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Cascade Synthesis of Polyoxygenated 6*H*,11*H*-[2]Benzopyrano-[4,3-*c*][1]benzopyran-11-ones

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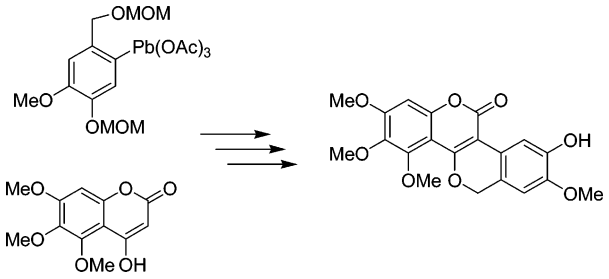

2-(Methoxymethoxymethyl)aryllead triacetates, obtained in situ from the corresponding arylboronic acids, reacted with 4-hydroxycoumarins, leading to 3-(2-methoxymethoxymethyl)aryl-4-hydroxycoumarin derivatives in good to high yields. These compounds underwent a cascade sequence of reactions, deprotection−halogenation−annulation, to afford polyoxygenated tetracyclic 6*H*,11*H*-[2]benzopyrano-[4,3-*c*] [1]benzopyran-11-ones in good yields. Some compounds showed a moderate cytotoxicity against human epithelial mammary HBL100 cells.

Introduction

Substituted furano-,[1] benzofurano-,[2] pyrano-,[3] and indolocoumarins[4] and their isostructural analogs[5] are present in plant, microorganism, and animal sources and manifest a wide range of pharmacological activities, including antitumoral, antibacterial, and antiviral (anti-HIV-1) properties. Acetylcholinesterase inhibitory activities potentially interesting for the treatment of neurodegenerative diseases such as Alzheimer's disease have been also reported.[6] The biological activities of these polycyclic

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[⊥] CNRS et Aix-Marseille Université, CISMET, Faculté de Pharmacie.

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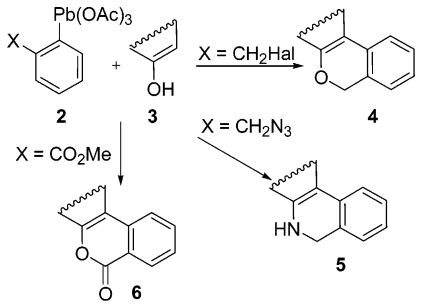
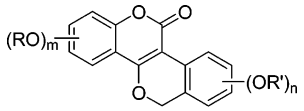
SCHEME 1



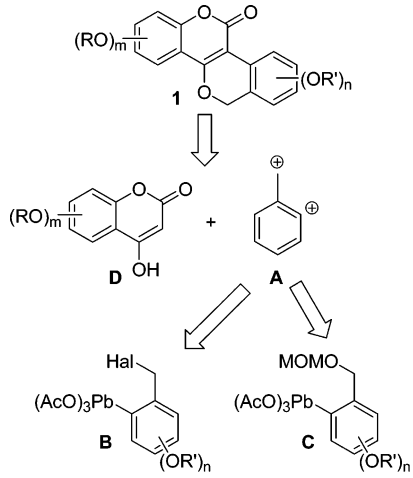
coumarin-containing heterocycles are strongly dependent upon the number and positions of alkoxyl and/or hydroxyl substituents.[1−5] Although these compounds are seldom isolated from natural sources, relatively few examples of synthesis of these types of biologically active compounds have been devised. Here we describe a flexible synthetic pathway to polyoxygenated tetracyclic 6*H*,11*H*-[2]benzopyrano-[4,3-*c*][1]benzopyran-11-ones **1**, which are built up by the combination of polymethoxy-containing coumarin and 1*H*-2-benzopyran structural subunits.



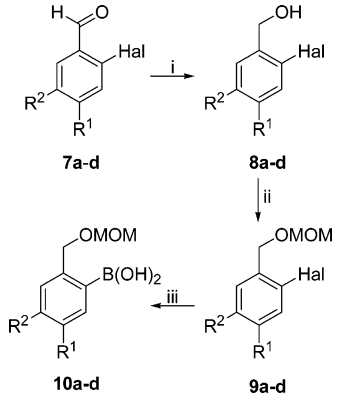
1, R = H, Me, Bn

Two approaches to these benzopyrano-[4,3-*c*][1]benzopyran-11-ones have been reported.[7,8] In the first one, the key step is a free-radical type of cyclization performed on 4-(2′-bromobenzyloxy)benzopyran-2-ones.[7] This method was useful for the synthesis of non-substituted or alkyl-substituted tetracyclic isochromanocoumarin type compounds. However, the synthesis of polyoxygenated derivatives was not reported. The second approach to this type of compounds was recently developed in our group.[8] It involves the arylation reaction of 4-hydroxycoumarins with 2-(halogenomethyl)aryllead triacetates **2** (X = CH_2-Hal), derived from arylboronic acids (Scheme 1). However, the scope of this method is restricted by the accessibility to polyoxygenated 2-(halogenomethyl)arylboronic acids and their poor stability. Moreover, despite the attractiveness of this cascade procedure, the yields of final products were moderate.

SCHEME 2



SCHEME 3. Synthesis of Arylboronic Acids 10a−d[a]



[a] Reaction conditions: (i) $NaBH_4$, THF/MeOH/H_2O, rt; (ii) NaH, THF, 0 °C, 10 min, then $ClCH_2OCH_3$, 50 °C, 4 h; (iii) *n*BuLi, THF, −78 °C, then B(O*i*Pr)$_3$, −78 °C, 1.5 h, then rt, overnight.

On the other hand, application of aryl derivatives of main-group metal elements, containing easily functionalizable groups in the *ortho* position of the aryl moiety, allowed the synthesis of a variety of heterocyclic systems, via a cascade sequence of reactions with a ligand coupling reaction as one of the key steps (Scheme 1).[8−10] Therefore, elaboration of polyfunctionalized arylation agents, in which the aryl moiety possess two different electrophilic centers with selective reactivities, is of significant interest for synthetic organic chemistry.

Results and Discussion

The key step for the synthesis of type **1** compounds is the preparation of an arylating agent able to generate the synthetic equivalent of the dicationic synthon **A** (Scheme 2). We considered that application of 2-(methoxymethoxymethyl)-aryllead triacetates **C** instead of the unstable 2-(halogenomethyl)aryllead triacetates[8] **B** could importantly contribute to broadening the scope of this synthetic pathway to the synthesis of type **1** compounds *via* reductive ligand coupling reactions.[11] The methoxymethyl (MOM) protecting group should afford

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TABLE 1. Synthesis of Aryl Halides 8a−d and 9a−d and Arylboronic Acids 10a−d

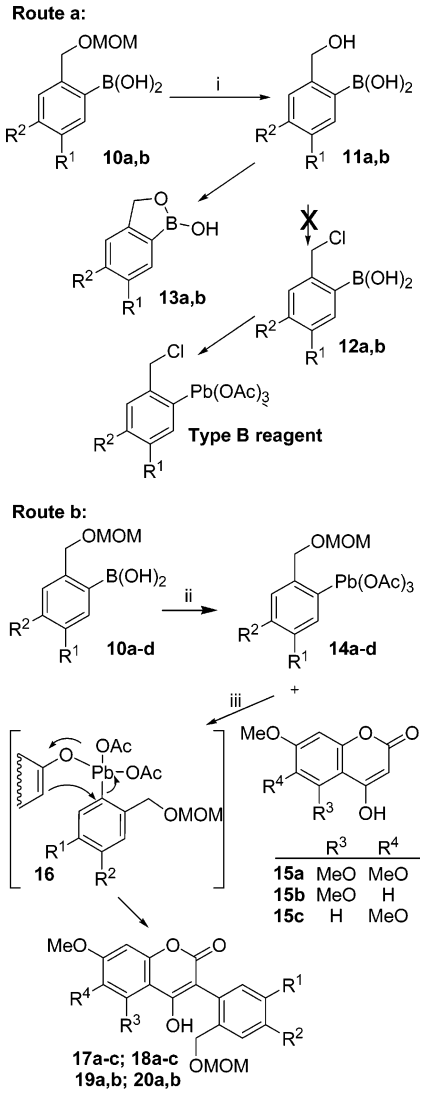
no.	halide	R^1	R^2	yield (%)
8a	I	OBn	OMe	91
8b	Br	OMe	OMe	97
8c	Br	OH	OMe	69
8d	Br	OMe	OH	78
9a	I	OBn	OMe	65
9b	Br	OMe	OMe	81
9c	Br	OMOM	OMe	38
9d	Br	OMe	OMOM	36
10a		OBn	OMe	61
10b		OMe	OMe	55
10c		OMOM	OMe	38
10d		OMe	OMOM	41

more easily handled reagents with the possibility of selective derivatization at a later stage of the sequence of reactions.

The 2-(methoxymethoxymethyl)arylboronic acids **10a−d**, necessary for the synthesis of the appropriate aryllead triacetates, were prepared in three steps from 2-halogenobenzaldehydes **7a−d**[12] (Scheme 3). Reduction of the carbonyl function of compounds **7a−d** and protection of the benzylic alcohol as a MOM-ether followed by a sequence of bromine−lithium exchange and transmetallation afforded the arylboronic acids **10a−d** in relatively good yields (Table 1). The yields of aryl halides **9c** and **9d**, containing two methoxymethyl fragments in the benzylic and phenolic positions, were relatively lower than the yields of the **9a** and **9b** analogs, bearing only one MOM group on the benzylic position of the molecules (Table 1). A similar trend was also observed for the subsequent conversion of these compounds into the corresponding arylboronic acids **10a**, **10b** and **10c**, **10d**.

Two pathways can be envisioned to transform the MOM-protected arylboronic acids **10a−d** into the aryllead triacetates that are required for the synthesis of benzopyranocoumarins **1**. In the first route, direct deprotection of the MOM group[13] should give 2-(hydroxymethyl)arylboronic acids **11**, which could be transformed into the corresponding 2-(halogenomethyl)arylboronic acids **12** (Scheme 4, route a). Then, boron-to-lead transmetallation should give access to type B aryllead reagents, capable of transferring the 2-(halogenomethyl)aryl fragment on the C-3 position of the 4-hydroxycoumarin skeleton. The 3-aryl-4-hydroxycoumarin intermediates thereby generated could undergo spontaneous annelation to afford type **1** tetracyclic compounds. However, when organoboron compounds **10a** and **10b** were treated with concentrated HCl or HBr in acetone, formation of the corresponding 2-(halogenomethyl)arylboronic acids **12a** and **12b** was not observed (Scheme 4, route a). Instead, the first formed 2-(hydroxymethyl)arylboronic acids **11a** and **11b** underwent spontaneous acid-catalyzed cyclization to afford the benzoxaborole derivatives **13a** and **13b** respectively. Unfortunately, all attempts of boron-to-lead transmetallation performed on organoboron compounds **13a** and **13b** met with failure.

SCHEME 4. Reactions of Arylboronic Acids 10a−d and Synthesis of 3-Aryl-4-hydroxycoumarins 17−20[a]



[a] Reaction Conditions: (i) conc HCl, acetone, 40 °C; (ii) $Pb(OAc)_4$, $Hg(OAc)_2$ (0.1 equiv), $CHCl_3$, 40 °C, 1.5 h, then rt overnight; (iii) pyridine, $CHCl_3$, 60 °C.

On the other hand, direct boron-to-lead transmetallation reaction between the MOM-protected arylboronic acids **10a−d** (Scheme 4, route b) and lead tetraacetate performed in the presence of a catalytic amount of $Hg(OAc)_2$, according to Pinhey's procedure,[14] generated in situ the aryllead triacetates **14a−d**. Subsequent treatment of these aryllead triacetates **14a−d** with 4-hydroxycoumarins **15a−c** in the presence of pyridine afforded the different 3-aryl-4-hydroxycoumarins **17−20** in good to high yields (Table 2). The latter step involves a reductive coupling C-arylation reaction on the α-position of the enolized substrate through formation of a covalent organolead intermediate **16**.[11,15] Although organolead-mediated arylation reactions sometimes give complex mixtures of mono- and polyarylated products,[11,15b,16] only mono-α-arylation products **17−20** were isolated in all of the presently reported cases. One should note that 3-aryl-4-hydroxycoumarins **17c** and **18c**, derived from 4-hydroxy-6,7-dimethoxycoumarin **15c**, were

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TABLE 2. Synthesis of Derivatives 17−20

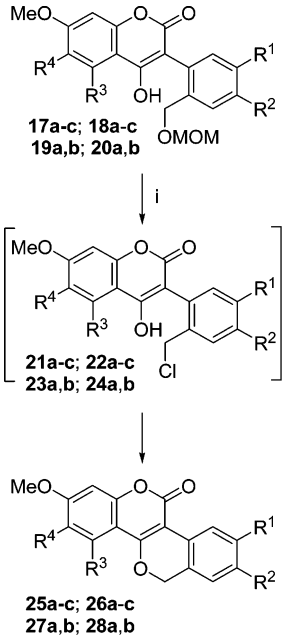
no.	R^1	R^2	R^3	R^4	yield (%)
17a	OBn	OMe	OMe	OMe	82
17b	OBn	OMe	OMe	H	70
17c	OBn	OMe	H	OMe	51
18a	OMe	OMe	OMe	OMe	78
18b	OMe	OMe	OMe	H	62
18c	OMe	OMe	H	OMe	42
19a	OMOM	OMe	OMe	OMe	62
19b	OMOM	OMe	OMe	H	67
20a	OMe	OMOM	OMe	OMe	48
20b	OMe	OMOM	OMe	H	45

isolated in lower yields than their analogs **17a** and **18a** obtained from 5,6,7-trimethoxycoumarin **15a** and also lower than **17b** and **18b** derived from 5,7-dimethoxycoumarin **15b**. Use of polar aprotic solvents[17] (DMF, DMA, DMSO) did not improve the yields of **17c** and **18c** or even of their analogs **17a**, **17b** and **18a**, **18b**. It is likely that the 5-methoxy group present in substrates **15a** and **15b** plays a role, as it can compete with the side chain MOM group for coordinating the lead atom during formation of intermediate **16**. By contrast, in absence of the 5-methoxy group, the MOM group can stabilize the aryloxylead-(IV) intermediate **16c**, and decomposition instead of ligand coupling may then become a significant competing pathway.

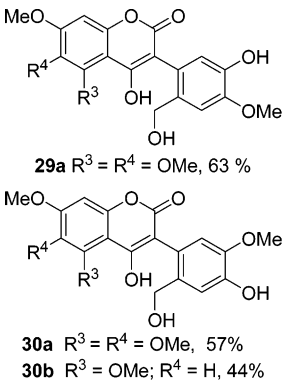
Deprotection of the MOM groups of **17a−c**, **18a−c**, and **19a**, **19b** was realized by acid-catalyzed treatment using the HCl−acetone system, leading to the desired tetracyclic compounds **25a−c**, **26a−c**, and **27a**, **27b**, respectively, in a three-step one-pot cascade sequence of reactions in good overall yields (Table 3). Attempts to deprotect the benzyl fragment in compounds **25a−c**, employing Pd/C−H_2, Pd/C−HCO_2NH_4 systems[13] or concentrated HBr[18] were unsuccessful.

One should note that the tetracyclic compounds **25a−c** and **26a−c** were obtained in higher overall yields than the analogs **27a** and **27b** containing a phenolic group in the benzopyran moiety (Table 3). This fact could be explained by a lower stability of the intermediate 3-[2′-(chloromethyl)-5′-hydroxy-4′-methoxyphenyl]-4-hydroxycoumarins **23a**, **23b** in contrast to coumarins **21a−c** and **22a−c** that do not exhibit a phenolic group substituting the B aryl moiety, present on the C-3 position of the coumarin skeleton (Scheme 5). On the other hand, when the 3-aryl-4-hydroxycoumarin **19a**, precursor of the tetracyclic product **27a**, was treated with dilute HCl (15−20%), the non-cyclized 3-[2′-(hydroxymethyl)aryl]-4-hydroxycoumarin **29a** was obtained. In the case of **20a** and **20b**, acid-catalyzed treatment did not lead to the tetracyclic compounds **28a**, **28b** (Table 3). Whatever the conditions, only hydrolysis to the benzylic alcohol derivative occurred, leading to coumarins **30a** and **30b**, respectively. The difference of reactivity between the two pairs of substrates **19a**, **19b** and **20a**, **20b** may result from the possibility for compounds **19a**, **19b** to form, during the acid-catalyzed hydrolysis, highly reactive p-methylenequinone that are suitable for cyclization.

SCHEME 5. Cyclization of the 3-Aryl-4-hydroxycoumarins 17−20[a]



[a] Reaction conditions: (i) conc HCl, acetone, 40 °C.



These tetracyclic systems can be viewed as rigid analogs of polymethoxylated natural products, such as colchicine or

TABLE 3. Synthesis of Derivatives 25−28

no.	R^1	R^2	R^3	R^4	yield (%)
25a	OBn	OMe	OMe	OMe	75
25b	OBn	OMe	OMe	H	74
25c	OBn	OMe	H	OMe	53
26a	OMe	OMe	OMe	OMe	82
26b	OMe	OMe	OMe	H	73
26c	OMe	OMe	H	OMe	64
27a	OH	OMe	OMe	OMe	46
27b	OH	OMe	OMe	H	35
28a	OMe	OH	OMe	OMe	
28b	OMe	OH	OMe	H	

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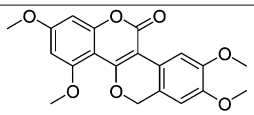
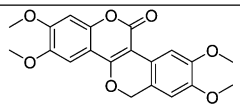
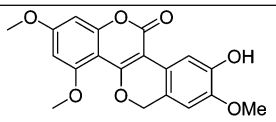
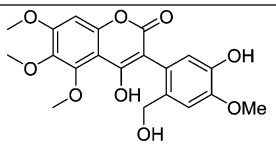
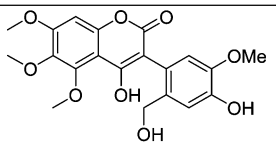
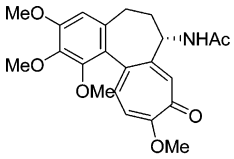
These tetracyclic systems can be viewed as rigid analogs of polymethoxylated natural products, such as colchicine or

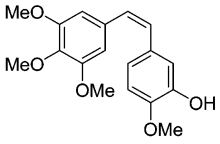
TABLE 4. Cytotoxicity of Selected Compounds toward HBL100 Cells

Compound	Structure	IC50 (μM)
26b		6.31 ± 0.32
26c		> 50
27b		> 50
29a		> 50
30a		10.09 ± 0.50

combretastatin A-4, that inhibit the polymerization of microtubules participating in mitotic spindle formation during cell division.[19]



Colchicine



Combretastatin A-4

For example, combretastatin A-4, a natural *cis*-stilbene isolated from the South African bush willow tree *Combretum caffrum*, exhibits a potent cytotoxicity against various cancer cells, including multi-drug-resistant cell lines.[20] Structure−activity studies have shown that some characteristic structural features are mandatory for the biological activity (three methoxyl groups on the A-ring, a *cis* configuration of the olefin inducing a non-coplanar conformation between A and B aryl rings), whereas the substitution pattern on the B-ring is more flexible to structural variations.[21] As part of our efforts to discover novel cytotoxic anticancer chemotherapeutic agents that could act by inhibition of tubulin polymerization,[18,22] we selected some of our compounds for preliminary biological screening. The cytotoxicity of these compounds was tested against HBL100 human epithelial mammary cells, and the results are reported in Table 4. Two compounds showed an interesting cytotoxicity, compound **26b** being slightly more active than compound **30a**. Unfortunately, a number of compounds were not sufficiently soluble in the assay buffer to allow the evaluation of their activity. Thus, the preliminary biological screening did not reveal any new lead compound justifying further developments for optimizing the biological anti-cancer activity.

Conclusion

The use of MOM-protected *o*-tolyllead derivatives is an efficient way to generate dicationic equivalents of polyoxygenated aryllead triacetates, required for the synthesis of highly oxygenated dibenzo[*b,d*]pyran derivatives. The presence of a MOM group in the vicinity of the lead metallic center does not interfere with the arylating properties of this type of reagents, which are especially effective for the transfer of highly electron-rich aryl fragments.[11,15] Moreover, the synthesis of polyfunctionalized arylboronic acids of type **10**, used for the in situ generation of the aryllead reagents, can be useful in Suzuki−Miyaura catalytic transformations[23] or in copper-mediated N-, O, and S-arylation reactions[24] for the synthesis of heterocyclic compounds.

Experimental Section

General Methods. All commercially available reagents were used as received without further purification. All solvents were purified by standard techniques. Crude materials were purified by column chromatography (CC) using silicagel 60 (70−230 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 200.13 and 50.32 MHz, respectively. Chemical shifts (δ) are reported in ppm for a solution of the compound in $CDCl_3$ with $SiMe_4$ as internal reference unless otherwise stated. *J* values are given in hertz. 2-Halogenarylbenzaldehydes **7a**−**d**[12] and 4-benzyloxy-2-iodo-5-methoxybenzyl alcohol **8a**[25] were synthesized as previously reported. The 4-hydroxycoumarins **15a**−**c** were prepared as previously reported: 4-hydroxy-5,6,7-trimethoxycoumarin **15a**,[26] 4-hydroxy-5,7-dimethoxycoumarin **15b**[27] and 4-hydroxy-6,7-dimethoxycoumarin **15c**.[16]

2-Bromo-4,5-dimethoxybenzyl Alcohol (8b). $NaBH_4$ (0.20 g, 5.2 mmol) was added by small portions to a solution of benzaldehyde **7b** (2.54 g, 10.4 mmol) in THF (90 mL) and 20% aqueous

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methanol (90 mL). The mixture was stirred for 1 h at room temperature, then diluted with water (50 mL), and concentrated under reduced pressure. The aqueous layer was extracted with AcOEt (4 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the solid residue was recrystallized in AcOEt/hexanes to afford **8b** as colorless plates (2.50 g, 97%): mp 141 °C; ^{1}H NMR (200.13 MHz) δ 3.87 (3H, s), 3.88 (3H, s), 4.68 (2H, s), 7.01 (2H, s); ^{13}C NMR (50.32 MHz) δ 56.1, 56.2, 64.9, 111.9, 112.5, 115.4, 131.8, 148.6, 149.0. Anal. Calcd for $C_9H_{11}BrO_3$ (247.09 g mol^{-1}): C, 43.75; H, 4.49. Found: C, 43.66; H, 4.60.

2-Bromo-4-hydroxy-5-methoxybenzyl Alcohol (8c). Prepared by the same procedure as for **8b**. Before the aqueous workup, the water layer was acidified to pH ∼5. Recrystallization in AcOEt/hexanes afforded **8c** as colorless prismatic crystals (69%): mp 107−109 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.90 (3H, s), 4.67 (2H, s), 5.62 (1H, s), 6.98 (1H, s), 7.11 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.1, 65.0, 111.3, 113.2, 118.4, 131.2, 145.7, 146.1. Anal. Calcd for $C_8H_9BrO_3$ (233.06 g mol^{-1}): C, 41.23; H, 3.89. Found: C, 41.11; H, 3.93.

2-Bromo-5-hydroxy-4-methoxybenzyl alcohol (8d). Prepared by the procedure used for **8c**. Recrystallization in AcOEt/hexanes afforded **8d** as grayish prismatic crystals (78%): mp 105 °C; ^{1}H NMR (200.13 MHz) δ 3.88 (3H, s), 4.64 (2H, s), 5.59 (1H, br. s), 7.00 (1H, s), 7.04 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.3, 64.8, 111.6, 114.9, 115.3, 132.7, 145.1, 146.5. Anal. Calcd for $C_8H_9BrO_3$ (233.06 g mol^{-1}): C, 41.23; H, 3.89. Found: C, 41.16; H, 4.04.

4-Benzyloxy-2-iodo-5-methoxy-1-(methoxymethoxymethyl)benzene (9a). Sodium hydride (0.067 g of a 60% emulsion in oil, 1.58 mmol) was added to a cooled (0 °C) solution of **8a**[25] (0.53 g, 1.43 mmol) in anhydrous THF (15 mL) under argon. The reaction mixture was stirred for 15 min, and then a solution of chloromethoxymethane (0.12 g, 1.43 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 2 h at room temperature and for 3 h at 60 °C. After addition of a 10% aqueous solution of Na_2CO_3 (10 mL), the organic solvent was distilled under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (3 × 7 mL). The organic phase was dried over Na_2SO_4, the solvent was distilled under reduced pressure, and the crude product was purified by CC (eluent ether/hexane, 1/1) to afford **9a** (0.39 g, 65%): mp 75 °C; ^{1}H NMR (200.13 MHz) δ 3.46 (s, 3H), 3.89 (s, 3H), 4.54 (s, 2H), 4.77 (s, 2H), 5.11 (s, 2H), 7.02 (s, 1H), 7.30−7.42 (m, 6H); ^{13}C NMR (50.32 MHz) δ 55.6, 56.0, 71.3, 73.1, 86.0, 96.1, 112.6, 124.2, 127.4, 128.0, 128.6, 133.3, 136.4, 148.2, 150.1. Anal. Calcd for $C_{17}H_{19}IO_4$ (414.23 g mol^{-1}): C, 49.29; H, 4.62. Found: C, 49.14; H, 4.60.

2-Bromo-4,5-dimethoxy-1-(methoxymethoxymethyl)benzene (9b). Prepared under the same reaction conditions using **8b** (2.50 g, 10.1 mmol), NaH (0.44 g of a 60% emulsion in oil, 11.1 mmol), and chloromethoxymethane (0.89 g, 11.1 mmol). After the usual aqueous workup the crude product was purified by CC (eluent ether/hexane, 1/1) to afford **9b** as a colorless oil (2.4 g, 81%): ^{1}H NMR (200.13 MHz) δ 3.40 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 4.57 (2H, s), 4.71 (2H, s), 6.96 (1H, s), 6.97 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.5, 56.0, 56.2, 68.7, 96.0, 112.3, 113.2, 115.4, 129.2, 148.4, 149.0. Anal. Calcd for $C_{11}H_{15}BrO_4$ (291.14 g mol^{-1}): C, 45.38; H, 5.19. Found: C, 45.18; H, 5.37.

2-Bromo-5-methoxy-4-(methoxymethoxy)-1-(methoxymethoxymethyl)benzene (9c). Sodium hydride (0.94 g of a 60% emulsion in oil, 23.6 mmol) was added to a cooled (0 °C) solution of **8c** (5.0 g, 21.5 mmol) in anhydrous THF (70 mL) under argon. After the reaction mixture was stirred for 15 min, a solution of chloromethoxymethane (1.77 g, 22.0 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 30 min at room temperature and 3 h at 60 °C (TLC monitoring) and then cooled to 0 °C, and a second portion of sodium hydride (0.94 g of a 60% emulsion in oil, 23.6 mmol) was added. After the reaction mixture was stirred for 15 min, a solution of chloromethoxymethane (1.77 g, 22.0 mmol) in THF (10 mL) was added, and the reaction was stirred for 5 h at 60 °C and overnight at room temperature. Then a 10% aqueous solution of Na_2CO_3 (30 mL) was added to the reaction mixture, and the organic solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with water (3 × 30 mL). The organic layer was dried over Na_2SO_4, the solvent was distilled under reduced pressure, and the crude product was purified by CC (eluent AcOEt/hexanes, 3/7) to afford **9c** (2.62 g, 38%): mp 70 °C; ^{1}H NMR (200.13 MHz) δ 3.44 (3H, s), 3.50 (3H, s), 3.88 (3H, s), 4.60 (2H, s), 4.75 (2H, s), 5.20 (2H, s), 7.03 (1H, s), 7.34 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.5, 56.0, 56.3, 68.7, 95.6, 96.1, 112.5, 112.9, 120.2, 131.0, 146.3, 149.1. Anal. Calcd for $C_{12}H_{17}BrO_5$ (321.16 g mol^{-1}): C, 44.88; H, 5.34. Found: C, 44.66; H, 5.52.

2-Bromo-4-methoxy-5-(methoxymethoxy)-1-(methoxymethoxymethyl)benzene (9d). Prepared under the same reaction conditions as **9c** using 5.0 g (21.5 mmol) of **8d**, two portions of NaH (0.94 g of a 60% emulsion in oil, 23.6 mmol), and two portions of a solution of chloromethoxymethane (1.77 g, 22.0 mmol) in THF (10 mL). After the usual aqueous workup, the crude product was purified by CC (eluent AcOEt/hexanes, 3/7) to afford **9d** as a colorless solid (2.48 g, 36%): mp 38−39 °C; ^{1}H NMR (200.13 MHz) δ 3.42 (3H, s), 3.50 (3H, s), 3.86 (3H, s), 4.57 (2H, s), 4.74 (2H, s), 5.22 (2H, s), 7.06 (1H, s), 7.25 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.5, 56.2, 56.3, 68.7, 95.5, 96.1, 115.2, 115.9, 117.5, 129.4, 145.8, 149.8. Anal. Calcd for $C_{12}H_{17}BrO_5$ (321.16 g mol^{-1}): C, 44.88; H, 5.34. Found: C, 44.61; H, 5.61.

Synthesis of Arylboronic Acids 10a−d. General Procedure. *n*BuLi (6.3 mL of a 1.6 M solution in hexanes, 10.1 mmol) was added dropwise to a solution of **9a** (4.0 g, 9.7 mmol) in THF (50 mL) at −78 °C under an inert gas. The solution was stirred for 10−15 min, and then triisopropyl borate (2.3 mL, 0.01 mmol) was added. The mixture was stirred at −78 °C for 1.5 h and then warmed to room temperature overnight. Water (10 mL) was added to the reaction mixture, and the solvents were distilled under reduced pressure. AcOEt (80 mL) was added, and the mixture was vigorously shaken with water (3 × 20 mL) during 5 min. The organic layer was dried over Na_2SO_4, and the solvent was distilled under reduced pressure. The crude product was recrystallized in AcOEt/hexanes to afford 5-benzyloxy-4-methoxy-2-(methoxymethoxymethyl)phenylboronic acid **10a** as a colorless powder (1.96 g, 61%): mp 105 °C; ^{1}H NMR (200.13 MHz) δ 3.40 (3H, s), 3.90 (3H, s), 4.66 (2H, s), 4.67 (4H, s), 5.18 (2H, s), 6.33 (2H, s), 6.83 (1H, s), 7.33−7.50 (6H, m); ^{13}C NMR (50.32 MHz) δ 55.9, 56.0, 69.8, 70.9, 94.1, 114.5, 120.9, 127.5, 127.9, 128.5, 134.5, 137.0, 147.6, 150.9. Anal. Calcd for $C_{17}H_{21}BO_6$ (332.16 g mol^{-1}): C, 61.47; H, 6.37. Found: C, 61.22; H, 6.63.

4,5-Dimethoxy-2-(methoxymethoxymethyl)phenylboronic Acid (10b). Prepared under the same reaction conditions using **9b** (2.4 g, 8.20 mmol), BuLi (5.6 mL of a 1.6 M solution in hexanes, 9 mmol), and triisopropyl borate (2 mL, 8.6 mmol). The usual aqueous workup and recrystallization of the crude product in $CHCl_3$/hexanes afforded **10b** as a colorless powder (1.15 g, 55%): mp 126 °C; ^{1}H NMR (200.13 MHz) δ 3.41 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 4.66 (2H, s), 4.68 (2H, s), 6.59 (2H, s), 6.81 (1H, s), 7.41 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.7, 55.8, 55.9, 69.8, 94.0, 113.9, 118.3, 134.0, 148.3, 150.2. Anal. Calcd for $C_{11}H_{17}BO_6$ (256.06 g mol^{-1}): C, 51.60; H, 6.69. Found: C, 51.55; H, 6.78.

4-Methoxy-5-(methoxymethoxy)-2-(methoxymethoxymethyl)-phenylboronic Acid (10c). Prepared under the same reaction conditions using **9c** (2.4 g, 7.5 mmol), BuLi (5.1 mL of a 1.6 M solution in hexanes, 8.2 mmol) and triisopropyl borate (1.9 mL, 8.2 mmol). The usual aqueous workup was followed by recrystallization in AcOEt/petroleum ether to afford **10c** as a colorless solid (0.81 g, 38%): mp 72−74 °C; ^{1}H NMR (200.13 MHz) δ 3.41 (3H, s), 3.52 (3H, s), 3.91 (3H, s), 4.66 and 4.67 (2 × 2H, 2 s), 5.27 (2H, s), 6.55 (2H, s), 6.84 (1H, s), 7.64 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.9, 56.0, 56.3, 69.7, 94.1, 95.3, 114.4, 123.5,

135.5, 145.8, 151.0. Anal. Calcd for $C_{12}H_{19}BO_7$ (286.09 g mol^{-1}): C, 50.38; H, 6.69. Found: C, 50.11; H, 6.74.

5-Methoxy-4-(methoxymethoxy)-2-(methoxymethoxymethyl)-phenylboronic Acid (10d). Prepared under the same reaction conditions using **9d** (2.2 g, 6.9 mmol), BuLi (4.7 mL of a 1.6 M solution in hexanes, 7.5 mmol), and triisopropyl borate (1.73 mL, 7.5 mmol). The usual aqueous workup followed by CC of the crude product (eluent AcOEt/petroleum ether, 1/1) afforded **10d** as a slightly yellow oil that slowly solidified to a colorless powder (0.81 g, 41%): mp 62−63 °C; ^{1}H NMR (200.13 MHz) δ 3.40 (3H, s), 3.51 (3H, s), 3.93 (3H, s), 4.66 and 4.67 (2 × 2H, 2 s), 5.26 (2H, s), 6.80 (2H, s), 7.10 (1H, s), 7.45 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.9 (strong), 56.3, 69.8, 94.3, 95.1, 118.5, 118.9, 133.9, 147.6, 148.9. Anal. Calcd for $C_{12}H_{19}BO_7$ (286,09 g mol^{-1}): C, 50.38; H, 6.69. Found: C, 50.29; H, 6.83.

1,3-Dihydro-6-benzyloxy-1-hydroxy-5-methoxy-2,1-benzoxaborole (13a). Several drops of concentrated hydrochloric acid were added to a solution of **10a** (0.5 g, 1.5 mmol) in acetone (3 mL). The mixture was stirred at 40 °C for 1 h (TLC monitoring). The organic solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL) and washed with water (3 × 5 mL). The organic layer was dried over Na_2SO_4, the solvent was distilled under reduced pressure, and the residue was recrystallized in $CHCl_3$/hexanes to afford **13a** as a colorless powder (0.29 g, 67%): mp 143−144 °C; ^{1}H NMR (200.13 MHz) δ 3.92 (3H, s), 4.60 (1H, s), 5.01 (2H, s), 5.18 (2H, s), 6.86 (1H, s), 7.20 (1H, s), 7.33−7.45 (5H, m); ^{13}C NMR (50.32 MHz) δ 56.0, 70.9, 71.0, 114.0, 127.2, 127.3, 127.8, 128.5, 137.0, 148.1, 148.4, 153.1. Anal. Calcd for $C_{15}H_{15}BO_4$ (270.09 g mol^{-1}): C, 66.70; H, 5.60. Found: C, 66.52; H, 5.82.

1,3-Dihydro-1-hydroxy-4,5-dimethoxy-2,1-benzoxaborole (13b). Prepared under the same reaction conditions in a 65% yield; colorless powder: mp 149 °C; ^{1}H NMR (200.13 MHz) δ 3.91 (3H, s), 3.92 (3H, s), 5.05 (2H, s), 5.35 (1H, br. s), 6.85 (1H, s), 7.19 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.9, 56.0, 70.9, 103.6, 111.3, 147.7, 148.9, 152.4. Anal. Calcd for $C_9H_{11}BO_4$ (193.99 g mol^{-1}): C, 55.72; H, 5.72. Found: C, 55.65; H, 5.93.

Two-Step One-Pot Organolead-Mediated Arylation Reactions. Typical Procedure. A mixture of **10a** (0.10 g, 0.30 mmol), $Pb(OAc)_4$ (0.13 g, 0.3 mmol), and $Hg(OAc)_2$ (0.01 g, 0.03 mmol) was stirred in anhydrous $CHCl_3$ (1.5 mL) for 1.5 h at 40−45 °C and for 15 h at room temperature under nitrogen. Pyridine (0.07 mL, 0.90 mmol) and 4-hydroxy-5,6,7-trimethoxycoumarin **15a** (0.07 g, 0.27 mmol) were added to the reaction mixture, which was stirred for 10−12 h at 65 °C. The solvent was distilled under reduced pressure, and the residue was purified by CC (eluent AcOEt/petroleum ether, 1/1) to afford 3-[5′-benzyloxy-4′-methoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,6,7-trimethoxychromen-2-one **17a** as a colorless polycrystalline solid (0.12 g, 82%): mp 134−135 °C; ^{1}H NMR (200.13 MHz) δ 3.32 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 3.95 (3H, s), 4.16 (3H, s), 4.50 (2H, s), 4.63 (2H, s), 5.10 (1H, d, J = 12.1), 5.15 (1H, d, J = 12.1), 6.70 (1H, s), 6.85 (1H, s), 7.14 (1H, s), 7.31−7.42 (5H, s), 9.96 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 56.0, 56.4, 61.4, 62.8, 66.9, 71.1, 95.7, 96.7, 101.0, 102.8, 111.9, 116.3, 121.9, 127.5, 127.7, 128.4, 130.7, 137.1, 137.5, 147.6, 149.0, 149.6, 150.3, 157.0, 161.5, 162.3. Anal. Calcd for $C_{29}H_{30}O_{10}$ (538.54 g mol^{-1}): C, 64.68; H, 5.61. Found: C, 64.51; H, 5.82.

3-[5′-Benzyloxy-4′-methoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,7-dimethoxychromen-2-one (17b). CC (AcOEt/Petroleum ether, 1/1). Colorless crystalline solid (70%): mp 126 °C; ^{1}H NMR (200.13 MHz) δ 3.32 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 4.50 (2H, s), 4.63 (2H, s), 5.06 (1H, d, J = 11.8), 5.15 (1H, d, J = 11.8), 6.38 (1H, d, J = 2.0), 6.53 (1H, d, J = 2.0), 6.85 (1H, s), 7.13 (1H, s), 7.30−7.46 (5H, m), 9.49 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 55.9, 56.0, 56.9, 67.0, 71.1, 94.3, 95.6, 95.7, 98.7, 101.9, 111.9, 116.4, 122.2, 127.5, 127.7, 128.4, 130.8, 137.2, 147.5, 149.5, 155.9, 157.1, 161.9, 162.3, 163.2. Anal. Calcd for $C_{28}H_{28}O_9$ (508.52 g mol^{-1}): C, 66.13; H, 5.55. Found: C, 66.01; H, 5.78.

3-[5′-Benzyloxy-4′-methoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-6,7-dimethoxychromen-2-one (17c). CC (AcOEt/Petroleum ether, 7/3). Yellow crystalline solid (51%): mp 173 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.27 (3H, s), 3.93 (3H, s), 3.94 (3H, s), 3.97 (3H, s), 4.37 (1H, d, J = 11.6), 4.52 (1H, d, J = 11.5), 4.62 (1H, d, J = 6.7), 4.70 (1H, d, J = 6.7), 5.05 (1H, d, J = 12.1), 5.15 (1H, d, J = 12.1), 6.84 (1H, s), 6.86 (1H, s), 7.09 (1H, s), 7.23 (1H, s), 7.30−7.47 (5H, m); ^{13}C NMR (50.32 MHz) δ 55.8, 56.1, 56.3, 56.4, 68.6, 71.0, 96.6, 99.6, 102.7, 103.7, 107.4, 113.5, 116.6, 121.1, 127.6, 128.0, 128.5, 131.3, 136.5, 146.2, 148.5, 149.1, 150.3, 153.4, 160.9, 162.9. Anal. Calcd for $C_{28}H_{28}O_9$ (508.52 g mol^{-1}): C, 66.13; H, 5.55. Found: C, 65.87; H, 5.85.

3-[4′,5′-Dimethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,6,7-trimethoxychromen-2-one (18a). CC (AcOEt/ Petroleum ether, 1/1). Slightly yellow crystalline solid (78%): mp 132 °C; ^{1}H NMR (200.13 MHz) δ 3.31 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 3.95 (3H, s), 4.17 (3H, s), 4.49 (2H, s), 4.62 (2H, s), 6.71 (1H, s), 6.78 (1H, s), 7.10 (1H, s), 10.01 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 55.9, 56.4, 61.4, 62.8, 66.9, 95.6, 96.7, 101.0, 102.9, 111.4, 113.7, 122.1, 130.1, 137.5, 148.2, 148.9, 149.0, 150.3, 157.0, 161.5, 162.3. Anal. Calcd for $C_{23}H_{26}O_{10}$ (462.45 g mol^{-1}): C, 59.74; H, 5.67. Found: C, 59.46; H, 5.91.

3-[4′,5′-Dimethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,7-dimethoxychromen-2-one (18b). CC (AcOEt/petroleum ether, 1/1). Slightly yellow crystalline solid (62%): mp 140 °C; ^{1}H NMR (200.13 MHz) δ 3.31 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 4.49 (2H, s), 4.62 (2H, s), 6.38 (1H, d, J = 2.0), 6.53 (1H, d, J = 2.1), 6.77 (1H, s), 7.09 (1H, s), 9.53 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 55.8 (strong), 55.9, 56.9, 66.9, 94.3, 95.5, 95.6, 98.6, 101.9, 111.3, 113.7, 122.2, 130.1, 148.1, 148.8, 155.9, 157.1, 162.0, 162.4, 163.2. Anal. Calcd for $C_{22}H_{24}O_9$ (432.42 g mol^{-1}): C, 61.11; H, 5.59. Found: C, 60.85; H, 5.72.

3-[4′,5′-Dimethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-6,7-dimethoxychromen-2-one (18c). CC (AcOEt/petroleum ether, 1/1). Yellow crystalline solid (42%): mp 79−81 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.27 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 3.96 (3H, s), 4.38 (1H, d, J = 11.4), 4.52 (1H, d, J = 11.4), 4.63 (1H, d, J = 6.8), 4.70 (1H, d, J = 6.7), 6.76 (1H, s), 6.86 (1H, s), 7.05 (1H, s), 7.25 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.6, 55.9 (strong), 56.3, 56.4, 68.7, 96.6, 99.6, 102.9, 103.8, 107.4, 113.0, 114.2, 121.3, 130.7, 146.2, 149.1, 149.3, 149.6, 153.4, 160.9, 163.0. Anal. Calcd for $C_{22}H_{24}O_9$ (432.42 g mol^{-1}): C, 61.11; H, 5.59. Found: C, 60.92; H, 5.84.

3-[4′-Methoxy-5′-methoxymethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,6,7-trimethoxychromen-2-one (19a). CC (AcOEt/petroleum ether, 1/1). Slightly yellow crystalline solid (62%): mp 147−148 °C; ^{1}H NMR (200.13 MHz) δ 3.32 (3H, s), 3.50 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 3.95 (3H, s), 4.17 (3H, s), 4.50 (2H, s), 4.63 (2H, s), 5.21 (1H, d, J = 6.7), 5.25 (1H, d, J = 6.7), 6.70 (1H, s), 7.07 (1H, s), 7.14 (1H, s), 9.99 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.3, 55.9, 56.2, 56.4, 61.4, 62.8, 66.9, 95.6, 95.7, 96.7, 101.1, 102.8, 111.7, 118.7, 122.1, 131.9, 137.5, 145.8, 149.1, 149.6, 150.3, 157.0, 161.6, 162.2. Anal. Calcd for $C_{24}H_{28}O_{11}$ (492.47 g mol^{-1}): C, 58.53; H, 5.73. Found: C, 58.28; H, 5.96.

3-[4′-Methoxy-5′-methoxymethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,7-dimethoxychromen-2-one (19b). CC (AcOEt/petroleum ether, 2/1). Slightly yellow crystalline solid (67%): mp 115 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.29 (3H, s), 3.47 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 3.98 (3H, s), 4.48 (2H, s), 4.60 (2H, s), 5.18 (1H, d, J = 6.6), 5.22 (1H, d, J = 6.6), 6.35 (1H, d, J = 2.2), 6.48 (1H, d, J = 2.2), 7.04 (1H, s), 7.11 (1H, s), 9.51 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.1, 55.7, 55.8, 56.0, 56.9, 66.8, 94.1, 95.4, 95.5, 95.6, 98.5, 101.6, 111.4, 118.7, 122.2, 131.8, 145.5, 149.3, 155.7, 157.0, 162.0, 162.2, 163.1. Anal. Calcd for $C_{23}H_{26}O_{10}$ (462,45 g mol^{-1}): C, 59.74; H, 5.67. Found: C, 59.71; H, 5.89.

3-[5′-Methoxy-4′-methoxymethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,6,7-trimethoxychromen-2-one (20a). CC (AcOEt/petroleum ether, 1/1). Yellow viscous oil (48%); ^{1}H NMR (200.13 MHz) δ 3.29 (3H, s), 3.52 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 4.17 (3H, s), 4.46 (2H, s), 4.60 (2H, s), 5.27 (2H, s), 6.71 (1H, s), 6.81 (1H, s), 7.36 (1H, s), 10.01 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 55.9, 56.2, 56.4, 61.4, 62.8, 66.9, 95.3, 95.6, 96.7, 100.9, 102.9, 114.1, 116.3, 123.8, 130.2, 137.5, 146.5, 148.9, 149.0, 150.3, 157.1, 161.5, 162.3. Anal. Calcd for $C_{24}H_{28}O_{11}$ (492.47 g mol^{-1}): C, 58.53; H, 5.73. Found: C, 58.27; H, 5.97.

3-[5′-Methoxy-4′-methoxymethoxy-2′-(methoxymethoxymethyl)phenyl]-4-hydroxy-5,7-dimethoxychromen-2-one (20b). CC (AcOEt/petroleum ether, 1/1). Yellow viscous oil that crystallized in $CHCl_3$/ether/petroleum ether mixture during 4 days in refrigerator to afford a slightly yellow solid (45%): mp 134−135 °C; ^{1}H NMR (200.13 MHz) δ 3.30 (3H, s), 3.53 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 4.02 (3H, s), 4.46 (2H, s), 4.60 (2H, s), 5.28 (2H, s), 6.39 (1H, d, J = 2.2), 6.54 (1H, d, J = 2.2), 6.80 (1H, s), 7.36 (1H, s), 9.54 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.2, 55.9, 56.0, 56.2, 57.0, 67.0, 94.3, 95.3, 95.6, 95.7, 98.6, 102.0, 114.2, 116.2, 124.0, 130.3, 146.4, 148.8, 156.0, 157.1, 162.0, 162.4, 163.2. Anal. Calcd for $C_{23}H_{26}O_{10}$ (462,45 g mol^{-1}): C, 59.74; H, 5.67. Found: C, 59.61; H, 5.92.

Three-Step One-Pot Deprotection−Halogenation−Annulation Sequence for Synthesis of Compounds 25a−c and 26a−c. Typical Procedure. Several drops of concentrated hydrochloric acid were added to a solution of **17a** (0.1 g, 0.18 mmol) in acetone (3 mL). The mixture was stirred at 40 °C for 1 h (TLC monitoring). The organic solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (15 mL) and washed with water (5 mL), 5% aqueous NaOH (2 × 4 mL), 5% aqueous HCl (4 mL), and water (2 × 5 mL). The organic layer was dried over Na_2SO_4, the solvent was distilled under reduced pressure, and the residue was recrystallized in $CHCl_3$/hexanes to afford 9-benzyloxy-2,3,4,8-tetramethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one **25a** as a slightly yellow powder (0.066 g, 75%): mp 169−170 °C; ^{1}H NMR (200.13 MHz) δ 3.88 (3H, s), 3.90 (6H, s), 3.92 (3H, s), 5.23 (2H, s), 5.30 (2H, s), 6.65 (1H, s), 6.67 (1H, s), 7.28−7.40 (3H, m), 7.49−7.55 (2H, m), 8.24 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.2, 56.3, 61.4, 62.3, 69.4, 70.8, 96.3, 100.8, 103.5, 107.6, 110.5, 119.8, 119.9, 127.8, 128.5, 136.9, 140.1, 148.2, 149.2, 150.5, 150.6, 156.8, 160.2, 161.5. Anal. Calcd for $C_{27}H_{24}O_8$ (476.47 g mol^{-1}): C, 68.06; H, 5.08. Found: C, 67.83; H, 5.42.

9-Benzyloxy-2,4,8-trimethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (25b). Recrystallization in $CHCl_3$/petroleum ether. Yellow crystalline solid (74%): mp 214−216 °C; ^{1}H NMR (200.13 MHz) δ 3.85 (3H, s), 3.87 (6H, s), 5.22 (2H, s), 5.24 (2H, s), 6.30 (1H, d, J = 1.8), 6.43 (1H, d, J = 1.8), 6.62 (1H, s), 7.31−7.40 (3H, m), 7.50−7.57 (2H, m), 8.23 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.7, 56.2, 56.3, 69.3, 70.9, 93.0, 95.9, 99.6, 99.8, 107.6, 110.4, 119.7, 120.1, 127.8, 127.9, 128.4, 137.0, 148.2, 148.9, 156.1, 158.6, 160.3, 162.8, 163.2. Anal. Calcd for $C_{26}H_{22}O_7$ (446.45 g mol^{-1}): C, 69.95; H, 4.97. Found: C, 69.67; H, 5.19.

9-Benzyloxy-2,3,8-trimethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (25c). Recrystallization in $CHCl_3$/ether/petroleum ether. Yellow crystalline solid (59%): mp 180−181 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.90 (3H, s), 3.95 (6H, s), 5.24 (2H, s), 5.33 (2H, s), 6.64 (1H, s), 6.83 (1H, s), 7.18 (1H, s), 7.28−7.40 (3H, m), 7.49−7.55 (2H, m), 8.32 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.2, 56.3, 56.4, 69.4, 70.9, 99.5, 100.3, 102.9, 107.4, 107.8, 110.4, 119.7, 119.8, 127.8, 127.9, 128.5, 136.9, 146.3, 148.2, 148.7, 149.1, 153.2, 160.2, 160.8. Anal. Calcd for $C_{26}H_{22}O_7$ (446.45 g mol^{-1}): C, 69.95; H, 4.97. Found: C, 69.74; H, 5.16.

2,3,4,8,9-Pentamethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (26a). Recrystallization in $CHCl_3$/ether/petroleum ether. Yellow crystalline solid (82%): mp 172−174 °C; ^{1}H NMR (200.13 MHz) δ 3.88 (3H, s), 3.91 (6H, s), 3.93 (3H, s), 3.97 (3H, s), 5.32 (2H, s), 6.64 (1H, s), 6.69 (2H, s), 8.16 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.0, 56.1, 56.3, 61.4, 62.3, 69.5, 96.3, 100.8, 103.5, 107.0, 108.3, 119.4, 119.9, 140.2, 148.6, 149.0, 150.5, 150.7, 156.9, 160.3, 161.6. Anal. Calcd for $C_{21}H_{20}O_8$ (400.38 g mol^{-1}): C, 63.00; H, 5.03. Found: C, 62.73; H, 5.26.

2,4,8,9-Tetramethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (26b). Recrystallization in $CHCl_3$/ether/petroleum ether. Yellow crystalline solid (73%): mp 178−179 °C; ^{1}H NMR (200.13 MHz) δ 3.84 (3H, s), 3.89 (6H, s), 3.95 (3H, s), 5.24 (2H, s), 6.30 (1H, d, J = 1.9), 6.44 (1H, d, J = 1.9), 6.60 (1H, s), 8.13 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.7, 56.0 (strong), 56.3, 69.4, 93.0, 95.9, 99.6, 99.8, 107.0, 108.2, 119.3, 120.2, 148.3, 149.0, 156.1, 158.6, 160.4, 162.9, 163.2. Anal. Calcd for $C_{20}H_{18}O_7$ (370.35 g mol^{-1}): C, 64.86; H, 4.90. Found: C, 64.61; H, 5.18.

2,3,8,9-Tetramethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (26c). Recrystallization in $CHCl_3$/ether/petroleum ether. Yellow crystalline solid (64%): mp 214−216 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.90 (3H, s), 3.95 (6H, s), 3.97 (3H, s), 5.33 (2H, s), 6.61 (1H, s), 6.82 (1H, s), 7.17 (1H, s), 8.22 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.0, 56.1, 56.3, 56.4, 69.4, 99.5, 100.3, 102.9, 107.2, 107.4, 108.3, 119.3, 119.9, 146.3, 148.5, 148.7, 149.0, 153.3, 160.3, 160.8. Anal. Calcd for $C_{20}H_{18}O_7$ (370.35 g mol^{-1}): C, 64.86; H, 4.90. Found: C, 64.61; H, 5.18.

Synthesis of Compounds 27a, 27b, 29a, 30a, and 30b. Typical Procedure. Several drops of concentrated hydrochloric acid were added to a solution of **19a** (0.1 g, 0.20 mmol) in acetone (3 mL). The mixture was stirred at 40 °C for 1.5 h (TLC monitoring), and then $CHCl_3$ (15 mL) was added. The mixture was washed with water (3 × 5 mL), the organic layer was dried over Na_2SO_4, the solvent was distilled under reduced pressure, and the residue was recrystallized in $CHCl_3$/petroleum ether to afford 9-hydroxy-2,3,4,8-tetramethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one **27a** as a yellow crystalline solid (0.036 g, 46%): mp 236−237 °C; ^{1}H NMR (200.13 MHz) δ 3.88 (3H, s), 3.92 (9H, s), 5.29 (2H, s), 5.81 (1H, s), 6.63 (1H, s), 6.68 (1H, s), 8.15 (1H, s); ^{13}C NMR (50.32 MHz) δ 56.1, 56.3, 61.4, 62.3, 69.5, 96.3, 100.9, 103.5, 106.6, 111.8, 119.2, 120.5, 140.2, 145.9, 146.3, 150.5, 150.7, 156.9, 160.2, 161.7. Anal. Calcd for $C_{20}H_{18}O_8$ (386,35 g mol^{-1}): C, 62.17; H, 4.70. Found: C, 61.88; H, 4.96.

9-Hydroxy-2,4,8-trimethoxy-6*H*,11*H*-[2]benzopyrano[4,4-*c*][1]benzopyran-11-one (27b). Recrystallization in $CHCl_3$/ether/petroleum ether. Yellow crystalline solid (35%): mp 253 °C (dec); ^{1}H NMR (200.13 MHz, DMF-d$_7$) δ 3.81 (1H, br. s), 4.02 (3H, s), 4.10 (3H, s), 4.11 (3H, s), 5.48 (2H, s), 6.70 (1H, d, J = 2.1), 6.76 (1H, d, J = 2.1), 7.13 (1H, s), 8.15 (1H, s); ^{13}C NMR (50.32 MHz, DMF-d$_7$) δ 55.9, 56.0, 56.4, 69.1, 93.3, 96.1, 99.3, 99.6, 108.6, 112.1, 119.2, 120.4, 147.0, 147.7, 156.2, 159.2, 159.7, 163.2, 163.9. Anal. Calcd for $C_{19}H_{16}O_7$ (356.33 g mol^{-1}): C, 64.04; H, 4.53. Found: C, 63.77; H, 4.75.

4-Hydroxy-3-[5′-hydroxy-2′-(hydroxymethyl)-4′-methoxyphenyl]-5,6,7-trimethoxychromen-2-one (29a). Synthesized under the same reaction conditions, except using dilute HCl (15−20%) as deprotection agent. Recrystallization in $CHCl_3$/petroleum ether. Slightly yellow crystalline solid (63%): mp 143−144 °C (dec); ^{1}H NMR (200.13 MHz) δ 3.06 (1H, br. s), 3.88 (3H, s), 3.93 (3H, s), 3.95 (3H, s), 4.18 (3H, s), 4.37 (1H, d, J = 12.1), 4.47 (1H, d, J = 12.1), 5.69 (1H, s), 6.72 (1H, s), 6.86 (1H, s), 7.09 (1H, s), 10.15 (1H, s); ^{13}C NMR (50.32 MHz) δ 55.9, 56.5, 61.4, 62.9, 63.7, 96.8, 101.0, 102.9, 112.3, 117.0, 122.6, 132.5, 137.7, 145.2, 146.9, 149.0, 150.1, 162.2, 163.7. Anal. Calcd for $C_{20}H_{20}O_9$ (404.37 g mol^{-1}): C, 59.40; H, 4.99. Found: C, 59.25; H, 5.17.

4-Hydroxy-3-[4′-hydroxy-2′-(hydroxymethyl)-5′-methoxyphenyl]-5,6,7-trimethoxychromen-2-one (30a). Recrystallization in $CHCl_3$/petroleum ether. Slightly yellow crystalline solid (57%): mp 121−123 °C (dec); ^{1}H NMR (200.13 MHz) δ 2.15 (1H, br. s), 3.89 (6H, s), 3.96 (3H, s), 4.18 (3H, s), 4.47 (2H, s), 5.71 (1H, br. s), 6.73 (1H, s), 6.77 (1H, s), 7.10 (1H, s), 10.10 (1H, s); ^{13}C NMR (50.32 MHz) δ 44.7, 56.0, 56.5, 61.4, 62.9, 96.8, 100.9, 102.4, 113.5, 116.1, 122.5, 130.2, 137.5, 145.7, 146.6, 149.1, 150.4, 157.2, 162.2, 162.4. Anal. Calcd for $C_{20}H_{20}O_9$ (404.37 g mol^{-1}): C, 59.40; H, 4.99. Found: C, 59.13; H, 5.21.

4-Hydroxy-3-[4′-hydroxy-2′-(hydroxymethyl)-5′-methoxyphenyl]-5,7-dimethoxychromen-2-one (30b). Recrystallization in $CHCl_3$/petroleum ether. Slightly yellow crystalline solid (44%): mp 127 °C (dec); ^{1}H NMR (200.13 MHz) δ 1.96 (1H, br. s), 3.87 (3H, s), 3.89 (3H, s), 4.03 (3H, s), 4.48 (2H, s), 5.68 (1H, br. s), 6.39 (1H, d, J = 2.0), 6.55 (1H, d, J = 2.0), 6.76 (1H, s), 7.10 (1H, s), 9.61 (1H, s); ^{13}C NMR (50.32 MHz) δ 44.7, 55.9, 56.0, 57.0, 94.3, 95.7, 98.6, 101.6, 113.5, 116.0, 122.7, 130.3, 145.6, 146.6, 156.0, 157.2, 162.5, 162.6, 163.4. Anal. Calcd for $C_{19}H_{18}O_8$ (374.34 g mol^{-1}): C, 60.96; H, 4.85. Found: C, 60.72; H, 5.07.

Cell Culture. Human epithelial mammary HBL100 cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 10% foetal bovine serum (FBS), 2 mM l-glutamine, and 1% penicillin/streptomycin (Gibco) and maintained in a humidified incubator at 37 °C with 5% CO_2. For cytotoxicity experiments, exponentially growing cell cultures (2.6×10^4 cells/cm^2) were trypsinized with 0.25% trypsin/2 mM EDTA and seeded 24 h before treatment with the drug.

Cytotoxicity Tests. The HBL100 cells were seeded in 96-well plates to be treated during 72 h. The compounds were dissolved in DMSO at a 10 mM concentration and diluted in the tissue culture medium before use. The number of viable cells were estimated by using the colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma) assay, and absorbance was measured at 550 nm with a Dynatech MR 7-000 plate reader. At least three independent experiments were performed for each compound, and the IC_{50} values (i.e., concentration half-inhibiting cell proliferation) were graphically determined.

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