, a thorough evaluation of the factors influencing the reaction was undertaken (Scheme 10).[28] It was quickly determined that CH_2Cl_2 was critical for the reaction to proceed with a useful level of enantioselectivity. The original optimization was conducted with a cinchonine-derived catalyst (**35**), although quinine, quinidine, and cinchonidine were also studied. It was also determined that the free secondary alcohol was necessary and that the 1-naphthyl derivative on the tertiary nitrogen was optimal for a high level of conversion and enantioselectivity. Finally, the preferred substrate proved to have the primary alcohol protected as the 3,4-dimethoxybenzoate. As previously reported,[28] the absolute configuration of the product was secured through elucidation of the X-ray crystal structure of a bromobenzoate derivative.

The final synthesis proceeds as shown in Scheme 11. Alcohol **7** was acylated using acid chloride **36** to provide ester **37**, which underwent a smooth Friedel–Crafts acylation to afford crystalline acetophenone **38** in 97% yield over two steps. It is interesting to note that, by having an electron-rich ester as the

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(25) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137–3138.
(26) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666–667.
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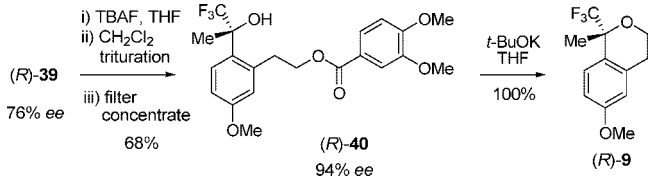
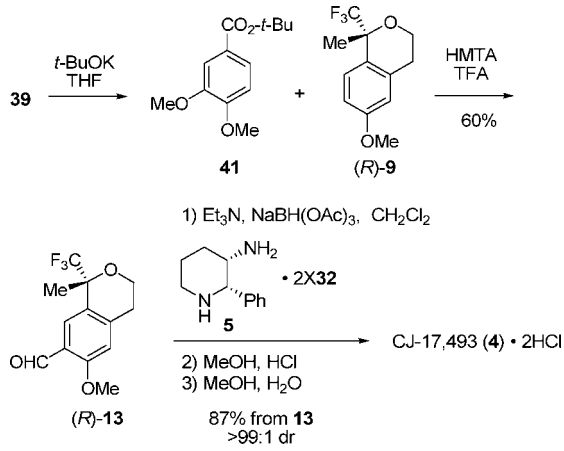
Scheme 12



Scheme 13



protecting group, regioselectivity increased to the level of 20:1. The trifluoromethylation reaction was conducted at −50 °C in the presence of 2 equiv of CF_3TMS and 4 mol % of the catalyst, affording the crude **39** in 92% ee and 97% yield.

Cleavage of the trimethylsilyl ether of **39** proceeded smoothly, and the enantiomeric excess could be increased by precipitation and filtration of the racemic alcohol, which had very poor solubility in CH_2Cl_2. For example, when starting from **39** of only 76% ee, the alcohol (*R*)-**40** could be isolated as an oil in 94% ee and 68% yield (Scheme 12). Furthermore, the 3,4-dimethoxybenzoate was identified as an acceptable leaving group for the direct conversion of ester (*R*)-**40** to isochroman (*R*)-**9** using either KHMDS or *t*-BuOK.

Surprisingly, it was found that the tertiary silyl ether of **39** could be cleaved when treated with *t*-BuOK, which resulted in direct conversion to (*R*)-**9** (Scheme 13). The byproduct, *tert*-butyl ester **41**, can be explained if the reaction proceeds through intramolecular silyl transfer, as depicted in Figure 4. Although migration of a tertiary TMS to a secondary alcohol is precedented under basic conditions,[29] we believe that this is the first example of the deprotection of a tertiary silyl ether using *t*-BuOK in THF. The crude mixture could be taken directly in the Duff reaction, where the acidic conditions cleaved the *tert*-butyl ester and simplified removal of the carboxylic acid as part of the extractive workup. The chiral aldehyde (*R*)-**13** was obtained in 60% yield over the two steps and was progressed through the reductive amination and salt formation sequence, which proceeded in 87% yield.

In summary, several syntheses of CJ-17,493 were investigated in the course of the development of this new NK1 candidate. A diastereoselective crystallization approach allowed for the identification of a regioselective acylation and rapid

(29) Kuramochi, K.; Saito, F.; Takeuchi, R.; Era, T.; Takemura, M.; Kobayashi, J. i.; Sakaguchi, K.; Kobayashi, S.; Sugawara, F. *Tetrahedron* **2006**, *62*, 8006–8015.

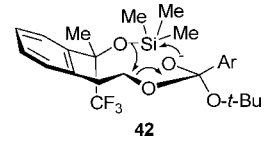


Figure 4

preparation of the candidate. A chiral chromatography permitted the evaluation of the properties of scalemic intermediates and minimized the utilization of the chiral aminopiperidine. Finally, an enantioselective trifluoromethylation was achieved, followed by a direct base-mediated isochroman formation. This sequence allowed for a seven-step synthesis of CJ-17,493 (**4**) from the commercially available alcohol **7** in 49% overall yield.

Experimental Section

1-(2- (2-Chloroethyl)-4-methoxyphenyl)ethanone (17). To a solution of $AlBr_3$ (19.8 g, 74.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C was slowly added AcCl (3.27 mL, 46 mmol). The reaction mixture was warmed to 15 °C, and 1-(2-chloroethyl)-3-methoxybenzene (**15**; 5.61 g, 32.9 mmol) in CH_2Cl_2 (75 mL) was added over 20 min. The reaction mixture was stirred for 1 h and then poured over ice (100 mL). To the mixture was added 1 N aqueous HCl (100 mL). The aqueous layer was removed, and the organic layer was washed with 1 N aqueous NaOH (50 mL), dried over $MgSO_4$, filtered, and concentrated to afford 1-(2-(2-chloroethyl)-4-methoxyphenyl)ethanone (**17**; 6.18 g, 88%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3), 3.38 (t, 2, J = 6.9), 3.82 (t, 2, J = 6.9), 3.90 (s, 3), 6.85 (m, 1), 6.85–7.29 (m, 1), 7.85 (d, 1, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.15, 39.60, 46.38, 56.69, 112.95, 119.68, 130.60, 134.47, 143.01, 163.30, 200.54.

Acetic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (21). This compound was prepared by modification of a known procedure.[13] To a solution of $AlBr_3$ (43.8 g, 164 mmol) in CH_2Cl_2 (70 mL) at 0 °C was slowly added AcBr (14.6 mL, 197 mmol). The reaction mixture was warmed to 15 °C, and 2-(3-methoxyphenyl)ethanol (**7**; 10.0 g, 65.7 mmol) in CH_2Cl_2 (20.0 mL) was added over 45 min. The reaction mixture was stirred for 1 h and then poured over ice (100 mL). To the mixture was added 1 N aqueous HCl (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were washed with 1 N aqueous NaOH (100 mL), dried over $MgSO_4$, filtered through Celite and concentrated to afford acetic acid 2-(2-acetyl-5-methoxyphenyl)ethyl ester (**21**) as an oil (14.8 g, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ 2.05(s, 3), 2.59 (s, 3), 3.29 (t, 2, J = 6.9), 3.89 (s, 3), 4.33 (t, 2, J = 6.9), 6.81 (d, 1, J = 2.5), 8.85 (dd, 1, J = 8.6, 2.6), 7.82 (d, 1, J = 8.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.28, 30.37, 35.36, 56.63, 66.11, 101.21, 112.63, 119.17, 131.00, 134.23, 142.90, 163.24, 172.32. IR: 1737, 1674, 1604, 1567, 1358, 1239, 1037 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.71; H, 7.21.

1,1,1-Trifluoro-2-[2-(2-hydroxyethyl)-4-methoxyphenyl] propan-2-ol ((+/−)-22). To a solution of acetic acid 2-(2-acetyl-5-methoxyphenyl)ethyl ester (**21**; 7.21 g, 30.5 mmol) and cesium fluoride (0.550 g, 3.62 mmol) in DMF (40 mL) at 0 °C was slowly added (trifluoromethyl)trimethylsilane (5.90 mL,

39.9 mmol). The reaction mixture was stirred for 40 min, after which GC/MS and HPLC analysis showed no starting material. For characterization purposes, the reaction mixture was poured into water and extracted with MTBE (100 mL). The organic layer was washed with H_2O (2 × 75 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to provide acetic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]ethyl ester as a crude oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9), 1.93 (s, 3), 2.10 (s, 3), 3.23–3.33 (m, 1), 3.42–3.52 (m, 1), 3.83 (s, 3), 4.26–4.32 (m, 2), 6.77 (dd, 1, J = 8.9, 2.8), 6.86 (d, 1, J = 2.9), 7.32 (d, 1, J = 8.9). ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.03, 21.03, 24.64, 32.86, 55.11, 65.54, 78.90 (q, J = 30.3), 111.26, 117.44, 125.70 (q, J = 287), 129.56, 129.79, 139.77, 159.17, 171.09. IR: 2961, 1741, 1610, 1383, 1286, 1255, 1165, 1140, 1039, 864, 846 cm^{-1}. Anal. Calcd for $C_{17}H_{25}F_3O_4Si$: C, 53.95; H, 6.66. Found: C, 53.72; H, 6.53.

To the reaction mixture containing a solution of acetic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]ethyl ester was added TBAF (31.0 mL of a 1.0 M solution in tetrahydrofuran, 31.0 mmol). The reaction mixture was stirred for 1 h, after which GC/MS and HPLC analysis showed no starting material. For characterization purposes, the reaction mixture was poured into water and extracted with MTBE (75 mL). The organic layer was washed with H_2O (75 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to provide a crude oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 3), 2.01 (s, 3), 2.98–3.06 (m, 2), 3.55 (dt, 1, J = 13.7, 6.8), 3.79 (s, 3), 4.27–4.34 (m, 2), 6.73–6.77 (m, 2), 7.28 (d, 1, J = 8.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.92, 25.50, 34.16, 55.10, 66.49, 76.67 (q, J = 30.3), 111.55, 118.25, 126.02 (q, J = 286), 128.67, 129.56, 139.70, 159.20, 171.32. IR: 3453, 1720, 1610, 1249, 1161, 1134, 1038 cm^{-1}. Anal. Calcd for $C_{14}H_{17}F_3O_4$: C, 54.90; H, 5.59. Found: C, 55.03; H, 5.85.

To the reaction mixture containing acetic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl]ethyl ester was added 1 N aqueous NaOH (35 mL, 35 mmol). The reaction mixture was warmed to room temperature and was stirred until reaction completion. The mixture was poured into H_2O (100 mL) and extracted with MTBE (150 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated. To the crude solid was added hexanes (25 mL) and MTBE (5 mL), and the solid was triturated, filtered, and dried to provide 1,1,1-trifluoro-2-[2-(2-hydroxyethyl)-4-methoxyphenyl]propan-2-ol (5.70 g, 71% overall yield from acetic acid 2-(2-acetyl-5-methoxyphenyl)ethyl ester (**21**)): mp 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3), 2.91 (dt, 1, J = 13.7, 3.9), 3.76 (ddd, 1, J = 13.7, 9.3, 4.4), 3.85 (s, 3), 3.85–3.93 (m, 1), 4.08 (dt, 1, J = 9.3, 3.7), 6.80–6.83 (m, 2), 7.38 (d, 1, J = 8.4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.01, 36.12, 55.19, 64.13, 76.52 (q, J = 28.9), 111.47, 117.43, 125.99 (q, J = 287), 129.69, 129.94, 140.86, 159.55. IR: 3395, 3162, 1610, 1513, 1467, 1248, 1157, 1087, 1046 cm^{-1}. Anal. Calcd for $C_{12}H_{15}F_3O_3$: C, 54.54; H, 5.72. Found: C, 54.65; H, 5.70.

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman ((+/−)-9). To a solution of 1,1,1-trifluoro-2-[2-(2-hydroxyethyl)-4-methoxyphenyl]-propan-2-ol (**22**; 3.12 g, 11.8 mmol) in CH_2Cl_2 (18 mL) was added Et_3N (5.70 mL, 41.1 mmol). The solution was cooled to 0 °C, and MsCl (1.00 mL, 12.9 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 20 h. The formation of methanesulfonic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenyl]ethyl ester was rapid and its disappearance monitored by HPLC (retention time 4.5 min, Zorbax Rx-C6 column 4.6 × 150 mm, 40 °C, 50% CH_3CN/50% (0.2% Et_3N, 0.1% H_3PO_4 aqueous pH 3.2 buffer, 1 mL/min). At the end of the reaction, the mixture was poured into 1 N aqueous HCl (20 mL) and was extracted with MTBE (30 mL). The organic extracts were washed with H_2O (20 mL), dried over $MgSO_4$, filtered, and concentrated to afford 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman ((+/−)-**9**) as an oil (2.89 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3), 2.85–2.90 (m, 2), 3.85 (s, 3), 3.90–3.98 (m, 1), 4.14–4.21 (m, 1), 6.72 (d, 1, J = 2.6), 6.85 (dd, 1, J = 8.7, 2.6), 7.31 (d, 1, J = 8.7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.25, 29.42, 55.19, 61.37, 76.10 (q, J = 27.4), 112.84, 113.43, 124.85, 125.96 (q, J = 289), 127.86, 136.49, 158.98. IR: 2946, 2839, 1738, 1611, 1505, 1162, 1137, 1101 cm^{-1}. Anal. Calcd for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32. Found: C, 58.27; H, 5.35.

(2-Acetyl-5-methoxyphenyl)acetic Acid (24). To a solution of $AlBr_3$ (57.6 g, 216 mmol) in CH_2Cl_2 (90 mL) at 0 °C was slowly added AcCl (11.5 mL, 162 mmol). To the reaction mixture was added (3-methoxyphenyl)acetic acid (**23**; 17.9 g, 108 mmol) in CH_2Cl_2 (20.0 mL). The reaction mixture was stirred for 1 h and then poured over ice (100 mL). The organic layer was separated, and 1 N aqueous NaOH (100 mL) was added. The biphasic mixture was stirred vigorously for 90 min, and the layers were separated. The organic layer was discarded, and concentrated HCl was added to the aqueous layer until the pH reached 1. A solid precipitated and was filtered and air-dried to afford (2-acetyl-5-methoxyphenyl)acetic acid (**24**; 16.8 g, 75%): mp 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3), 3.91 (s, 3), 3.92 (s, 2), 6.92–6.95 (m, 2), 7.88 (d, 1, J = 9.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.33, 41.43, 55.46, 112.54, 118.26, 129.17, 133.08, 136.94, 162.65, 174.80, 200.96. IR: 3435, 1704, 1663, 1609, 1568, 1258 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.46.

(2-Acetyl-5-methoxyphenyl)acetic Acid Methyl Ester (25). To a solution of (2-acetyl-5-methoxyphenyl)acetic acid (**24**; 11.0 g, 52.8 mmol) in MeOH (55 mL) was added concentrated H_2SO_4 (2.2 mL). The reaction mixture was stirred at room temperature for 3 h, after which it was concentrated to a low volume, EtOAc (50 mL) was added and the mixture concentrated to a low volume. EtOAc (50 mL) was added, and the solution was washed with 1 N aqueous NaOH (50 mL). The layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil. Hexanes (70 mL) was added, a precipitate formed, and the mixture was stirred for 2 h. The product was filtered to afford (2-acetyl-5-methoxyphenyl)acetic acid methyl ester (**25**; 10.6 g, 91%): mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3), 3.74 (s, 3), 3.89 (s, 3), 3.95 (s, 2), 6.78 (d, 1, J = 2.6), 6.89 (dd, 1, J =

8.7, 2.6), 7.89 (d, 1, J = 8.6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.65, 42.35, 53.11, 56.69, 113.17, 120.00, 130.52, 134.39, 138.90, 163.54, 173.23, 200.35. IR: 1739, 1665, 1605, 1568, 1321, 1247, 1165 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C, 65.85; H, 6.35. Found: C, 64.87; H, 6.44.

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-one (26). To a solution of (2-acetyl-5-methoxyphenyl)acetic acid methyl ester (**25**; 2.00 g, 9.00 mmol) and CsF (96.0 mg, 0.632 mmol) in DMF (12 mL) at 0 °C was slowly added (trifluoromethyl)trimethylsilane (1.73 mL, 11.7 mmol). The reaction mixture was stirred at 0 °C for 7 h. For characterization purposes, the reaction mixture was poured into water and extracted with MTBE (50 mL). The organic layer was washed with H_2O (2 × 75 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to provide [5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]acetic acid methyl ester as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 9), 1.89 (s, 2), 3.68 (s, 3), 3.77 (s, 3), 3.98 (d, 1, J = 17.2), 4.28 (d, 1, J = 17.0), 6.74–6.77 (m, 2), 7.29 (d, 1, J = 9.1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.87, 24.25, 39.32, 51.75, 55.12, 78.67 (q, J = 30.3), 111.97, 118.30, 125.70 (q, J = 286), 129.50, 129.57, 136.10, 159.17, 172.81. IR: 2956, 1745, 1611, 1577, 1467, 1436, 1290, 1256, 1166, 1092, 989, 863, 847 cm^{-1}. Anal. Calcd for $C_{16}H_{23}F_3O_4Si$: C, 52.73; H, 6.36. Found: C, 52.84; H, 6.36.

To the reaction mixture containing a solution of [5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]acetic acid methyl ester was added TBAF (9.00 mL of a 1.0 M solution in THF, 9.00 mmol). The reaction mixture was stirred for 1 h, after which it was poured into H_2O (50 mL) and extracted with MTBE (50 mL). The organic layer was washed with H_2O (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-one (**26**) as an oil (1.26 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (s, 3), 3.71 (d, 1, J = 20.6), 3.79 (s, 3), 3.89 (d, 20.8), 6.65 (d, 1, J = 1.5), 6.85–6.89 (m, 1), 7.29 (d, 1, J = 8.7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.45, 34.32, 55.33, 83.01 (q, J = 30.3), 112.21, 113.88, 120.57, 124.68 (q, J = 285.7), 127.73, 132.18, 160.75, 167.45. IR: 1765, 1614, 1509, 1322, 1301, 1274, 1259, 1183, 1101, 997, 813 cm^{-1}. Anal. Calcd for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.03; H, 4.54.

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-ol (28). To a solution of 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-one (**26**; 1.50 g, 5.76 mmol) in THF (30 mL) at 0 °C was added $NaBH_4$ (0.240 g, 6.34 mmol) followed by $BF_3 \cdot Et_2O$ complex (0.992 g, 8.07 mmol). The reaction mixture was warmed to room temperature and was stirred overnight. The reaction mixture was added to H_2O (75 mL) and extracted with MTBE (75 mL). The layers were separated, and the organic layer was washed with 1 N aqueous HCl (50 mL), dried over $MgSO_4$, filtered, and concentrated to afford 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-ol (**28**) as an oil and a mixture of α and β anomers (1.19 g, 79%). Data are reported for the major diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 3), 2.85 (dd, 1, J = 15.7, 4.3), 2.88–2.99 (m, 1), 3.11 (dd, 1, J = 15.7, 3.2), 3.80 (s, 3), 5.63 (t, 1, J = 3.7), 6.69 (d, 1, J = 2.7), 6.82 (dd, 1, J = 8.7, 2.7), 7.22–7.27 (m, 1). ^{13}C NMR (100 MHz, $CDCl_3$,data reported for identifiable signals of the major diastereoisomer): δ 24.52, 35.46, 55.16, 90.71, 113.11, 113.98, 125.22, 127.57, 132.98, 159.59. IR: 3439, 2949, 1735, 1613, 1506, 1166, 1141, 1070 cm^{-1}

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman ((+/−)-9). To a solution of 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-3-ol (**28**; 8.36 g, 31.9 mmol) in CH_2Cl_2 (84 mL) was added triethylsilane (15.3 mL, 95.8 mmol) followed by TFA (14.7 mL, 191 mmol). The reaction was stirred at room temperature for 2 h and was poured into 1 N aqueous NaOH (250 mL). The organic layer was separated and washed with 1 N aqueous NaOH (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman (**9**) as an oil (6.88 g, 88%). Spectroscopic data were identical with those of the material prepared by the previous method.

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde ((+/−)-13). *Method A.* To HMTA (31.3 g, 223 mmol) was added TFA (400 mL), and the mixture was heated to 70 °C for 90 min. A solution of 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman (**9**; 50.0 g, 203 mmol) in TFA (100 mL) was then added to the reaction mixture over 40 min. The solution was stirred for 3 h, and H_2O was added (450 mL). The reaction mixture was stirred for 16 h, cooled to room temperature, and poured into MTBE (500 mL). The organic layer was separated and washed with H_2O (3 × 300 mL). The organic layer was poured into a round-bottom flask and cooled to 0 °C. NaOH (6 N) was added in portions until the pH rose to 10 (~500 mL). The organic layer was separated, washed with H_2O (200 mL), dried over $MgSO_4$, filtered, and concentrated to afford 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (**13**) as an oil (54.2 g of a 12:1 mixture of regioisomers, 97%): mp 82–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 3), 2.95 (dt, 2, J = 2.6, 5.3), 3.90–3.97 (m, 1), 3.97 (s, 3), 4.19 (dt, 1, J = 11.2, 5.6), 6.81 (d, 1, J = 1.2), 10.4 (s, 1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.07, 29.98, 55.73, 60.83, 76.03 (q, J = 27.4), 111.81, 112.50, 123.65, 125.32, 125.64 (q, J = 287), 127.06, 160.89, 188.92. IR: 1683, 1616, 1498, 1296, 1271, 1163, 1149, 1120, 1096, 874 cm^{-1}. Anal. Calcd for $C_{13}H_{13}F_3O_3$: C, 57.13; H, 5.05. Found: C, 56.94; H, 4.78.

Method B. A mixture of $CuCl_2$ (52.7 g, 309 mmol) and *N*′-1-[(*E*)-1-(6-methoxy-1,1-dimethyl-3,4-dihydro-1*H*-isochromen-7-yl)methylidene]-4-methyl-1-benzenesulfonohydrazide (**29**; 45.5 g, 103 mmol) in *t*-BuOH (910 mL) and H_2O (228 mL) was heated to 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, concentrated to about 300 mL, and poured into MTBE (500 mL) and H_2O (500 mL). The mixture was stirred for 15 min and filtered. The filtrate was poured into MTBE (200 mL), and the layers were separated. The organic layer was washed with water (4 × 250 mL), dried over $MgSO_4$, filtered, and concentrated to provide 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (**13**) as an oil which solidified on standing (26.8 g, 95%). Spectroscopic data were identical with those of the material reported above.

(*E*)-*N*′-((6-Methoxy-1-methyl-1-(trifluoromethyl)-3,4-dihydro-1*H*-isochromen-7-yl)methylene)-4-methylbenzenesulfonohydrazide (29). To a solution of the crude 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (**13**) (8.97 g, 32.7 mmol) in methanol (90 mL) was added *p*-toluenesulfonhydrazide (6.09 g, 32.7 mmol) followed by 2% aq. AcOH (14.0 mL). The reaction mixture was heated to reflux for 1 h and cooled to room temperature. H_2O (90 mL) was added dropwise, and the mixture was stirred for 2 h. The solid was isolated, stirred in MTBE (62 mL) at reflux for 2 h, stirred overnight at room temperature, and filtered to provide (*E*)-*N*′-((6-methoxy-1-methyl-1-(trifluoromethyl)-3,4-dihydro-1*H*-isochromen-7-yl)methylene)-4-methylbenzenesulfonohydrazide (**29**) (7.87 g, 54%): mp 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3, J = 0.7), 2.44 (s, 3), 2.85–2.89 (m, 2), 3.84 (s, 3), 3.93 (dt, 1, J = 11.2, 5.6), 4.16 (dt, 1, J = 11.2, 5.6), 6.65 (s, 1), 7.33 (d, 2, J = 8.1), 7.79 (d, 1, J = 1.2), 7.89 (d, 2, J = 8.4), 8.13 (s, 1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.48, 23.07, 29.50, 55.47, 60.99, 76.02 (q, J = 27.4), 110.91, 120.45, 124.74, 125.04, 125.72 (q, J = 287), 127.95, 129.45, 134.97, 138.97, 143.34, 144.22, 157.04. IR: 3223, 1623, 1505, 1417, 1325, 1289, 1275, 1172, 1157, 1123, 1098, 918, 658 cm^{-1}. Anal. Calcd for $C_{20}H_{21}F_3N_2O_4S$: C, 54.29; H, 4.78; N, 6.33. Found: C, 54.34; H, 4.73; N, 6.37.

(2*S*,3*S*)-[((1*R*)-6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl](2-phenylpiperidin-3-yl)amine (*S*)-(+)-mandelate (4·32). Sodium triacetoxyborohydride (10.28 kg, 55.0 mol) was added in one portion to a slurry of 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (**13**; 6.59 kg, 24.0 mol) and (2*S*-3*S*)-2-phenylpiperidin-3-ylamine (**5**) dimandelate (**32**) (11.66 kg, 24.2 mol) in CH_2Cl_2 (230 L). Within 15 min most starting material was dissolved and slow precipitation of product began shortly after. The reaction mixture was stirred for 2.5 h at room temperature and cooled to 0 °C, and 2 N NaOH (60 L) was added slowly. The layers were separated. The organic extracts were stirred for 15 min with 2 N aqueous NaOH (120 L), the layers were separated, and the organic layer was washed with H_2O (2 × 30 L). EtOH 2B (187 L) was added, and the CH_2Cl_2 was distilled. The mixture was cooled to 18–22 °C, and (*S*)-(+)-mandelic acid (**32**) (7.35 kg, 48.3 mol) was added. The mixture was stirred, and crystallization began to proceed. After it was stirred overnight, the mixture was filtered to yield 6.38 kg (45%) of ((6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl)(2-phenylpiperidin-3-yl)amine (*S*)-(+)-mandelate (**4·32**) as a mixture of diastereomers (76:24 ratio by HPLC analysis). ^{1}H NMR (400 MHz, $CDCl_3$, data reported for major diastereoisomer): δ 1.42–1.64 (m, 2), 1.53 (s, 3), 1.72–1.79 (m, 1), 1.94–1.98 (m, 1), 2.46–2.89 (m, 4), 3.15–3.28 (m, 3), 3.45 (s, 3), 3.47–3.78 (m, 1), 3.92–3.97 (m, 2), 4.27 (bs, 1), 4.52 (s, 1), 6.66 (s, 1), 7.04–7.19 (m, 4), 7.27–7.36 (m, 7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.99, 22.53, 25.96, 28.58, 45.05, 45.46, 53.52, 53.95, 55.08, 60.61, 61.86, 73.25, 75.54 (q, J = 28.2), 110.36, 126.02, 126.27, 126.32, 126.42, 126.55, 127.01, 127.43, 127.57, 128.27, 135.04, 137.83, 143.16, 156.51, 174.59. IR: 3441, 1576, 1358, 1160, 1136, 1098, 1038, 775, 756, 698 cm^{-1}. Anal. Calcd for $C_{32}H_{37}F_3N_2O_5$: C, 65.52; H, 6.36; N, 4.78. Found: C, 65.55; H, 6.03; N, 4.84.

(2*S*,3*S*)[((1*R*)-6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl](2-phenylpiperidin-3-yl)amine Dihydrochloride (4·2HCl). ((6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl)(2-phenylpiperidin-3-yl)amine (*S*)-(+)-mandelate (**4·32**; 6.25 kg of a 76:24 mixture of diastereoisomers, 10.7 mol) was stirred overnight in MTBE (62.5 L) and 0.5 N aqueous NaOH (62.5 L). The layers were separated, and the organic layer was washed with 0.5 N aqueous NaOH (50 L) and H_2O (2 × 50 L). The organic layer was concentrated to a low volume, and methanol (20 L) was added. The solution was stirred at room temperature, and a solution of 1.89 L of concentrated HCl in H_2O (9.77 L) was slowly added. The mixture was stirred for 6 h, and the solids were filtered. The solids were stirred for 20 h in 3:1 MeOH/H_2O (31.2 L), filtered, and dried to afford ((6-methoxy-1-methyl-1-(trifluoromethyl) isochroman-7-yl)methyl)(2-phenylpiperidin-3-yl)amine dihydrochloride (**4·2HCl**; 3.02 kg, 56%) as a 98:2 mixture of diastereoisomers. The diastereomeric ratio could be further increased by crystallization from methanol/water (75:25). ^{1}H NMR (400 MHz, D_2O, data reported for major diastereoisomer): δ 1.52 (s, 3), 1.80–1.92 (m, 2), 1.95–2.50 (m 1), 2.21–2.26 (m, 1), 2.63–2.71 (m, 2), 3.04–3.11 (m, 1), 3.36 (s, 3), 3.45–3.49 (m, 1), 3.65–3.81 (m, 3), 3.90–3.96 (m, 1), 4.09 (d, 1, J = 13.5), 6.46 (s, 1), 6.98–7.07 (m, 3), 7.23–7.25 (m, 2), 7.30 (t, 1, J = 7.5). IR: 2958, 1457, 1377, 1143, 749, 692 cm^{-1}. Anal. Calcd for $C_{24}H_{31}Cl_2F_3N_2O_2$: C, 56.81; H, 6.16; Cl, 13.97; N, 5.52. Found: C, 56.69; H, 6.31; Cl, 14.13; N, 5.55.

3,4-Dimethoxybenzoic Acid 2-(3-Methoxyphenyl)ethyl Ester (37). To a solution of 3-methoxyphenethyl alcohol (**7**; 21.24 g, 139.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (23.3 mL, 167 mmol), DMAP (3.22 g, 26.4 mmol), and 3,4-dimethoxybenzoyl chloride (33.57 g, 167.3 mmol). The reaction mixture was warmed slowly to room temperature and stirred for 16 h. To the reaction mixture was added H_2O (200 mL). The aqueous layer was removed, and the organic layer was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to afford 3,4-dimethoxybenzoic acid 2-(3-methoxyphenyl)ethyl ester (**37**) as a crude brown oil (44.16 g, 100%). This material was used without further purification. ^{1}H NMR: δ 3.08 (t, 2, J = 7.0), 3.82 (s, 3), 3.95 (s, 3), 3.97 (s, 3), 4.54 (t, 2, J = 7.0), 6.80 (dd, 1, J = 2.6, 0.8), 6.83 (dd, 1, J = 2.6, 0.8), 6.87 (t, 1, J = 1.9), 6.90 (d, 1, J = 8.6), 7.24 (d, 1, J = 7.8), 7.54 (d, 1, J = 1.9), 7.69 (dd, 1, J = 8.4, 2.0).

3,4-Dimethoxybenzoic Acid 2-(2-Acetyl-5-methoxyphenyl)ethyl Ester (38). To a solution of the crude 3,4-dimethoxybenzoic acid 2-(3-methoxyphenyl)ethyl ester (**37**; 44.16 g, 139.6 mmol) in CH_2Cl_2 (400 mL) at 0 °C was added $TiCl_4$ (23.0 mL, 209 mmol) and AcCl (19.8 mL, 279 mmol). After 2 h, the reaction mixture was poured over ice (100 mL). To the mixture was added 1 N aqueous HCl (200 mL), and the resulting mixture was stirred for 2 h. The organic layer was separated and washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to afford 3,4-dimethoxybenzoic acid 2-(2-acetyl-5-methoxyphenyl)ethyl ester (**38**) as a pale peach solid (48.4 g, 97%): mp 110–111 °C (6:1 *i*-PrOH/hexanes). ^{1}H NMR: δ 2.57 (s, 3), 3.39 (t, 2, J = 6.6), 3.79 (s, 3), 3.90 (s, 3), 3.92 (s, 3), 4.54 (t, 2, J = 6.6), 6.81 (dd, 1, J =

8.3, 2.5), 6.84 (d, 1, J = 2.5), 6.86 (d, 1, J = 8.3), 7.49 (d, 1, J = 2.1), 7.64 (dd, 1, J = 8.7, 2.1), 7.80 (d, 1, J = 8.7). ^{13}C NMR: δ 29.33, 34.56, 55.52, 56.13, 56.20, 65.37, 110.37, 111.62, 112.10, 118.37, 123.17, 123.72, 129.90, 133.30, 142.13, 148.71, 153.04, 162.16, 166.47, 199.53. IR: ν 1709, 1672, 1602, 1270, 1223, 1031, 533 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.27; H, 6.27.

(1*R*)-3,4-Dimethoxybenzoic Acid 2-[5-Methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]ethyl Ester ((*R*)-39). To a solution of 3,4-dimethoxybenzoic acid 2-(2-acetyl-5-methoxyphenyl)ethyl ester (**38**; 200 mg, 0.558 mmol) and catalyst **35** (10.1 mg, 4 mol %) in CH_2Cl_2 (2.0 mL) at −50 °C was added CF_3TMS (0.12 mL, 8.1 mmol). The solution was stirred at −50 °C for 3 h and warmed to room temperature overnight. HPLC analysis showed a 97% conversion and 92% ee. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extract was concentrated to provide an oil. For analytical purposes, the material was purified by chromatography on SiO_2 (EtOAc/Hex, 20:80). ^{1}H NMR: δ 0.22 (s, 9), 1.96 (s, 3), 3.42 (ddd, 1, J = 13.4, 8.4, 6.5), 3.56–3.65 (m, 1), 3.81 (s, 3), 3.97 (s, 3), 3.98 (s, 3), 4.44–4.59 (m, 2), 6.78 (dd, 1, J = 9.0, 2.8), 6.94 (d, 1, J = 8.4), 6.96 (d, 1, J = 2.8), 7.34 (d, 1, J = 9.0), 7.60 (d, 1, J = 1.9), 7.74 (dd, 1, J = 8.4, 1.9). ^{13}C NMR: δ 2.31, 24.84, 33.40, 55.29, 56.13, 56.20, 66.09, 79.24 (q, J = 30.1), 110.45, 111.53, 112.13, 117.92, 123.10, 123.79, 124.18 (q, J = 286), 129.76, 130.05, 140.09, 148.80, 153.15, 159.43, 166.56. IR: 1711, 1604, 1515, 1270, 1223, 1174, 1134, 1027, 861, 846, 763 cm^{-1}. Anal. Calcd for $C_{24}H_{31}F_3O_6Si$: C, 57.58; H, 6.24. Found: C, 57.16; H, 6.30.

6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (*R*)-(13). To a solution of (1*R*)-3,4-dimethoxybenzoic acid 2-[5-methoxy-2-(2,2,2-trifluoro-1-methyl-1-((trimethylsilanyl)oxy)ethyl)phenyl]ethyl ester ((*R*)-**39**; 2.16 g, 4.31 mmol) in THF (20 mL) at 0 °C was added *t*-BuOK (0.734 g, 6.54 mmol). The reaction mixture was warmed slowly to room temperature and was stirred overnight. To the reaction mixture was added 1 N NaOH (10 mL), and the mixture was stirred vigorously for 30 min and was partitioned between H_2O (10 mL) and toluene (20 mL). The organic layer was washed with 1 N HCl (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to a brown oil, which was taken directly into the next step. To HMTA (0.738 g, 5.26 mmol) was added TFA (9.0 mL), and the mixture was heated to 70 °C for 2 h. A solution of the crude mixture of **9** and **41** in TFA (5 mL) was then added to the reaction mixture. The solution was stirred for 4 h at 70 °C, after which GC/MS and HPLC analyses showed no remaining starting material. Water (10 mL) was added to the reaction mixture at 70 °C. After 4 h at 70 °C, the resulting reaction mixture was cooled to room temperature and stirred overnight. The reaction mixture was partitioned between H_2O (10 mL) and toluene (30 mL). The organic layer was separated and washed with H_2O (3 × 10 mL). The organic layer was then transferred into a flask and cooled to 0 °C, and 1 N NaOH was added to raise the pH to 12. The organic layer was separated, washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide a crude oil. Purification via filtration through SiO_2 with 40% EtOAc/hexanes as eluent afforded 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde ((*R*)-**13**) as an amorphous solid (0.709 g, 60% from **39**). Spectroscopic data were identical with those of material prepared from the previous method.

(2*S*,3*S*)[((1*R*)-6-Methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl](2-phenylpiperidin-3-yl)amine Dihydrochloride (4·2HCl). To a solution of 6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-carbaldehyde (**13**; 50.0 g, 182 mmol) and (2*S*,3*S*)-(2-phenylpiperidin-3-yl)amine dimandelate (**5·32**; 80.6 g, 219 mmol) in CH_2Cl_2 (1.0 L) was added TEA (61.0 mL, 437 mmol). The mixture was stirred for 15 min, sodium triacetoxyborohydride (77.0 g, 363.0 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction was quenched by addition of 4 N NaOH (456 mL), and the layers were separated. The organic layer was washed with 1 N HCl (500 mL to pH 6). The CH_2Cl_2 was displaced with MeOH until absence of CH_2Cl_2. To the mixture (375 mL) was added a solution of concentrated HCl (33 mL) in H_2O (90 mL), and the mixture was stirred overnight, cooled to 10 °C, and filtered. The crude solid was triturated in 3:1 MeOH/H_2O (2 × 500 mL) and filtered to afford ((6-methoxy-1-methyl-1-(trifluoromethyl)isochroman-7-yl)methyl)(2-phenylpiperidin-3-yl)amine dihydrochloride (**4**·2HCl; 80.8 g, 87%) as a >99:1 mixture of diastereoisomers. The spectroscopic and other analytical data were identical with those of the material prepared by the previous route.

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