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Asymmetric synthesis of *cis*-aminochromanol

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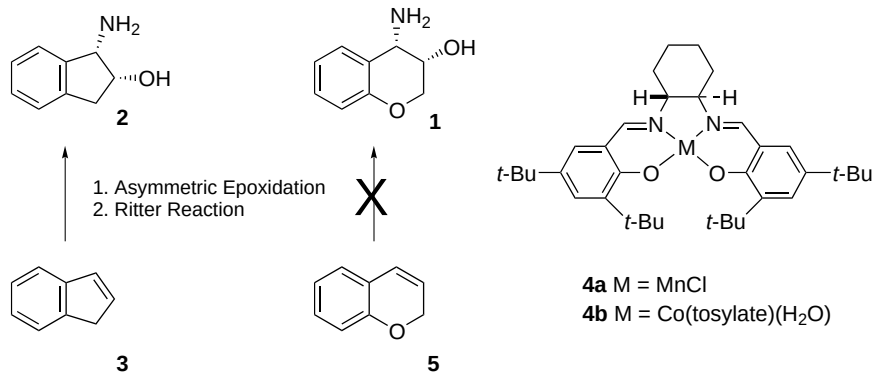
Abstract—An efficient asymmetric synthesis of *cis*-aminochromanol was achieved in seven steps. The absolute stereochemistry of *cis*-aminochromanol was derived from (salen)Co(III)-catalyzed phenol opening of methyl glycidate.

We recently wished to develop a synthesis of *cis*-aminochromanol **1** in enantiomerically enriched form. While **1** has been synthesized as a racemate,[1] we wished to develop an efficient asymmetric synthesis which used inexpensive and readily available starting materials. *cis*-Aminochromanol **1** is structurally similar to *cis*-aminoindanol **2**, which has been prepared in our laboratories on large scale from indene **3** by asymmetric epoxidation catalyzed by (salen)Mn(III) complex **4a**[2] followed by a unique Ritter reaction (Scheme 1).[3] Unfortunately, an analogous route from chromene **5** to **1** is not tenable, given the propensity of **5** to oxidize at the methylene position under asymmetric epoxidation conditions.[4]

We recognized that **1** could be accessed by diastereoselectively reducing the oxime derived from hydroxy chromanone **6**,[1b] which in turn, could be constructed via cyclization of hydroxy acid **7a** (Scheme 2).[5] The kinetic resolution of methyl glycidate **8** via asymmetric ring opening (ARO) with phenol-catalyzed by chiral (salen)Co(III) complex **4b** has been reported to afford α-hydroxy ester **7b** in good chemical and optical yield.[6] Herein we describe the elaboration of **7a** to *cis*-aminochromanol using the (salen)Co(III)-catalyzed ARO to establish the stereochemistry of **1**. The synthesis presented is amenable to large scale since it employs inexpensive, readily available starting materials and reagents, requires no chromatography and uses a recyclable catalyst to establish the stereochemistry of **1**.

Methyl glycidate **8** was prepared in 50–55% yield by addition of bleach to methyl acrylate, followed by extraction and distillation (Scheme 3).[7] A solution of **8** in methyl-*tert*-butyl ether (MTBE) was then treated at −10°C with 0.45 equiv. of phenol in the presence of 6.6 mol% (*R*,*R*)-**4b**.[8] Upon complete conversion of phenol (24 h), the solution was concentrated and the methyl



Scheme 1.

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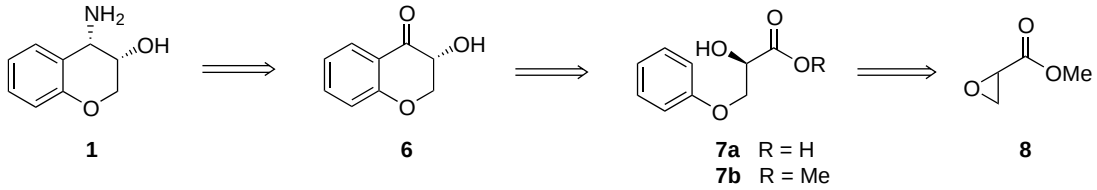
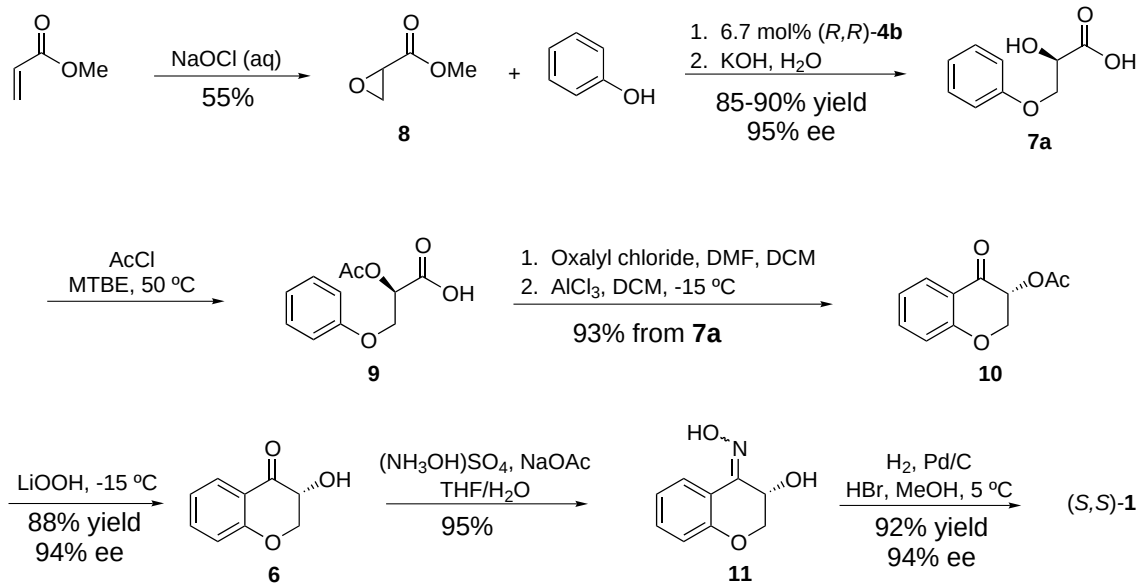


Scheme 2.



Scheme 3.

ester hydrolyzed with 1.2 equiv. of aqueous KOH. The catalyst was removed and recovered by extracting with dichloromethane (DCM). Adjusting the aqueous layer to pH 1 by addition of concentrated HCl afforded α-hydroxy acid **7a** as an off-white crystalline solid in 95% ee and 85–90% yield (based on phenol).[9]

Attempts to cyclize **7a** to **10** directly under acidic conditions using polyphosphoric acid met with little success.[10] We therefore protected the hydroxyl group of **7a** as its acetate **9** and performed an intramolecular Friedel–Crafts acylation in order to form **10**.[11] Hydrolysis of the acetate provided **6** in good chemical yield, however, we discovered the ee of **6** had been compromised. Further investigation revealed that racemization occurred during acylation, cyclization and deacylation, therefore conditions were developed for each step to avoid racemization. Use of amine bases, including dimethylaminopyridine (DMAP), for the acetylation of **7a** with either acetyl chloride or acetic anhydride resulted in diminished ee of the acetoxy acid product. Acylation of **7a** without a loss of optical purity was achieved by treatment with several equivalents (6–8) of acetyl chloride in MTBE in the absence of any base at 50°C. Removal of solvent in vacuo followed by treatment with oxalyl chloride and catalytic DMF converted **9** to its corresponding acid chloride. A solution of the acid chloride was then added to 2 equiv. of $AlCl_3$ at −15°C in DCM with the reaction temperature controlled by the addition rate of the substrate. Upon careful quenching of the reaction with dilute hydrochloric acid, enantiomerically enriched acetoxy chromanone **10** was isolated in 93% yield with no racemization detected.[12] Cleavage of the acetate under both acidic and basic conditions, also resulted in **6** isolated with diminished ee. Epimerization could be avoided by using lithium hydroperoxide at −10°C in THF to afford **6** in 94% yield and <1% racemiziation.[13]

In order to install the nitrogen at C-4, **6** was treated with 2 equiv. of $(NH_3OH)_2SO_4$ in aqueous THF buffered with 4 equiv. NaOAc at room temperature to give a mixture of *E* and *Z* oximes **11**.[14] This mixture was then hydrogenated at 5°C and 40 PSIG H_2 with 10% palladium on carbon in the presence of 1 equiv. HBr, affording **1** as its HBr salt with 25:1 *cis*:*trans* ratio and a 94% yield and 94% ee for the desired *cis*-isomer.[15] The material could be crystallized from methanol/MTBE to afford **1** as a single diastereomer with >99% ee[16] with 77% recovery.[17]

In summary, we have demonstrated the first asymmetric synthesis of aminochromanol **1** which derives the absolute stereochemistry of the molecule from an asymmetric catalytic reaction. Despite the tendency of many of the intermediates to epimerize, we have developed conditions which convert hydroxy acid **7a** to *cis*-aminochromanol in 72% yield with less than 1% racemization. The synthesis described is efficient, requires no chromatography, uses inexpensive, readily available

starting materials and a recyclable catalyst **4b** to install the stereochemistry of **1**.

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References

1. (a) Julian, D. R.; Matusiak, Z. S. *J. Heterocycl. Chem.* **1975**, *12*, 1179; (b) Ghosh, A. K.; McKee, S. P.; Sanders, W. M. *Tetrahedron Lett*. **1991**, *32*, 711.
2. Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; Fredenburgh, L. E.; Liu, J.; Roberts, F. E.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1996**, *37*, 3271.
3. Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 3993.
4. Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett*. **1991**, *32*, 6533.
5. (a) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Synlett* **1998**, 51; (b) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 1093.
6. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1999**, *121*, 6086.
7. Nemes, A.; Czibula, L.; Visky, G.; Farkas, M.; Kreidl, J. *Heterocycles* **1991**, *32*, 4329.
8. Catalyst **4b** was prepared by treating a solution of commercially available (salen)Co(II) complex in DCM with 1 equiv. of lutidine *para*-toluenesulfonic acid salt, stirring for 1 h open to air and concentrating to a dark brown solid.
9. The ee of **7a** was measured by re-esterification in methanol with catalytic H_2SO_4 and analysis of **7b** by the procedure described in Ref. 6.
10. Kabuto, K.; Kikuchi, Y.; Yamaguchi, S.; Inoue, N. *Bull. Chem. Soc. Jpn*. **1973**, *46*, 1839.
11. Loubinoux, B.; Viriot-Chauveau, C.; Sinnes, J. L. *Tetrahedron Lett*. **1992**, *33*, 2145.
12. Analysis of acetoxy chromanone was performed by chiral HPLC: (*R*,*R*)-Whelko, 1% EtOH/hexanes, 1.5 ml/min flow rate.
13. The ee of **6** was measured by chiral supercritical fluid chromatography (SFC): Chiralpak AD, 300 Bar CO_2 at 35°C, 4–40% MeOH at 2% MeOH/min, 1.5 ml/min flow rate.
14. No epimerization of the α-hydroxyl center was observed under these reaction conditions. The ee of **9** was measured by chiral SFC: Chiralpak AS, 300 Bar CO_2 at 35°C, 4–40% MeOH at 2% MeOH/min, 1.5 ml/min flow rate.
15. The relative stereochemistry of **3** was determined by ^{1}H NMR. For a study on the effect of acid in this diastereoselective hydrogenation, see: Davies, I; Taylor, M.; Marcoux, J.; Matty, L.; Wu, J.; Hughes, D.; Reider, P. J. *Tetrahedron Lett*. **2000**, *41*, 8021.
16. ^{1}H NMR (CD_3OD): δ 7.43 (dd, $J=7.9$, 1.3 Hz, 1H), 7.30 (m, 1H), 7.02 (m, 1H), 6.89 (dd, $J=8.3$, 1.1 Hz, 1H), 4.62 (d, $J=4.9$ Hz, 1H), 4.35 (m, 1H), 4.22 (ddd, $J=11.6$, 3.4, 1.0 Hz, 1H), 4.07 (dd, $J=11.6$, 8.2 Hz, 1H). ^{13}C NMR (CD_3OD): δ 154.3, 130.4, 129.3, 121.1, 116.9, 116.3, 65.4, 61.7, 48.8. The ee of **3** was measured by chiral HPLC: DAICEL Crownpak CR analytical column eluted with pH 2 $HClO_4$.
17. This yield is unoptimized. *cis*-Aminochromanol can also be isolated as a mandalate salt. See Ref. 15.