Efficient and general asymmetric syntheses of (R)-chroman-4-amine salts

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ABSTRACT

Starting from a variety of substituted chroman-4-ones, a highly enantioselective CBS reduction using in situ-generated B–H catalyst gave (S)-chroman-4-ols. Azide inversion and reduction gave crude (R)-chroman-4-amines, which could be purified without chromatography by isolation as the (R)-mandelic or D-tartaric acid salts with good yields and excellent ee.

Chiral chroman-4-amines have been utilized as core scaffolds in an increasing number of recent drug discovery programs (Fig. 1). For example, chroman-4-amine sulfonamide **1** was found to be a potent $K_v1.5$ potassium channel blocker ($IC_{50} = 0.11$ μM) with good selectivity over the block of hERG.[1] Also, diaminochroman carboxamide **2** is a 0.8 nM inhibitor of the human bradykinin B1 receptor showing in vivo efficacy against hypotension and inflammatory pain.[2]

We required an efficient, general, scalable, and highly enantioselective synthesis of an array of structurally diverse (R)-chroman-4-amines **3** for our own drug discovery efforts (Fig. 2). We hoped to obtain these from readily available chroman-4-ones **4**.[3] Conceptually, an imine (i.e., **5**) or enamine (i.e., **6**) derived from **4** could be reduced enantioselectively to give **3**. Alternatively, enantioselective ketone reduction to (S)-chroman-4-ol **7** followed by amine inversion would also yield **3**.

Several recently disclosed methods for 2-unsubstituted chroman-4-amine preparation were initially investigated,[4] but 2,2-disubstituted chromans (Fig. 2, R = alkyl) were unsuitable substrates for these methods in our hands. Initial results with asymmetric enamine hydrogenation were encouraging and could provide a general route upon further optimization.[5] Finally, we decided to investigate the previously reported asymmetric ketone reduction/azide inversion route disclosed by Gerlach and co-workers,[6] aware that low reduction ee was observed with electron-withdrawing aryl substituents. Of equal concern, low azide inversion yield and ee were reported in several examples. These drawbacks would need to be overcome to provide a practical and general route.

Initially, the published CBS reduction[7] conditions for chroman-4-one **8** were employed (Table 1, entry 1, Scheme 1), using the commercially available B–Me CBS catalyst (5 mol %) and borane–methyl sulfide (1 equiv).[6] These conditions gave (S)-chroman-4-ol **9** with the reported 96% ee and quantitative yield. Aware that other substrates were more problematic under these conditions, we sought to further optimize the reaction. Without changing the solvent, the in situ-generated B–H CBS catalyst derived from the free aminoalcohol ligand (5 mol %) and N,N-diethylaniline borane (also serving as stoichiometric reducing agent) gave comparable results (Table 1, entry 2).[8] Finally, switching to methyl t-butyl ether (10
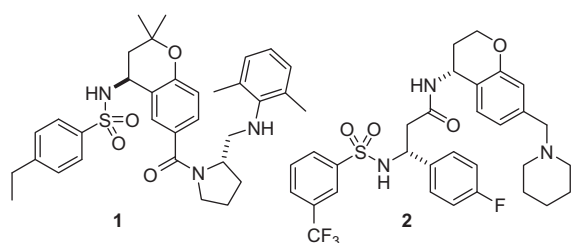

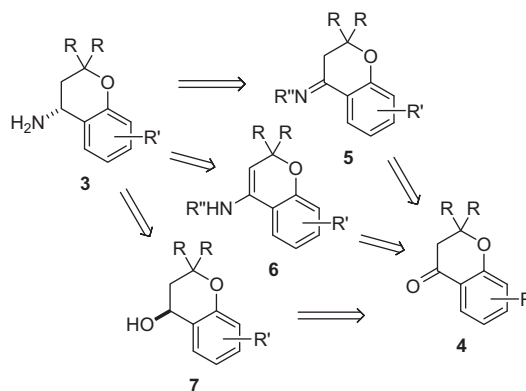**Figure 1.** Biologically active chroman-4-amine-containing compounds.

Figure 2. Chroman-4-amines (3) from chroman-4-ones (4).

* Corresponding author. Tel.: +1 847 938 6741; fax: +1 847 935 0548.
 E-mail address: eric.a.voight@abbott.com (E.A. Voight).

Table 1
Asymmetric chroman-4-one reduction according to Scheme 1

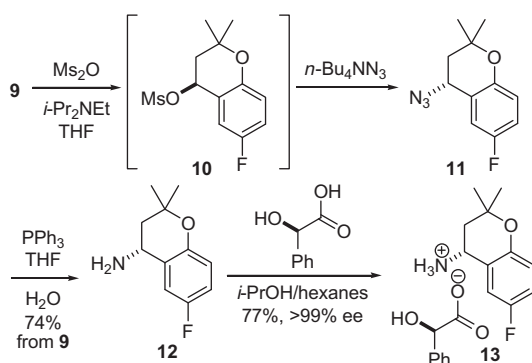| Entry	Conditions[a]	%ee[b]	Yield[c] (%)
1	(R)-2-Me-CBS-oxazaborolidine (5 mol %), BH3·SMe₂ (1 equiv), toluene, 0 °C	96	>99
2	(R)-Diphenyl(pyrrolidin-2-yl)methanol (5 mol %), BH₃·NEt₂Ph (1.2 equiv), toluene, 45 °C	96	>99
3	(R)-Diphenyl(pyrrolidin-2-yl)methanol (5 mol %), BH₃·NEt₂Ph (1.2 equiv), MTBE, 45 °C	99	>99

[a] Slow inverse addition (30–75 min) of substrate to reagent for all reactions.
[b] Enantiomeric excess was determined by chiral HPLC.
[c] Isolated yield.
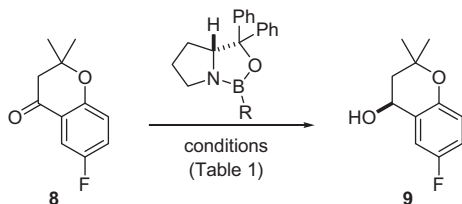
Scheme 1. Asymmetric reduction of chroman-4-one **8**.

Scheme 2. Preparation of (R)-chroman-4-amine salt **13**.

Figure 3. Chromanone substrates for Scheme 2 procedure.

Table 2
CBS reduction, n-Bu₄NN₃ inversion, (R)-mandelic acid salt formation according to Schemes 1 and 2 (substrates in Fig. 3)

Entry	Substrate	Reduction %ee[a]	Crude amine yield % (%ee)[a]	Amine salt yield % (%ee)[a]
1	**14**	>99	67 (87)	82 (>99)
2	**15**	>99	71 (95)	65 (99)
3	**16**	97	59	65 (>99)
4	**17**	99	68 (94)	80 (98)
5	**18**	>99	56 (98)	75 (>99)
6	**19**	>99	79	64 (98)

[a] Enantiomeric excess was determined by chiral HPLC.

volumes) as the solvent under the same conditions increased the ee to 99% and was conveniently carried out on a large scale (Table 1, entry 3). Besides increasing the ee, this procedure displayed no moisture sensitivity, avoided the safety and volume productivity concerns associated with conventional CBS reductions,[8] and required no product purification beyond conventional aqueous workup.[9]

From (S)-chroman-4-ol **9**, the published procedure was followed, generating mesylate **10** at −25 °C in THF followed by the addition of tetra-N-butylammonium azide to produce inverted (R)-azide **11** (Scheme 2).[6] Azide reduction under Staudinger conditions gave (R)-chroman-4-amine **12** in 74% overall yield from **9**.[10] Chiral HPLC versus a racemic reference demonstrated that **12** was produced in 91% ee, a degradation we expected based on the published result. In order to upgrade the ee and to avoid chromatography, salt crystallization conditions were explored (Scheme 3). A patent procedure described a racemate resolution with low recovery and good ee using (R)-mandelic acid.[11] From crude amine **12** (after acid/base workup), the (R)-mandelic acid salt of **12** was formed in i-PrOH (10 volumes) at 50 °C. Addition of hexanes (10 volumes) as an antisolvent and slow cooling to room temperature allowed the filtration of **13** in 77% yield and high purity. Chiral HPLC of this material was not able to detect the minor enantiomer.

This chromatography-free process was applied successfully to chroman-4-ones **14–19**, efficiently providing (R)-chroman-4-amine salts (Table 2, Fig. 3). Both 2-unsubstituted (entries 1 and 2) and 2,2-dimethyl (entries 3–6) chromans were tolerated, as well as a variety of aryl substituents. In all cases, ee degradation in the
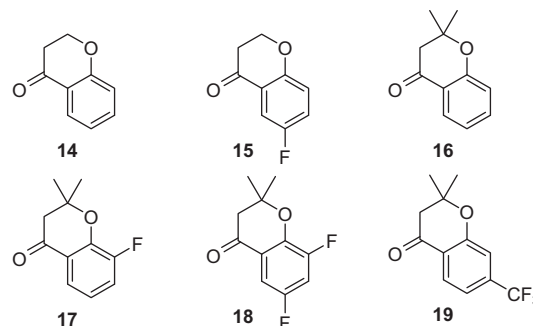
azide inversion step was observed to some extent, however, the (R)-mandelic acid salt isolation improved the ee and provided good recovery and purity. All reactions were carried out on a 5–10 g scale and required no chromatography. In comparison to the Gerlach procedure,[6] this method provided modest improvements in overall yield while significantly improving ee and scalability.

While this procedure worked well for all substrates in Figure 3, more lipophilic chroman-4-amine mandelic acid salts often formed oils instead of crystalline solids. A screen of several chiral and achiral acids identified D-tartaric acid as a suitable alternative. Also, the acid/base workup employed for the crude amines to reject the phosphine oxide reduction byproduct was unsuccessful, since lipophilic HCl salts did not show sufficient water solubility. Azide hydrogenation provided an alternative. Finally, a diphenylphosphoryl azide procedure was identified to improve the azide inversion step for some substrates.[12] An example of this procedure starting from chromanone **20** is shown in Scheme 3, providing amine salt **24** in 76% overall yield from **20** and 98% ee.[13]

With this modified method in hand, several (R)-chroman-4-amine D-tartaric acid salts were prepared in good overall yield and excellent ee (Fig. 4). In addition to 2,2-bis(monofluoromethyl) substitution (Scheme 3), 2,2-diethyl (**25–28**), 2,2-dipropyl (**29**), and 2,2-dimethyl (**30**) chroman substitution were well tolerated. Chromans with aryl substitution at the 6, 7, or, 8 position were all good substrates for this chemistry, reliably providing (R)-chro-
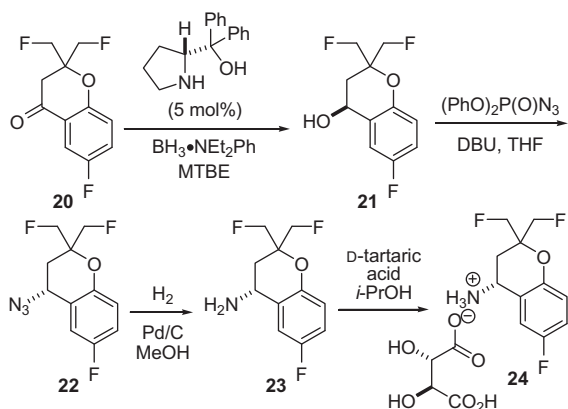
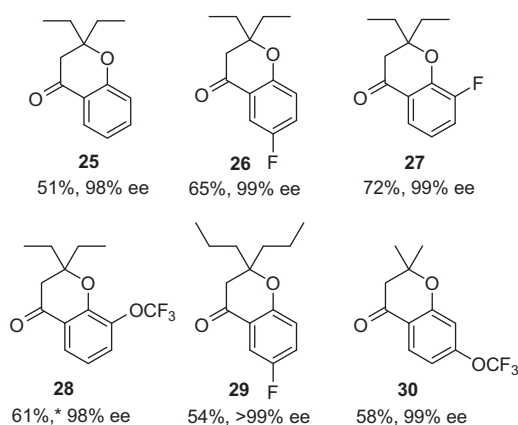**Scheme 3.** Alternative procedure to D-tartaric acid salt **24**.

Figure 4. Chromanone substrates for Scheme 3 procedure (* = Ms₂O/n-Bu₄NN₃ inversion protocol).

man-4-amine D-tartaric acid salts on multigram scale without chromatography from chroman-4-ones **25–30**.

In conclusion, a known method for the preparation of chiral chroman-4-amines from chroman-4-ones was optimized to provide a general, scalable, and highly enantioselective route. Alternative procedures for each step of the synthesis were identified to make the approach more practical, including an improved CBS reduction protocol, a DPPA azide inversion, azide hydrogenation, and chiral salt isolation. The (R)-mandelic and D-tartaric acid salt isolation procedures provided convenient and reliable methods for chemical and chiral purification. The modified procedure (Scheme 3) has been carried out successfully on kilogram scale, highlighting the utility of this route.

Acknowledgment

References and notes

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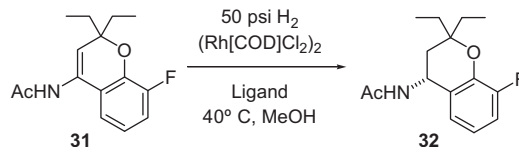
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9. Typical CBS reduction procedure: A solution of methyl tert-butylether (34 mL), (R)-diphenyl(pyrrolidin-2-yl)methanol (1.10 g, 4.35 mmol) and borane-N,N-diethylaniline complex (18.5 mL, 104 mmol) was heated to 45 °C and chroman-4-one **8** (16.9 g, 87.0 mmol) in methyl tert-butylether (136 mL) was added over 75 min via an addition funnel. After 15 min at 45 °C, the reaction mixture was cooled to 10 °C and treated with MeOH (85 mL) over 10 min (H₂ evolution). After stirring for 30 min at room temperature, 2 N HCl (85 mL) was added and the reaction mixture was stirred for 10 min. Methyl tert-butylether (170 mL) was added and the layers were separated. The organic layer was washed with 2 N HCl (85 mL) and brine (35 mL). The aqueous layers were back-extracted with methyl tert-butylether (85 mL). The combined organic portions were dried (Na₂SO₄), filtered, and concentrated, to provide (S)-chroman-4-ol **9** (17.4 g, 89.0 mmol). Analysis by analytical chiral HPLC (Chiralcel OJ 4.6 × 25 mm, 20% isopropanol/hexane, 23 °C, 0.5 mL/min) showed 99% ee versus a racemic reference.
10. Typical azide inversion, reduction, salt formation procedure according to Scheme 2: A solution of chroman-4-ol **9** (17.1 g, 87.0 mmol) in THF (340 mL) was cooled to −30 °C followed by the addition of methanesulfonic anhydride (16.7 mL, 131 mmol). N,N-Diisopropylethylamine (21.3 mL, 122 mmol) was slowly added (internal temperature ⩽ −24 °C) to the reaction mixture. After 50 min, additional Ms₂O (3.00 g, 0.2 equiv) and N,N-diisopropylethylamine (4.2 mL, 0.3 equiv) were added and the reaction mixture was stirred for 30 min at 0 °C. The dark solution of mesylate **10** was cooled to −30 °C and treated with tetra-N-butylammonium azide (49.5 g, 174 mmol). The resulting slurry was allowed to slowly warm to ambient temperature overnight. After 14 h, methanol (85 mL) was added followed by 2 N NaOH. After 30 min, MTBE (340 mL) and water (170 mL) were added. The layers were separated and the organic layer was washed with water (85 mL), 2 N HCl (2 × 85 mL), water (85 mL), and brine (34 mL). The acidic washes were back-extracted with MTBE (85 mL). The combined organic portions were dried (Na₂SO₄), filtered, and concentrated to give azide **11** as a yellow oil that was used without further purification. The crude azide **11** was dissolved in THF (305 mL) and water (34 mL) and treated with triphenylphosphine (25.1 g, 96.0 mmol). The yellow solution was heated to 60 °C for 2.5 h. The reaction mixture was cooled and concentrated to remove THF. Dichloromethane (170 mL), 2 N HCl (85 mL), and water (425 mL) were added and the layers were separated. The aqueous portion was washed with dichloromethane (85 mL). 2 N NaOH (100 mL) was added to the aqueous layer, followed by extraction with dichloromethane (5 × 85 mL). The organic layers were dried (Na₂SO₄), filtered, and concentrated to give amine **12** (12.6 g, 64.3 mmol, 74%). Analytical chiral HPLC showed 91% ee versus a racemic reference. Amine **12** (12.6 g, 64.3 mmol) and isopropanol (126 mL) were heated to 50 °C while (R)-(−)-mandelic acid (9.79 g, 64.3 mmol) was added. At 43 °C, solids were observed, and heating continued to 50 °C. The mixture was aged at 50 °C for 10 min, then hexanes (126 mL) were added for over 45 min at 50 °C. Following the addition, the reaction mixture was cooled to ambient temperature for over 90 min, and the precipitated solids were filtered and washed with 1:1 isopropanol–hexanes. The solid was dried in a vacuum oven at 45 °C overnight with an air bleed, to give (R)-chroman-4-amine salt **13** (17.2 g, 49.5 mmol, 77%) as a crystalline white solid. The solid had no detectable minor isomer by chiral HPLC and the mother liquor showed ∼50% ee in favor of the desired isomer. ¹H NMR (300 MHz, DMSO-d₆) δ 7.44–

7.37 (m, 3H), 7.30–7.17 (m, 3H), 7.01 (td, J = 8.5, 3.1 Hz, 1H), 6.78–6.73 (m, 1H), 4.70 (s, 1H), 4.21 (dd, J = 11.5, 6.3 Hz, 1H), 2.13 (dd, J = 13.2, 6.3 Hz, 1H), 1.65 (t, J = 12.3 Hz, 1H), 1.37 (s, 3H), 1.17 (s, 3H); MS (DCI/NH$_3$) m/z 179 (M−16)+.

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12. For example, see Ref. 2.
13. Typical azide inversion, reduction, salt formation procedure according to Scheme 3: A solution of (S)-chroman-4-ol **21** (12.56 g, 54.1 mmol) and THF (190 mL) was cooled to <5 °C, and 1,8-diazabicyclo[5.4.0]undec-7-ene (12.11 mL, 81 mmol) and diphenylphosphoryl azide (15.18 mL, 70.3 mmol) were added. After 2 h, the yellow slurry was warmed to room temperature. After 14 h, the mixture was concentrated, diluted with MTBE (250 mL), and washed with 2 N NaOH (2 × 125 mL), brine (50 mL), 2 N HCl (2 × 125 mL), and brine (50 mL). The organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated,

giving crude azide **22** as a yellow oil. A solution of crude azide **22** (13.92 g) in MeOH (150 mL) was shaken with 5% Pd on carbon (4.17 g, 15 wt % dry basis) under hydrogen (30 psi) at 50 °C for 3 h. The mixture was filtered and concentrated with an isopropyl alcohol chase to yield crude amine **23**. Isopropyl alcohol (125 ml) was added, the solution heated to 50 °C, and D-(−)-tartaric acid (8.12 g, 54.1 mmol) was added. The slurry was heated to 70 °C, then cooled slowly to room temperature and stirred for 1 h. The solid was filtered, washed with isopropyl alcohol, and dried in a vacuum oven at 60 °C, giving (R)-chroman-4-amine salt **24** (15.7 g, 41.2 mmol, 76% yield) as a white crystalline solid. Chiral HPLC showed 98% ee. ^{1}H NMR (300 MHz, MeOH-d_6) δ 7.23 (dd, J = 6, 3 Hz, 1H), 7.10–6.90 (m, 2H), 4.43–4.71 (m, 5H), 4.41 (s, 2H), 2.52 (dd, J = 12, 6 Hz, 1H), 2.06 (ddd, J = 15, 12, 3 Hz, 1H); MS (DCI/NH$_3$) m/z 232 (M+NH$_3$−H$_2$O)$^+$.