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Development of a Scalable Synthetic Process for Selective Bromination of 4-Methyl-3,7-Substituted Coumarins

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Abstract:

The hydroxyl-protected coumarin derivatives 6a−e of 4-methyl-3-(2,4-dihydroxyphenyl)-7-hydroxycoumarin (4) are key intermediates in the synthesis of unsymmetrical benzopyranobenzopyran compounds, a novel series of selective estrogen receptor modulators (SERMs). Free radical bromination of the 4-methyl group on 7-acetoxy-3-[(2,4-diacetoxy)phenyl]-4-methylcoumarin (6a) with NBS resulted in incomplete reactions and low to moderate yields (25−44%) of 4-bromomethyl product 7a. Lithiation of the 4-methyl group of coumarins 6b (R = SEM), 6c (R = MOM) and 6d (R = Bz) with LDA (1.1−1.7 equiv) or LHMDS (1.2−1.7 equiv) generated carbanion in THF at −76 °C, which was quenched with bromine (1.5−2.0 equiv) to afford 4-bromomethyl derivatives 7b−d in good yields (80∼90%) in small scale reactions (2−20 g). The reaction yields declined to ∼70% when the scale was increased to ≥ 80 g. Furthermore, treatment of 3-[(2,4-dimethoxy)phenyl]-7-methoxy-4-methylcoumarin (6e) with LHMDS (1.08 equiv) in THF followed by rapid inverse quenched with NBS (1.10 equiv) in THF at −76 °C, selectively produced the desired 4-bromomethyl compound 7e in excellent yield (> 90%) in both small (2−8 g) and large (80−150 g) scale reactions. A non-chromatographic process was developed to prepare 6e. This selective and efficient procedure was successfully transferred to the pilot plant to produce multi-kilograms of 4-bromomethyl coumarin 7e.

Introduction

4-Methyl-3,7-substituted coumarins (**6a**−**e**, R = Ac, SEM, MOM, Bz, Me), key intermediates for the construction of unsymmetrical benzopyranobenzopyran ring systems,[1,2] have played an important role in the discovery of novel molecules as selective estrogen receptor modulators (SERMs).[1−3] Key to this synthesis was the conversion of the 4-methyl group of a 3,7-substituted courmarin to a functional group, typically a 4-halogenated or 4-oxygenated methyl moiety, to allow for ring closure to benzopyranobenzopyrans. Although free radical brominations of 4-methyl or 4-methylene (4-CH_2R) functionalities of 7-,[4,5] 5,7-,[6] and 5,6,7-substituted[6,7] courmarins have been reported, the selective bromination of a 4-methyl group of 3,7-substituted coumarins has not been investigated. Our interests focused on selective transformation of the 4-methyl group of coumarins **6a**−**e** to their corresponding 4-bromomethyl analogues **7a**−**e**, identify the best bromination conditions, and the best R-group substrate among coumarins **6a**−**e**, as well as develop a reproducible and non-chromatographic scale-up process. We wish to report our results of method development and scale-up.

Results and Discussion

The convenient base-catalyzed Perkin condensation of 2,4-dihydroxyacetophenone (**1**) and 2,4-dimethoxyphenylacetic acid (**2**) in refluxing acetic anhydride was selected to synthesize the backbone structure of coumarin **3** in 77% isolated yield.[1,8,9] Deacetylation and demethylation of compound **3** in a one-pot reaction with pyridine hydrochloride produced 4-methyl-3-(2,4-dihydroxyphenyl)-7-hydroxycoumarin (**4**) in nearly quantitative yield.[1,9] This trihydroxy coumarin **4** was converted to its hydroxyl-protected derivatives **6a**−**d** (R = Ac, SEM, MOM, Bz) in only moderate yields (42−68%), probably due to steric congestion between the 4-methyl group and the 2-hydroxy group of the 3-(2,4-dihydroxy)phenyl group. Under these reaction conditions, chromatographic purification of the crude reaction mixture was required in order to obtain pure **6a**−**d** (Scheme 1). A nonchromatographic scale-up process was developed where the 7-acetoxy **3** was deacetylated with K_2CO_3 in MeOH to afford 7-hydroxy compound **5** in 38% isolated yield. This moderate yield of **5** was not further refined due to limited time. Methylation of **5** with MeI and K_2CO_3 in DMF afforded the desired trimethoxy material **6e** in 80% isolated yield with excellent chemical purity (>98%). The protecting groups (R) were chosen because they could be easily removed under either alkaline (NaOH, K_2CO_3) or acidic (HCl, HBr, and/or BBr_3) cleavage conditions after the bromination reaction.

A brief literature survey revealed that bromination of the 4-methyl group of 7-substituted[4,5] and 5,7-substituted cou-

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‡ Reproductive Therapeutics.

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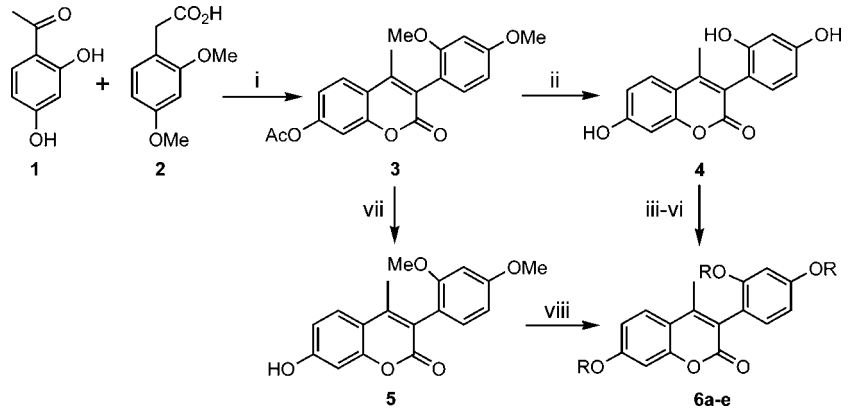
Scheme 1[a]



[a] Reagents and conditions: i) Ac_2O, Et_3N, 148 °C, 48 h, 77%; ii) pyridine hydrochloride, 180−210 °C, 1 h, >95%; iii) **6a**, R = Ac, Ac_2O, pyridine, 89 °C, 4 h, 59%; iv) **6b**, R = SEM, K_2CO_3, SEMCl, acetone, 56 °C, 3 h, 42%; v) **6c**, R = MOM, K_2CO_3, MOMBr, 87 °C, 3 h, 68%; vi) **6d**, R = Bz, BzCl, Et_3N, CH_2Cl_2, 20 °C, 4 h, 48%; vii) K_2CO_3, MeOH, 38%; viii) **6e**, R = Me, K_2CO_3, DMF, MeI, 20 °C, 2 h, 80%.

Table 1. **Results of free radical bromination of 4-methyl-3,7-substituted coumarin 6a (R = Ac)**

entry	conditions	**7a** (%)[a]	**6a/8a/10a** (%)[a]
1	NBS (1.3 equiv), $(BzO)_2$, CCl_4, *hν*, 76 °C, 100 h	44	40/8/0
2	NBS (1.3 equiv), $(BzO)_2$, C_6H_5Cl, *hν*, 100 °C, 48 h	<5	90/0/0/
3	NBS (1.3 equiv), AIBN, CCl_4, *hν*, 76 °C, 21 h	43	40/8/0
4	Br_2 (1.1 equiv), *hν*, *o*-xylene, 125 °C, 24 h	25	3/40/25
5	Br_2 (1.1 equiv), $La(OAc)_3$, *hν*, heptane, 60 °C, 6 h	30	5/40/25
6	NCS (1.3 equiv), $(BzO)_2$, CCl_4, *hν*, 76 °C, 100 h	0	99/0/0

[a] HPLC area%.

marins were classically conducted under free radical conditions using NBS that resulted in moderate to good yields (45−74%) of 4-bromomethyl products; however, with poor selectivity since both the 4-dibromomethyl and 3-brominated coumarins were often generated as byproducts. Although radical bromination of 4-methylene (4-CH_2R) containing 5,6,7-substituted courmarins to 4-BrCHR− proceeded with good selectivity in excellent yield (>95%).[6,7] In practice, bromination of the 4-methyl group of 3,7-substituted triacetoxy compound **6a** with NBS in the presence of dibenzoyl peroxide under light and refluxing in CCl_4 for 100 hours, resulted in 44% of **7a** and recovered 40% of **6a**. (entry 1, Table 1).[1,2] Elevating the reaction temperature (100 °C) or using AIBN as an initiator did not improve the reaction yields (entries 2 and 3).[11] Replacement of NBS with bromine in hot *o*-xylene under light afforded 25% of **7a** (determined by HPLC) along with 40% of 4-dibromomethyl **8a** and 25% of aromatic bromination product **10a** (Scheme 2).[12] The addition of $La(OAc)_3$, a catalyst reported that benefits radical benzylic bromination, did not significantly change the product/byproducts ratio (entries 4 and 5).[13] The attempt to convert **6a** to its corresponding 4-chloromethyl derivative using NCS was also unsuccessful (entry 6, Table 1). The incomplete reaction and low reaction yields of free radical bromination on **6a** with NBS may be attributed to the 2-acetoxy group of the 3-(2,4-acetoxy)phenyl substituent, which adds steric congestion around the 4-methyl group on the coumarin ring. On the other hand, bromine displayed the powerful brominating capability to **6a** and led the reaction close to a completed conversion, which however, also resulted in low yields of **7a** due to the lack of selectivity to 4-methyl group and 3-phenyl ring.

Due to the disappointing results in Table 1, we decided to explore the preparation of **7b**−**e** via the 4-methyl carbanion of **6b**−**e**. Since the 4-methyl group is at the *beta*-position of the α,*β*-unsaturated conjugated lactone ring of coumarins **6b**−**e**, the 4-methyl protons may be deprotonized by a strong Bronsted base, such as LDA. Moreover, the regiospecific preparation of α-bromo ester[14] as well as α-bromo ketone[15] by bromination of lithium enolates has been reported with good to excellent yields (80−97%). To examine this hypotheses, the SEM-protected coumarin **6b** was treated with LDA (1.1 equiv) in THF at −8 °C and the generated anion was quenched with bromine (2.0 equiv) at −76 °C to give 50% of the desired coumarin **7b**, 42% of starting material **6b**, and 8% of aromatic bromination product **10b** (entry 7, Table 2).[14,15] Increasing the amount of LDA from 1.1 to 1.5 or 1.7 equiv improved the yield of **7b** to 80%, but 10% of **6b** still remained as well as 10% of aromatic bromide **10b** (entries 8 and 9). This result was encouraging, however, for scale-up purposes we needed to accomplish complete lithiation of the 4-methyl group and minimize the aromatic bromination. We decided to use LHMDS, a more hindered base than LDA, for the deprotonation. Treatment of **6b** with LHMDS (1.7 equiv) in THF

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Scheme 2

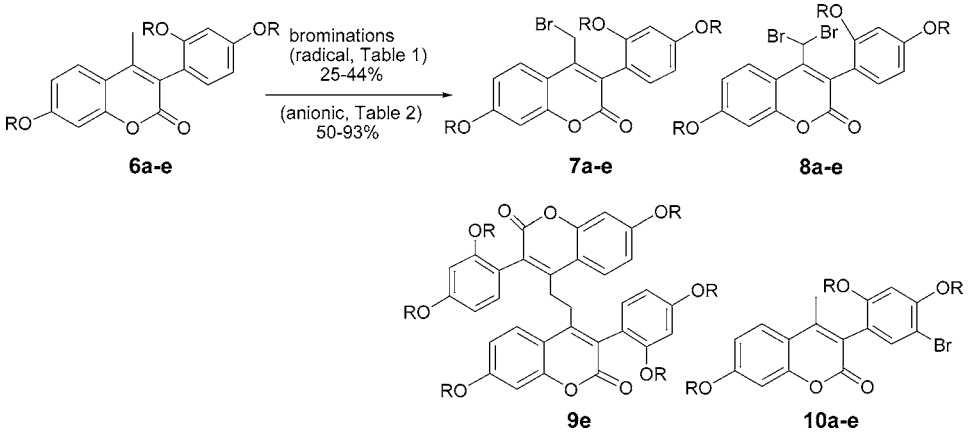

Table 2. **Results of anionic bromination of 4-methyl-3,7-substituted coumarins 6b−e (R = SEM, MOM, Bz, Me)**

entry	R	reagents	**7b−e** (%)[d]	**6b−e/8b−e/9e/10b−e** (%)[d]
7	SEM	LDA (1.1 equiv)/Br_2 (2.0 equiv)[a]	50	42/0/0/8
8	SEM	LDA(1.5 equiv)/Br_2 (2.0 equiv)[a]	80	10/0/0/10
9	SEM	LDA (1.7 equiv)/Br_2 (2.0 equiv)[b]	80	10/0/0/10
10	SEM	LHMDS (1.7 equiv)/Br_2 (1.7 equiv)[b]	82	0/10/0/8
11	MOM	LHMDS (1.5 equiv)/Br_2 (1.5 equiv)[b]	78	0/0/0/22
12	MOM	LHMDS (1.5 equiv)/Br_2 (1.02 equiv)[b]	90 (2.0 g) 83 (10.0 g)	0/0/0/8 8/0/0/9
13	Bz	LHMDS (1.2 equiv)/Br_2 (1.5 equiv)[b]	62	38/0/0/0
14	Bz	LHMDS (1.5 equiv)/Br_2 (2.0 equiv)[b]	80	17/0/0/3
15	Bz	LHMDS (1.7 equiv)/Br_2 (2.0 equiv)[b]	90(8−20 g) 70−80 (80−100 g)	8/0/0/0 20−30/0/0/0
16	Me	LHMDS (1.5 equiv)/Br_2 (1.1 equiv)[c]	80	1/5/14/0
17	Me	LHMDS (1.08 equiv)/NBS (1.3 equiv)[c] (regular quench, 1 min addition time)	81	12/<1/6/0
18	Me	LHMDS (1.08 equiv)/NBS (1.3 equiv)[c] (inverse quench, 1 min addition time)	93	≤1/5/0.7/0
19	Me	LHMDS (1.2 equiv)/NBS (1.1 equiv)[c] (inverse quench, 8 min addition time)	67	5/ 15/11/0
20	Me	LHMDS (1.08 equiv)/NBS (1.10 equiv)[c] (inverse quench, 1−2 min addition time)	91	1.3/5.8/0.7/0[e]

Conditions: [a]Compound **6b** was treated with LDA in THF at −8 °C for 1 h and then quenched with Br_2 at −76 °C. [b] Compounds **6b−d** were treated with LDA or LHMDS in THF at −70 °C for 1 h and then quenched only with Br_2 at −76 °C. [c] Compound **6e** was treated only with LHMDS in THF at −30 °C for 1 h and then quenched with Br_2 or NBS at −76 °C. [d] HPLC area%. [e] A result of eight runs in 150 g of **6e** and under the same reaction conditions.

at −70 °C followed by bromine (1.7 equiv) quench at −76 °C gave 82% of the desired **7b**, plus 10% of 4-dibromo **8b** and 8% of aromatic **10b** as side products (entry 10). A comparison of the SEM group to the smaller MOM group was investigated. Coumarin **6c** produced 78% of **7c** with no unreacted **6c** detected and 22% of aromatic **10c** (entry 11) when treated with LHMDS (1.5 equiv) followed by bromine (1.5 equiv) quench at −76 °C. If the amount of bromine was reduced to 1.0 equiv and the anion of **6c** was quenched in CH_2Cl_2 a high yield of **7c** (90%) with only 8% of aromatic bromide **10c** (2.0-g run) was produced. However, this result was irreproducible at a 10-g scale and the yield of **7c** declined to 83% with 8% of **6c** and 9% of **10c** (entry 12, Table 2).

Since both MOM and SEM protecting groups add electron-donating character to the 3-phenyl ring system that increase the possibility of ring bromination, the electron-withdrawing benzoyl group was introduced to reduce the aromatic bromination on coumarin **6d**. Treatment of **6d** with LHMDS (1.2 equiv) in THF at −70 °C followed by bromine (1.5 equiv) quench at −76 °C resulted in only 62% of 4-bromomethylcoumarin **7d** with 38% of starting **6d** recovered; however, none of the aromatic ring brominated **10d** was detected by HPLC (entry 13). The use of more LHMDS (1.5 equiv) and bromine (2.0 equiv) afforded 80% of **7d** with 17% of **6d** and a small amount (3%) of **10d** (entry 14). The best reaction conditions for the small scale (8−20 g) transformation of tribenzoyl compound **6d** was found to use 1.7 equiv of LHMDS, which achieved 90% of **7d** and 8% of **6d**. Unfortunately, this reaction yield declined again to 70−80% with recovered 20−30% of **6d** when repeated on an 80−100 g scale (entry 15). All the above results on anionic bromination of coumarins **6b−d** suggested that no one protecting group was any superior than another when considering the yields of desired product 4-bromomethyl compounds **7b−d** verses minimizing recovered starting materials **6b−d**, and byproducts **8b−d** and **10b−d**. Therefore, trimethxoy coumarin **6e** was prepared and subjected to LHMDS (1.5 equiv) in THF at −30 °C for 1 h followed

by bromine (1.8 equiv) quench in THF at −76 °C. This reaction gave a good yield of **7e** (80%) with a trace of starting **6e** (1%), 4-dibrommethyl **8e** (5%), and a new byproduct, the dimer **9e** (14%) (entry 16). The formation of dimer **9e** may be a consequence of the reaction of less sterically encumbered **6e** anion with the reactive bromomethyl compound **7e**. Furthermore, we decided to investigate the replacement of bromine with NBS, a larger but also a milder source of electrophilic bromine. The anion of **6e** was generated with LHMDS (1.08 equiv) and quickly (1.0 min) quenched with NBS (1.3 equiv) in THF at −76 °C to afford **7e** (81%) with a trace of dibromomethyl **8e** (>1%), **6e** (12%), and dimer **9e** (6%) (entry 17). One final variation; inverse quench of the anion **6e** quickly (1 to 2 min) into THF containing NBS (1.3 equiv) at −76 °C achieved an excellent yield of **7e** (93%) with a trace amount of **6e** (1.0%), 4-dibrommethyl **8e** (5.0%), and dimer **9e** (0.7%) (entry 18). This inverse quench was an exothermic process, and the reaction temperature usually increased to about −62 °C after the addition of **6e** anion solution in THF. On the other hand, the solution of NBS in THF needs to be freshly prepared and kept at −76 °C for each reaction, since NBS was found unstable in THF at above 0 °C after the solution was stocked for more than 1 h. Furthermore, the inverse addition rate of anion **6e** was proven to be very critical to the profile of product/byproducts. For example, slow inverse quench of anion of **6e** into NBS/THF at −76 °C over an 8-min period, formed only a moderate yield of **7e** (67%) along with a higher amount of 4-dibromo **8e** (15%) and dimer **9e** (11%) (entry 19). The best condition for this selective transformation was finalized with the use of 1.08 equiv of LHMDS and 1.10 equiv of NBS (entry 20, Table 2). A large quantity of **6e** (150 g × 8 runs) was reproducibly brominated to **7e** in quantitative isolated yield (100−105%) and excellent chemical purity (91−93% of **7e**, HPLC area%) with acceptable quantities of unreacted **6e** (1.0−1.45%), 4-dibrommethyl **8e** (5.8−6.3%), and dimer **9e** (0.5−0.8%). 4-Bromomethylcoumarin **7e** was made by this selective method and was used in the next synthetic step without chromatographic purification. Furthermore, this method was transferred to pilot plant, where both NBS and NCS[16] were successfully used for multikilogram production of 4-bromomethyl/4-chloromethyl[16] 3,7-substituted coumarins. In addition, this anion method was successfully extended to the scale-up of one-carbon homologation on 4-methylcoumarin that afforded a high yield and chemically pure product.[1,3]

Conclusions

In summary, the free radical bromination of 7-acetoxy-3-[(2,4-diacetoxy)phenyl]-4-methylcoumarin(**6a**) with NBS produced incomplete reaction and low to moderate yields (25−44%) of desired 4-bromomethyl **7a**. Although the reaction went to almost completion with bromine, it also resulted in low yields (25−30%) of **7a** due to the formation of undesired 4-dibromomethyl **8a** (40%) and aromatic brominated **10a** (25%) as side products. In contrast, lithiation of the 4-methyl group of **6b**−**d** (R = SEM, MOM, Bz) with LDA (1.1−1.7 equiv) or LHMDS (1.2−1.7 equiv) in THF and then quenched with bromine (1.5−2.0 equiv) afforded 4-bromomethyl coumarins **7b**−**d** in very good yields (80∼90%) on small scale (2−20 g); however, these reactions were problematic when increased by 5-fold. On the other hand, reproducible anionic bromination conditions were found for **6e** (R = Me) where treatment with LHMDS (1.08 equiv) in THF at −30 °C for 1 h, followed by quick inverse quench of the anion into THF containing NBS (1.10 equiv) at −76 °C. These conditions afforded the desired 4-bromomethyl coumarin **7e** in excellent yield (> 90%) on either small (2−20 g) or large scale (100−150 g) reactions. A nonchromatographic scale-up process was developed to prepare **6e** in moderate to good yield. We have demonstrated that NBS was a better source of electrophilic bromine than bromine molecule for the preparation of **7e**. This selective method may be applied for brominating or chlorinating those compounds having similar structural features or where free radical bromination is disfavored.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. 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. Mass spectra were recorded on an Agilent Series 180 LC−MS instrument (positive/negative modes). The chemical purity/impurity were determined on an Agilent Series 1100 system at UV_{max} = 254 and 340 nm, using a ZORBAX Ecilipse 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.

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-Acetoxy-3-(2,4-dimethoxyphenyl)-4-methylcoumarin (3).[8] A 22-L RBF was charged with 2,4-dihydroxyacetophone **1** (99%, 1100 g, 7.23 mol), 2,4-dimethoxyphenylacetic acid **2** (1420 g, 7.23 mol), and acetic anhydride (99%, 3440 mL, 36.4 mol) with agitation under a nitrogen atmosphere. Triethylamine (99%, 1008 mL, 7.23 mol) was added to the mixture via the addition funnel over 8 min, and the reaction mixture was heated to reflux (148 °C internal temperature) for 24 h. Additional Et_3N (150 mL, 1.08 mol) was added to the reaction mixture after 8 h and cooling, and the reflux was resumed for the overnight period. The excess reagents were removed by distillation under reduced pressure (160 mmHg) at 140 °C (2400 mL). The resulting material was cooled to 30 °C and then diluted with ether (10.0 L). The resulting mixture was agitated for 16 h, and the solid was collected by filtration. The tan solid was washed with ether (4.0 L × 3) and dried at 40 °C for 48 h to afford 1968 g (77% yield) of compound **3**. ^{1}H NMR (300 MHz, $CDCl_3$) δ

(16) Unpublished results.

2.21 (s, 3 H), 2.36 (s, 3 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 6.56 (s, 1 H), 6.59 (dd, $J = 0.8, 8.9$, 1 H), 7.08 (dd, $J = 0.8, 8.8$, 1 H), 7.8 (d, $J = 8.8$, 1 H), 7.10 (d, $J = 0.6$, 1 H), 7.68 (d, $J = 8.7$, 1 H). LC−MS *m*/*z* 355 (MH^+), 377 (MNa^+), 313.

3-(2,4-Dihydroxyphenyl)-7-hydroxy-4-methylcoumarin (4).[1,9] A 12-L RBF was charged with compound **3** (484.0 g, 1.367 mol) and pyridine hydrochloride (98%, 1844 g, 15.957 mol) under a nitrogen atmosphere. The solid mixture was gradually heated to 180−210 °C (internal temperature) and stirred for 1 h with fast agitation. After cooling to 22 °C, the reaction was diluted with water (4.0 L) and extracted with EtOAc (4.0 L × 1, 2.0 L × 1). The combined organic phase was washed with brine (2.0 L) and concentrated to dryness in vacuo at 50 °C. The resulting dark gelatinous material was placed under high vacuum (8 mmHg) at 22 °C overnight to afford crude **4** (388 g, 99% yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 2.18 (s, 3 H), 4.80 (br, 3 H), 6.36 (dd, $J = 0.3, 8.0$, 1 H), 6.38 (s, 1 H), 6.72 (s, 1 H), 7.78−6.98 (m, 2 H), 7.62 (d, $J = 8.4$, 1 H). LC−MS *m*/*z* 285 (MH^+), 307 (MNa^+).

3-[(2,4-Dimethoxy)phenyl]-7-hydroxy-4-methylcoumarin (5). A 22-L RBF was charged with crude 7-acetoxy coumarin **3** (2.0 kg, 5.64 mol), MeOH (9.0 L), and K_2CO_3 (1.01 kg, 7.28 mol; 325 mesh). The reaction was heated to reflux at 65 °C for 1.5 h, and then the mixture was cooled to 20 °C; one-half of the mixture was transferred to a 22-L separatory flask and diluted with EtOAc (8.0 L). This mixture was carefully treated with 2 N HCl (4.0 L), and the organic phase was separated and then concentrated in vacuo at 50 °C to give a crude product. The second half of the reaction mixture was worked up in the same fashion; the combined crude products was triturated with ether (1.0 L) to afford 676.5 g (38% isolated yield; HPLC = 95%, area%) of **5** as off-white solid, which was suitable for use in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3 H), 2.60 (s, 1 H), 3.78 (s, 6 H), 6.29 (s, 1 H), 6.40 (d, $J = 8.6$, 1 H), 7.0 (s, 1 H), 7.08 (d, $J = 9.0$, 1 H), 7.22 (d, $J = 8.5$, 1 H), 7.64 (d, $J = 9.1$, 1 H). LC−MS *m*/*z* 313 (MH^+), 335 (MNa^+).

7-Acetoxy-3-[(2,4-diacetoxy)phenyl]-4-methylcoumarin (6a).[1] A 5-L RBF was charged with crude coumarin **4** (132.0 g, 0.464 mol) and acetic anhydride (99%, 459.6 g, 4.5 mol). The mixture was stirred under nitrogen at 22 °C, treated with pyridine (99.8%, 113.0 g, 1.43 mol) over a 5-min period, and then heated to 89 °C and stirred for 6 h. The progress of the reaction was monitored by HPLC. The excess amount of reagents was removed by distillation under reduced pressure (160 mmHg) at 140 °C. The resulting mixture was cooled to 22 °C, dissolved in EtOAc (2.0 L), and washed with saturated $NaHCO_3$ (1.0 L), 0.5 N HCl solution (1.0 L × 2), and brine (1.0 L). Concentration of the organic phase gave 187.7 g of crude material, which was purified by chromatography (2.0 kg of SiO_2; EtOAc/hexane, 30%/70% (8.0 L), 40%/60% (6.0 L), 50%/50% (8.0 L) to afford 110.0 g (59% yield) of triacetate coumarin **6a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.8 (s, 3 H), 2.25 (s, 3 H), 2.30 (s, 3 H), 2.36 (s, 3 H), 7.08−7.18 (m, 4 H), 7.24 (d, $J = 8.1$, 1 H), 7.69 (d, $J = 8.7$, 1 H). LC−MS *m*/*z* 411 (MH^+), 433 (MNa^+), 369.

3-[2,4-Bis(2-trimethylsilylethoxymethoxy)phenyl]-4-methyl-7-(2-trimethylsilanylethoxymethoxy)coumarin (6b). A 2-L RBF was charged with crude trihydroxy coumarin **4** (41.4 g, 0.0336 mol), acetone (400 mL), and K_2CO_3 (23.2 g, 0.168 mol; 325 mesh) with stirring under nitrogen. 2-Trimethylsilylethoxymethyl chloride (SEM-Cl, 24 mL, 0.134 mol) was added dropwise over a 20-min period, and then the reaction was refluxed at 59 °C for 3 h. The mixture was cooled to 20 °C, and the solid was filtered through a Celite pad, which was washed with acetone (200 mL); the combined filtrate was concentrated in vacuo at 50 °C. The resulting crude mixture (37.6 g) was purified by chromatography (580 g of SiO_2; EtOAc/hexane, 2%/98% (1.0 L), 8%/90% (1.0 L)). There was obtained 17.1 g (42% yield) of coumarin **6b** as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.05 (s, 9 H), 0.08 (s, 9 H), 0.78−0.85 (m, 6 H), 2.16 (s, 3 H), 3.42−3.60 (m, 6 H), 6.05 (s, 6 H), 6.30 (s, 1 H), 6.36 (d, $J = 8.6$, 1 H), 6.73 (s, 1 H), 6.75 (d, $J = 9.3$, 1 H), 7.22 (d, $J = 8.4$, 1 H), 7.55 (d, $J = 9.2$, 1 H). LC−MS *m*/*z* 675 (MH^+), 697 (MNa^+).

3-[2,4-Bis(methoxymethoxy)phenyl]-7-methoxymethoxy-4-methylcoumarin (6c). A 500-mL RBF was charged with crude trihydroxy coumarin **4** (10.1 g, 0.0084 mol) and K_2CO_3 (5.8 g, 0.042 mol). Bromomethyl methyl ether (MOM-Br, 90%, 4 mL, 0.044 mol) was added dropwise over an 8-min period, and then the reaction was warmed to reflux at 87 °C for 3 h. The mixture was cooled to 20 °C and diluted with EtOAc (500 mL). The organic phase was washed with brine (300 mL × 2) and then concentrated in vacuo at 50 °C. There was obtained 10.1 g (68% yield) of coumarin **6c** as a brown tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 3.38 (s, 3 H), 3.48 (s, 3 H), 3.50 (s, 3 H), 5.19 (s, 2 H), 5.24 (s, 2 H), 5.26 (s, 2 H), 6.78 (dd, $J = 0.3, 7.6$, 1 H), 6.92 (d, $J = 0.4$, 1 H), 7.01 dd, $J = 0.2, 8.0$, 1 H), 7.03−7.10 (m, 2 H) 7.58 (d, $J = 8.2$, 1 H). LC−MS *m*/*z* 417 (MH^+), 439 (MNa^+), 385.

7-Benzoyloxy-3-[(2,4-dibenzoyloxy)phenyl]-4-methylcoumarin (6d). A 22-L RBF was charged with crude trihydroxy coumarin **7** (388 g, 1.37 mol), CH_2Cl_2 (5.0 L), and Et_3N (946 mL, 6.78 mol) under nitrogen. The mixture was cooled to 0 °C with stirring and was treated with benzoyl chloride (632 mL, 5.45 mol) over a 1-h period. Additional CH_2Cl_2 (1.0 L) was added, and the mixture was warmed to 20 °C and stirred for 18 h. The mixture was further diluted with CH_2Cl_2 (3.0 L) and then carefully quenched with water (2.5 L). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (1.0 L); the combined organic extracts were washed with saturated $NaHCO_3$ (2.0 L × 2) and then dried over Na_2SO_4. The solvent was concentrated in vacuo at 50 °C to afford the crude tribenzoate, that was dissolved in hot EtOAc (950 mL) and then allowed to stand at 0 °C for 16 h. The solid was collected by filtration and washed with ether, air-dried, and dried in a vacuum oven at 50 °C overnight. There was obtained 387.6 g (48% yield) of tribenzoxy coumarin **6d** as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3 H), 7.14 (dd, $J = 0.8, 6.8$, 1 H),

7.18 (dd, J = 0.5, 8.0, 1 H), 7.27−7.47 (m, 5 H), 7.48−7.60 (m, 5 H), 7.61−7.72 (m, 3 H), 8.01 (d, J = 0.5, 1 H), 8.03 (s, 1 H), 8.16−8.28 (m, 4 H). LC−MS m/z 597 (MH^+), 619 (MNa^+).

3-[(2,4-Dimethoxy)phenyl]-7-methoxy-4-methylcoumarin (6e). A 12-L RBF was first purged with nitrogen and then charged with compound **5** (886.5 g, 2.8 mol), DMF (2.7 L), and K_2CO_3 (1160.9 g, 8.4 mol). The well-stirred mixture was slowly treated with MeI (516.5 g, 3.64 mol) via a syringe at 20 °C. After stirring for 2 h, the reaction mixture was cooled to 0 °C with an ice bath and diluted with D.I. water (4.0 L) followed by EtOAc (4.0 L). The mixture was transferred to a 22-L separatory flask, and an additional amount of D.I. water (4.0 L) and EtOAc (4.0 L) was added. After the phases were separated, the aqueous phase was extracted with EtOAc (4.0 L × 2), and the combined organic phases were washed with D.I. water (4.0 L × 2) followed by brine (4.0 L). The solvent was concentrated in vacuo at 50 °C to afford 883.0 g of the crude product, which was further digested in warm ether (2.0 L). After cooling, the solid was collected by filtration and air dried to afford 733.9 g (80% isolated yield) of **6e** (HPLC = 98.6%, area %), that was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 3.78 (s, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 6.56 (s, 1 H), 6.58 (dd, J = 0.2, 8.2, 1 H), 6.88 (s, 1 H), 6.89 (dd, J = 0.4, 8.5, 1 H), 7.8 (d, J = 8.1, 1 H), 7.56 (d, J = 8.4, 1 H). LC−MS m/z 327 (MH^+), 349 (MNa^+).

7-Acetoxy-4-bromomethyl-3-[(2,4-diacetoxy)phenyl]-coumarin (7a).[6−8] A 5-L RBF (connected to a heated/refrigerated circulator) was charged with CCl_4 (2.5 L), triacetate **6a** (163.0 g, 0.397 mol), *N*-bromosuccinimide (99%, 70.7 g, 0.397 mol), and benzoyl peroxide [$(BzO)_2$, 97%, 4.81 g, 0.0198 mol) under nitrogen with agitation. The mixture was heated to 76 °C and irradiated with light (2 × 300 W, Philips Sparkling Clear) for 100 h (additional NBS (8.0 g) and $(BzO)_2$ (1.0 g) were added to the reaction after each 24 h interval), and the progress of the reaction was monitored by HPLC. After cooling to 22 °C, the mixture was diluted with CH_2Cl_2 (2.0 L) and stirred vigorously for 8 min and then transferred to a 12-L separatory flask. The organic phase was washed with 1 N NaOH solution (2.0 L), D.I. water (2.0 L × 2), and brine (2.0 L × 2). The solvent was concentrated in vacuo at 400 °C to give 170.0 g of crude material, which after chromatographic purification (2.0 kg of SiO_2; EtOAc/CH_2Cl_2, 5%/95% (8.0 L)) afforded 85.7 g (44% isolated yield) of triacetate 4-bromomethyl coumarin **7a**, plus 15.9 g (8%) of 4-dibromomethyl **8a** and 65.2 g (40%) of the recovered **6a**. ^{1}H NMR of **7a** (300 MHz, $CDCl_3$) δ 2.8 (s, 3 H), 2.30 (s, 3 H), 2.36 (s, 3 H), 4.44 (dd, J = 8.2, 38.7, 2 H), 7.8−7.22 (m, 4 H), 7.46 (d, J = 8.4, 1 H), 7.81 (d, J = 8.9, 1 H). LC−MS m/z 489 (MH^+), 511 (MNa^+), 447, 403.

7-Benzoyloxy-4-bromomethyl-3-[(2,4-dibenzoyloxy)-phenyl]coumarin (7d).[14,15] A 1-L RBF was charged with THF (50 mL, anhydrous) and lithium bis(trimethylsilyl)amide (40.3 mL, 0.0403 mol, 1 *M* in THF) solution. The mixture was cooled to −70 °C, and a solution of tribenzoate **6d** (20.0 g, 0.0336 mol) in THF (250 mL) was added dropwise over a 50-min period, while the reaction temperature was maintained between −70 to −72 °C. The mixture was stirred at −70 °C for 1 h, bromine (2.6 mL, 0.0503 mol) was added dropwise over an 8-min period, and the reaction was allowed to stir for 1 h at − 76 °C. The reaction was quenched with saturated NH_4Cl (80 mL) solution, and the mixture was warmed to 8 °C. The organic phase was separated and concentrated in vacuo at 50 °C. The resulting crude material was partitioned between CH_2Cl_2 (400 mL) and D.I. H_2O (300 mL). After phase separation, the organic phase was sequentially washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL × 2) and then concentrated in vacuo at 40 °C and placed under high vacuum (10 mmHg) at 60 °C for 30 min. There was obtained 24.1 g (106.5%) of crude material which after a chromatographic purification afforded 62% of **7d** and recovered starting tribenzoate **6d** (38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (dd, J = 8.6, 25, 2 H), 7.15−7.20 (m, 2 H), 7.27−7.47 (m, 5 H), 7.48−7.60 (m, 5 H), 7.61−7.72 (m, 3 H), 8.01 (d, J = 0.5, 1 H), 8.03 (s, 1 H), 8.16−8.30 (m, 4 H). LC−MS m/z 675 (MH^+), 697 (MNa^+).

3-[(2,4-Bis(2-trimethylsilylethoxymethoxy)phenyl]-4-bromomethyl-7-(2-trimethylsilylethoxymethoxy)coumarin (7b). This compound was prepared in the same manner as for **7d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.05 (s, 9 H), 0.08 (s, 9 H), 0.78−0.86 (m, 6 H), 3.40−3.62 (m, 6 H), 4.10 (dd, J = 9.6, 28.4, 2 H), 6.05 (s, 6 H), 6.30 (s, 1 H), 6.34 (d, J = 8.5, 1 H), 6.73 (s, 1 H), 6.76 (d, J = 9.0, 1 H), 7.20 (d, J = 8.3, 1 H), 7.56 (d, J = 9.1, 1 H). LC−MS m/z 753 (MH^+), 775 (MNa^+).

3-[2,4-Bis(methoxymethoxyphenyl]-4-bromomethyl-coumarin (7c). This compound was prepared in the same manner as for **7d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3 H), 3.49 (s, 3 H), 3.51 (s, 3 H), 4.16 (dd, J = 9.7, 36.8, 2 H), 5.18 (s, 2 H), 5.24 (s, 2 H), 5.24 (s, 2 H), 6.77 (dd, J = 0.3, 7.6, 1 H), 6.90 (d, J = 0.4, 1 H), 6.98 (dd, J = 0.2, 8.0, 1 H), 7.01−7.8 (m, 2 H), 7.56 (d, J = 8.2, 1 H). LC−MS m/z 495 (MH^+), 517 (MNa^+).

4-Bromomethyl-3-[(2,4-dimethoxy)phenyl]-7-methoxy-coumarin (7e). A 12-L RBF was connected to a 22-L RBF via a 0.25-in. Teflon tube (wrapped with cotton and aluminum foil) and two inlet adapters. The 12-L flask was charged with trimethoxy coumarin **6e** (98.6%, 150.0 g, 0.460 mol) and THF (5.6 L, anhydrous, inhibitor free) under nitrogen atmosphere. The brownish solution was stirred and cooled to −30 °C in an acetone/dry ice bath. After a lithium bis(trimethylsilyl)amide (500.0 mL, 0.497 mol, 1 *M* in THF) solution was added as a small stream via the addition funnel over a 15-min period, the mixture was stirred for 1.0 h at −30 °C and then cooled to −76 °C. Meantime, the 22-L flask was charged with anhydrous THF (3.4 L, inhibitor free) and NBS (99%, 92.6 g, 0.515 mol) under nitrogen and quickly cooled to −76 °C. With fast agitation, the above freshly prepared anion solution of **6e** was quickly transferred into the NBS/THF solution under a negative pressure (via house vacuum) over a 1−2 min period. The reaction was stirred at −76 °C for an additional 1 h. The progress of the reaction was determined by HPLC and ^{1}H NMR. A saturated

solution of sodium sulfite (900 mL) was added to the above reaction mixture, followed by the addition of EtOAc (6.0 L) and 1 N HCl (2.0 L). The acetone/dry ice bath was replaced with a water bath, and the mixture was allowed to warm to 4 °C with stirring. This solution was transferred to a 22-L three-neck separatory flask, the aqueous phase (pH 2−3) was separated, and the organic phase was sequentially washed with 1 N HCl (2.0 L), saturated $NaHCO_3$ solution (2.0 L × 3), and brine (2.0 L × 2). The organic phase (14.8 L) was concentrated at 46 °C under high vacuum (10 mmHg) to afford 196.9 g (105.7% isolated yield; HPLC = 91%, area %) of the product **7e**. HPLC (area %/retention time): **6e**, 1.3%/6.76 min; **7e**, 91.0%/7.10 min; **8e**, 5.8%/7.53 min; **9e**, 0.73%/8.06 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 9 H), 4.0 (dd, J = 6.8, 7.0, 2 H), 6.28 (s, 1 H), 6.32 (d, J = 8.3, 1 H), 6.70 (s, 1 H), 6.75 (d, J = 8.7, 1 H), 7.21 (d, J = 8.3, 1 H), 7.50 (d, J = 8.9, 1 H). LC−MS m/z 405 (MH^+), 427 (MNa^+), 833 ($2M + Na^+$).

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