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Convenient synthetic route to a dehydrorotenoid via selective intramolecular aldol condensation of 1,2-diaryl diketone

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Abstract—Synthesis of dehydrorotenoid (**1**) was successfully achieved via an intramolecular aldol reaction of the corresponding 1,2-diaryl diketone intermediate. The 1,2-diaryl diketone was prepared using a ruthenium-catalyzed oxidation of the corresponding substituted diaryl acetylene. Treatment of this 1,2-diketone with L-proline induced a selective intramolecular aldol condensation reaction, forming the desired benzopyranone over the alternative benzofuran. Deprotection, cyclization, and dehydration gave the target compound in good overall yield.

1. Introduction

Rotenoids are an important class of natural products found principally in the Stemonaceae family[1] and also in certain unrelated families such as Leguminosae and Nyctaginaceae.[2] Rotenoids possess a variety of biological activities including insecticidal,[3] antiviral,[4] anticancer,[5] antiplasmodial,[6] antibacterial,[7] antifungal,[8] and anti-inflammatory activities.[9] Recent reports revealed the pharmacological properties of the dehydrorotenoids whose structures are illustrated in Figure 1. Boeravinones G and H have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy.[10] Boeravinone E has anti-spasmolytic activity, inhibiting the contractions of smooth muscle induced by acetylcholine (Ach).[11] 6-Hydroxy-2,3,9-trimethoxy-[1]-benzopyrano[3,4-*b*][1]benzo-pyran-12(6*H*)-one (**1**), the focus of our synthetic efforts, was isolated from *Clitoria fairchildiana* with an anti-inflammatory activity based on capillary permeability assay.[9a]

Our laboratory[12] and others[13] have investigated the synthesis of rotenoids, although previous approaches do not permit access to dehydrorotenoids containing an actetal moiety in ring B (e.g., **1**). To date, the only report concerning the synthesis of this structure was the synthesis of coccineone B (Fig. 1)

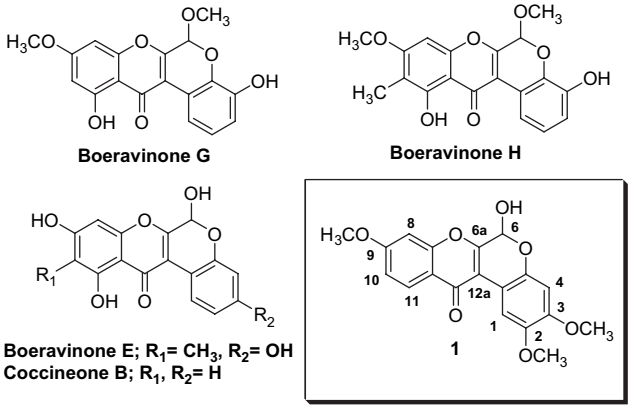

Figure 1. Naturally occurring rotenoids.

using 2-benzoyloxybenzyl-2,4,6,-trihydroxy phenyl ketone as intermediate.[14] In this report, we describe the methodological challenges associated with the synthesis of dehydrorotenoid **1**, which was achieved in three steps using the corresponding 1,2-diaryl diketone as a key intermediate. Several features of our synthetic strategy were attractive: (i) the convergent pathway minimizes the number of linear synthetic steps while maximizing product yields; (ii) the availability, using an oxidation protocol described herein, of functionalized 1,2-diaryl substituted diketones provided abundant starting materials that could be used for the synthesis of a variety of dehydrorotenoid-based natural products,

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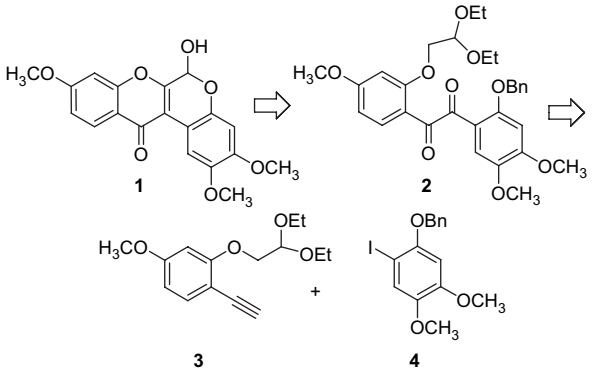
implying further uses in preparing many related compounds for biological study.

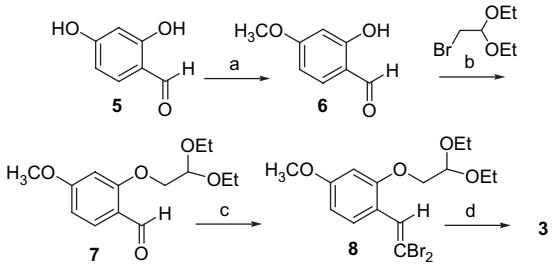
The retrosynthetic approach adopted for compound **1** is outlined in Scheme 1. The synthetic strategy is based on two key successive intramolecular cyclization steps of 1,2-diaryl diketone (**2**), which was obtained from the corresponding substituted diaryl acetylene. The preparation of the desired substituted diaryl acetylene was accomplished by the Sonogashira coupling reaction between monoaryl substituted acetylene (**3**) and aryl iodide (**4**).



Scheme 1. Retrosynthesis of rotenoid (**1**).

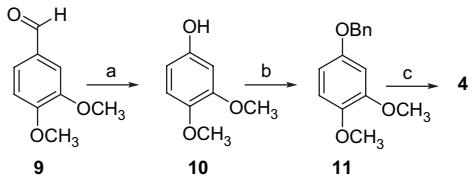
2. Results and discussion

The synthesis of aryl acetylene **3** is presented in Scheme 2. To realize this approach, commercially available **5** was treated with methyl iodide under basic condition to obtain compound **6** in 64% yield. Treatment of **6** with bromoacetaldehyde diethyl acetal in the presence of potassium carbonate in DMF at 150 °C gave ether **7** in excellent yield.[15] Conversion of **7** to **3** was accomplished by the Corey–Fuchs alkynylation via dibromide **8**.[16]



Scheme 2. (a) CH_3I, K_2CO_3, acetone, 64%; (b) K_2CO_3, DMF, 150 °C, 91%; (c) CBr_4, PPh_3, Zn, CH_2Cl_2, 88%; (d) *n*-BuLi, THF, −78 °C, 80%.

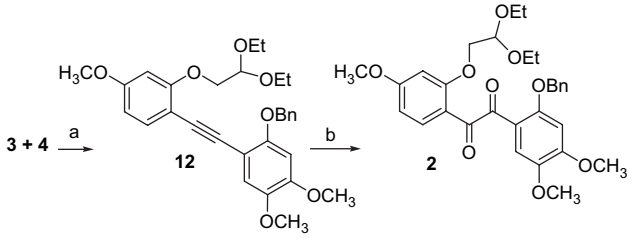
The preparation of **4** is outlined in Scheme 3. 3,4-Dimethoxybenzaldehyde (**9**) was converted to 3,4-dimethoxyphenol



Scheme 3. (a) (i) *m*-CPBA, CH_2Cl_2; (ii) then K_2CO_3, MeOH, 96%; (b) BnBr, K_2CO_3, acetone, 96%; (c) NIS, TFA, CH_2Cl_2, 98%.

(**10**) in 96% yield using an *m*-CPBA-mediated Baeyer–Villiger oxidation[17] followed by hydrolysis under basic conditions. The phenolic hydroxyl moiety of compound **10** was protected as its benzyl derivative (96%),[18] then iodinated with NIS in the presence of trifluoroacetic acid to give compound **4** in 98% yield.[19]

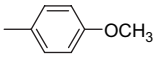
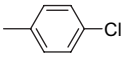
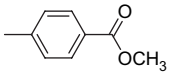
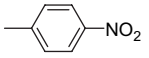
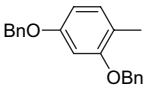
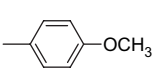
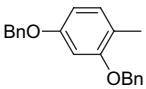
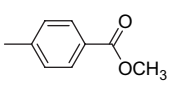
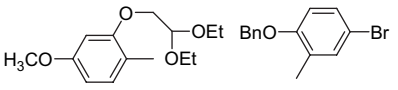
Sonogashira coupling of monoaryl substituted acetylene (**3**) and aryl iodide (**4**) afforded the substituted diaryl acetylene (**12**) in excellent yield (98%).[20] Compound **12** was oxidized with $RuCl_3$ (1 mol %), $NaIO_4$, $H_2O/CH_3CN/CCl_4$ according to a reported procedure[21] to obtain diketone **2** in moderate yield (45%). To improve the yield of diketone **2**, this oxidation reaction was buffered with $NaHCO_3$ and $MgSO_4$.[22] Under this optimized condition, the desired diketone (**2**) was obtained in 86% yield (Scheme 4).[23]



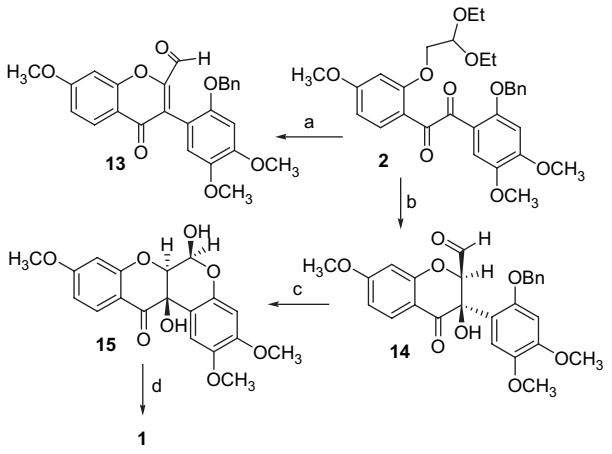
Scheme 4. (a) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, CH_3CN, 98%; (b) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, $MgSO_4$, $NaHCO_3$, 86%.

The scope of this oxidation procedure for the conversions of various substituted diaryl acetylenes into the corresponding diketones was examined (Table 1). Arylalkynes substituted

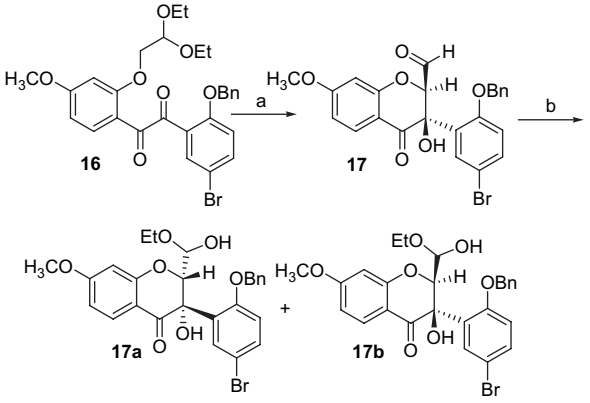
Table 1. Oxidation of various substituted diaryl acetylenes by $RuCl_3/NaIO_4$, $H_2O/CH_3CN/CCl_4$ buffered with $NaHCO_3$, $MgSO_4$

Entry	Ar^1	Ar^2	Time (h)	Yield (%)
1			3	93
2			1	91
3			2	87
4			1	79
5			4	62
6			3	95
7			1	74
8			3	83

Each product gave expected spectroscopic data.



Scheme 5. (a) 2 M H_2SO_4, H_2O, THF, reflux; (b) (i) 2 M H_2SO_4, H_2O, THF; (ii) L-proline, THF, 71%; (c) H_2, Pd/C, IPA, 80%; (d) 0.5 M H_2SO_4, THF, 93%.



Scheme 6. (a) (i) 2 M H_2SO_4, H_2O/THF; (ii) L-proline, THF, **17** (75%); (b) recryst CH_2Cl_2/EtOH.

with an electron-donating group have been transformed into the corresponding diketones in good yield and with shorter reaction time. On the other hand, the presence of a nitro group on the aryl moiety (entry 3) resulted in a significantly lower yield of diketone product.

Scheme 5 depicts the final transformations leading up to synthetic rotenoid **1**. Aldol cyclization of **2** under acidic conditions afforded benzopyranone **13** through cyclization onto the distal ketone and dehydration. Notably, none of the corresponding five-membered ring (benzofuran) was observed. In order to avoid potential conflictions in the removal of the benzyl ether, a stepwise aldol sequence was then employed. Compound **2** was treated with 2 M H_2SO_4, H_2O/THF to transform the diethyl acetal moiety into an aldehyde intermediate, which was followed by treatment with L-proline in THF to initiate an intramolecular aldol condensation leading to **14** in 71% yield.[24] Attempts to establish the stereochemistry of **14** by X-ray analysis were unsuccessful due to the non-crystalline, unstable nature of compound **14**. Thus, a bromo analog (**16**) was prepared and subjected to identical L-proline catalyzed-intramolecular aldol reaction as shown in Scheme 6. 1,2-Diketone **16** gave the aldol reaction product **17** in 73% yield as a white amorphous solid. Compound **17** was recrystallized from dichloromethane and ethanol (1:4) to give single crystals. The *syn* stereochemistry of compound **17** (carbonyl at C-2 and OH-C3) was ascertained from the correlation of X-ray diffraction data of **17a** and **17b** (Fig. 2).[25] Thus, the stereochemistry of compound **14** (carbonyl at C-2 and OH-C3) was assigned to be *syn* by analogy.[26] However, the stereogenic centers of compound **14** will be destroyed in the final step.

Preparation of the rotenoid hemiacetal **15** was accomplished in 80% yield by removing the benzyl group from compound **14** using 10% Pd/C under H_2 atmosphere.[27] The stereochemistry indicated for compound **15** was confirmed by the NOESY correlations; the hemiacetal at C-6 was formed almost exclusively with only small amount of epimer being observed in the NMR spectrum. To explain this stereochemical outcome, we invoke an intramolecular H-bond between the hydroxyl at position C-3 and the aldehyde carbonyl (Fig. 3), which locked the carbonyl and exposed it to be attacked by phenolic-OH leading to 6β-OH of a hemiacetal moiety. This new hydroxyl group can engage in a similar intramolecular

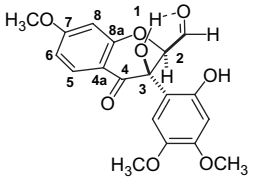


Figure 3. Probable reactive conformation.

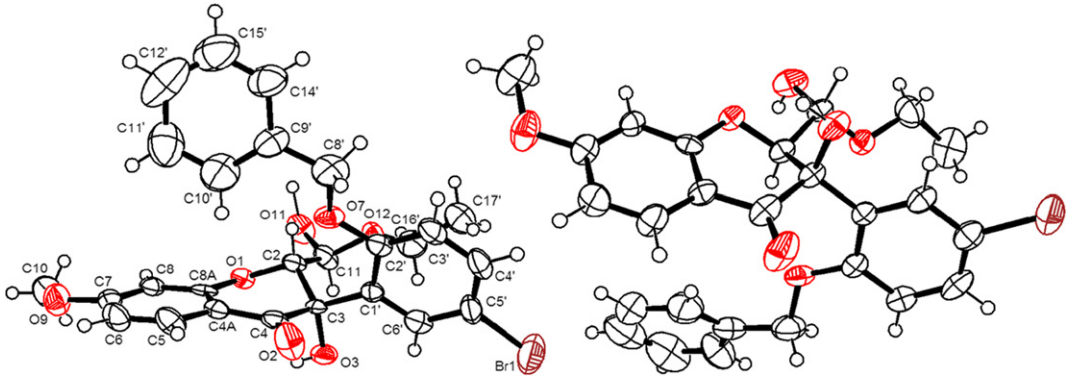


Figure 2. ORTEP diagram for compounds **17a** and **17b**.

hydrogen bond (not shown) to stabilize the product (**15**). However, the ratio of 6α-OH was increased when the compound was purified under acidic condition. This result indicated that 6β-OH was the kinetic product.

Finally, dehydration of **15** was performed in 0.5 M H_2SO_4 in THF to provide the target molecule **1** in 93% yield. Synthetic **1** exhibited ^1H and ^{13}C NMR spectral data in agreement with those of the natural product.[9b]

3. Conclusion

We have developed a novel and concise methodology for the synthesis of dehydrorotenoid (**1**) using the corresponding 1,2-diaryl diketone as a key intermediate in good yield. This synthetic strategy should be applicable to the synthesis of rotenoid and isoflavanoid analogs. Moreover, the corresponding 1,2-diaryl diketone was easily accessed by the ruthenium-catalyzed oxidation of diaryl acetylenes in buffer media.

4. Experiment

4.1. General experimental methods

All reactants and reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous solvents were distilled immediately prior to use: tetrahydrofuran (THF) from sodium/benzophenone, dichloromethane and acetonitrile from calcium hydride. Flash chromatography was performed on silica gel 60 (Merck, 230–400). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used for NMR data: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad. IR data were obtained with an FTIR spectrometer. High-resolution mass spectra (TOF MS (ESI)) and low resolution mass spectra (MS (ESI)) were performed on instruments from the National Center for Genetic Engineering and Biotechnology. Melting points of crystalline compounds are uncorrected.

4.1.1. 2-Hydroxy-4-methoxy-benzaldehyde (6). 2,4-Dihydroxybenzaldehyde (**5**) (1.5 g, 10.81 mmol) and K_2CO_3 (1.5 g, 10.81 mmol) were first dissolved in acetone (20 mL) then treated with methyl iodide (677 μL, 10.81 mmol), and the mixture was stirred at room temperature for 24 h. After removal of solvent, the residue was dissolved in EtOAc (2×50 mL) and then washed with H_2O (2×50 mL) and brine (2×20 mL) and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to provide compound **6** (1.05 g, 64%), mp=39–40 °C; TLC, R_f 0.55 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 11.48 (s, 1H), 9.70 (s, 1H), 7.42 (d, 1H, J=8.4 Hz), 6.53 (dd, 1H, J=8.4, 2.4 Hz), 6.42 (d, 1H, J=2.4 Hz), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.4, 166.8, 164.5, 135.3, 115.4, 108.4, 100.6, 55.7; IR (neat) 3081, 2850, 1638 cm^{-1}; MS (ESI) calcd for $C_8H_9O_3$ $(M+H)^+$ m/z 153.16; found 153.33.

4.1.2. 2-(2,2-Diethoxy-ethoxy)-4-methoxy-benzaldehyde (7). To a solution of compound **6** (509 mg, 3.34 mmol) in DMF (3 mL) were added K_2CO_3 (1.85 g, 13.38 mmol) and bromoacetaldehyde diethyl acetal (410 μL, 3.68 mmol). The mixture was stirred under refluxing at 150 °C for 2 h. The reaction mixture was worked up with ice, neutralized with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (3×15 mL), the combined organic extract was washed with H_2O (2×10 mL) and brine (1×20 mL), and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to give compound **7** (813 mg, 91%) as a yellow oil. TLC, R_f 0.43 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 10.30 (s, 1H), 7.78 (d, 1H, J=8.8 Hz), 6.53 (dd, 1H, J=8.8, 2.0 Hz), 6.42 (d, 1H, J=2.0 Hz), 4.86 (t, 1H, J=5.6 Hz), 4.05 (d, 2H, J=5.6 Hz), 3.83 (s, 3H), 3.77 (m, 2H), 3.63 (m, 2H), 1.23 (t, 6H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 188.2, 166.1, 162.7, 130.3, 119.1, 106.7, 100.4, 98.6, 69.2, 63.2×2, 55.6, 15.3×2; IR (neat) 2968, 2875, 1684, 1597, 1438 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}O_5$ $(M+H)^+$ m/z 269.1389; found 269.1380.

4.1.3. 1-(2,2-Dibromo-vinyl)-2-(2,2-diethoxy-ethoxy)-4-methoxy-benzene (8). A mixture of Zn dust (886 mg, 13.56 mmol), triphenylphosphine (3.06 g, 13.56 mmol), and carbon tetrabromide (4.50 g, 13.56 mmol) in dried CH_2Cl_2 (35 mL) was stirred at room temperature under N_2 for 6 h. To this mixture was added compound **7** (1.21 g, 4.52 mmol) and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed to give a residue. This mixture was dissolved in EtOAc 80 mL and filtered. The solvent was removed and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to yield compound **8** (1.68 g, 88%) as a yellow solid, mp=40–41 °C; TLC, R_f 0.63 (EtOAc/hexane, 3:7); ^1H NMR ($CDCl_3$) δ 7.60 (d, 1H, J=9.2 Hz), 7.47 (s, 1H), 6.43 (dd, 1H, J=9.2, 2.4 Hz), 6.34 (d, 1H, J=2.4 Hz), 4.76 (t, 1H, J=5.6 Hz), 3.90 (d, 2H, J=5.6 Hz), 3.72 (s, 3H), 3.71 (m, 2H), 3.58 (m, 2H), 1.19 (t, 6H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 161.1, 156.9, 132.3, 129.6, 117.4, 105.1, 100.6, 99.1, 87.7, 69.3, 63.3×2, 55.4, 15.4×2; IR (neat) 2972, 2890, 1617 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Br_2O_4Na$ $(M+Na)^+$ m/z 444.9626; found 444.9636.

4.1.4. 2-(2,2-Diethoxy-ethoxy)-1-ethynyl-4-methoxybenzene (3). Compound **8** (1.68 g, 3.97 mmol) was dissolved in dried THF (10 mL) at −78 °C under N_2, and then *n*-butyllithium (7.5 mL of a 0.56 M hexane solution, 4.17 mmol) was added and the solution was stirred at −78 °C for 30 min. The reaction mixture was worked up with water (5 mL) and the mixture was extracted with EtOAc (2×25 mL). The combined organic extract was washed with water (20 mL) and brine (20 mL) and finally dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:9 EtOAc/hexane) to obtain compound **3** (839 mg, 80%) as a yellow solid, mp=66–67 °C; TLC, R_f 0.53 (EtOAc/hexane, 1:9); ^1H NMR ($CDCl_3$) δ 7.32 (dd, 1H, J=9.6, 1.6 Hz), 6.41 (d, 1H, J=9.6 Hz), 6.40 (d, 1H, J=1.6 Hz), 4.83 (t, 1H, J=5.6 Hz), 4.01 (d, 2H, J=5.6 Hz), 3.78 (m, 2H), 3.75 (s, 3H), 3.66 (m, 2H), 3.14 (s,

1H), 1.22 (t, 6H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 161.3, 161.0, 134.7, 105.8, 104.2, 100.8, 99.5, 80.1, 79.6, 69.9, 63.4×2, 55.4, 15.3×2; IR (neat) 3281, 2983, 2880, 2110 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}O_4$ (M+H)$^+$ m/z 265.1440; found 265.1447.

4.1.5. 3,4-Dimethoxyphenol (10).[28] To a solution of 3,4-dimethoxybenzaldehyde (**9**) (2.00 g, 12.04 mmol) in CH_2Cl_2 (32 mL) was added *m*-chloroperbenzoic acid (3.26 g with 25–30% of H_2O, ca. 13.24 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with dimethyl sulfide (1 mL) and then successively washed with saturated aqueous Na_2SO_3 solution (3×20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH (30 mL), and then treated with K_2CO_3 (3.32 g, 24.07 mmol), and the mixture was stirred at room temperature for 30 min. After removal of MeOH, the residue was dissolved in EtOAc (30 mL), washed with H_2O (2×20 mL) and brine (20 mL), and dried over Na_2SO_4. The organic phase was filtered and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:1 EtOAc/hexane) to provide compound **10** (1.78 g, 96%) as a white solid, mp=80–82 °C; TLC, R_f 0.50 (EtOAc/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, 1H, J=8.8 Hz), 6.46 (d, 1H, J=2.4 Hz), 6.34 (dd, 1H, J=8.8, 2.4 Hz), 5.84 (br s, 1H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 149.8, 142.9, 112.5, 105.9, 100.6, 56.6, 55.7; IR (neat) 3726–3034, 2983, 2839, 1608, 1508, 1465 cm^{-1}; MS (ESI) calcd for $C_8H_{11}O_3$ (M+H)$^+$ m/z 155.07; found 155.33.

4.1.6. 4-Benzyloxy-1,2-dimethoxy-benzene (11).[29] Compound **10** (857 mg, 5.56 mmol) and K_2CO_3 (844 mg, 6.11 mmol) were first dissolved in acetone (20 mL) and then treated with benzyl bromide (727 μL, 6.12 mmol), and the mixture was stirred at room temperature for 24 h. After removal of solvent, the residue was dissolved in water (30 mL). The aqueous phase was extracted with EtOAc (2×30 mL), washed with brine (2×20 mL), and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **11** (1.31 g, 96%) as a white solid, mp=43.5 °C; TLC, R_f 0.48 (EtOAc/hexane, 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 6.77 (d, 1H, J=8.4 Hz), 6.62 (d, 1H, J=1.6 Hz), 6.48 (dd, 1H, J=8.4, 1.6 Hz), 5.00 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 149.9, 143.7, 137.2, 128.6×2, 128.0, 127.6×2, 111.8, 104.1, 101.2, 70.6, 56.4, 55.8; IR (neat) 2834, 1611, 1519, 1463 cm^{-1}; MS (ESI) calcd for $C_{15}H_{17}O_3$ (M+H)$^+$ m/z 245.12; found 245.31.

4.1.7. 1-Benzyloxy-2-iodo-4,5-dimethoxy-benzene (4). To a solution of compound **11** (557 mg, 2.28 mmol) in dried CH_2Cl_2 (4 mL) were added *N*-iodosuccinimide (446 mg, 2.51 mmol) and TFA (5.2 μL, 0.58 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous $NaHSO_3$ (1 mL). The resulting mixture was washed with H_2O (2×10 mL) and brine (10 mL), and dried over Na_2SO_4. The organic phase was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to give compound **4** (827 mg, 98%) as a white solid, mp=50–51 °C; TLC, R_f 0.30 (EtOAc/hexane, 1:4); ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 2H, J=7.2 Hz), 7.39 (t, 2H, J=7.2 Hz), 7.32 (t, 1H, J=7.2 Hz), 7.21 (s, 1H), 6.51 (s, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.0, 150.0, 144.6, 136.7, 128.5×2, 128.0, 127.4×2, 121.5, 100.2, 74.4, 72.4, 56.6, 56.1; IR (neat) 2939, 2847, 1508, 1439, 1208 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}IO_3Na$ (M+Na)$^+$ m/z 392.9964; found 392.9969.

4.1.8. 1-Benzyloxy-2-[2-(2,2-diethoxy-ethoxy)-4-methoxy phenylethynyl]-4,5-dimethoxybenzene (12). To a N_2-degassed solution of CH_3CN (5 mL) and triethylamine (500 μL) were added compound **3** (338 mg, 1.28 mmol), compound **4** (338 mg, 0.91 mmol), $Pd(PPh_3)_2Cl_2$ (13 mg, 2 mol %), and CuI (3 mg, 1.7 mol %), and the mixture was stirred at room temperature for 12 h. The mixture was filtered, concentrated, and the residue was purified by flash chromatography on silica gel (elution with 3:7 EtOAc/hexane) to give compound **12** (456 mg, 98%) as a brown solid, mp=53–54 °C; TLC, R_f 0.28 (EtOAc/hexane, 3:7); ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 2H, J=6.8 Hz), 7.38–7.26 (m, 4H), 6.97 (s, 1H), 6.51 (s, 1H), 6.48–6.47 (m, 2H), 5.20 (s, 2H), 4.79 (t, 1H, J=6.0 Hz), 4.06 (d, 2H, J=6.0 Hz), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (m, 2H), 3.64 (m, 2H), 1.18 (t, 6H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 160.8, 160.2, 154.2, 149.7, 143.6, 137.4, 133.9, 128.4×2, 127.8, 127.4×2, 115.4, 106.1, 105.9, 101.1, 100.8×2, 99.7, 88.9, 88.4, 72.6, 70.1, 63.3×2, 56.3, 55.9, 55.4, 15.4×2; IR (neat) 2967, 2372, 1606, 1514 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}O_7Na$ (M+Na)$^+$ m/z 529.2202; found 529.2208.

4.1.9. General procedure for oxidation of alkynes to 1,2-diketones. To the alkyne substrate (2.0 mmol), $NaHCO_3$ (13.2 mg, 0.1571 mmol), $MgSO_4$ (59 mg, 0.4937 mmol), and $NaIO_4$ (1.2833 mg, 6 mmol) in CH_3CN (3 mL), CCl_4 (3 mL), and H_2O (4 mL) was added $RuCl_3$ stock solution in water (2 mL, 1 mol %, 0.01 M). The reaction mixture was stirred at room temperature until complete conversion. The reaction mixture was extracted with EtOAc (2×30 mL), washed with H_2O, and dried over Na_2SO_4. After the organic solvent was removed the crude residue was purified by flash chromatography on silica gel to obtain the pure product.

4.1.9.1. 1-(2-Benzyloxy-4,5-dimethoxy-phenyl)-2-[2-(2,2-diethoxy-ethoxy)-4-methoxyphenyl]-ethane-1,2-dione (2). General procedure was followed employing 300 mg (0.59 mmol) of compound **12**. Purification by flash chromatography on silica gel (elution with 1:1 EtOAc/hexane) to obtain compound **2** (274 mg, 86%) as a yellow solid, mp=119–120 °C; TLC, R_f 0.43 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1H, J=8.8 Hz), 7.57 (s, 1H), 7.14–7.11 (m, 3H), 7.05 (d, 2H, J=6.8 Hz), 6.48 (s, 1H), 6.43 (dd, 1H, J=8.8, 2.0 Hz), 6.29 (d, 1H, J=2.0 Hz), 4.87 (s, 2H), 4.20 (t, 1H, J=5.6 Hz), 3.91 (s, 3H), 3.86 (s, 3H), 3.82 (d, 2H, J=5.6 Hz), 3.81 (s, 3H), 3.47 (m, 2H), 3.21 (m, 2H), 1.07 (t, 6H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 191.7, 191.4, 165.7, 161.0, 155.8, 155.1, 143.9, 135.3, 132.3, 128.2×2, 127.8, 127.6×2, 116.9, 115.8, 111.3, 107.1, 100.3, 98.9, 97.7, 71.9, 70.1, 62.8×2, 56.3, 56.1, 55.6, 15.2×2; IR (neat) 2967, 1647, 1605, 1514,

1442 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}O_9Na$ $(M+Na)^+$ *m/z* 561.2101; found 561.2105.

4.1.9.2. 1-(4-Methoxy-phenyl)-2-phenyl-ethane-1,2-dione.[30] Light yellow crystal, mp=47–48 °C; TLC, R_f 0.48 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 7.54–7.50 (m, 4H), 7.35 (m, 3H), 6.91–6.89 (dd, 2H, *J*=8.8, 1.2 Hz), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.9, 193.2, 165.0, 134.8, 133.1, 132.3×2, 129.9×2, 129.0×2, 126.0, 114.4×2, 55.6; IR (neat) 3061, 2834, 1674, 1695, 1513, 1260, 1169 cm^{-1}.

4.1.9.3. 1,2-Diphenyl-ethane-1,2-dione.[30] Light yellow crystal, mp=76–80 °C; TLC, R_f 0.50 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 7.60–7.58 (m, 4H), 7.70–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 131.6×4, 128.4×4, 128.3×2, 123.3×2, 89.4×2; IR (neat) 3060, 1600, 1504, 1443 cm^{-1}.

4.1.9.4. 1-(4-Chloro-phenyl)-2-phenyl-ethane-1,2-dione.[30] Yellow crystal, mp=64–65 °C; TLC, R_f 0.38 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 7.96 (dd, 2H, *J*=7.6, 1.6 Hz), 7.92 (dd, 2H, *J*=6.8, 0.8 Hz), 7.67 (t, 1H, *J*=7.6 Hz), 7.54–7.48 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 193.9, 193.1, 141.6, 135.1, 132.8, 131.3, 131.2×2, 129.9×2, 129.4×2, 129.1×2; IR (neat) 2995, 1769, 1674, 1587, 1456 cm^{-1}.

4.1.9.5. 4-(2-Oxo-2-phenyl-acetyl)-benzoic acid ethyl ester. Light yellow crystal, mp=64–65 °C; TLC, R_f 0.48 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 8.08 (d, 2H, *J*=8.0 Hz), 7.95 (d, 2H, *J*=8.4 Hz), 7.89 (d, 2H, *J*=7.6 Hz), 7.59 (t, 1H, *J*=7.6 Hz), 7.44 (t, 2H, *J*=8.0 Hz), 4.32 (q, 2H, *J*=7.2 Hz), 1.32 (t, 3H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 193.8, 193.7, 165.4, 135.9, 135.7, 135.1, 132.7, 130.0×2, 129.9×2, 129.7×2, 129.14×2, 61.7, 14.2; IR (neat) 2922, 1717, 1674, 1600, 1452, 1278 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}O_4Na$ $(M+Na)^+$ *m/z* 305.0790; found 305.0793.

4.1.9.6. 1-(4-Nitro-phenyl)-2-phenyl-ethane-1,2-dione.[30] Yellow crystal, mp=139–140 °C; TLC, R_f 0.43 (EtOAc/hexane, 3:7); ^1H NMR ($CDCl_3$) δ 8.33 (d, 2H, *J*=1.2 Hz), 8.15 (d, 2H, *J*=8.4 Hz), 7.97 (d, 2H, *J*=8.4 Hz), 7.70 (t, 1H, *J*=7.6 Hz), 7.54 (t, 2H, *J*=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 192.9, 192.1, 151.1, 137.3, 135.5, 132.3, 131.0×2, 130.0×2, 129.2×2, 124.1×2; IR (neat) 3109, 1665, 1600, 1521, 1356 cm^{-1}.

4.1.9.7. 1-(2,4-Bis-benzyloxyphenyl)-2-(4-methoxy-phenyl)-ethane-1,2-dione. Colorless crystal, mp=97–98 °C; TLC, R_f 0.18 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 8.05 (d, 1H, *J*=9.2 Hz), 7.64 (d, 2H, *J*=8.4 Hz), 7.40–7.35 (m, 5H), 7.26–7.16 (m, 3H), 7.00 (d, 2H, *J*=6.8 Hz), 6.77 (d, 2H, *J*=8.8 Hz), 6.71 (dd, 1H, *J*=8.8, 1.6 Hz), 6.52 (d, 1H, *J*=1.6 Hz), 5.10 (s, 2H), 4.82 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.6, 192.6, 165.6, 163.8, 161.4, 135.8, 134.7, 132.8, 131.7×2, 128.8×2, 128.4, 128.3×2, 128.0, 127.9×2, 127.5×2, 126.1, 117.5, 113.8×2, 107.7, 99.9, 71.0, 70.5, 55.5; IR (neat) 3030, 2926, 1665, 1596, 1517, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{24}O_5Na$ $(M+Na)^+$ *m/z* 475.1521; found 475.1524.

4.1.9.8. 4-[2-(2,4-Bis-benzyloxyphenyl)-2-oxo-acetyl]-benzoic acid ethyl ester. Light yellow oil. TLC, R_f 0.25 (EtOAc/hexane, 1:4); ^1H NMR ($CDCl_3$) δ 7.96 (d, 1H, *J*=8.4 Hz), 7.82 (d, 2H, *J*=8.4 Hz), 7.56 (d, 2H, *J*=8.0 Hz), 7.31–7.25 (m, 5H), 7.16–7.11 (m, 1H), 7.05 (t, 2H, *J*=7.6 Hz), 6.85 (d, 2H, *J*=7.2 Hz), 6.65 (dd, 1H, *J*=9.2, 2 Hz), 6.43 (d, 1H, *J*=1.6 Hz), 5.02 (s, 2H), 4.68 (s, 2H), 4.31 (q, 2H, *J*=7.2 Hz), 1.33 (t, 3H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 192.9×2, 166.0, 165.7, 161.5, 136.1, 135.7, 134.3, 134.1, 132.7, 129.5×2, 129.1×2, 128.8×2, 128.4×3, 128.3, 128.1×2, 127.5×2, 117.0, 108.0, 99.7, 71.1, 70.5, 61.4, 14.3; IR (neat) 3052, 2934, 2874, 1721, 1683, 1643, 1591, 1439, 1269 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{26}O_6Na$ $(M+Na)^+$ *m/z* 517.1627; found 517.1626.

4.1.10. 1-(2-Benzyloxy-5-bromo-phenyl)-2-[2-(2,2-diethoxyethoxy)-4-methoxyphenyl]-ethane-1,2-dione (16). General procedure was followed employing 650 mg (1.24 mmol) of 1-(2-benzyloxy-5-bromophenylethynyl)-2-(2,2-diethoxyethoxy)-4-methoxy-benzene. Purification by flash chromatography on silica gel (elution with 2:3 EtOAc/hexane) to give 1-(2-benzyloxy-5-bromo-phenyl)-2-[2-(2,2-diethoxy-ethoxy)-4-methoxy-phenyl]-ethane-1,2-dione (572 mg, 83% yield) as a white solid, mp=84–85 °C; TLC, R_f 0.33 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$) δ 8.18 (d, 1H, *J*=2.3 Hz), 7.67 (d, 1H, *J*=8.6 Hz), 7.60 (dd, 1H, *J*=8.6, 2.3 Hz), 7.15–7.10 (m, 3H), 7.03 (d, 2H, *J*=6.2 Hz), 6.87 (d, 1H, *J*=8.6 Hz), 6.43 (dd, 1H, *J*=8.6, 1.6 Hz), 6.25 (s, 1H), 4.87 (s, 2H), 4.18 (t, 1H, *J*=4.7 Hz), 3.18 (s, 3H), 3.77 (d, 2H, *J*=4.7 Hz), 3.49 (q, 2H, *J*=7.8 Hz), 3.20 (q, 2H, *J*=7.8 Hz), 1.06 (t, 6H, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 191.0, 190.7, 165.9, 161.0, 158.3, 137.7, 134.5, 133.2, 132.2, 128.3×2, 128.0, 127.7×2, 125.3, 116.4, 114.9, 113.6, 107.2, 100.1, 98.8, 71.3, 69.9, 62.9×2, 55.6, 15.2×2; IR (neat) 2978, 2927, 1668, 1704, 1653 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{29}O_7BrNa$ $(M+Na)^+$ *m/z* 579.0989; found 579.0997.

4.1.11. 3-(2-Benzyloxy-4,5-dimethoxy-phenyl)-7-methoxy-4-oxo-4*H*-chromene-2-carbaldehyde (13). To a solution of 0.5 M H_2SO_4 in THF was added compound **2** (200 mg, 0.37 mmol), and the reaction mixture was stirred at room temperature for 24 h. This mixture was diluted with H_2O, and then extracted with EtOAc (2×15 mL). The combined organic layer was concentrated, and the mixture was purified by flash chromatography on silica gel (elution with 1:4 EtOAc/hexane) to give compound **13** (131 mg, 79% yield) as a yellow solid, mp=127–128 °C; TLC, R_f 0.48 (EtOAc/hexane, 1:1); ^1H NMR ($CDCl_3$) δ 9.59 (s, 1H), 8.13 (d, 1H, *J*=9.6 Hz), 7.21–7.19 (m, 5H), 7.02 (s, 1H), 7.01 (d, 1H, *J*=9.6 Hz), 6.86 (s, 1H), 6.67 (s, 1H), 4.99 (d, 1H, *J*=11.6 Hz), 4.93 (d, 1H, *J*=11.6 Hz), 3.93 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 186.3, 177.4, 165.1, 157.1, 151.9, 151.2, 150.9, 143.7, 136.4, 128.5×2, 128.0, 127.8, 127.7, 127.5×2, 118.1, 115.7, 115.3, 109.2, 100.3×2, 72.7, 56.4, 56.1, 56.0; IR (neat) 3396, 1741, 1661, 1604, 1579, 1268 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{28}O_8Na$ $(M+Na)^+$ *m/z* 563.1682; found 563.1676.

4.1.12. 3-(2-Benzyloxy-4,5-dihydroxy-phenyl)-3-hydroxy-7-methoxy-4-oxo-chroman-2-carbaldehyde (14). To a solution of 2 M H_2SO_4 in H_2O (1 mL) and THF

(4 mL) was added compound **2** (200 mg, 0.37 mmol), and the reaction mixture was stirred at room temperature for 18 h. This mixture was diluted with H_2O (30 mL), and then extracted with EtOAc (2×20 mL), washed sequentially with water (4×20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated to give crude aldehyde. This crude aldehyde was dissolved in THF (4 mL), followed by addition of L-proline (3 mg, 0.03 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was added with H_2O (15 mL) and then the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (2×10 mL). The combined organic phase (THF and $CHCl_3$) was washed with H_2O (2×15 mL), and then dried over Na_2SO_4, filtered, and concentrated. The residue was recrystallized with hexane and EtOAc to give compound **14** as a white solid (122 mg, 71%), mp=192–193 °C; TLC, R_f 0.28 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ +4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H), 7.69 (d, 1H, *J*=8.8 Hz), 7.18–7.16 (m, 6H), 6.62 (s, 1H), 6.58 (d, 1H, *J*=8.8 Hz), 6.52 (s, 1H), 5.39 (s, 1H), 4.98 (d, 1H, *J*=11.2 Hz), 4.89 (d, 1H, *J*=11.2 Hz), 3.86 (s, 6H), 3.84 (s, 3H), 3.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 195.6, 186.7, 166.3, 161.0, 150.1, 148.8, 143.7, 135.8, 129.8, 128.4×2, 128.0, 127.4×2, 117.1, 113.1, 111.5, 111.1, 100.8, 99.1, 84.8, 76.1, 71.6, 56.5, 56.1, 55.8; IR (neat) 3560–3242, 1747, 1682, 1600, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}O_8Na$ (M+Na)$^+$ *m*/*z* 487.1369; found 487.1376.

4.1.13. 6,12a-Dihydroxy-2,3,9-trimethoxy-6a,12a-dihydro-6*H*-chromeno[3,4-*b*]chromen-12a-one (15). To a solution of compound **14** (100 mg, 0.27 mmol) in distilled isopropanol (2 mL) was added Pd/C (10% on charcoal, 10 mg), and the mixture was stirred under a balloon pressure of H_2 at room temperature for 12 h. The mixture was filtered and concentrated to give compound **15** (69 mg, 80%) as a white solid, mp=84–86 °C; TLC, R_f 0.23 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ +4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H, *J*=8.8 Hz), 7.73 (s, 1H), 6.66 (dd, 1H, *J*=8.8, 2.4 Hz), 6.55 (d, 1H, *J*=2.4 Hz), 6.42 (s, 1H), 5.81 (br s, 1H), 5.34 (d, 1H, *J*=6.0 Hz), 4.57 (d, 1H, *J*=2.8 Hz), 4.28 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 186.1, 166.2, 161.9, 151.2, 145.0, 144.1, 130.5, 113.3, 112.8, 111.1, 110.0, 101.1, 100.6, 91.8, 76.8, 67.3, 56.3, 55.9, 55.8; IR (neat) 3686, 3070, 1617, 1582, 1443 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}O_8Na$ (M+Na)$^+$ *m*/*z* 397.0899; found 397.0905.

4.1.14. 6-Hydroxy-2,3,9-trimethoxy-6*H*-chromeno[3,4-*b*]chromen-12-one (1). To a solution of 0.5 M H_2SO_4 in THF was added compound **15** (50 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 24 h. This mixture was diluted with H_2O, and then extracted with EtOAc (2×15 mL). The combined organic layer was concentrated, and the mixture was purified by flash chromatography on silica gel (elution with 95:5 $CHCl_3$/MeOH) to give compound **1** (44 mg, 93% yield) as a yellow solid, mp=211–212 °C; TLC, R_f 0.48 ($CHCl_3$/MeOH, 95:5); $[\alpha]_D^{20}$ 0 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$+$(CD_3)_2SO$) δ 8.48 (s, 1H), 8.03 (d, 1H, *J*=8.8 Hz), 6.87 (dd, 1H, *J*=8.8, 2.0 Hz), 6.77 (d, 1H, *J*=2.0 Hz), 6.53 (s, 1H), 6.04 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$+$(CD_3)_2SO$) δ 175.4, 164.0, 156.8, 155.1, 149.0, 143.8, 143.2, 127.2, 118.1, 114.7, 110.5, 109.5, 108.8, 101.2, 100.2, 88.9, 56.2, 55.8×2; IR (neat) 3286, 2913, 1626, 1591, 1513, 1447 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}O_7Na$ (M+Na)$^+$ *m*/*z* 379.0794; found 379.0795.

4.1.15. 3-(2-Benzyloxy-5-bromo-phenyl)-3-hydroxy-7-methoxy-4-oxo-chroman-2-carbaldehyde (17). White amorphous (150 mg, 75%), mp=190–192 °C; TLC, R_f 0.30 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ +10 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.77 (d, 1H, *J*=2.0 Hz), 7.70 (d, 1H, *J*=8.8 Hz), 7.48 (dd, 1H, *J*=8.4, 2.0 Hz), 7.19–7.11 (m, 5H), 6.88 (d, 1H, *J*=8.4 Hz), 6.66 (dd, 1H, *J*=8.8, 2.0 Hz), 6.52 (d, 1H, *J*=2.0 Hz), 5.33 (s, 1H), 4.98 (d, 1H, *J*=11.2 Hz), 4.90 (d, 1H, *J*=11.2 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 196.7, 187.0, 166.2, 161.1, 154.1, 136.1, 132.6, 131.1, 129.9, 129.8, 128.5×2, 128.1, 127.7×2, 115.2, 113.1, 112.1, 111.4, 101.2, 84.6, 75.8, 70.7, 56.4; IR (neat) 3674–3172, 2950, 1738, 1659, 1602–1446, 1256 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{19}O_6BrNa$ (M+Na)$^+$ *m*/*z* 505.0263; found 505.0257.

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26. Products **14** and **17** display optical activity, presumably as a function of employing L-proline for the aldol cyclization. We were unable to assign the absolute stereochemistry of the major enantiomer.
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