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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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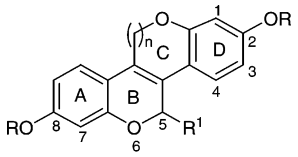
Abstract:

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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(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. F.; Ng, R.; Sui, Z.; Xu, J. WO2003053977, 2003.

(4) (a) Li, X.; Jain, N.; Russell, R. K.; Ma, R.; Branum, S.; Xu, J.; Sui, Z. *Org. Process Res. Dev.* **2006**, *10*, 354. (b) Horváth, A.; De Smet, K.; Ormerod, D.; Depré, D.; Pérez-Balado, C.; Govaerts, T.; Van den Heuvel, D.; Schorpion, I. *Org. Process Res. Dev.* **2005**, *9*, 356.

(5) Li, X.; Reuman, M.; Russell, R. K.; Adams, R.; Ma, R.; Beish, S.; Branum, S.; Youells, S.; Roberts, J.; Jain, N.; Kanojia, R.; Sui, Z. *Org. Process Res. Dev.* **2007**, *11*, 414−421, part 1 of this publication.

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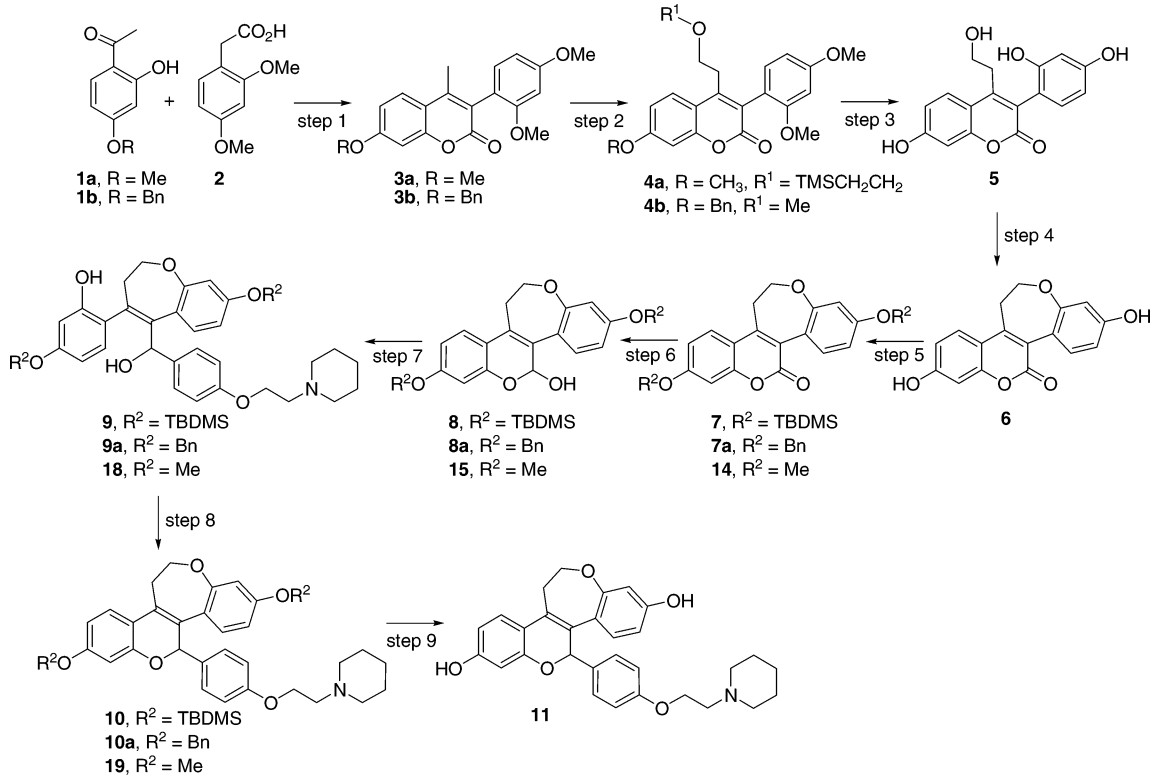
Table 1. **Summary of the reaction conditions and yields for the preparation of compounds 11 and 19**

	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

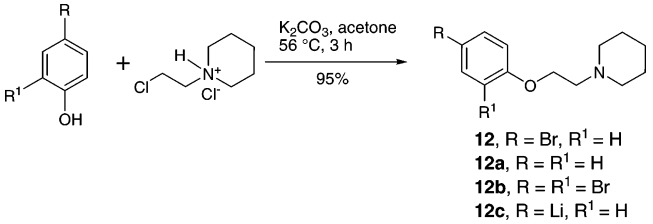
Scheme 1). During pilot production, the unstable and carcinogenic MOM-Br was replaced with the stable and less harmful pivaloyoxymethyl chloride (POM-Cl), which also produced the POM-homologated compound in high yield (93%) and good chemical purity (85.4%).[4b]

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

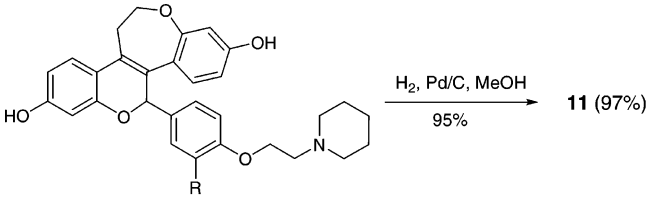


12, R = Br, R^1 = H
12a, R = R^1 = H
12b, R = R^1 = Br
12c, R = Li, R^1 = H

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

(6) (a) Fieser, M. *Fieser and Fieser's Reagents for Organic Synthesis;* John Wiley & Sons: New York, 1982; Vol. 10, pp 56−57. (b) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976.
(7) Suzuki, A.; Hara, S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; John Wiley & Sons: New York, 1995; Vol. 1, pp 645−648.
(8) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(9) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 273−275.
(10) Li, H.-Y. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; John Wiley & Sons: New York, 1995; Vol. 7, pp 4728−4732.

Scheme 3



11 (R = H, 94%) + **13** (R = Br, 3.1%)

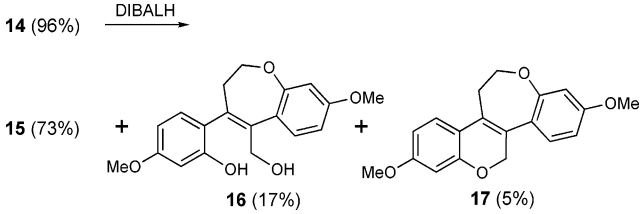
to afford highly pure (>97%, HPLC area %) of the desired **11** in quantitative isolated yield (Scheme 3).

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

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 76−86.
(12) (a) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746. (b) Schmidhammer, H.; Brossi, A. *J. Org. Chem.* **1983**, *48*, 1469.

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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