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Synthesis of Tetracyclic Heterocompounds as Selective Estrogen Receptor Modulators. Part 1. Process Development for Scale-up of 2,5,8-Substituted 5,11-Dihydrochromeno[4,3-*c*]chromene Derivatives

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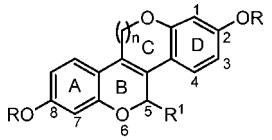
Abstract:

Unsymmetrical benzopyranobenzopyran compounds are novel selective estrogen receptor modulators (SERMs). A reproducible and nonchromatographic process was developed to prepare multihundred gram quantities of 5-(4-(2-(piperidin-1-yl)ethoxy)-phenyl)-5,11-dihydrochromeno[4,3-*c*]chromene-2,8-diyl-bis(2,2-dimethylpropanoate) (14). The overall yield of this 11-step synthesis was improved from 0.17% to 7.1% after three scale-up campaigns.

Introduction

Recently, the Discovery medicinal chemists at Johnson & Johnson Pharmaceutical R&D reported the preparation of substituted 5,11-dihydrochromeno[4,3-*c*]chromene derivatives **I** (where R = H, CH_3, or $COC(CH_3)_3$; $R^1 = C_6H_4$-$OCH_2CH_2N(CH_2)_5$ or other structurally similar substituents; and n = 1, 2, 3) as novel selective estrogen receptor modulators (SERMs).[1−3]



I

As a continuation of this research, large quantities of 5-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-5,11-dihydrochromeno[4,3-*c*]chromene-2,8-diol (**13**) and its corresponding 2,8-bis(2,2-dimethylpropanoate) ester **14** were requested for advanced in vivo biological studies.[1c] The original Discovery route that started with the base-catalyzed Perkin condensation of 2,4-dihydroxyacetophenone (**1**) and 2-benzyloxy-4-methoxyphenylacetic acid (**2a**) resulted in only 0.17% overall yield of compound **13**, after a 10-step linear synthesis which required nine chromatographic purifications (Discovery route in both Schemes 1 and 2, and Tables 1 and 2).[3] A brief review of this chemistry identified some large-scale synthesis improvement opportunities: (1) develop a scaleable and safer route to prepare bulk quantities of **2b**, since **2a** was not commercially available and the Discovery preparation of **2a** used highly toxic thallium(III) nitrate;[4] (2) reduce or eliminate the number of chromatographic purifications throughout the preparation; (3) increase the bromination efficiency of 4-methyl **6a** to 4-bromomethyl derivative **7a**, since the yields were generally low (<44% of **7a**); (4) look for alternatives of Grignard reagent **20a**, since the preparation was problematic; and (5) improve the Discovery yield of the Mitsunobu cyclization of **11** to **12** (17% after chromatographic purification). Herein, we report our improved and reproducible process, which requires no chromatography and is amendable to large-scale production of 2,8-bis(2,2-dimethylpropanoate) ester **14**.

Results and Discussion

The purpose of the first campaign was to prepare a 10-g amount of racemic 2,8-diol compound **13** within a limited time frame and the Discovery synthetic strategy was adopted with the intention to improve the overall yield. Attention was focused on the optimizations of the two lowest reaction yields (steps 8 and 9) as well as to remove the column chromatographic purifications required for both steps. To achieve this goal, 3.3 kg of starting material **2a** was required for the synthesis; however, the availability of **2a** became an issue when commercial suppliers had neither material on-hand nor any plan to make the necessary amounts within our timeline. The Discovery preparation of **2a** was accomplished by the conversion of 2-benzyloxy-4-methoxyacetophenone (**16**, another compound which was unavailable commercially in bulk quantity) using thallium(III) nitrate[4] in 52% isolated yield over two steps after chromatographic purifications (Scheme 3, steps i and ii). These problems were overcome when a low-cost commercially available 2,4-dimethoxyacetophenone (**17**) was used in a modified Willgerodt reaction[5] to prepare **2b** from its thioamide intermediate **18** in 80% overall yield without chromatographic purification (Scheme 3, steps iii and iv). This modified process was later used by a contract research organization to prepare bulk quantities of **2b**.

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† High Output Synthesis.

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(1) (a) Chen, N.; Jain, N.; Xu, J.; Reuman, M.; Li, X.; Russell, R. K.; Sui, Z. *Tetrahedron Lett.* **2006**, *47*, 5909. (b) Jain, N.; Xu, J.; Sui, Z. WO2006055694, 2006. (c) Jain, N.; Kanojia, R. M.; Xu, J.; Gou, J.-Z.; Pacia, E.; Lai, M.-T.; Du, F.; Musto, A.; Allan, G.; Hahn, D.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2006**, *49*, 3056.

(2) Kanojia, R. M.; Jain, N.; Xu, J.; Sui, Z. *Tetrahedron Lett.* **2004**, *45*, 5837.

(3) Kanojia, R. M.; Jain, N.; Ng, R.; Sui, Z.; Xu, J. WO2003053977, 2003.

(4) McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340.

(5) King, F. E.; Neill, K. G. *J. Chem. Soc.* **1952**, 4752.

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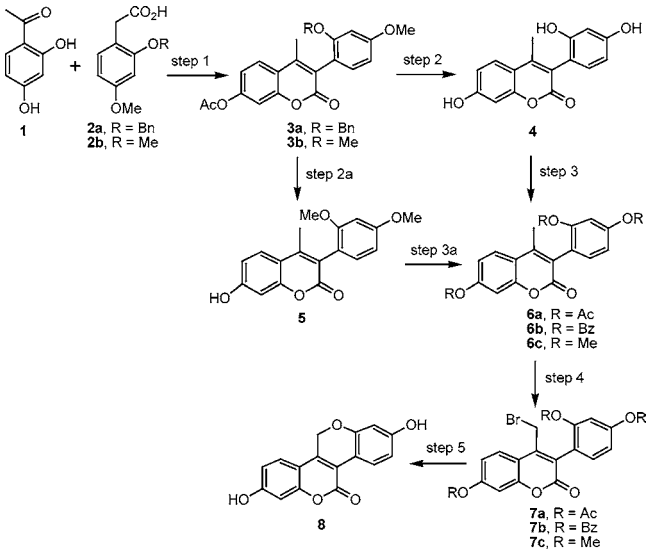
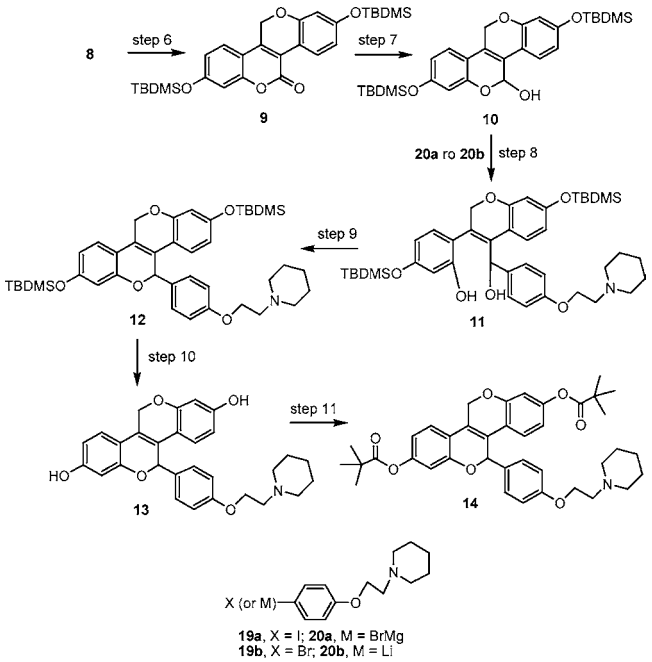
Scheme 1



Scheme 2



Following the Discovery methods,[1,3] coumarin **3b** was prepared by base-catalyzed Perkin condensation of 2,4-dihydroxyacetophenone (**1**) and **2b** in 55% isolated yield after silica gel chromatography. Deacetylation and demethylation of compound **3b** using pyridine hydrochloride produced 4-methyl-3-(2,4-dihydroxyphenyl)-7-hydroxycoumarin (**4**) in nearly quantitative yield. This trihydroxy coumarin **4** was converted to its triacetoxy derivative **6a** (R = Ac) in moderate yield (59%) after chromatographic purification (acetoxy route in Scheme 1, Table 1). Radical bromination of **6a** with NBS and $(BzO)_2$ resulted in 44% of 4-bromomethyl compound **7a** after chromatographic purification.[3] Deacetylation and C-ring closure were achieved in a one-pot reaction by first treatment of **7a** with K_2CO_3 in a mixture of acetone and methanol, followed by HCl treatment to afford 2,8-dihydroxy-5,11-dihydrochromeno[4,3-*c*]chromen-5-one (**8**) in excellent yield (95%) after chromatographic purification. Silylation of 2,8-dihydroxy **8** with a large excess of *tert*-butyldimethylsilyl chloride (TBDMSCl, 5.22 equiv) afforded its 1,8-bisTBDMS ether **9** in 61% isolated yield (acetoxy route: steps 1−6). Direct addition of Grignard reagent **20a** to the B-ring lactone carbonyl in THF or Et_2O from −20 to 20 °C were unsuccessful;[6] neither a 1,2- nor a 1,4-addition product of **9** was formed,[6,7] probably due to carbonyl conjugation with aromatic A- and D-rings, which deactivates its electrophilicity.

Although the above results of Grignard addition **20a** to carbonyl were disappointing, a literature survey revealed that 2,4-dialkyl-isoflav-3-enes could be prepared in a moderate yield (42−50%) by DIBALH reduction of 4-alkyl-3-aryl-coumarins, a ring system similar to that of compound **9**, followed by in situ addition of a Grignard reagent and acid-catalyzed cyclization without separation of intermediates.[8] Therefore, the carbonyl of **9** was reduced with DIBALH in toluene to its corresponding bis-silyl lactol **10** in almost quantitative yield with high chemical purity (95%) (acetoxy route: step 7 in Scheme 2, Table 2). The bis-silyl lactol **10** was stable at room temperature and did not need to be protected as its alkyl or aryl ether.[9] The Grignard reagent **20a** was freshly prepared from the reaction of **19b**, a coupling product of 4-bromophenol with 1-(2-chloroethyl)piperidine (Scheme 4), with magnesium turnings in the presence of catalytic amount of CH_3I in anhydrous THF.[10] Addition of excess **20a** to lactol **10** in anhydrous THF afforded 156% isolated yield of crude material after workup (the isolated yield > 100% of theory was due to the crude material containing solvent residues and other unidentified impurities); HPLC and ^1H NMR analyses indicated that this crude product contained 65% (area %) of the desired diol **11**, ∼30% of 1-(2-phenoxyethyl)piperidine (**19c**), plus ∼10% of homocoupled dimer **19d**. However, the presence of **19c** and **19d** did not impact the B-ring reclosure when a large excess of acid was used.

Treatment of crude diol **11** with concentrated HCl in toluene resulted in 106% isolated yield of crude **12** as a mixture of 2- and/or 8-monodesilylated products of **12** (3−5%) and final product **13** (∼1%) (acetoxy route: steps 8, 9, determined by HPLC and LC/MS analyses compared to standard reference samples). Interestingly, the byproducts **19c** and **19d** were removed as water-soluble HCl salts during aqueous workup. Desilylation of **12** with tetrabutylammonium fluoride (TBAF) in THF resulted in a 121% isolated yield of crude product **13**,[12] which after chromatographic purification afforded the first batch (14.9 g) of pure **13** in 52% isolated yield over three steps. It was found that when a large excess of TBAF (such as 5.0 equiv) or long reaction time (more than 6 h) was used, a lower yield of **13** was isolated, due to the formation of undesired side products. In

(6) Alberola, A.; Ortega, A. G.; Pedrosa, R.; Bragado, J. L. P.; Amo, J. F. R. *J. Heterocycl. Chem.* **1983**, *20*, 715.
(7) Cook, C. E.; Corley, R. C.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 4114.
(8) Cook, C. E.; Twine, C. E., Jr. *J. Chem. Soc., Chem. Commun.* **1968**, 791.
(9) Grese, T. A.; Pennington, L. D. *Tetrahedron Lett.* **1995**, *36*, 8913.
(10) Prat, D.; Benedetti, F.; Girard, G. F.; Bouda, L. N.; Larkin, J.; Wehrey, C.; Lenay, J. *Org. Process Res. Dev.* **2004**, *8*, 219.
(11) Li, X.; Jain, N.; Russell, R. K.; Ma, R.; Branum, S.; Xu, J.; Sui, Z. *Org. Process Res. Dev.* **2006**, *10*, 354.
(12) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

Table 1. **Summary of the reaction conditions and yields for steps 1−5**

	route			
step	discovery route[a]	acetoxy route[b] (1st campaign)	benzoyloxy route[c] (2nd campaign)	methoxy route[d] (3rd campaign)
1	**2a**, Ac_2O, Et_3N 41% of **3a**	**2b**, Ac_2O, Et_3N 55% of **3b**	**2b**, Ac_2O, Et_3N 77% of **3b**	**2b**, Ac_2O, Et_3N 77% of **3b**
2	**3a**, pyridine·HCl >95% of **4**	**3b**, pyridine·HCl 96% of **4**	**3b**, pyridine·HCl 99% of **4**	
2a				**3b**, K_2CO_3, MeOH 38% of **5**
3	**4**, Ac_2O, pyridine 59% of **6a**	**4**, Ac_2O, pyridine 59% of **6a**	**4**, BzCl, Et_3N, CH_2Cl_2 48% of **6b**	
3a				**5**, K_2CO_3, DMF, MeI 80% of **6c**
4	**6a**, NBS, *hν*, $(BzO)_2$ CCl_4, 42% of **7a**	**6a**, NBS, *hν*, $(BzO)_2$ CCl_4, 44% of **7a**	**6b**, LHMDS, Br_2, THF 62% of **7b** (plus 38% of **6b**)	**6c**, LHMDS, NBS, THF 91−93% of **7c** (inverse quench)
5	1) **7a**, K_2CO_3, acetone, MeOH 2) HCl, 92% of **8**	1) **7a**, K_2CO_3, acetone, MeOH 2) HCl, 95% of **8**	1) **7a**, K_2CO_3, acetone, MeOH 2) HCl, 62% of **8**	1) **7c**, BBr_3, CH_2Cl_2 2) NaOH, 88% of **8**

[a] Four chromatographic purifications were required (steps 1, 3, 4, and 5). [b] Three chromatographic purifications were required (steps 1, 3, and 4). [c] Two chromatographic purifications were required (steps 4 and 5). [d] Zero chromatographic purification was required.

Table 2. **Summary of the reaction conditions and yields from steps 6−11**

	route			
step	discovery route[a]	acetoxy route[b] (1st campaign)	benzoyloxy route[c] (2nd campaign)	methoxy route[d] (3rd campaign)
6	**8**, TBDMSCl, Et_3N, CH_2Cl_2 80% of **9**	**8**, TBDMSCl, Et_3N, CH_2Cl_2 61% of **9**	**8**, TBDMSCl, Et_3N, CH_2Cl_2 19% of **9**	**8**, TBDMSCl, Et_3N, CH_2Cl_2 67% of **9**
7	**9**, DIBALH, toluene 80% of **10**	**9**, DIBALH, toluene 96% of **10**	**9**, DIBALH, toluene 96% of **10**	**9**, DIBALH, toluene 79% of **10**
8	**10**, **19a**, $BrMgCH(CH_3)_2$, THF 22% of **11**	**10**, **19b,** Mg, CH_3I, THF	**10**, **19a,** *n*-BuLi, THF	**10**, **19b,** *n*-BuLi, THF
9	**11**, DEAD, $P(Ph)_3$, Mol. S. 4Å, THF 17% of **12**	**11**, HCl, toluene	**11**, HCl, toluene	**11**, HCl, toluene
10	**12**, TBAF, THF. 78% of **13**	**12**, TBAF,THF 52% of **13** (3 steps)	**12**, TBAF, THF.	**12**, TBAF, THF.
11			**13**, *t*-BuCOCl, Et_3N 40% of **14** (4 steps)	**13**, *t*-BuCOCl, Et_3N 72% of **14** (4 steps)

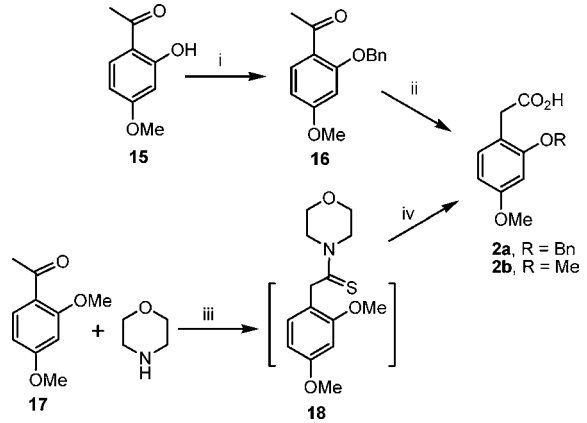
[a] Five chromatographic purifications were required (steps 6−10). [b] Two chromatographic purifications were required (steps 6 and 10). [c] One chromatographic purification was required (step 11). [d] Zero chromatographic purification was required.

summary, the acetoxy route afforded 3.9% isolated yield of racemic 2,8-dihydroxy **13** over 10 steps, with the yield of steps 8−10 significantly improved from 8.7% to 52% and three chromatographic purifications eliminated. However, 2,8-dihydroxy **13** was found unstable to the ambient conditions after long standing and also decomposed during the chiral separation process. The pro-drug **14**, a 2,8-bis-pivaloyl ester of **13**, was chosen to be used in advanced in vitro and in vivo tests, which thus far, granted highly reproducible results (IC_{50}'s) to the biological assays.[1c]

The second campaign objective was, therefore, changed to prepare ≥5.0 g each of (*5S*)-enantiomer **21** and (*5R*)-enantiomer **22**, which could be obtained by chiral chromatographic separation of racemate 2,8-bis(2,2-dimethylpropanoate) ester **14** (Scheme 5). The focus for this campaign was to increase the selectivity as well as the yield of the **6a** radical bromination in the acetoxy route (first campaign) and further reduce the number of chromatographic purifications.

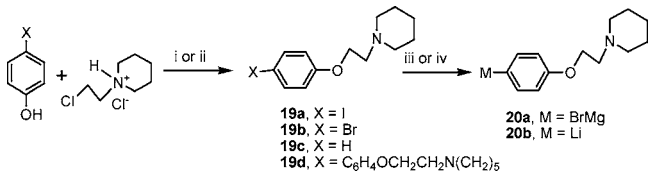
The first goal was achieved after changing the radical bromination of triacetoxy compound **6a** to anionic bromi-

Scheme 3[a]



[a] Reagents and conditions: i) BnBr, K_2CO_3, DMF, 20 °C, 18 h, 87%; ii) $Tl(NO_3)_3$, HNO_3, MeOH, 20 °C, 18 h, 60%; iii) S, 130 °C, 6 h; iv) NaOH, H_2O, 102 °C, 3 h; then HCl, 80% (over two steps).

Scheme 4[a]



[a] Reagents and conditions: i) **19a**, K_2CO_3, acetone, 56 °C, 3 h, 95%; ii) **19b**, K_2CO_3, acetone, 56 °C, 3 h, 95%; iii) **20a**, Mg, CH_3I (cat.), THF, > 95%; iv) **20b**, *n*-BuLi, THF, −78 °C, 2 h, > 95%.

nation of tribenzoyloxy derivative **6b** as described in a previous publication, since the preferred protecting group was Bz (vs SEM and or MOM).[11] Therefore, trihydroxy compound **4** was converted to its tribenzoyloxy derivative **6b** in a moderate yield without chromatographic purification. Treatment of **6b** with LHMDS in THF and then quenching with Br_2 afforded 4-bromomethyl compound **7b** in 62% yield along with 38% of recovered starting material **6b** after a column separation (benzoyloxy route: steps 3 and 4 in Scheme 1, Table 1). Debenzoylation and C-ring cyclization of **7b** was accomplished in the same fashion as in the acetoxy route (K_2CO_3, MeOH/acetone) to afford a 62% isolated yield of 2,8-dihydroxy **8** after column purification. This material was then also treated with a large excess of TBDMSCl (5.22 equiv) to provide 2,8-bis-silyl ether **9** in only 19% isolated yield after low-temperature pentane slurry clean up (−10 °C); albeit, without column chromatographic purification. The unexpected low yield of **9** here, probably, was due to the presence of a large amount of TBDMS-related byproducts in the crude material, which caused more difficulty in recovering **9** from the purification solvent. The B-ring lactone of **9** was reduced to lactol **10** in quantitative yield and high chemical purity (>95%). In the meantime, Discovery chemists demonstrated that the addition of lithium reagent **20b** to lactol **10** afforded a higher yield of diol **11** with less byproduct **19d**. Reagent **20b** was easily prepared in an almost quantitative manner by simply treating iodo compound **19a** with *n*-BuLi in THF at −78 °C (Scheme 4, step iv).[13] After treatment with concentrated HCl, the crude diol **11** was dehydrated to give B-ring cyclized intermediate **12** in 186% isolated yield, which was used crude in the next step. Treatment of crude **12** with 2 equiv of TBAF in THF gave compound **13** in situ, which was then reacted with pivaloyl chloride in the presence of Et_3N to afford a crude reaction mixture (228% isolated yield) after work up. Chromatographic purification of this crude material afforded the desired racemate **14** in 40% yield over four steps (benzoyloxy route: steps 8−11). In summary, the second campaign demonstrated that anionic bromination of **6b** was more efficient than radical bromination, in terms of reaction time and isolated yield of the 4-bromomethyl product **7b**. In addition, the number of column chromatographic purifications was reduced from five in the acetoxy route to three in this benzoxy route. However, the overall yield for 11 steps was 0.73%, due to low recovery yield of **9** in step 6.

The above two campaigns (5−20 g scale) provided an excellent understanding of all intermediates as well as the final product and allowed for further improvement in the third campaign, which was for the preparation of at least 250 g of racemate **14** to provide ∼115 g each of (*5S*)-enantiomer **21** and (*5R*)-enantiomer **22**. In order to accomplish this task, the following problems had to be solved: (1) the reaction conditions for deacetylation/demethylation of compounds **3a**/**3b** to trihydroxy **4** were difficult due to a high reaction temperature (180−210 °C) and a large volume of gas (CH_3Cl) released from the system in a short time period, (2) the yield of anionic bromination (step 4) needed to be improved, and (3) two column purifications (steps 4 and 11 of the benzoyloxy route) needed to be removed. Since phenol alkyl ethers can be cleaved with a strong Lewis acid, such as BBr_3 or $AlCl_3$,[14] an alternative strategy to 2,8-dihydroxy intermediate **8** was undertaken by converting **3b** to intermediate **5** and then trimethoxy compound **6c**. In practice, trimethoxy **6c** was prepared in 23.4% overall isolated yield, starting from compound **1** and **2b** without chromatographic purifications (methoxy route: steps 2a and 3a in Scheme 1, Table 1).[11,15] More importantly, the further improved anionic bromination conditions (which involving lithiation with LHMDS followed by *rapid inverse quench with NBS* in THF at −76 °C) using **6c** successfully achieved a reproducible quantitative yield of 4-bromomethyl **7c** with high chemical purity (91−93%), which could be used in next step without further purification.[11] Treatment of **7c** with BBr_3 in CH_2Cl_2 at 34−36 °C for 24−48 h afforded 88% isolated yield of compound **8** in high chemical purity (90−95%) as determined by both ^1H NMR and HPLC (methoxy route: steps 4 and 5).[1,14]

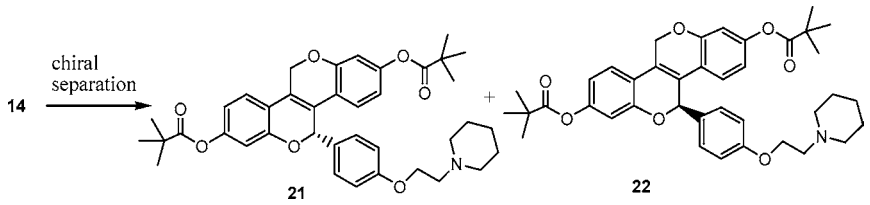
Treatment of **8** with a slight excess of TBDMSCl (2.16 equiv) afforded 2,8-bis-silyl ether **9** in 67% isolated yield and 95% chemical purity, after slurry of the crude reaction product in pentane and hexane without additional purification. DIBALH reduction of **9** produced crude lactol **10**, which after EtOAc crystallization afforded pure lactol **10** in 79% yield (methoxy route: steps 6 and 7). One more modification of Discovery's preparation of lithium reagent **20b** was to

(13) Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Duisenbery, A. J. M.; van Lenthe, J. H. *Organometallics* **1990**, *9*, 511.

(14) Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem*. **1979**, *44*, 4444.

(15) MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *Tetrahedron* **1986**, *42*, 3259.

Scheme 5



use the cheaper bromo compound **19b** to react with a stoichiometric amount of *n*-BuLi (steps iii and iv, Scheme 4). As before, the addition of **20b** to lactol **10** in THF at below −70 °C produced 165% isolated yield (of theory) of crude diol **11**. This crude diol was further treated with concentrated HCl in toluene and then diluted in EtOAc, followed by $NaHCO_3$ wash to afford the crude cyclized product **12** in 106.5% isolated yield, which was used without further purification (methoxy route: steps 8 and 9). Finally, treatment of the THF solution of crude **12** with TBAF resulted quantitatively in bis-hydroxy compound **13**, which, without workup, was reacted with pivaloyl chloride and Et_3N to afford the crude 2,8-bis(2,2-dimethylpropanoate) ester **14** in 73.2% yield. This crude material was crystallized from IPA to produce the desired racemate **14** as an off-white solid in 72% isolated yield over four steps. This reaction was repeated multiple times to afford 569 g of racemate **14** that was separated by chiral chromatography to produce 257.8 g of the (*5S*)-enantiomer **21** and 239.9 g of (*5R*)-isomer **22**.

Conclusions

Three synthetic routes were used to prepare racemates **13**/**14**, with significant improvements made throughout the three campaigns. In the acetoxy scale-up route, an economic and nonchromatographic process was developed to prepare a large quantity of starting material **2b**.[5] In addition, a three-step one-pot synthetic procedure was used to prepare intermediate **12**[8] and enough of compound **13** in a short time period. The overall yield of the acetoxy route was increased to greater than 50% versus the Discovery's 2.3% over four steps from intermediate **9**, and the number of column purifications was reduced from nine to five.

In the second campaign, the target product was changed to the 2,8-bis(2,2-dimethylpropanoate) ester **14**. The selective anionic bromination of benzoyloxy compound **6b** produced better results[10] than that of radical bromination, which was demonstrated by a shorter reaction time and an increased yield of the desired 4-bromomethyl **7b** (62% vs 44%). In addition, the chromatographic purification steps were further reduced to three, although the BzCl protection of trihydroxy **4** to **6b** and the 2,8-bissilylation of **8** to **9** were problematic with a low isolated yield (19%) of intermediate **9**.

The experience of the first and second campaigns benefited the third scale-up preparation of **14** in several ways: (1) a safer process was developed for large-scale preparation of trimethoxy compound **6c**, (2) anionic bromination of **6c** was improved to afford quantitatively 4-bromomethyl **7c** with high chemical purity (91−93%), (3) C-ring demethylation/cyclization of **7c** using BBr_3 produced 2,8-dihydroxy **8** in high yield (88%) without chromatographic purification, (4) the yield of bis-silyl ether **9** was improved to 67% with high purity (>95%) by modifying the workup, and (5) the racemate **14** was prepared in 72% yield with high chemical purity (>97%) using crude products in each step for four consecutive steps. The overall yield of the 11-step synthesis of racemate **14** was improved from 0.17% to 7.1%, and all chromatographic purifications were eliminated. This methoxy route was safe, reproducible, lower in cost, and allowed for multikilogram production of racemates **13**/**14**.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. The melting points are uncorrected and determined on a MEL-TEMP 3.0 apparatus. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 instrument, and mass spectra were recorded on an Agilent Series 180 LC/MS instrument (positive/negative modes). The chemical purity was determined on an Agilent series 1100 system at UV_{max} = 254 and 340 nm, using a ZORBAX Eclipse XDB-phenyl column (4.6 mm i.d. × 5 cm, 3.5 μ) at 40 °C with flow rate of 1.0 mL/min and run time of 10.0 min. Solvent system: A, 80% H_2O + 0.1% TFA; B, 20% CH_3CN; Gradient: B 20% /0.0 min, B 20%/1.0 min, B 90%/6.0 min, B 90%/8.0 min, B 55%/9.0 min, B 20%/10.0 min. The optical purity was determined on an Agilent series 1100 system at UV_{max} = 254 and 340 nm, using a CHIRALPAK AD column (2.1 mm i.d. × 150 mm, 3.5 μ) at 40 °C with flow rate of 0.5 mL/min and run time of 12 min with 2-propanol (IPA, 100%). Rochelle's solution (40%, wt/vol) was prepared by dissolving potassium sodium tartrate tetrahydrate (×400 g) in deionization water (D.I. water, × 1 L) at 20 °C.

All reactions were carried out in a four-neck round-bottom flask (RBF, 1−22 L), equipped with a thermocouple controller, an overhead mechanical stirrer, a condenser, and a pressure-equalization addition funnel and nitrogen inlet/outlet whenever they were required.

2,4-Dimethoxyphenylaectic acid (2b).[5] A 3-L RBF was charged with 2,4-dimethoxyacetophenone (**17**) (98%, 333.0 g, 1.848 mol), sulfur (99%, 117.0 g, 3.650 mol), and morpholine (99%, 319.4 g, 3.666 mol) (the mixing process was endothermic, and the final temperature of the mixture was 0 °C). The reaction mixture was heated to reflux (130 °C, internal temperature) for 6 h, and the progress of the reaction was monitored by TLC and LC/MS. After completion, the excess morpholine was removed by distillation under reduced pressure (40 mmHg) at 136 °C (150 mL of distillate was collected) to afford the crude thioamide **18** as a viscous oil, which was used in the next step without further purification. LC/MS *m*/*z* 282 (MH^+), 304 (MNa^+).

After crude **18** was transferred to a 12-L RBF, D.I. H_2O (4.4 L) and NaOH (591.3 g, 14.78 mol) were added with rapid stirring (this was an exothermic process, the final temperature of the solution was about 68 °C). This mixture was heated to 100−102 °C and refluxed for 3 h (or until both TLC and LC/MS showed complete hydrolysis). The H_2S gas generated from the reaction was scrubbed through a bleach solution. After completion, the reaction was cooled to 25 °C and extracted with CH_2Cl_2 (1.0 L, 0.5 L) to remove water-insoluble organic impurities. The aqueous phase was then cooled to 10 °C in an ice bath and acidified to pH 1 by dropwise addition of 37% HCl solution (1.1 L) over 1.5 h with fast agitation. During this addition, the reaction temperature was maintained between 15 and 20 °C. The slightly yellowish solid was collected by filtration, and the wet cake was washed with D.I. water (100 mL × 3), air-dried, and then placed in a vacuum oven at 50 °C for 72 h under house vacuum. There was obtained 290.7 g (80% yield) of acid **2b** as a pale-yellow solid, which was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.58 (s, 2 H), 3.79 (s, 6 H), 6.44 (d, J = 7.9, 1 H), 6.47 (s, 1 H), 7.08 (d, J = 8.0, 1 H), 9.8−10.9 (br s, 1 H). LC/MS m/z 197 (MH^+), 219 (MNa^+).

The preparation of substituted coumarins **3a**, **3b**, **4**, **5**, **6a**−**c**, and **7a**−**c** was reported in an earlier publication.[11]

2,8-Dihydroxy-11*H*-chromeno[4,3-c]chromen-5-one (8).[14] A 22-L RBF was charged with 4-bromomethyl **7c** (322.1 g, 0.795 mol) and CH_2Cl_2 (14.7 L). The solution was stirred under nitrogen while the vessel was evacuated and filled with nitrogen three times. Boron tribromide (1.05 kg, 4.19 mol) was added from reagent bottles to the reaction by a cannula over 10−15 min period under a positive nitrogen pressure (the BBr_3 addition was slightly exothermic, and the internal temperature increased from 20 °C to 28 °C). The septum was replaced with a Teflon stopper, and the reaction was heated gently to just below reflux. The progress of the reaction was monitored by NMR and HPLC, which was typically done in 24−48 h.

Two 22-L three-neck separatory flasks equipped with an overhead stirrer were both charged with saturated $NaHCO_3$ (4 L) and D.I. water (4 L). Approximately half of the contents of the above reaction mixture was added, in portions, via a Teflon tube under a positive nitrogen pressure to each of the separatory flasks with stirring. The reaction flask was rinsed with a minimal volume of CH_2Cl_2 and saturated $NaHCO_3$, and this was added to one of separatory flasks. The pH of each half-saturated $NaHCO_3$ mixture in each flask was adjusted to strongly basic (pH >12) by the addition of 10 N NaOH to afford a clean separation of the aqueous and CH_2Cl_2 layers. The lower CH_2Cl_2 layer in each flask was separated and discarded. The pH of aqueous layer was then adjusted to acidic (pH = 1) by the addition of concentrated HCl; the resulting fine yellow-green precipitate was collected by filtration, washed with D.I. H_2O (4 L), and dried to a constant weight at 40 °C to afford 197.2 g (88% isolated yield), of which ^{1}H NMR indicated a 90−95% purity, while HPLC determined 90% (area %) purity of 2,8-dihydroxy **8**. (**All efforts should be taken to avoid contact with this product as it may be a possible skin irritant.**) ^{1}H NMR (300 MHz, CD_3OD) δ 4.79 (br s, 2 H), 5.26 (s, 2 H), 6.39 (s, 1 H), 6.48 (d, J = 7.8, 1 H), 6.74 (s, 1 H), 6.83 (d, J = 7.6, 1 H), 7.40 (d, J = 8.0, 1 H), 8.24 (d, J = 7.9, 1 H). LC/MS m/z 283 (MH^+), 305 (MNa^+), 587 ($2MNa^+$).

2,8-Bis(*tert*-butyldimethylsilyloxy)-11*H*-chromeno[4,3-c]chromen-5-one (9).[3,16] A 5-L RBF was charged with 2,8-dihydroxy **8** (410.6 g. 1.45 mol), CH_2Cl_2 (2 L), and Et_3N (470 mL, 3.37 mol). While the mixture was stirred under nitrogen, TBDMSCl (473 g, 3.14 mol) was added to the reaction portionwise (approximately 30 g each at 5-min intervals), while the internal temperature was maintained below 36 °C with a cold water bath. After the TBDMSCl addition, the reaction was allowed to stir at room temperature for 24 h (the reaction was monitored by HPLC). The mixture was transferred to a 12-L three-neck separatory flask equipped with an overhead stirrer and was washed with 0.1 N HCl (1 L × 2) followed by saturated $NaHCO_3$ (1 L). The organic phase was concentrated to give the crude product as a tan-brown solid (724 g, 98%). This crude material was suspended in pentane and filtered (this initial filtration was difficult, since the filter paper and filter funnel both clogged with a brown, gummy material). The recovered solid from the filtration was dissolved in CH_2Cl_2, reconcentrated, and then suspended in hexane (500 mL); the solid was collected by filtration and washed with hexane (500 mL). The product was dried under vacuum at 40 °C to give 496.0 g (67% isolated yield) of 2,8-bis-silyl ether **9** as a tan solid, which was 95% chemically pure by ^{1}H NMR and HPLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6 H), 0.25 (s, 6 H), 0.99 (s, 18 H), 5.24 (s, 2 H), 6.47 (d, J = 2.3, 1 H), 6.58 (dd, J = 2.4, 8.6, 1 H), 6.82 (d, J = 8.8, 1 H), 6.84 (s, 1 H), 7.32 (d, J = 8.3, 1 H), 8.43 (d, J = 8.4, 1 H). LC/MS m/z 511 (MH^+), 533 (MNa^+).

2,8-Bis(*tert*-butyldimethylsilyloxy)-11*H*-chromeno[4,3-c]chromen-5-ol (10).[3,8] A 3-L RBF was charged with CH_2Cl_2 (1.6 L) and lactone **9** (100.0 g, 0.196 mol), and the mixture was stirred under nitrogen and cooled to −40 °C in a dry-ice/CH_3CN bath. Diisobutylaluminum hydride (DIBALH, 1.0 M solution in toluene, 234.8 mL, 0.2348 mol) was added dropwise over a 45-min period, while the reaction temperature was maintained at −40 °C. After the addition, the reaction was stirred at −40 °C for 1.5 h and checked by TLC and LC/MS. If reaction was not complete, additional DIBALH was added and allowed to stir an additional 30 min. The reaction was quenched with 40% Rochelle's solution (800 mL) (the temperature of mixture increased from −40 to −6 °C) and was agitated at room temperature for 2 h; then the mixture was transferred to a 12-L separatory flask equipped with an overhead mechanical stirrer that contained Rochelle's solution (7.2 L). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 2.0 L), and the combined organic phase was washed with Rochelle's solution (1 × 1.0 L) and brine (1 × 2.0 L). After concentration of the solvents, the resulting material (136.9 g) was crystallized from EtOAc (2.2 L). The solution was gradually cooled to 20 °C and then placed in an ice−water

(16) Kendall, P. M.; Johnson, J. V.; Cook, C. E. *J. Org. Chem.* **1979**, *44*, 1421.

bath until the solution temperature was 8 °C. The solids were collected by filtration, washed with hexanes (200 mL), and dried in an oven under house vacuum at 40 °C for 20 h. There was obtained 79.3 g (79% isolated yield) of 2,8-bis-silyl lactol **10**, which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 12 H), 0.99 (s, 18 H), 3.03 (d, J = 8.2, 1 H), 5.17 (m, 2 H), 6.36 (d, J = 8.2, 1 H), 6.43 (d, J = 2.4, 1 H), 6.47 (dd, J = 2.3, 8.0, 1 H), 6.54 (dd, J = 2.3, 8.1, 1 H), 6.62 (d, J = 2.3, 1 H), 6.95 (d, J = 8.3, 1 H), 7.16 (d, J = 8.4, 1 H). LC/MS m/z 495 [(M − OH)H$^+$], 513 (MH$^+$), 535 (MNa$^+$).

2-(4-(Hydroxy(4-(2-(piperidin-1-yl)ethoxy)phenyl)methyl)-7-(*tert*-butyldimethylsilyloxy-*2H*-chromen-3-yl)-5-(*tert*-butyldimethylsilyloxy)phenol (11). A 12-L Morton RBF was placed under house vacuum and was heated to 100 °C for at least 1 h prior to addition of any reagents, while the attached components were dried with a heat gun. To the above reaction flask via a cannula under a positive nitrogen pressure was added 2-(4-bromophenoxy)ethyl piperidine (**19b**) (189.25 g, 0.67 mol) followed by the addition of anhydrous THF (1.5 L). The system was purged with nitrogen by evacuating and filling with nitrogen (×3). The addition funnel was charged with *n*-BuLi (2.5 *M* in hexane, 240 mL, 0.60 mol) via a cannula; during this time the reaction flask was chilled in a dry ice−IPA bath. After the internal temperature reached −75 °C, the *n*-BuLi was added at a rate such that the internal temperature did not exceed −72 °C. After the *n*-BuLi addition, the reaction was checked for the extent of the lithium−bromine exchange to form **20b**[13] by ^{1}H NMR ($CDCl_3$) (used the integration of the starting bromide doublet at δ 7.35 versus the ether methylene singlet at δ 4.1), and more *n*-BuLi was added if the analysis showed that it was needed. A solution of lactol **10** (150 g, 0.29 mol) in anhydrous THF (6 L) was transferred to the addition funnel portionwise (2 L × 3) and then was added at a rate such that the internal reaction temperature did not exceed −70 °C. After the addition was complete, the batch was allowed to stir for 30 min and then was quenched with saturated NH_4Cl (600 mL). The cooling bath was removed, and the mixture was stirred while slowly warming to room temperature overnight. The mixture was filtered to remove salts, and the phases were separated; the flask and solids were rinsed with EtOAc (200 mL), and the combined organic phases were concentrated in vacuo. The resulting oil was diluted with EtOAc (3 L), transferred to a 12-L separatory flask equipped with an overhead stirrer, and agitated with D.I. H_2O (3 L). The layers were separated, and the mixture was subjected to a second water wash followed by a brine (2 L) wash. The aqueous layers were combined and back extracted with EtOAc (1.5 L × 2), and the combined EtOAc solution was concentrated at 60 °C to afford the crude diol **11** (347.0 g, 166.7% isolated yield) as orange oil, which was carried on to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 6 H), 0.19 (s, 6 H), 0.91 (s, 9 H), 0.96 (s, 9 H), 1.45 (m, 2 H), 1.64 (m, 4 H), 2.53 (m, 4 H), 2.78 (t, J = 6.0, 2 H), 4.12 (t, J = 6.2, 2 H), 4.78 (m, 2 H), 5.63 (br s, 1 H), 6.31−6.42 (m, 4 H), 6.70−7.41 (m, 8 H), 7.08 (m, 4 H). LC/MS m/z 718 (MH$^+$), 740 (MNa$^+$).

2,8-Bis(*tert*-butyldimethylsilyloxy)-5-[4-(2-(piperidin-1-yl)ethoxy)phenyl]-5,11-dihydrochromeno[4,3-*c*]chromene (12).[8] A 5-L RBF was charged with the above crude diol **11** (347.0 g) in toluene (2.9 L) and cooled to 17 °C. Concentrated HCl (186 mL) was added dropwise via an addition funnel at a rate to keep the temperature between 20 and 22 °C while cooling with an ice−water bath (LC/MS analysis indicated that the reaction was complete in 20 min). The reaction mixture was diluted with EtOAc (1 L) and transferred to a 22-L three-neck separatory flask along with additional EtOAc (4 L) and D.I. H_2O (5 L). After phase separation, the organic layer was washed with saturated $NaHCO_3$ (4 L) followed by brine (4 L) and then dried over Na_2SO_4 (500 g). After filtration, the solvent was concentrated to dryness to give the crude cyclized product **12** (218.0 g, 106.5% isolated yield), which was carried on to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6 H), 0.19 (s, 6 H), 0.93 (s, 9 H), 0.96 (s, 9 H), 1.42 (m, 2 H), 1.58 (m, 4 H), 2.48 (m, 4 H), 2.73 (t, J = 6.0, 2 H), 4.03 (t, J = 6.0, 2 H), 5.10 (dd, J = 1.7, 13.8, 1 H), 5.29 (d, J = 13.9, 1 H), 6.15 (s, 1 H), 6.29 (m, 2 H), 6.38 (m, 2 H), 6.71 (d, J = 8.3, 1 H), 6.80 (d, J = 8.4, 2 H), 6.88 (d, J = 8.2, 1 H), 7.30 (d, J = 8.6, 2 H). LC/MS m/z 701 (MH$^+$), 723 (MNa$^+$).

2,2-Dimethylpropionic Acid, 8-(2,2-Dimethylpropionyloxy)-5-[4-(2-(piperidin-1-yl)ethoxy)phenyl]-5,11-dihydrochromeno[4,3-*c*]-chromene-2-yl ester (14).[12] A 12-L RBF was charged with a solution of crude **12** (218.0 g) in THF (2.3 L). TBAF (626 mL, 0.626 mol, 1.0 *M* in THF) was added via an addition funnel to the above solution over 20 min (the mixture started as a thick, orange solution and changed to a red, homogeneous solution). The mixture was stirred for an additional 30 min; the formation of 2,8-diol **13** was complete by this time as determined by HPLC and LC/MDS. Pivaloyl chloride (115 mL, 0.93 mol) was added over 12 min while an ice−water bath was used to maintain the reaction temperature below 5 °C during this addition, followed by Et_3N (130 mL, 0.93 mol) over 10 min. The mixture was stirred for an additional 30 min, while the reaction progress was monitored by HPLC and LC/MS analyses for the disappearance of **13** and the formation of 2,8-bis(2,2-dimethylpropanoate) **14**. The solids were removed by filtration, and the filtrate was concentrated to give a mixture of crude **14** with other components (468.0 g). This crude material **14** was dissolved in CH_2Cl_2 (5 L), transferred to a 12-L three-neck separatory flask, and sequentially washed with D.I. H_2O (3 L × 6), saturated $NaHCO_3$ (3.5 L), and brine (3.5 L) (the extraction was followed by LC/MS to verify the near removal of the residual TBAF). The CH_2Cl_2 layer was separated and concentrated to give a 2,8-bis(2,2-dimethylpropanoate) **14** (184.0 g), which was further slurried in IPA at 70 °C for 30 min to remove residual TBAF. The slurry was cooled, and the solid was collected by filtration. The filter cake was treated with IPA (350 mL), and the resulting solid was washed with additional IPA (50 mL × 2) and dried under vacuum at 60 °C for 20 h to afford pure 2,8-bis(2,2-dimethylpropanoate) **14** (133.4 g, 72% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9 H),

1.33 (s, 9 H), 1.42 (m, 2 H), 1.58 (m, 4 H), 2.47 (m, 4 H), 2.72 (t, J = 5.8, 2 H), 4.03 (t, J = 5.7, 2 H), 5.14 (d, J = 13.9, 1 H), 5.37 (d, J = 14.0, 1 H), 6.20 (s, 1 H), 6.42−6.53 (m, 2 H), 6.61 (d, J = 2.3, 1 H), 6.63 (dd, J = 2.4, 8.4, 1 H), 6.77−6.82 (m, 3 H), 7.0 (d, J = 8.4, 1 H), 7.31 (d, J = 8.5, 2 H). LC/MS m/z 640 (MH^+), 662 (MNa^+).

(5*S*)-2,2-Dimethylpropionic Acid, 8-(2,2-Dimethylpropionyloxy)-5-[4-(2-(piperidin-1-yl)ethoxy)phenyl]-5,11-dihydrochromeno[4,3-*c*]-chromene-2-yl ester (21). The optical purity was determined on an Agilent series 1100 system at UV_{max} = 254 and 340 nm, using a CHIRALPAK AD column (2.1 mm i.d. × 150 mm, 3.5 μ) at 40 °C with flow rate of 0.5 mL/min and run time of 12 min with IPA (100%). Preparative chiral separation of racemate **14** (569.0 g) was conducted by using a CHIRALPAK AD column (5 cm i.d. × 50 cm, 20 μ) at 20 °C with flow rate of 90 mL/min and run time of 30 min with IPA (100%), which afforded 257.8 g of pure (5*S*)-**21** as beige, amorphous solid with 98.5% of chemical purity and 99.6% ee optical purity (chiral HPLC retention time = 3.83 min), mp 213−214 °C (decomposition). [α] = +72.0°, (c = 0.30 g/100 mL in $CHCl_3$ at 20 °C, 589 nm). LC/MS m/z 640.3 (MH^+). Anal. Calcd for $C_{39}H_{45}NO_7$: C, 73.22; H, 7.09; N, 2.19. Found: C, 73.00; H, 7.22; N, 2.13. In addition to the above material, there was obtained 239.9 g of pure **(5*R*)-enantiomer 22** as an off-white amorphous solid with 99.0% of chemical purity and 99.5% ee of optical purity (chiral HPLC retention time = 2.22 min), mp 208−209 °C (decomposition). [α] = −73.4°, (c = 0.31 g/100 mL in $CHCl_3$ at 20 °C, 589 nm). LC/MS m/z 640.3 (MH^+). Anal. Calcd for $C_{39}H_{45}NO_7$: C, 73.22; H, 7.09; N, 2.19. Found: C, 73.09; H, 7.17; N, 2.20.

5-[4-(2-(Piperidin-1-yl)ethoxy)phenyl]-5,11-dihydrochromeno[4,3-*c*]-chromene-2,8-diol (13). A 5-L RBF was charged with a solution of compound **12** (42.0 g, 0.06 mol) in anhydrous THF (1.5 L). Tetrabutylammonium fluoride (1.0 M in THF, 120 mL, 0.12 mol) was added dropwise over a 5-min period. The mixture was stirred at 20 °C for 20 min, while the progress of the reaction was monitored by HPLC and LC/MS. After completion, an ice-cooled 1 M H_3PO_4 (1.5 L) solution was added to the above reaction and stirred vigorously for 3 min. The acidic solution was transferred to a 12-L three-neck separatory funnel and extracted with EtOAc (4.0 L, 2.0 L × 2); the organic phases were combined and washed with brine (1.5 L). Solvent removal in vacuo gave 34.12 g (121% yield) of crude material, which after flash chromatographic purification (Si_2O, eluted with EtOAc/hexane/MeOH/NH_4OH, 45/45/10/0.2 to 65/20/15/0.5) afforded 14.9 g (52% yield, over three steps) of 2,8-diol **13** as a brown−cherry solid (mp 178−180 °C, decomposition). ^1H NMR (300 MHz, acetone-d_6) δ 1.36 (m, 2 H), 1.49 (m, 4 H), 2.42 (m, 4 H), 2.63 (t, J = 5.6, 2 H), 4.05 (t, J = 5.8, 2 H), 5.04 (dd, J = 1.7, 13.9, 1 H), 5.36 (d, J = 14.0, 1 H), 6.12 (d, J = 2.4, 2 H), 6.21 (dd, J = 2.4, 8.3, 1 H), 6.23 (d, J = 2.3, 1 H), 6.28 (dd, J = 2.4, 8.4, 1 H), 6.71 (d, J = 6.7, 3 H), 7.00 (d, J = 8.0, 1 H), 7.32 (d, J = 8.1, 2 H), 7.96−9.10 (br s, 2 H). LC/MS m/z 472 (MH^+), 494 (MNa^+).

1-[2-(4-Bromophenoxy)ethyl]piperidine (19b).[3,10] A 5-L RBF was charged with acetone (2.5 L), D.I. H_2O (25 mL), 4-bromophenol (98%, 150.0 g, 0.867 mol), 1-(2-chloroethyl)-piperidine monohydrochloride (98%, 159.6 g, 0.867 mol), and potassium carbonate (99%, 325 mesh, 239.7 g, 1.734 mol) under nitrogen with agitation. The mixture was heated to reflux (56 °C) for 3 h. The progress of the reaction was followed by TLC and LC/MS. After filtration, the solvent was removed in vacuo, and the resulting oil was diluted in EtOAc (2 L), washed with 1 N NaOH solution (2 L), and washed with brine (2 L × 2). Concentration of the solvent afforded 234.0 g (95% isolated yield) of bromide **19b**, which was placed under high vacuum (∼20 mmHg) at 22 °C for 18 h and used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (m, 2 H), 1.61 (m, 4 H), 2.52 (t, J = 5.8, 4 H), 2.74 (t, J = 6.0, 2 H), 4.08 (t, J = 6.1, 2 H), 6.78 (d, J = 8.2, 2 H), 7.34 (d, J = 8.3, 2 H). LC/MS m/z 284 (MH^+), 286 [$(M + 2)H^+$].

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Note Added after ASAP Publication: There were production errors in Table 2 and the Scheme 4 footnote in the version published on the Web March 31, 2007. The correct version posted April 5, 2007 and the print version are correct.

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