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Synthesis of Tetracyclic Heterocompounds as Selective Estrogen Receptor Modulators. Part 2. Process Improvement for Scale-Up Of 2,5,8-Substituted 11,12-Dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta-[1,2-*a*]naphthalene Derivatives

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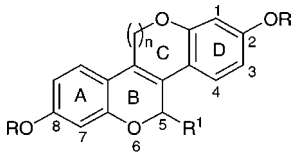
Abstract:

An improved, reproducible nonchromatographic process for scale-up synthesis of 2,5,8-substituted 11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene derivatives as selective estrogen receptor modulators (SERMs) is described. The titled compounds were prepared in 9−21% overall yield with high chemical purity (>97%) after nine consecutive synthetic steps.

Introduction

Tetracyclic heterocompounds **I** (where R = H, CH_3, or $COC(CH_3)_3$; $R^1 = C_6H_4OCH_2CH_2N(CH_2)_5$ or other structurally similar substituents) have attracted our interest since they represent a novel class of compounds with biological properties as selective estrogen receptor modulators (SERMs).[1−3]

The development of nonchromatographic processes for



I, n = 1
II, n = 2

the scale-up production of 2,5,8-substituted 5,11-dihydrochromeno[4,3-*c*]chromene derivatives (**I**) ($n = 1$) was reported in our previous work.[4,5] Recently the 2,5,8-substituted 11,12-dihydro-5*H*-6,13-dioxabenzo 3,4]cyclohepta[1,2-*a*]naphthalene series **II** ($n = 2$), the C-ring homolog to compounds **I**, was also identified as a new class of highly potent in vitro SERM candidates, and multi-hundred gram quantities of racemates **11** and **19** were requested for in vivo biological evaluations. The original Discovery preparation for **11** was a 9-step, low yielding (1.1%) synthesis that had four steps with yields in the range of 35−45%. These low yields were in part due to the need for silica gel chromatographic purification for intermediates **3a**, **4a**, **6**, and **7** as well as the additional purification of compound **11** since it was contaminated with tetrabutylammonium ion, a byproduct from the tetrabutylammonium fluoride (TABF) cleavage of the Si−O ether bond in the last step (Table 1, Discovery route). The above-mentioned issues required a fresh look at the synthesis before starting a large-scale production of compounds **11** and **19**. It was believed that the synthetic methods used to prepare compounds **I**[5] could also be used for the production of the seven-member analogue **II**. However, the structural difference in a single methylene group on the C-ring of the compound **II** afforded an unexpected number of synthetic challenges. Herein, we report our results for the improved large-scale preparation of racemates **11** and **19**.

Results and Discussion

During our previous scale-up preparation of the six-member C-ring chromene derivatives **I**, 3-(2,4-dimethoxy)-7-methoxycoumarin **3a** was identified as the best candidate and converted to its corresponding 4-bromomethyl analogue in quantitative yield with high chemical purity under anionic bromination conditions (LHMDS/NBS); however, **3a** was obtained in only 23% yield after four steps.[1,4] This anionic chemistry could also be applied to help construct the seven-member C-ring of compounds **II** by means of trapping a **3a** anion with a carbon electrophile (such as a $POCH_2^+$, P = protecting group) to give one carbon hydroxyl-protected homologue 4-(2-hydroxyethyl)coumarins **4a**. The development of a one-step synthesis of **3a** with higher yield was necessary to benefit the first non-GMP campaign for racemate **11** (≥250 g) as well as the second campaign for the racemate **19** (≥250 g). To achieve this immediate goal, 4-methoxy-2-hydroxyacetophenone (**1a**) was treated with 2,4-dimethoxyphenylacetic acid (**2**) under Perkin condensation conditions to afford compound **3a** in a slightly improved yield (36%) after a chromatographic purification.[4] Furthermore, when starting material **1a** was replaced with the 4-benzyloxy analogue **1b**, the desired 7-benzyloxycoumarin **3b** was isolated in ≥60% yield after crystallization of the crude reaction mixture from 2-propanol (IPA) (step 1 of Scheme 1).

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† High Output Synthesis.

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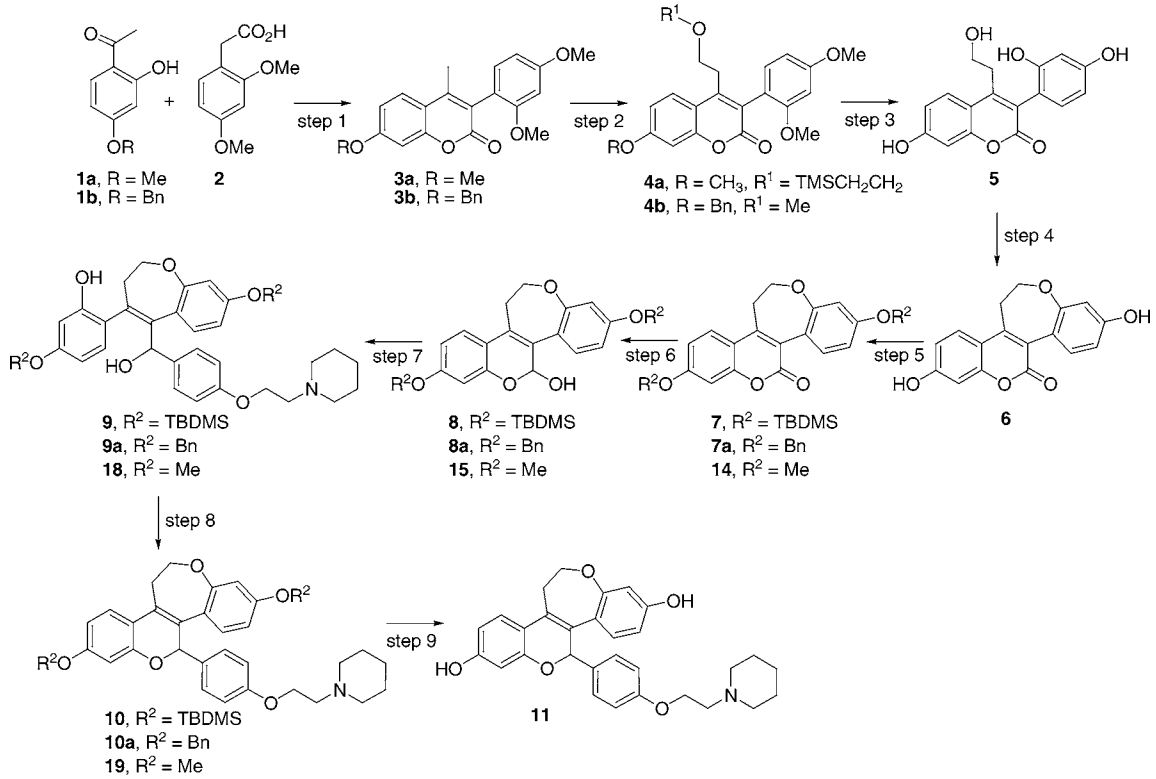
Table 1. **Summary of the reaction conditions and yields for the preparation of compounds 11 and 19**

	route			
step	discovery route[a]	scale-up (TBDMS route)[b]	scale-up (benzyloxy route)[c]	scale-up (methoxy route for **19**)[d]
1	**1a**, Ac_2O, Et_3N, 148 °C, 48 h; 36% of **3a**	**1b**, Ac_2O, Et_3N, 148 °C, 48 h; 60% of **3b**		
2	**3a**, $(TMS)_2NLi$, SEM-Cl, THF, −20 °C, 1 h; 45% of **4a**	**3b**, $(TMS)_2NLi$, MOM-Br, THF, −20 °C, 1 h; 95% of **4b**		
3	**4a**, BBr_3, CH_2Cl_2, 20 °C, 36 h >95% of **5** (workup by addition of water to the reaction mixture at −76 °C)	**4b**, BBr_3, CH_2Cl_2, 36−38 °C, 24 h; 90−99% of **5** (workup by addition of the boron complex into EtOH at 0 °C, or to water at 20 °C)		
4	**5**, Ph_3P, DIAD THF, 20 °C,18 h; 42% of **6**	**5**, Ph_3P, DIAD THF, 20 °C, 18 h; 97% of **6**		
5	**6**, TBDMS−Cl, Et_3N, CH_2Cl_2, 0−20 °C, 24 h; 35% of **7**	**6**, TBDMS-Cl, Et_3N, CH_2Cl_2, 0−20 °C, 24 h; 60% of **7**	**6**, BnBr, K_2CO_3, CH_2Cl_2, 38−40 °C, 24 h; 92% of **7a**	**6**, MeI, K_2CO_3, DMF, 20 °C, 4 h; 85% of **14**
6	**7**, DIBALH, CH_2Cl_2, −20 °C, 2 h; 95% of **8**	**7**, DIBALH, CH_2Cl_2, −20 °C, 2 h; 99% of 8	**7a**, DIBALH, CH_2Cl_2, −40 °C 1 h; 99% of **8a**	**14**, DIBALH, CH_2Cl_2, −76 °C, 6 h; 73% of **15**
7	**8**, **12**, nBuLi, THF, −78 °C, 1 h	**8**, **12**, nBuLi, THF, −78 °C, 1 h	**8a**, **12**, nBuLi, THF, −78 °C, 1 h	**15**, **12**, nBuLi, THF, −78 °C, 8 h; 95% of **18**
8	**9**, HCl, CH_2Cl_2, 0−20 °C, 1 h	**9**, HCl, CH_2Cl_2, 0−20 °C, 1 h	**9a**, HCl, toluene 20 °C, 1 h	**18**, HCl, CH_2Cl_2, 10−15 °C, 45 min; 56% of **19** (2 steps)
9	**10**, TBAF, THF, 20 °C, 18 h; 50% of **11** (3 steps)	**10**, TBAF, THF, 20 °C, 18 h, 72% of **11** (3 steps)	**10a**, Pd/C, H_2, 3.06 atm, EtOAc/CH_3OH, 20 °C, 20 h; 41% of **11** (3 steps)	

[a] Five chromatographic purifications were required (steps 1, 2, 4, 5, and 9). [b] One chromatographic purification was required (step 9). [c] Zero chromatographic purification was required. [d] Zero chromatographic purification was required.

Scheme 1



Originally, the one carbon homologation on the 4-methyl group was accomplished by treating **3a** anion with SEM-Cl, which resulted in a moderate isolated yield (45%) of compound **4a** after chromatography. When SEM-Cl was replaced with the more active alkylating reagent, MOM-Br,[1a,6] a doubled isolated yield (95%) of **4b** was obtained in high chemical purity (96%, HPLC area %) without chromatographic separation (scaled-up TBDMS route, step 2 of

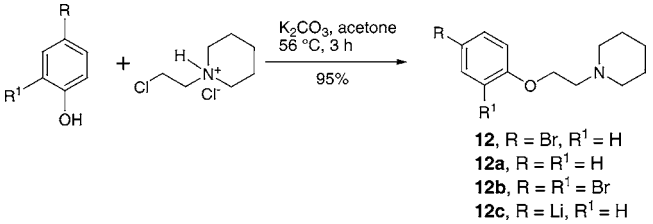
Scheme 1). During pilot production, the unstable and carcinogenic MOM-Br was replaced with the stable and less harmful pivaloyoxymethyl chloride (POM-Cl), which also produced the POM-homologated compound in high yield (93%) and good chemical purity (85.4%).[4b]

The Discovery deprotection of **4a** using BBr_3 (6 equiv) in CH_2Cl_2 was complete after 36 h at room temperature,[7] and then addition of water (≥12 mL/g of **4a**) to the reaction mixture at −76 °C afforded >95% isolated yield of crude tetraol **5**. The scaled-up deprotection of **4b** with reduced amounts of BBr_3 (4 equiv) in CH_2Cl_2 was complete in 24 h at 36−38 °C; however, less than 10% of crude **5** was isolated after acidic aqueous−organic solvent extraction, when a large volume of water (≥80 mL/g of **4b**) was used in the workup. The tetraol **5** was identified as a major component in the aqueous phase (pH ≤ 3), which was very difficult to extract into any organic solvent (such as CH_2Cl_2, EtOAc, and *n*-butyl alcohol) even when the aqueous phase pH was ≤1 or saturated with solid NaCl. This problem was resolved by the isolation of the crude boron complex of **5** as a solid and then careful portionwise addition of this crude complex to EtOH (200 proof) at 0 °C. Ethanol removal in vacuo and repeated chasing of the resulting material with MeOH (×4) produced tetraol **5** in quantitative yield with 86% chemical purity (HPLC area %). Another improvement was realized during the preparation of racemate **19**, where the slurry of crude boron complex **5** was directly quenched into a limited volume of water (≥25 mL/g but ≤57 mL/g of **4b**), and the resulting aqueous phase was allowed to stand at least 20 h; the desired tetraol **5** was isolated as a crystalline solid in 72−86% yield with good purity (>80%, HPLC area %).

The tetraol **5** was converted to 2,8-bisphenol **6** using modified Mitsunobu cyclization conditions (DIAD and Ph_3P in THF)[8] to afford cyclic 2,8-bisphenol **6** in 97% isolated yield with good quality (82%, HPLC area %). The protection of the 2,8-bisphenol groups of **6** was best accomplished with 2.3 equiv of TBDMSCl in an acceptable yield (60%) of 2,8-bis-silyl lactone **7** as a yellowish solid without chromatographic purification (scaled-up TBDMS route, steps 4 and 5 of Scheme 1).[9]

The addition of freshly prepared Grignard reagent of **12** to lactone **7** was unsuccessful (cf. the six-member C-ring series **I**[5]), probably due to the high oxidation level on 2-carbonyl and/or carbonyl conjugation with aromatic A- and D-rings that deactivates its electrophilicity. Lactone **7** was therefore reduced to lactol **8**, a compound with low oxidation level at C-2 where nucleophilic acceptability is also increased, with DIBALH (1.2 equiv) in a quantitative yield with high chemical purity (96%, HPLC area %). Similar to the 6-member C-ring process,[5] an excess of lithium reagent **12c** (Scheme 2) was added to lactol **8** under the well-

Scheme 2



12, R = Br, R^1 = H
12a, R = R^1 = H
12b, R = R^1 = Br
12c, R = Li, R^1 = H

developed conditions to give a 138% recovery yield of crude diol **9**, which contained about 30% of 1-(2-phenoxyethyl)-piperidine (**12a**) as determined by ^{1}H NMR and HPLC analyses (the isolated yield >100% of theory was due to the crude material containing solvent residues and other uncharacterized impurities. The yields were calculated based on pure products). The crude diol **9** was cyclized to 2,8-bis-silyloxy benzopyran derivative **10** in quantitative yield, and at this point, **12a** was removed as its HCl salt during workup. Following the Discovery procedure, the silyl protecting groups of **10** were cleaved using TBAF (2 equiv) in THF to afford crude **11** (158% isolated yield) after workup, which contained 84% (HPLC area %) of **11**.[10] However, an approximate 8% of tetrabutylammonium group (TBA^+) was observed in the ^{1}H NMR, an impurity that was not reported in the original preparation. It was found impossible to remove this impurity from compound **11** by either organic acid−base aqueous solvent partition or crystallization. This result was due to the reaction of the phenolic groups of **11** (pK_a of 2-OH = 10.19 and pK_a of 8-OH = 9.88, unpublished internal communication) with the tetrabutylammonium group to create a salt that is soluble in both organic and aqueous solvents. Instead of using TBAF, several other reagents (such as KF/HBr/DMF, CBr_4/CH_3OH, and/or HCl/CH_3OH) were investigated for this step, but either an incomplete reaction or a complicated mixture was observed. This problem was resolved by converting crude **11** to its 2,8-dibenzyloxy **10a** (R^2 = Bn) or 2,8-bis-acetoxy **10b** (R^2 = Ac) derivatives, followed by organic/aqueous partitioning, and then cleavage of the protecting groups to give a pure **11**. This protection/deprotection process was not used on scale due to limited time and other results (vide supra). It was realized that when the reaction was run with less than 1 equiv of TBAF (0.6 equiv) at a longer reaction time the tetrabutylammonium group contamination of crude **11** was minimized to ±2%, which was removed by chromatographic purification to afford **11** (85% isolated yield; 94%, HPLC area %) on 250-g scale. After solving this issue, monobromo compound **13** was identified as another major impurity (3.1%) that presented in the above-obtained **11** (Scheme 3) by ^{1}H NMR and LC/MS spectroscopic analyses. The batch of **12** used for this step was checked and found to contain ~3% of the undesired dibromo compound **12b**. The side chain **12** was simply redistilled to remove the dibromo side product **12b**. Finally, the impurity **13** could be cleanly removed by debromination of the mixture under a catalytic hydrogenation

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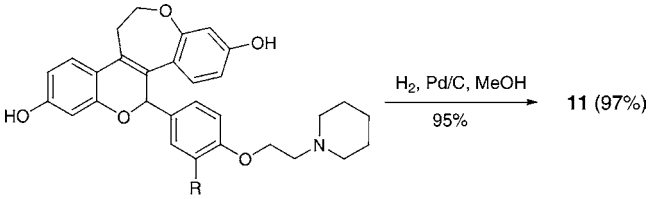
Scheme 3



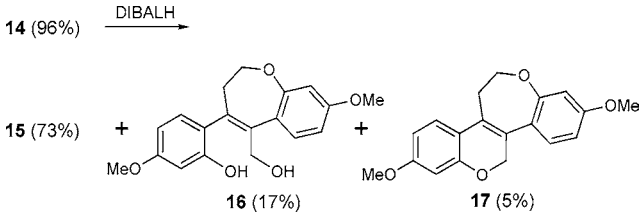
to afford highly pure (>97%, HPLC area %) of the desired **11** in quantitative isolated yield (Scheme 3).

Since the 2,8-dibenzyloxy compound **10a** could be converted to **11** by hydrogenolysis without over-reduction, a non-TABF process was developed to prepare compound **11** (Scheme 1).[11] 2,8-Bisphenol **6** was converted to 2,8-dibenzyloxy derivative **7a** in quantitative isolated yield, after treatment with benzyl bromide and K_2CO_3 in CH_2Cl_2. DIBALH reduction of **7a** resulted in quantitative preparation of the desired lactol **8a**, which was further treated with the lithium reagent **12c** to produce the crude diol **9a**. Acid-catalyzed ring-closure of **9a** afforded compound **10a**, which after removal of the benzyl protecting groups under catalytic hydrogenation conditions (5% Pd/C in MeOH)[11,12] and crystallization from EtOAc and IPA (9:1) afforded compound **11** in 41% (over three steps starting from compound **6**) with >97% chemical purity. Since this benzyloxy route was more cost effective and also provided more chemically robust intermediates (**7a**, **8a**, **9a**, and **10a**), it was recommended to the pilot plant for the GMP campaign of compound **11**.

The second campaign was changed to prepare more than 250 g of 2,8-dimethoxy racemic **19**, due to the in vitro screening results which concluded that compound **19** was the preferred candidate for the advanced biological studies in vivo. To achieve this goal, cyclic 2,8-bisphenol **6** was prepared as before from tetraol **5** under Mitsunobu cyclization conditions in quantitative yield with 88% chemical purity (HPLC area %). Since the tetraol **5** used in this campaign was prepared by the crystallization from water, it was necessary to determine the contents of boronic acid and/or water in **5** by combustion analysis before use in this reaction, because the success of this Mitsunobu cyclization reaction was water- and $B(OH)_3$ dependent. If tetraol **5** was contaminated with a high residue of either boron (>2−3%, 1.0 equiv of $B(OH)_3$) or water (>6.8%, 1.3 equiv of water) this cyclization failed. The 2,8-bisphenol **6** was converted to its 2,8-bis-methoxy lactone **14,** which was isolated as a solid by filtration in 85% yield and high chemical purity (96%, HPLC area %) (Scheme 1).

When the reduction of lactone **14** to lactol **15** was done under conditions (DIBALH/CH_2Cl_2 at −20 °C) similar to those used to prepare lactol **8** in the first campaign, the desired lactol **15** was obtained only in 18% yield along with two unexpected major side products **16** (19%) and **17** (52%). Several solvent and temperature combinations, as well as nonconventional reducing agents were investigated, but none of them provided a clean reduction. Optimized DIBALH reduction conditions were developed where the reaction temperature was rigorously controlled below −70 °C to achieve a high conversion (95%) of **14** after 6 h to the desired lactol **15** in 73% (HPLC area %), while the formation of side products **16** and **17** were minimized to 17% and 5%, respectively (Scheme 4). This crude **15** was used in next step without further purification.

Scheme 4



Addition of the side chain to the crude lactol **15** was also accomplished using the lithium reagent **12c**. This addition required at least 2.0 equiv of the lithium reagent and was conducted below −70 °C in THF. After the workup, it was difficult to remove the excess des-bromo **12a** from diol **18**. A method was developed where the crude product mixture was partitioned between CH_3CN and heptane; des-bromo **12a** was extracted into the heptane phase, and the more polar diol product **18** remained in the CH_3CN phase. This method afforded crude diol **18** (>70% chemical purity, plus 17% of **16**, 5% of **17**, and 8% of unidentified unknowns; HPLC area %) as a thick amber oil that was used in the next step without further purification.

Acid-catalyzed B-ring closure of crude diol **18** was accomplished with concentrated HCl in CH_2Cl_2, which resulted in near a quantitative isolation of crude **19** that was with 80% chemical purity. Crude **19** was purified by the same partition method as applied to diol **18** to afford the desired product **19** in 97% chemical purity (HPLC area %) and a moderate yield (67%), since some of **19** was extracted into the heptane layer. This 97% pure material was further partitioned between heptane and CH_3CN to afford the final product **19** (99.5%) in 56% isolated yield over two steps.

Conclusions

A reproducible process was developed for the scale-up synthesis of compound **11** in 21.4% isolated yield over nine steps with >97% chemical purity and required only one chromatographic purification to remove tetrabutylammonium impurity from the crude product **11**. The desired compound **19** was also prepared by the nonchromatographic "methoxy route" process in reproducible 41% isolated yield and >99.5% chemical purity. And finally, the benzyl-protected series provided the best impurity-free, nonchromatographic route, which was used for large-scale GMP preparation of compound **11** after some additional improvements were made during the pilot production.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further

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purification, except for 4-bromophenol that was used to prepare side-chain **12**. All the melting points are uncorrected and determined on a MEL-TEMP 3.0 apparatus. ^{1}H 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 ID × 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. 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.

7-(Benzyloxy)-3-(2,4-dimethoxyphenyl)-4-methyl-*2H*-chromen-2-one (**3b**)**.** A 5-L Morton flask was charged with 2,4-dimethoxyphenylacetic acid (**2**) (254.0 g, 1.29 mol, 98%), *o*-xylene (1.0 L), Et_3N (310.0 mL, 2.18 mol), and Ac_2O (145.0 mL, 1.41 mol) and was stirred at 20 °C for 30 min. 2-Hydroxy-4-benzyloxyacetophenone (**1b**) (314.0 g, 1.29 mol, 99%) was added to the reaction mixture and brought to reflux (150 °C) for 50 h, while Et_3N (1033 mL, 5.0 equiv) and Ac_2O (655 mL, 5.0 equiv) were added continuously via syringe pumps in a ratio of ∼1:2 (vol/vol) over the same time period (50 h); meanwhile, ∼50 mL of distillate was removed via a Dean Stark trap at intervals every 60 min during the daytime. The progress of the reaction was monitored by LC/MS and HPLC. After completion, the mixture was cooled to 20 °C, the solvents were removed by distillation under high vacuum (2−4 mmHg), and the resulting crude semisolid was crystallized from IPA (3.0 L) to afford 307.2 g (60%) of 7-benzyloxycoumarin **3b** as a brown solid with 99% (HPLC, area %) chemical purity, which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 5.16 (s, 2 H), 6.56 (s, 1 H), 6.58 (dd, J = 1.0, 8.1, 1 H), 6.88−6.98 (m, 2 H), 7.09 (d, J = 8.4, 1 H), 7.32−7.54 (m, 5 H), 7.56 (d, J = 8.4, 1 H). LC/MS *m*/*z* 403 (MH^+), 425 (MNa^+).

7-(Benzyloxy)-3-(2,4-dimethoxyphenyl)-4-(2-methoxyethyl)-*2H*-chromen-2-one (4b). A 5-L RBF was cooled to −20 °C (dry ice/acetone) and charged with lithium bis(trimethylsilyl)amide ($(TMS)_2NLi$, 1.12 L, 1.12 mol, 1.0 M in THF). Compound **3b** (345.0 g, 0.858 mol) in anhydrous THF (1.5 L) was added to the reaction mixture over a 10-min period and stirred at −20 °C for 45 min. Bromomethyl methyl ether (MOMBr, 90%, 125.0 mL, 1.12 mol) was added to the reaction mixture over a 10-min period (there was a mild exotherm, the final internal temperature was 0 °C), and stirring was continued at −20 °C for 1 h (the reaction was monitored by LC/MS and HPLC). The reaction mixture was quenched with saturated NH_4Cl (2.0 L) and extracted with EtOAc (2.0 L). The organic phase was condensed in vacuo at 60 °C to give 395.0 g of crude product, which was crystallized in IPA/EtOAc (1400 mL/200 mL). The solid was collected by filtration and dried in an oven under house vacuum (∼120 mmHg) at 60 °C for 18 h. There was obtained 341.0 g (89% isolated yield; 96% HPLC area %) of coumarin **4b** as a slightly tan solid. Recrystallization of the material from the mother liquor (∼160.0 g) again in IPA/EtOAc (1000 mL/200 mL) afforded an additional 24.4 g (6.4%) of pure compound **4b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76−3.0 (m, 2 H), 3.19 (s, 3 H), 3.46 (t, J = 6.8, 2 H), 3.74 (s, 3 H), 3.86 (s, 3 H), 5.15 (s, 2 H), 6.55 (s, 1 H), 6.57 (dd, J = 0.8, 8.1, 1 H), 6.88−6.98 (m, 2 H), 7.08 (d, J = 8.4, 1 H), 7.32−7.56 (m, 5 H), 7.61 (d, J = 8.3, 1 H). LC/MS *m*/*z* 447 (MH^+), 469 (MNa^+).

3-(2,4-Dihydroxyphenyl)-7-hydroxy-4-(2-hydroxyethyl)-*2H*-chromen-2-one (**5**)**.** A 12-L RBF was charged with CH_2Cl_2 (4.8 L) and compound **4b** (250.0 g, 0.56 mol). The solution was stirred at 20 °C under N_2, BBr_3 (99+%, 561.2 g, 2.24 mol) was added via a double-tipped needle under very mild N_2 pressure over a 20-min period (this was a mildly exothermic process; the final internal temperature was 34 °C). This mixture was gradually heated to 38 °C and gently refluxed for 20 h. The reaction was monitored by LC/MS and HPLC. The reaction was cooled to 20 °C, and the solid was filtered under N_2 atmosphere (*This operation must be done under N_2 atmosphere in a hood with good ventilation, due to the presence of excess BBr_3 that will decompose to HBr when it meets with atmospheric moisture in the atmosphere. The filtrate must be cooled to 0 °C and, with stirring under N_2, quenched with IPA (>500 mL) dropwise. This quenched solution is then stirred at 20 °C for 18 h, before disposal.*), washed with CH_2Cl_2 (1.0 L × 2), and dried under N_2 for 20 min. Another 12-L RBF was charged with EtOH (200 proof, 2.0 L) and cooled to 0 °C in an ice bath. The above solid was added portionwise over a 10-min period with fast agitation (this was an exothermic process; the final internal temperature was ∼26 °C), and the cherry solution was stirred at 20 °C for 18 h. The solvent was concentrated at 65 °C under house vacuum and then under high vacuum (10 mmHg); the resulting material was redissolved in MeOH (×4) and concentrated until the solid reached a constant weight. There was obtained 182.5 g (104% isolated yield) of crude tetraol **5** with 86% chemical purity (HPLC, area %) as a foamy solid. This crude material was used in the next step without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 2.84−3.06 (m, 2 H), 3.56−3.78 (m, 2 H), 4.88 (br s, 4 H), 6.41 (dd, J = 0.9, 8.2, 1 H), 6.43 (s, 1 H), 6.77 (d, J = 1.0, 1 H), 6.82−6.93 (m, 2 H), 7.74 (d, J = 8.3, 1 H). LC/MS *m*/*z* 315 (MH^+), 337 (MNa^+).

An Alternative Workup Process. The completed reaction mixture of compound **4b** (355.1 g, 0.795 mol) with BBr_3 (1074.6 g, 4.29 mol) in CH_2Cl_2 (8 L) was quenched by cautiously transferring the material to a 22-L separatory flask containing water (8 L) via a 1/4-in. Teflon tube. After the transfer was complete, the CH_2Cl_2 layer was removed, and the water layer was filtered into a 19-L filter flask. The

separatory flask was rinsed with hot water (2 × 500 mL); these additional extracts were added to the 19-L flask, and the combined mixture was allowed to crystallize overnight. The solid was collected by filtration and dried under house vacuum at 45 °C to give 178.7 g (72% isolated yield) of the tetraol **5** as a pale-yellow solid with 72% chemical purity (HPLC, area %).

2,8-Dihydroxy-11,12-dihydro-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-one (6). A 12-L RBF was charged with tetraol **5** (251.7 g, 0.802 mol) and anhydrous THF (4.0 L). This suspension was cooled to −5−0 °C, diisopropyl azodicarboxylate (DIAD, 664.5 mL, 3.206 mol) was added over a 35-min period, and the mixture was stirred at −5 °C for 30 min followed by the addition of triphenylphosphine (841.0 g, 3.206 mol) solution in THF (1.6 L) over a 30-min period. After the addition, the mixture was warmed to 20 °C and stirred for 18 h, and the progress of the reaction was monitored by LC/MS and HPLC. The solvent was concentrated in vacuo at 60 °C, and the resulting material was dissolved in CH_2Cl_2 (6.0 L) and washed with 2 N NaOH solution (4 L, 2 L, 1 L). The aqueous phases were combined and back-extracted with CH_2Cl_2 (1.6 L). This alkaline phase was cooled to 0 °C, acidified to pH ∼1−2 with concentrated HCl solution (37%, ∼1.8 L) (the final internal temperature was 16 °C), and the resulting slurry was stirred at 10 °C for 1 h. The solid was collected by filtration, and the filter cake was washed with D.I. H_2O (500 mL × 5, or until pH ∼6−7). This solid was dried by air-suction for 18 h and then placed in a vacuum oven at 70 °C under house vacuum for 72 h until a constant weight was achieved. There was afforded 230.7 g (97.2% isolated yield, 82% by HPLC area %) of 2,8-bisphenol lactone **6** as a yellow-green solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.94 (t, J = 5.9, 2 H), 4.56 (t, J = 5.8, 2 H), 6.52 (d, J = 0.9, 1 H), 6.68 (dd, J = 0.8, 8.2, 1 H), 6.78 (d, J = 1.0, 1 H), 6.86 (dd, J = 0.9, 8.8, 1 H), 7.44 (d, J = 8.3, 1 H), 7.81 (d, J = 8.4, 1 H), 9.7 (s, 1 H), 10.6 (s, 1 H). LC/MS m/z 297 (MH^+), 319 (MNa^+).

2,8-Bis(*tert*-butyldimethylsilyloxy)-11,12-dihydro-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-one (7). A 12-L RBF was charged with CH_2Cl_2 (2730 mL) and 2,8-bisphenol lactone **6** (82%, 411.2 g, 1.389 mol). This suspension was stirred at 20 °C for 5 min, and then Et_3N (449.2 mL, 3.223 mol) was added over a 5-min period. *tert*-Butyldimethylsilyl chloride (TBDMS-Cl, 97%, 466.3 g 3.001 mol) was added portionwise (40-g portions at 5-min intervals) over a 60-min period while the reaction temperature was maintained between 23 and 30 °C. After the addition, the mixture was stirred at 20 °C for 20 h. The reaction was monitored by LC/MS and ^{1}H NMR. The reaction mixture was transferred to a 12-L three-neck separatory flask, washed with 0.1 N HCl (1.36 L × 2), saturated $NaHCO_3$ (1.36 L), and brine (1.36 L). The solvent was concentrated in vacuo and kept under high vacuum (10 mmHg) at 60 °C for 1 h. The resulting semisolid material (791.0 g, 108% recovery yield) was triturated with pentane (780 mL) and stirred at 20 °C for 20 min and then at −10 °C for 30 min. The solid was collected by filtration, washed with pentane (20 mL × 3), and then placed in a vacuum oven under house vacuum at 60 °C for 18 h. There was obtained 230.0 g (39% isolated yield; 96% HPLC area %) of the desired 2,8-bissilyl lactone **7** as a yellowish fine powder. The mother liquor was concentrated to give a 610.0 of thick oil which contained ∼25−30% of lactone **7** as determined by ^{1}H NMR. Chromatographic purification (SiO_2, 2.0 kg, eluted with EtOAc/hexane (0/100 to 20/80)) of this oil gave crude **7** (321.0 g), which was slurried in pentane (260 mL) to give an additional 124.9 g (21.2%) of pure **7**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6 H), 0.27 (s, 6 H), 1.0 (s, 18 H), 2.93 (t, J = 6.0, 2 H), 4.68 (t, J = 6.1, 2 H), 6.66 (d, J = 1.1, 1 H), 6.78 (dd, J = 0.9, 8.1, 1 H), 6.82 (dd, J = 0.9, 8.2, 1 H), 6.88 (s, 1 H), 7.52 (d, J = 8.4, 1 H), 7.69 (d, J = 8.4, 1 H). LC/MS m/z 525 (MH^+), 547 (MNa^+).

2,8-Dibenzyloxy-11,12-dihydro-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-one (7a). Compound **7a** (8.9 g, 92% isolated yield; 90% HPLC, area %) was prepared in a similar manner as **7** from 2,8-bisphenol **6** (6.0 g, 20.3 mmol; 89%) with benzyl bromide (2.0 equiv) and K_2CO_3 (4.4 equiv) in CH_2Cl_2 at 38 °C for 24 h to afford **7a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (t, J = 5.8, 2 H), 4.68 (t, J = 5.9, 2 H), 5.10 (s, 2 H), 5.15 (s, 2 H), 6.78 (d, J = 0.8, 1 H), 6.91 (dd, J = 0.9, 8.3, 1 H), 6.92−7.01 (m, 2 H), 7.29−7.50 (m, 10 H), 7.56 (d, J = 8.4, 1 H), 7.72 (d, J = 8.3, 1 H). LC/MS m/z 477 (MH^+), 499 (MNa^+).

2,8-Dimethoxy-11,12-dihydro-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-one (14). Compound **14** (72.8 g, 85% isolated yield; 96%, HPLC area %) was prepared in a similar manner as **7** from 2,8-bisphenol **6** (78.0 g, 0.263 mol) with iodomethane (3.0 equiv) and K_2CO_3 (4.0 equiv) in DMF at 20 °C for 4 h to afford **14**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98 (t, J = 5.9, 2 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 4.64 (t, J = 6.0, 2 H), 6.75 (d, J = 0.9, 1 H), 6.85 (dd, J = 0.9, 8.0, 1 H), 7.01 (dd, J = 0.9, 8.1, 1 H), 7.08 (d, J = 0.8, 1 H), 7.59 (d, J = 8.3, 1 H), 7.93 (d, J = 8.4, 1 H). LC/MS m/z 325 (MH^+), 347 (MNa^+).

2,8-Bis(*tert*-butyldimethylsilyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-ol (8). A 12-L RBF was charged with CH_2Cl_2 (4.0 L) and lactone **7** (360.0 g, 0.687 mol); the solution was stirred under nitrogen and cooled to −20 °C in a dry ice/acetone bath. Diisobutylaluminum hydride (DIBALH, 1.0 M in CH_2Cl_2, 823.0 mL, 0.823 mol) was added dropwise over a 45-min period, while the reaction temperature was maintained at −20 °C. After the addition, the reaction was stirred at −20 °C for 1.5 h, and the reaction was monitored by LC/MS, TLC (EtOAc/hexane, 2/8), and ^{1}H NMR analyses. The reaction was quenched with Rochelle's solution (2.4 L, 40% of potassium sodium tartrate tetrahydrate in D.I. water) and transferred to a 22-L three-neck separatory flask. Additional Rochelle's solution (13.0 L) was added, and the mixture was agitated at room temperature for 2 h. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (1.6 L × 2), and the combined organic phases were washed with Rochelle's solution (3.0 L) and brine (3.0 L). The organic phase was concentrated in vacuo at 30 °C, and the resulting material was placed in a vacuum oven (under 10 mmHg) at 60 °C for 18 h. There was obtained 368.0 g (101% isolated yield,

96% HPLC area %) of 2,8-bissilyl lactol **8** as a slightly yellowish solid, which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 12 H), 1.0 (s, 18 H), 2.73−2.99 (m, 2 H), 3.01 (d, J = 7.6, 1 H), 4.46−4.60 (m, 2 H), 6.09 (d, J = 7.8, 1 H), 6.56 (dd, J = 1.1, 8.4, 1 H), 6.57−6.63 (m, 2 H), 6.68 (dd, J = 1.2, 8.3, 1 H), 7.2 (d, J = 8.3, 1 H), 7.42 (d, J = 8.4, 1 H). LC/MS m/z 527 (MH^+), 549 (MNa^+).

2,8-Dibenzyloxy-11,12-dihydro-5*H*-6,13-dioxabenzo-[3,4]-cyclohepta[1,2-*a*]naphthalene-5-ol (8a). Compound **8a** was prepared in a similar fashion as **8** from compound **7a** (4.0 g, 8.4 mmol, 90%) with DIBALH (1.2 equiv) in CH_2Cl_2 at below −40 °C for 1 h to afford **8a** (4.1 g, 102% isolated yield, 90% HPLC area %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (m, 2 H), 4.54 (m, 2 H), 5.06 (s, 2 H), 5.08 (s, 2 H), 6.08 (d, J = 8.9, 1 H), 6.65 (dd, J = 0.9, 8.3, 1 H), 6.66−6.76 (m, 2 H), 6.80 (dd, J = 1.0, 8.1, 1 H), 7.20−7.50 (m, 13 H). LC/MS m/z 479 (MH^+), 501 (MNa^+).

2,8-Dimethoxy-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-5-ol (15). Compound **15** was prepared in a similar fashion as **8** from compound **14** (32.4 g, 0.10 mol) with DIBALH (1.5 equiv) in CH_2Cl_2 at − 70 °C for 6 h to afford **15** (30.0 g, 92% isolated yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.72−2.98 (m, 2 H), 3.21 (d, J = 5.4, 1 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.40−4.57 (m, 2 H), 5.99 (d, J = 5.6, 1 H), 6.60 (d, J = 0.8, 1 H), 6.61−6.66 (m, 2 H), 6.79 (dd, J = 0.9, 8.2, 1 H), 7.18 (d, J = 7.9, 1 H), 7.46 (d, J = 8.3, 1 H). LC/MS m/z 327 (MH^+), 349 (MNa^+).

(*Z*)-2-(5-(Hydroxy(4-(2-(piperidin-1-yl)ethoxy)phenyl)-methyl)-(8-*tert*-butyldimethylsilyloxy-2,3-dihydrobenzo-[*b*]oxepin-4-yl)-5-(*tert*-butyldimethylsilyloxy)phenol (9). A 12-L RBF was charged with 1-[2-(4-bromophenoxy)ethyl]-piperidine (**12**) (233.6 g, 0.822 mol) and anhydrous THF (1.8 L) under N_2. The solution was stirred and cooled to −76 °C; *n*-butyllithium (*n*-BuLi, 2.5 M in hexane, 329.0 mL, 0.822 mol) was added dropwise over a 60-min period, while the internal reaction temperature was maintained between −76 to −73 °C. The mixture was stirred for 20 min, and a solution of lactol **8** (188.0 g, 0.357 mol) in anhydrous THF (1.8 L) was added dropwise over an 80-min period at < −73 °C. The reaction was stirred for an additional hour, and the progress of the reaction was monitored by LC/MS, TLC (CH_2Cl_2/CH_3OH, 9/1), and ^{1}H NMR. After completion, the reaction was quenched with saturated NH_4Cl solution (740 mL) at −78 °C and the mixture was allowed to warm to 20 °C with stirring. The solvent was concentrated in vacuo at 60 °C to give an oily material, which was redissolved in EtOAc (2.8 L) and washed with D.I. H_2O (2.8 L × 2). The aqueous phase was extracted with EtOAc (1.8 L × 2), and the combined organic phases were washed with brine (2.5 L). The solvent was concentrated in vacuo at 65 °C to give the crude diol **9** (359.8 g, 138%; of which the ^{1}H NMR spectra indicated ~30% of des-bromo **12a**), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6 H), 0.23 (s, 6 H), 0.96 (s, 9 H), 0.99 (s, 9 H), 1.46 (m, 2 H), 1.61 (m, 4 H), 2.53 (m, 4 H), 2.73−2.81 (m, 2 H), 2.80 (t, J = 6.2, 2 H), 3.98−4.14 (m, 2 H), 4.15 (t, J = 6.3, 2 H), 4.56 (m, 1 H), 5.68 (br s, 1 H), 641−6.48 (m, 2 H), 6.58 (d, J = 1.0, 1 H), 6.78 (d, J = 8.9, 2 H), 6.90−7.0 (m, 3 H), 7.06 (d, J = 8.4, 1 H), 7.18 (dd, J = 1.0, 8.3, 1 H), 7.24 (d, J = 8.3, 1 H). LC/MS m/z 732 (MH^+), 754 (MNa^+), and 206 (MH^+ of **12a**).

(*Z*)-2-(5-(Hydroxy(4-(2-(piperidin-1-yl)ethoxy)phenyl)-methyl)-(8-benzyoxy-2,3-dihydrobenzo[*b*]oxepin-4-yl)-5-benzyoxyphenol (9a). Compound **9a** was prepared in a similar fashion as **9** from compound **8a** (90%, 4.0 g, 8.36 mmol) with the side-chain **12** (2.3 equiv) and *n*-BuLi (2.3 equiv) in THF at −78 °C for 1 h to afford **9a** (8.37 g crude product, 146% isolated yield; 68%, HPLC area %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (m, 2 H), 1.63 (m, 4 H), 2.51 (m, 4 H), 2.64 (m, 2 H), 2.80 (t, J = 6.0, 2 H), 4.08 (m, 2 H), 4.12 (t, J = 6.1, 2 H), 4.98 (m, 1 H), 5.10 (s, 2 H), 5.12 (s, 2 H), 6.50−7.02 (m, 9 H), 7.10−7.51 (m 12 H). LC/MS m/z 684 (MH^+), 706 (MNa^+).

(*Z*)-2-(5-(Hydroxy(4-(2-(piperidin-1-yl)ethoxy)phenyl)-methyl)-(8-methoxy-2,3-dihydrobenzo[*b*]oxepin-4-yl)-5-methoxyphenol (18). Compound **18** was prepared in a similar fashion as **9** from compound **15** (87.0 g, 0.27 mol) with the side-chain **12** (2.44 equiv) and *n*-BuLi (2.31 equiv) in THF at −78 °C for 8 h to afford **18** (145.0 g crude product (102% isolated yield; 80%, HPLC area %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (m, 2 H), 1.62 (m, 4 H), 2.52 (m, 4 H), 2.75 (m, 2 H), 2.80 (t, J = 5.6, 2 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 4.04 (m, 2 H), 4.11 (t, J = 5.5, 2 H), 4.58 (m, 1 H), 5.69 (s, 1 H), 6.41−6.56 (m, 3 H), 6.62 (d, J = 0.8, 1 H), 6.76 (d, J = 9.0, 2 H), 6.91 (d, J = 8.1, 1 H), 6.96 (d, J = 7.9, 1 H), 7.08 (d, J = 8.4, 1 H), 7.16 (d, J = 8.9, 2 H). LC/MS m/z 532 (MH^+), 554 (MNa^+).

1-(2-{4-[2,8-Bis(*tert*-butyldimethylsilyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5-yl]phenoxy}ethyl)piperidine (10). A 12-L RBF was charged with CH_2Cl_2 (3.6 L) and the crude diol **9** (360.0 g, 0.3574 mol) under N_2, and the mixture was cooled to 10 °C. A solution of HCl (37%, 152.8 mL, 1.43 mol) was added dropwise over a 15-min period with fast agitation. After the addition, the reaction was stirred for 30 min at 20 °C, and the reaction was monitored by LC/MS, TLC (CH_2Cl_2/CH_3OH, 9/1), and ^{1}H NMR. The mixture was transferred to a 12-L three-neck separatory flask, diluted with CH_2Cl_2 (1.23 L), and washed with D.I. H_2O (4.0 L × 2), saturated $NaHCO_3$ solution (3.0 L), and brine (3.0 L). The organic phase was dried over Na_2SO_4 (1.0 kg) and then concentrated in vacuo at 50 °C. The resulting cherry, syrupy material was placed under high vacuum at 60 °C for 18 h to afford 252.0 g (98.9%) of crude compound **10**, which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 6 H), 0.22 (s, 6 H), 0.97 (s, 9 H), 0.99 (s, 9 H), 1.44 (m, 2 H), 1.61 (m, 4 H), 2.50 (m, 4 H), 2.66 (t, J = 6.0, 2 H), 2.89 (m, 2 H), 4.06 (t, J = 6.1, 2 H), 4.69 (m, 2 H), 6.04 (s, 1 H), 6.32 (d, J = 0.9, 1 H), 6.39 (dd, J = 1.0, 8.2, 1 H), 6.53 (dd, J = 0.9, 8.3, 1 H), 6.59 (d, J = 1.0, 1 H), 6.68 (d, J = 9.0, 2 H), 6.98 (d, J = 8.3, 1 H), 7.11 (d, J = 8.4, 1 H), 7.35 (d, J = 9.0, 2 H). LC/MS m/z 714 (MH^+), 736 (MNa^+).

1-(2-{4-[2,8-(Dibenzyloxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5-yl]-phenoxy}ethyl)piperidine (10a). Compound **10a** was prepared in a similar fashion as **10** from compound **9a** (8.37 g, 68%, HPLC area %) with concentrated HCl (4.9 mL) in toluene at 20 °C for 1 h to afford **10a** (5.46 g, 98% isolated yield; 96%, HPLC area %) (the excess of des-bromo **12a** was removed as HCl salt during aqueous workup). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (m, 2 H), 1.62 (m, 4 H), 2.49 (m, 4 H), 2.74 (m, 2 H), 2.81 (t, J = 5.7, 2 H), 4.06 (m, 2 H), 4.13 (t, J = 5.8, 2 H), 5.0 (s, 2 H), 5.08 (s, 2 H), 6.05 (s, 1 H), 6.46 (d, J = 0.8, 1 H), 6.53 (dd, J = 0.9, 8.2, 1 H), 6.68 (dd, J = 0.9, 8.2, 1 H), 6.73 (d, J = 0.9, 1 H), 6.78 (d, J = 8.9, 2 H), 6.92 (m, 1 H), 7.01 (d, J = 8.3, 1 H), 7.18 (d, J = 9.0, 2 H), 7.20−7.51 (m, 10 H). LC/MS m/z 666 (MH^+), 688 (MNa^+).

1-(2-{4-[2,8-(Dimethoxy)-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-5-yl]phenoxy}-ethyl)piperidine (19). Compound **19** was prepared in a similar fashion as **10** from compound **18** (132.0 g, 0.248 mol) with concentrated HCl (61 mL) in CH_2Cl_2 at 10−15 °C for 45 min to afford **19** (84.0 g, 56% isolated yield; 99.5%, HPLC area %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (m, 2 H), 1.58 (m, 4 H), 2.46 (m, 4 H), 2.71 (t, J = 6.0, 2 H), 2.89 (t, J = 5.8, 2 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.03 (t, J = 6.1, 2 H), 4.69 (t, J = 5.5, 2 H), 6.06 (s, 1 H), 6.36 (d, J = 1.0, 2 H), 6.48 (dd, J = 0.9, 8.3, 1 H), 6.58 (dd, J = 0.9, 8.2, 1 H), 6.68 (d, J = 9.1, 2 H), 7.02 (d, J = 8.4, 1 H), 7.17 (d, J = 8.3, 1 H), 7.36 (d, J = 9.0, 2 H). LC/MS m/z 514 (MH^+), 536 (MNa^+).

5-[4-(2-Piperidin-1-yl-ethoxy)phenyl]-11,12-dihydro-5*H*-6,13-dioxabenzo[3,4]cyclohepta[1,2-*a*]naphthalene-2,8-diol (11). A 12-L RBF was charged with compound **10** (253.0 g, 0.356 mol) in anhydrous THF (5.0 L) with agitation at 20 °C under nitrogen. Tetrabutylammonium fluoride (TBAF, 1.0 *M* in THF, 213 mL, 0.213 mol) was added dropwise over a 1-h period with fast agitation, and the reaction was then stirred for 18 h; the reaction was monitored by LC/MS, TLC (CH_2Cl_2/CH_3OH, 9/1), and HPLC ((retention time/area %): unknown (2.36 min, 1.9%), **11** (3.90 min, 94%), **13** (4.18 min, 3.1%), mono-TBDMS-**11** (5.11 min, 0.1), and **10** (6.08 min, 0.0%)). After the reaction was completed, EtOAc (2.5 L) and brine (2.5 L) were added to the reaction and stirred for 10 min. The mixture was transferred to a 12-L separatory flask, and the aqueous phase was separated; the organic phase was washed with brine (2.5 L, 1.0 L × 6). The organic phase was dried over Na_2SO_4 (1.0 kg), and then concentrated in vacuo at 50 °C. The resulting cherry-colored material was placed under high vacuum at 60 °C for 2 h to afford 273.8 g (158%, 84% of **11**, which contained residual EtOAc; HPLC area %) of crude **11**. Chromatographic purification (SiO_2 × 2.4 kg; eluted with CH_2Cl_2/CH_3OH (97/3 to 93/7)) of the above crude product afforded 139.3 g (81% isolated yield, 94% of **11** and 3.1% of **13**; HPLC area %) of tetrabutylammonium impurity contaminated **11**. LC/MS m/z 486 (MH^+), 243 (MH^+ of Bu_4N^+).

In addition, compound **11** was also prepared from the hydrogenolysis of **10a** (3.73 g, 5.61 mmol; 96%) using Pd/C (5 mol %) in EtOAc/MeOH (60/60, mL/mL) under hydrogen pressure (3.06 atm) at 20 °C for 20 h to afford the crude product **11** (3.68 g, 91% isolated yield). Crystallization of crude **11** in EtOAc/IPA (9:1) afforded pure **11** (2.28 g, 62% isolated yield; 98% HPLC area %), which compared exactly to the ^{1}H NMR and LC/MS spectroscopic data with the compound **11** prepared from the TBDMS-protected route.

Debromination of 13. A sample of monobromo **13** contaminated **11** (139.3 g, 0.287 mol) was dissolved in CH_3OH (600 mL), and the solution was transferred to a 2-L Parr glass hydrogenation bottle followed by the addition of the catalyst (5% palladium on carbon, 30.5 g) under N_2 atmosphere. The mixture was flushed with hydrogen (∼1.36 atm × 3) and then the shaker bottle was refilled with hydrogen to 3.06 atm and shaken for 16 h. The reaction was monitored by LC/MS and HPLC. After completion, the reaction vessel was vented with N_2 (∼1.36 atm × 3), and the suspension was filtered through a pad of Celite. After the filter cake was washed with CH_3OH (100 mL × 3), the combined filtrate was concentrated in vacuo at 50 °C, and the product was further dried for 2 h under high vacuum (2 mmHg) at 65 °C and then at 50 °C for 18 h. There was obtained 132.1 g (95% isolated yield) of pure racemate **11** as a pink, foamy solid (a partial HBr salt). ^{1}H NMR (300 MHz, CD_3OD) δ 1.46 (m, 2 H), 1.61 (m, 4 H), 2.53 (m, 4 H), 2.75 (t, J = 6.0, 2 H), 2.85 (m, 2 H), 4.07 (t, J = 6.1, 2 H), 4.61 (m, 2 H), 4.88 (s, 2 H), 6.02 (s, 1 H), 6.18 (d, J = 0.8, 1 H), 6.36 (dd, J = 0.7, 8.1, 1 H), 6.50 (dd, J = 0.6, 8.0, 1 H), 6.52 (d, J = 0.6, 1 H), 6.79 (d, J = 9.1, 2 H), 7.0 (d, J = 8.2, 1 H), 7.16 (d, J = 8.1, 1 H), 7.34 (d, J = 9.0, 2 H). LC/MS m/z 486 (MH^+), 508 (MNa^+). Elementary analysis Calcd for $C_{30}H_{31}N_1O_5$·1.0 H_2O (MW = 503.60): C, 71.55; H, 6.60; N, 2.78; %H_2O, 1.0. Found: C, 71.37; H, 6.52; N, 2.70; %H_2O, 1.52.

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