(d, 3, J_{vic} = 7 Hz, CH_3), 1.07 (d, 3, J_{vic} = 7 Hz, CH_3), 1.4-2.0 (m, 3, H-5, H-6), 2.2 (br s, 1, OH), 2.85 (m, 1, H-4), 3.3 (s, 2, H-8), 3.4-3.8 (m, 1, H-7), 4.55 (br s, OCH_2Ph), 5.71 (dd, 1, $J_{1(cis),2}$ = 5 Hz, $J_{1(trans),2}$ = 9 Hz, H-2), 6.32 (d, 1, $J_{1(cis),2}$ = 5 Hz, H-1), 6.38 (d, 1, $J_{1(trans),2}$ = 9 Hz, H-1), 7.35 (s, 5, phenyl); high-resolution mass spectrum *m/e* 155 ($C_9H_{15}O_2$), calcd *m/e* 155.1090, found *m/e* 155.1093.

(-)-α-Multistriatin (1). The enone **20** (119 mg, 0.43 mmol) was dissolved in absolute ethanol (20 mL), and a catalytic amount of 10% palladium on charcoal was added carefully to the solution. The reaction mixture was stirred under a hydrogen atmosphere. After 6 h a new compound with R_f 0.05 [ethyl acetate-petroleum ether (3:7)] had been formed. However, within 18 h this was replaced by a compound with R_f 0.70 which was identical with authentic multistriatin. The solution was filtered through Celite and reduced in volume to about 10 mL. This was poured into a separatory funnel, and ether was added. The ether was washed several times to remove the ethanol present, dried over sodium sulfate, and blown off. The residue was purified on preparative TLC to give 1 (53 mg, 77%).

GLC of the product (isothermal 100 °C) showed a peak at 1.3 min which coincided precisely with authentic α-multistrain when coinjected: $[\alpha]^{23}_D$ -19.0° (c 1.2, chloroform); R_f 0.70 [ethyl acetate-petroleum ether (bp 30-60 °C) (3:7)]; mass spectrum, *m/e* 170 (M^+), 140 ($C_9H_{16}O^+$), 128 ($C_7H_{12}O_2$), 96 ($C_7H_{12}^+$), 86 ($C_5H_{10}O^+$), 71 ($C_4H_7O^+$); NMR δ 0.81 (d, 6, $J_{2,11}$ = 7 Hz, $J_{4,12}$ = 7 Hz, H-11, H-12), 0.92 (t, 3, $J_{9,10}$ = 7 Hz, H-10), 1.4-2.2 (m, 6, H-2, H-3, H-4), 3.68 (m, 1, H-7), 3.82 (d, 1, H-8'), 4.14 (m, 1, H-1).

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Registry No. (-)-**1**, 59014-03-8; **3a**, 73657-02-0; **3b**, 68880-95-5; **3d**, 80516-19-4; **3e**, 73656-96-9; **4a**, 73679-59-1; **4b**, 73679-57-9; **5**, 73679-58-0; **6d**, 73657-05-3; **7a**, 66149-53-9; **7b**, 66149-54-0; **7c**, 80516-20-7; **7d**, 80516-21-8; **8a**, 80516-22-9; **8b**, 73656-99-2; **8c**, 80516-23-0; **8d**, 80516-24-1; **9**, 35303-94-7; **10**, 66149-56-2; **11**, 73656-98-1; **12**, 23339-15-3; **13a**, 80516-25-2; **13b**, 58871-17-3; **13c**, 39798-87-3; **17**, 80516-26-3; **18**, 80516-27-4; **19**, 80516-28-5; **20**, 73657-04-2.

New Syntheses of Coumarins

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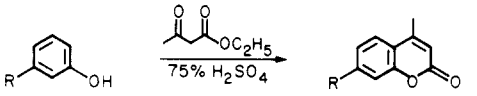
New, versatile coumarin syntheses have been developed which are based on the Claisen rearrangement of allylic or propargylic aryl ethers in which the allylic or propargylic α-carbon is further oxygenated. One proceeds by first ester exchange to the aryl dialkyl orthoacrylate which then thermally rearranges. Hydrolytic treatment gives the *o*-hydroxydihydrocinnamic acid from which the coumarin is obtained by ring closure and dehydrogenation. In parallel fashion, an orthopropiolate may be used, eliminating the dehydrogenation step. These processes have the advantage of avoiding the drastic acid conditions and orientation limitations of previous coumarin syntheses. They have been applied to syntheses in good yields of coumarins obtainable by previous methods in very poor yield or not at all.

The coumarin subunit is of interest because it is found in many natural products displaying diverse biological activities. The range of compounds includes antifungals,[1] anticoagulants,[2] compounds active against psoraris,[3] and carcinogens.[4] There have been many synthetic routes to the coumarins,[5,6] including the Perkin,[7] Knoevenagel,[8] Reformatsky,[9] and Pechmann[10] reactions. However, the Pechmann reaction has been the most widely applied method since it proceeds from simple and readily available educts. One can obtain in good yield coumarins substituted in either the pyrone or benzene ring or in both. The reaction, however, is dependent on the substituents on the phenol, on the condensing agent, and on the β-keto ester. For example, resorcinol (**1**) with 75% sulfuric acid and



1, R = OH
3, R = H

2, R = OH; 96%
4, R = H; 3%

ethyl acetoacetate gave 7-hydroxy-4-methylcoumarin (**2**) in 96% yield, while phenol (**3**) itself, when treated in an analogous fashion, afforded 4-methylcoumarin (**4**) in only 3% yield.[10] To avoid some of the adverse orienting effects and the harsh acid conditions of the Pechmann reaction, various other three-carbon moieties have been substituted for the β-keto ester component with some modest degree of success.[5,6]

With the objective of overcoming these deficiencies and difficulties, we have explored new routes to the coumarin ring system. The methods we have developed and now

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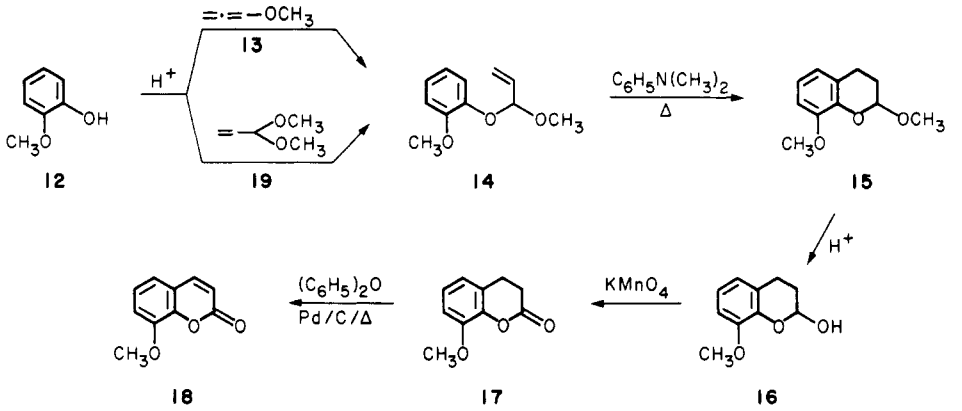
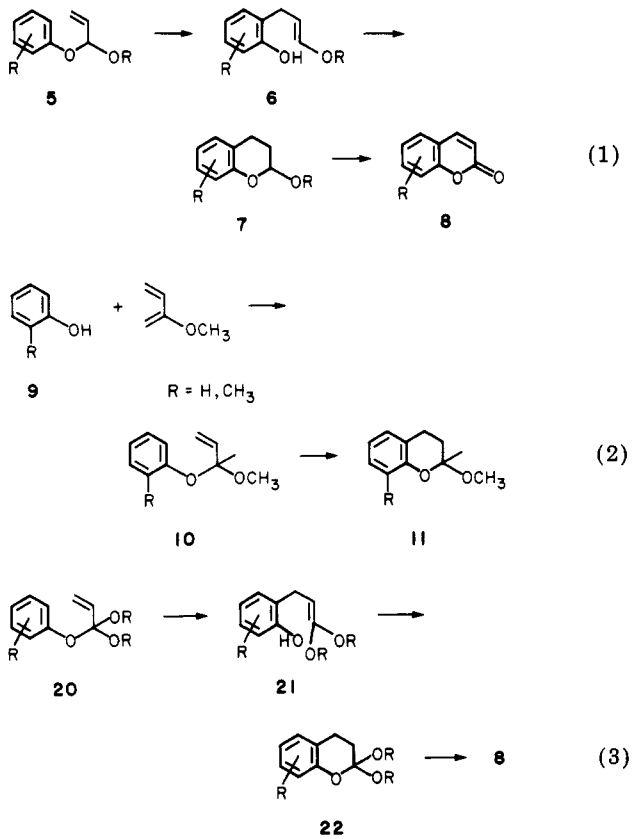
Scheme I. Preparation of 8-Methoxycoumarin (18) from Guaiacol (12) and Methoxyallene (13) or Acrolein Dimethyl Acetal (19)



report are based on a new application of the Claisen rearrangement using allyl or propargyl aryl ethers in which the allylic or propargylic α-carbon is further oxygenated. As a demonstration of our methods' utility, we have applied it to phenols (guaiacol, o-cresol, 2-methyl-4-chlorophenol, β-naphthol) which give essentially no coumarin in the Pechmann reaction.

Our first approach was based on rearrangement of the requisite α-oxygenated allyl aryl ether and is illustrated by sequence 1. The intermediate alkoxychroman 7 requires two oxidative transformations, introduction of carbon–carbon and carbon–oxygen double bonds, for conversion to the coumarin 8. Similar intermediates have been generated in frequently overlooked reports[11] of the preparation of 2-methoxychromans 11 (sequence 2). The presence of the 2-methyl group prevents the further elaboration of 11 to a pyrone; however, the α-methoxyallyl ether 10 is suggestive of the substrate we required.



Using guaiacol (12) as the first phenolic substrate, we pursued the formation of the α-methoxyallyl ether 14 by addition of methoxyallene (13)[12] as shown Scheme I. Since the acid-catalyzed addition of alcohols to methoxyallene (13) proceeds well to give good yields of the acrolein acetals,[13] we applied the same approach to the synthesis of the α-methoxyallyl aryl ether 14, a mixed methyl guaiacyl acetal of acrolein.

Conditions for the formation of ether 14 were thoroughly investigated. These included the effects of solvent (ether, methylene chloride), the concentration (0.5–20 mol %) and strength (acetic, chloroacetic, dichloroacetic, p-toluenesulfonic acids) of acid catalyst, temperature (0–40 °C), time (5 min–24 h), and concentration. In all cases, the final reaction mixture contained both phenol 12 and adduct 14, and polymeric material as well when higher acid concentrations were used. The best conditions we found led to a 1/1 mixture of 12/14 with no polymer, and the phenol could be easily recovered and recycled.

α-Methoxyallyl aryl ether 14 is quite unstable to traces of moisture and rapidly reverts to phenol 12 and polymeric material. This instability can be controlled by keeping 14 in solution and under nitrogen. It should be used in the next step without any further purification immediately following the alkaline wash to remove the phenol. This next step is the ring closure to chroman 15. It was effected by refluxing in dimethylaniline to induce Claisen rearrangement followed by intramolecular addition of the phenolic group to the ketene acetal of the intermediate.

Subsequent conversion of the 2-methoxychroman 15 to the coumarin 18 entailed a hydrolysis and two oxidations. Dilute aqueous acid gave the lactol 16, which was then oxidized to the dihydrocoumarin 17 with permanganate, the conversion of 15 to 17 being quantitative. Remaining was the second oxidation step, introduction of the carbon–carbon double bond. This was accomplished in 80% yield by catalytic dehydrogenation[14] in refluxing diphenyl ether. Thus 8-methoxycoumarin (18) was obtained from guaiacol (12) in 48% overall yield.

The only inconvenient step in this new coumarin synthesis is the instability of α-methoxyallyl aryl ether 14. We thought we might overcome this sensitivity by preparing 14 and rearranging it directly without further isolation or purification. Such a process has been applied in a related

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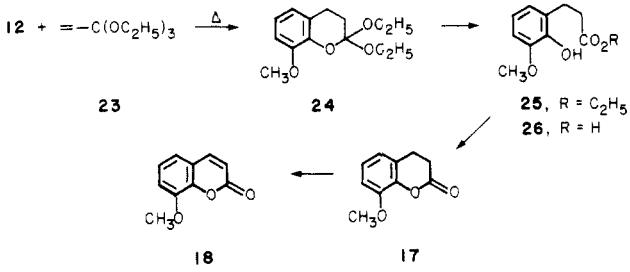
Scheme II. Preparation fo 8-Methoxycoumarin (18) from Guaiacol (12) and Triethyl Orthoacrylate (23)



case[15] where the first step was partial ketal exchange. For our purpose, we prepared acrolein dimethyl acetal (19) by addition of methanol to methoxyallene (13).[13] Acetal exchange did take place with guaiacol under acid catalysis to form allyl aryl ether 14, but the yield was only 20%, and it could not be induced to rearrange without going to the dimethylaniline conditions. Thus this approach was inferior to the previous method and was abandoned.

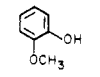
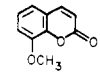
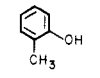
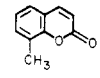
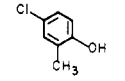
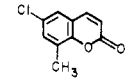
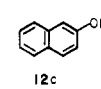
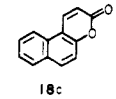
Our second approach was based on the rearrangement of the requisite α,α-dioxygenated allyl aryl ether and is illustrated by sequence 3. It would have the advantage of eliminating one of the oxidation steps, since the ultimate C-2 of the coumarin would be at the correct oxidation stage. To prepare the α,α-dialkoxyallyl vinyl ether 20, we considered exchange between an acrylic ortho ester and the phenol. A similar exchange has been reported[16] with a vinyl carbinol. Triethyl orthoacrylate (23) is the requisite three-carbon component, and it was readily prepared from triethyl orthopropionate.[17]

When triethyl orthoacrylate (23) and guaiacol (12) were mixed in refluxing toluene containing a catalytic amount of propionic acid, chromatography of the reaction mixture followed by spectral analysis indicated that exchange had occurred. Indeed, under the same conditions, reaction had proceeded through Claisen rearrangement and ring closure to the 2,2-diethoxychroman 24. However, 24 was found in only 50% yield. More acid catalyst (40–90 mol %) was added in an attempt to increase the conversion, but 50% was the maximum yield obtained. Presumably as exchange takes place the propionic acid catalyst is also consumed by esterification.

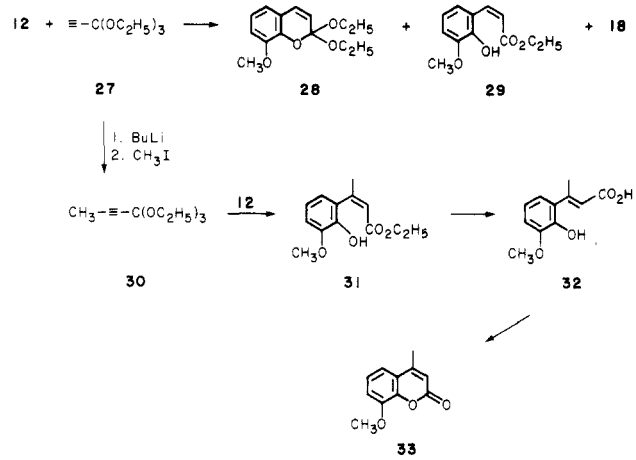
To mitigate this consumption of the acid catalyst, we turned to the more hindered pivalic acid. With this change, chroman 24 was formed directly in quantitative yield. The sequence then proceeded through hydrolysis, ring closure, and dehydrogenation to 8-methoxycoumarin (18) in 71% overall yield, as shown in Scheme II. Our first route via methoxyallene (13) had produced 18 in 48% overall yield, while under the Pechmann reaction conditions no 8-methoxycoumarin was formed.

We applied our new route to coumarins to three more phenols and triethyl orthoacrylate. The three phenols, in addition to guaiacol (12), were *o*-cresol (12a), 2-methyl-4-chlorophenol (12b), and β-naphthol (12c). These phenols were chosen because they give no, or very little, coumarin under Pechmann conditions.[10] In reaction with the orthoacrylate, and proceeding through the corresponding intermediates of Scheme II, coumarins were formed from each phenol in overall yields varying from 50 to 76% (Table I). The process was most conveniently effected

Table I. Preparation of Coumarins 18 from Phenols 12 and Triethyl Orthoacrylate (23)

phenol	coumarin	overall yield, %
 12	 18	71
 12a	 18a	76
 12b	 18b	50
 12c	 18c	62

Scheme III. Preparation of Coumarins from Phenols and Triethyl Orthopropiolates



by ring closure of the dihydrocinnamic acids and dehydrogenation of the dihydrocoumarins, without isolation, to the desired coumarins. Alternatively, the intermediate dihydrocoumarins could be isolated in good yield by heating the dihydrocinnamic acids in refluxing acetic anhydride for 2 h. Thus this new coumarin synthesis appears to be a general method applicable to a range of substitution patterns and groups.

One area for improvement still remained, and that was the dehydrogenation, the lowest yield step in the sequence. To avoid this dehydrogenation, it is necessary to bring in a three-carbon side chain at a higher oxidation state, that is, a propiolate instead of an acrylate. Such a substrate is available in triethyl orthopropiolate (27).[17] When 27 and guaiacol (12) were heated in refluxing toluene containing pivalic acid, three products were obtained in addition to recovered guaiacol. They were identified as 8-methoxy-2,2-diethoxychromene (28), ethyl 2-hydroxy-3-methoxycinnamate (29), and 8-methoxycoumarin (18). Increasing the reaction temperature to 160 °C (*p*-cymene) collapsed the reaction mixture to only coumarin 18 and cinnamate 29, which could be further converted to 18; the overall yield of coumarin 18 was 73%. Thus use of the propiolate simplified our method by eliminating the dehydrogenation step and increased the yield.

Another possibility offered by the orthopropiolate (Scheme III) was the ready extension of our method to the synthesis of some 4-substituted coumarins. This might be realized by substitution of the anion of 27 to form a new

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propiolate for incorporation into a coumarin. We applied this extension to one example, triethyl 2-butynoate (30), which was prepared by alkylating the 27 anion. Treating 30 and guaiacol (12) in refluxing *p*-cymene containing pivalic acid gave the cinnamate 31 in 75% yield. This was converted to 4-methyl-8-methoxycoumarin (33) via the cinnamic acid 32 in 49% overall yield. Although we have presented only one example of this extension to pyrone-ring-substituted coumarin, it appears that the method has considerable scope.

In summary, we have developed new, versatile, high-yield processes for the synthesis of coumarins. The methods proceed from readily available starting materials and afford coumarins which can be variously substituted in the benzene and pyrone nuclei.

Experimental Section

Melting points were determined in open capillaries by using a MelTemp Laboratory Devices apparatus and are uncorrected, IR spectra were recorded neat on a Perkin-Elmr 137 spectrophotometer, ^{1}H NMR (internal Me_4Si) spectra were taken in $CDCl_3$ on a Varian EM-390 instrument, ^{13}C NMR (internal Me_4Si) spectra were taken on a 270-MHz spectrometer, and UV spectra were taken in 95% EtOH on a Cary 118 instrument. Thin-layer chromatography (TLC) was done on E. Merck silica gel 60F-254 plates (0.2 mm), and preparative thin-layer chromatography (PTLC) was done on Analtech silica gel GF plates (2 mm). Unless otherwise specified, organic solutions were washed with brine and dried over Na_2SO_4 prior to evaporation on a Berkeley rotary evaporator. High-resolution mass spectra were obtained on a modified Kratos/AEI MS90Z mass spectrometer. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

1-Methoxy-2-[(1-methoxy-2-propenyl)oxy]benzene (14). To a solution of guaiacol (12; 711 mg, 5.7 mmol) in 20 mL of ether was added 206 mg (2.9 mmol) of methoxyallene (13),[12] the solution was stirred for 15 min at 0 °C, 0.5 mol % of *p*-toluenesulfonic acid (*p*-TSA) was added and the mixture was refluxed for 2 h. After the reaction mixture was cooled to room temperature, 20 mL of 5% aqueous NaOH was added, the ether fraction was separated and dried, and 2 mL of freshly distilled dimethylaniline was added. The ether was evaporated, leaving aryl allyl ether 14 dissolved in dimethylaniline: 50% yield; NMR (CCl_4) δ 6.5–6.9 (m, 4 H), 5.0–5.9 (m, 3 H), 3.65 (s, 3 H), 3.2 (s, 3 H).

2,8-Dimethoxychroman (15) and 2-Hydroxy-8-methoxychroman (16). The solution of 1-methoxy-2-[(1-methoxy-2-propenyl)oxy]benzene (14; 0.51 g, 2.8 mmol) in 2 mL of dimethylaniline prepared above was heated at reflux under N_2 for 6 h. Cooling, adding ether (10 mL), and extracting with cold 5% aqueous HCl (2 × 25 mL) left an organic layer which was washed with cold 5% aqueous NaOH (3 × 20 mL) and water (1 × 20 mL), dried, and evaporated. The two components 15 and 16 were present in a ratio of 4/1 in 60% overall yield and were separated by PTLC (hexane/Et_2O, 7/3). 15: NMR (CCl_4) δ 6.3–6.7 (m, 3 H), 4.9–5.1 (t, 1 H), 3.65 (s, 3 H), 3.3 (s, 3 H), 2.2–3.0 (m, 2 H) 1.6–2.1 (m, 2 H); mass spectrum, calcd for $C_{11}H_{14}O_3$, M^+, m/e 194.094 29, found 194.094 25. Lactol 16: NMR δ 6.4–6.75 (m, 3 H), 5.5–5.65 (t, 1 H), 3.7 (s, 3 H), 2.3–3.0 (m, 2 H), 1.75–2.1 (m, 2 H); mass spectrum, calcd for $C_{10}H_{12}O_3$, M^+, m/e 180.078 64, found 180.078 91.

Compound 15 can be converted to 16 in 100% yield by treatment with 5% aqueous HCl.

8-Methoxydihydrocoumarin (17). To 1.8 mL of H_2O and 0.2 mL of concentrated H_2SO_4 cooled to 15 °C was added 3.7 mg (.02 mmol) of 2-hydroxy-8-methoxychroman (16) in 1.0 mL of acetone followed by 2.3 mg (1.4 mmol) of $KMnO_4$. The reaction mixture was stirred at room temperature for 1 h, more $KMnO_4$ (2.3 mg, 0.14 mmol) was added, and the mixture was stirred for an additional 30 min. Sodium bisulfite was added until the solution became clear, and then it was extracted with ether (3 × 20 mL). The combined organic phase was washed with H_2O and evaporated to afford 100% yield of 8-methoxydihydrocoumarin (17). This was used directly in the dehydrogenation step to give coumarin 18 as described below by using 10% Pd/C in refluxing diphenyl ether: NMR δ 6.7–7.1 (m, 3 H), 3.9 (s, 3 H), 2.6–3.2 (m, 4 H); mass spectrum, m/e 178 (M^+).

Formation of Coumarins 18 from Phenols 12 and Triethyl Orthoacrylate (23). General Procedures. (A) 2,2-Diethoxychromans 24. A solution of 12 mmol of the phenol 12, 4.17 g (24 mmol) of triethyl orthoacrylate (23),[17] and 0.613 g (6 mmol) of pivalic acid in 15 mL of toluene was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, 25 mL of ether was added, and the organic phase was washed with cold 5% aqueous NaOH (3 × 30 mL), H_2O (1 × 30 mL), and brine (1 × 30 mL) and dried. Evaporation afforded crude product.

2,2-Diethoxy-8-methoxychroman (24): 100% yield; mp 82–83 °C (from hexane); IR 3010, 2990, 1600, 1490, 1060, 740 cm^{-1}, NMR (CCl_4) δ 6.3–6.7 (m, 3 H), 3.3–3.7 (m, 7 H), 2.55–2.8 (t, 2 H), 1.8–2.0 (t, 2 H), 1.0–1.3 (t, 6 H). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0; Found: C, 66.4; H, 7.9.

2,2-Diethoxy-8-methylchroman (24a): isolated by PTLC (hexane/Et_2O, 4/1) in 100% yield; NMR δ 6.4–6.9 (m, 3 H), 3.95 (q, 2 H), 2.65 (t, 2 H), 2.15 (s, 3 H), 1.95 (t, 2 H), 1.10 (t, 3 H); mass spectrum, calcd for $C_{14}H_{20}O_3$, M^+, m/e 236.141 24, found 236.141 04.

2,2-Diethoxy-6-chloro-8-methylchroman (24b): isolated by PTLC (hexane/Et_2O, 4/1) in 80% yield; NMR δ 6.7 (d, 2 H), 3.5–3.85 (m, 4H), 2.65 (t, 2 H), 2.10 (s, 3 H), 1.85 (t, 2 H), 1.1 (t, 6 H).

2,2-Diethoxy-5,6-benzochroman (24c): obtained in 94% yield by PTLC (hexane/Et_2O, 7/3); NMR δ 6.9–7.7 (m, 6 H), 3.6 (q, 4 H), 3.0 (t, 2 H), 2.15 (t, 2 H), 1.1 (t, 2 H); mass spectrum, calcd for $C_{17}H_{20}O_3$, M^+, m/e 272.141 24, found 272.141 25.

(B) Ethyl 2-Hydroxydihydrocinnamates 25 and 2-Hydroxydihydrocinnamic Acids 26. To 0.4 mmol of the 2,2-diethoxychroman 24 dissolved in 10 mL of ether was added 10 mL of 10% aqueous HCl. Stirring for 2 h at room temperature was followed by extraction with ether (3 × 10 mL), and the organic phase was washed with H_2O (1 × 10 mL) and evaporated to afford a quantitative yield of the esters 25 as clear liquids. In those cases where acids were isolated, this was done by heating at reflux for 2 h 0.9 mmol of the esters 25 in 5 mL of ethanol containing 75 mg of KOH. The solution was then cooled to room temperature, acidified with 10% aqueous HCl, and extracted with ether (3 × 50 mL). The combined organic extracts were washed, dried, and evaporated to leave the crude acid 26.

Ethyl 2-hydroxy-3-methoxydihydrocinnamate (25): IR 3450, 2920, 1720, 1620, 1270, 1070 cm^{-1}; NMR δ 6.65 (s, 3 H), 5.4 (br s, 1 H), 4.0 (q, 2 H), 3.75 (s, 3 H), 2.85 (t, 2 H), 2.5 (t, 2 H), 1.15 (t, 3 H).

2-Hydroxy-3-methoxydihydrocinnamic acid (26): 89% yield; mp 108–109 °C (from ethyl acetate); IR 3445, 1700, 1650, 1470, 1080, 795 cm^{-1}; NMR δ 6.65 (s, 3 H), 3.75 (s, 3 H), 2.8 (m, 2 H), 2.55 (m, 2 H). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2. Found: C, 61.3; H, 6.1.

Ethyl 2-hydroxy-3-methyldihydrocinnamate (25a): 99% yield; NMR δ 6.4–6.9 (m, 3 H), 3.95 (q, 2 H), 2.65 (m, 4 H), 2.15 (s, 3 H), 1.1 (t, 3 H).

2-Hydroxy-3-methyldihydrocinnamic Acid (26a): 92% yield; IR 3480, 1650, 1460, 1275, 850, 745 cm^{-1}; NMR δ 6.5–6.9 (m, 3 H), 2.45–2.85 (m, 4 H), 2.15 (s, 3 H).

Ethyl 2-hydroxy-3-methyl-5-chlorodihydrocinnamate (25b): IR 3400, 2980, 1705, 1475, 1380, 1190, 870 cm^{-1}; NMR δ 6.7 (d, 2 H), 3.95 (q, 2 H), 2.45–2.85 (m, 4 H), 2.2 (s, 3 H), 1.1 (t, 3 H); mass spectrum, calcd for $C_{12}H_{15}O_3Cl$, M^+, m/e 242.070 97, 244.068 02, found 242.070 91, 244.067 91.

2-Hydroxy-6-chloro-8-methyldihydrocinnamic acid (26b): 87% yield; NMR δ 6.7 (s, 2 H), 2.55 (m, 4 H), 2.1 (s, 3 H).

Ethyl 2-hydroxy-1-naphthalenepropionate (25c): IR 3350, 3000, 1710, 1620, 1080, 820 cm^{-1}; NMR δ 6.9–7.7 (m, 6 H), 3.9 (q, 2 H), 2.9–3.25 (m, 2 H), 2.5–2.8 (m, 2 H), 1.1 (t, 3 H).

2-Hydroxy-1-naphthalenepropionic acid (26c): 85% yield; NMR δ 6.9–7.8 (m, 6 H), 3.15 (t, 2 H), 2.75 (t, 2 H).

(C) Dihydrocoumarins 17 and Coumarins 18. The crude dihydrocinnamic acids 26 were heated in refluxing acetic anhydride (freshly distilled) for 2 h under N_2. The cooled reaction mixture was poured into 50 mL of water, the aqueous phase was extracted with ether (3 × 50 mL), and the combined organic phase was washed with 10% aqueous Na_2CO_3 (3 × 50 mL), dried, and evaporated to give the dihydrocoumarins 17. The dehydrogenation

was effected by heating 1.6 mmol of the dihydrocinnamic acids **26** or dihydrocoumarins **17** with 22 mg of 10% Pd/C in 4 mL of refluxing diphenyl ether for 20 h. The mixture was then cooled and filtered, and the residue was bulb to bulb distilled.

8-Methoxycoumarin (18): 80% yield from 26; mp 86–87 °C (lit.[18] mp 89 °C); UV λ_{max} 220 nm (sh, ϵ 7180), 250 (4960), 288 (6800), 350 (sh, 820); IR 3300, 1720, 1640, 1075 cm^{-1}; NMR δ 7.55 (d, 1 H, J = 9 Hz), 6.9 (s, 3 H), 6.25 (d, 1 H, J = 9 Hz), 3.85 (s, 3 H). Anal. Calcd for $C_{10}H_8O_3$: C, 68.2; H, 4.6. Found: C, 68.1; H, 4.7.

8-Methylcoumarin (18a): 83% yield from **26a**; mp 106–107 °C (lit.[19] mp 109–110 °C); UV λ_{max} 220 nm (ϵ 1040), 250 (248), 286 (640), 350 (sh, 160); IR 3440, 1670 cm^{-1}; NMR δ 7.55 (d, 1 H, J = 9 Hz), 6.9–7.3 (m, 3 H), 6.25 (d, 1 H, J = 9 Hz), 2.35 (s, 3 H). Anal. Calcd for $C_{10}H_8O_2$: C, 75.0; H, 5.04. Found: C, 75.2; H, 5.1.

6-Chloro-8-methylcoumarin (18b): 73% yield from **26b**; UV λ_{max} 222 nm (ϵ 4450), 275 (1950), 286 (sh, 1430), 325 (644); IR 3550, 1740, 1650, 875 cm^{-1}; NMR δ 7.35 (d, 1 H, J = 9 Hz), 7.0–7.15 (m, 2 H), 6.2 (d, 1 H, J = 9 Hz), 2.25 (s, 3 H); mass spectrum, calcd for $C_{10}H_7O_2Cl$, M^+, m/e 194.0134, 196.0105, found 194.0115, 196.0092.

5,6-Benzocoumarin (18c): 79% yield from **26c**; mp 116–117 °C (lit.[20] mp 118 °C); UV λ_{max} 231 nm (ϵ 5880), 304 (sh, 3410), 316 (4592), 346 (4850), 363 (sh 3300); IR 3500, 1740, 1640, 1560, 825 cm^{-1}; NMR δ 8.3 (d, 1 H, J = 9 Hz), 7.2–8.1 (m, 6 H), 6.4 (d, 1 H, J = 9 Hz); mass spectrum, calcd for $C_{13}H_8O_2$, M^+, m/e 196.052 43, found 196.052 62.

Ethyl 2-Hydroxy-3-methoxycinnamate (29). A solution of 0.25 g (2 mmol) of guaiacol (**12**), 0.69 g (4 mmol) of triethyl orthopropiolate (**27**),[17] and 0.15 g (1.5 mmol) of pivalic acid in 5 mL of *p*-cymene was heated at reflux for 24 h under N_2. The reaction mixture was cooled to room temperature, 20 mL of ether was added, and the organic phase was separated, washed with cold 5% aqueous NaOH (3 × 20 mL), H_2O (1 × 20 mL) and brine (1 × 20 mL), dried, and evaporated. Thin-layer chromatography (hexane/Et_2O, 7/3) showed the appearance of two products, the major spot being the desired cinnamate **29** and the minor component being 8-methoxycoumarin (**18**) by comparison with authentic material. Preparative thin-layer chromatography (hexane/Et_2O, 7/3) separated the two products and afforded cinnamate **29** in 81% yield: IR 3000, 1710, 1640, 1500, 1130 cm^{-1}; NMR δ 7.5 (d, 1 H, J = 10 Hz), 6.7–7.1 (m, 3 H), 5.25 (d, 1 H, J = 10 Hz), 4.0 (q, 2 H), 3.7 (s, 3 H), 1.15 (t, 3 H).

8-Methoxycoumarin (18) from Ethyl 2-Hydroxy-3-methoxycinnamate (29). To ester **29** (50 mg, 0.22 mmol) dissolved in 3 mL of 95% EtOH was added 35 mg (0.6 mmol) of KOH, and the solution was heated at reflux for 2 h. The mixture was cooled to room temperature, acidified with 10% aqueous HCl, and extracted with ether (3 × 20 mL). The combined ether extracts were washed with H_2O (1 × 20 mL) and brine (1 × 20 mL), dried, and evaporated to afford 28 mg (73%) of **18**, identical with previously prepared material.

Triethyl Orthobut-2-ynoate (30). To a solution of 1.0 g (5.8 mmol) of triethyl orthopropiolate (**27**)[17] in 10 mL of THF at −70 °C under N_2 was added dropwise 3.9 mL (6.3 mmol) of 1.6 M *n*-butyllithium in hexane, keeping the reaction temperature between −60 and −70 °C throughout the addition. The mixture was brought to 0 °C slowly and then returned to −70 °C. A solution of 0.89 g (6.3 mol) of methyl iodide in 7 mL of THF was added dropwise, the solution was stirred at −70 °C for 30 min, and then it was brought to room temperature over 2 h. After addition of 1.0 mL of methanol, the solution was poured into 22 mL of CH_2Cl_2 and 50 mL of 10% aqueous NaOH, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phase was washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), dried, and evaporated to afford 1.10 g (100% yield) of a pale yellow oil: bp 110–112 °C (18 mm); NMR δ 3.5 (q, 6 H), 1.8 (s, 3 H), 1.15 (t, 9 H).

Ethyl 2-Hydroxy-3-methoxy-β-methylcinnamate (31). A solution of 0.5 g (4 mmol) of guaiacol (**12**), 1.29 g (8 mmol) of triethyl ortho-2-butynoate (**30**) and 0.2 g (1.9 mmol) of pivalic acid in 7 mL of *p*-cymene was heated at reflux for 48 h under N_2. The solution was cooled to room temperature, 25 mL of ether was added, and the organic phase was washed with cold 5% aqueous NaOH (3 30 mL), H_2O (1 × 30 mL), and brine (1 × 30 mL) and dried. Evaporation and PTLC of the residue (hexane/Et_2O, 4/1) afforded 0.71 g (75% yield) of a clear oil: UV λ_{max} 220 nm (ϵ 9710), 235 (8270), 275 (sh, 1706), 278 (sh, 1310); IR 3020, 1730, 1640, 1495, 1160 cm^{-1}; ^1H NMR δ 7.15–7.2 (m, 1 H), 6.85–7.0 (m, 3 H), 4.8 (s, 1 H), 4.1 (q, 2 H), 3.8 (s, 3 H), 2.5 (s, 3 H), 1.2 (t, 3 H); ^{13}C NMR δ 172.2, 167.7, 151.2, 141.7, 139.86, 137.1, 128.8, 126.6, 122.95, 121.06, 112.80, 94.86, 59.38, 55.76, 18.13, 14.27; mass spectrum, calcd for $C_{13}H_{16}O_4$, M^+, m/e 236.104 86, found 236.104 62.

2-Hydroxy-3-methoxy-β-methylcinnamic Acid (32). To ethyl 2-hydroxy-3-methoxy-β-methylcinnamate (**31**; 100 mg, 0.4 mmol) dissolved in 3 mL of 95% EtOH was added KOH (100 mg, 1.7 mmol). The solution was heated at reflux for 3 h, cooled to room temperature, acidified with 10% aqueous HCl, and extracted with ether (3 × 20 mL). The combined organic phase was washed with H_2O (1 × 20 mL) and brine (1 × 20 mL), dried, and evaporated, leaving 67 mg (80% yield) of **32**: mp 138–139 °C; UV λ_{max} 210 nm (ϵ 12 500), 214 (sh, 10 100), 250 (sh, 2290), 257 (sh, 1875); IR 3500, 3000, 1690, 1620, 1500, 1260, 1025, 810, 750 cm^{-1}; NMR δ 6.95–7.1 (m, 1 H), 6.85–6.9 (m, 3 H), 4.7 (s, 1 H), 3.7 (s, 3 H), 2.4 (s, 3 H); mass spectrum, calcd for $C_{11}H_{12}O_4$, M^+, m/e 208.073 56, found 208.073 40.

8-Methoxy-4-methylcoumarin (33). A mixture of 2-hydroxy-3-methoxy-β-methylcinnamic acid (**32**; 89 mg, 0.4 mmol) and iodine (28 mg, 0.1 mmol) in 5 mL of freshly distilled acetic anhydride was heated at reflux for 2 h and then poured into 50 mL of warm water. The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic phase was washed with 10% aqueous Na_2CO_3 (2 × 50 mL), dried, and evaporated. PTLC (Et_2O) of the residue afforded 39 mg (51% yield) of coumarin **33**: mp 120–121 °C;[21] UV λ_{max} 230 nm (24 680), 251 (10 580), 307 (4780); IR 1695, 1600, 1510 cm^{-1}; NMR δ 7.0–7.2 (m, 3 H), 6.2 (s, 1 H), 3.95 (s, 3 H), 2.45 (s, 3 H); mass spectrum, calcd for $C_{11}H_{10}O_3$, M^+ m/e 190.062 99, found 190.063 81.

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Registry No. 12, 90-05-1; **12a**, 95-48-7; **12b**, 1570-64-5; **12c**, 135-19-3; **13**, 13169-00-1; **14**, 80515-72-6; **15**, 80515-73-7; **16**, 80515-74-8; **17**, 80515-75-9; **18**, 2445-81-0; **18a**, 1807-36-9; **18b**, 80515-76-0; **18c**, 4352-89-0; **19**, 6044-68-4; **23**, 42216-96-6; **24**, 80515-77-1; **24a**, 80515-78-2; **24b**, 80515-79-3; **24c**, 80515-80-6; **25**, 80515-81-7; **25a**, 80515-82-8; **25b**, 80515-83-9; **25c**, 80515-84-0; **26**, 21144-24-1; **26a**, 80515-85-1; **26b**, 80515-86-2; **26c**, 10441-53-9; **27**, 42217-00-5; **28**, 80515-87-3; **29**, 80515-88-4; **30**, 919-27-7; **31**, 80532-12-3; **32**, 80515-89-5; **33**, 1769-77-3.

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(21) This compound has been reported (Bevan, C. W. L.; Ekong, D. E. U. *Chem. Ind. (London)* **1965**, 383) as a natural product (mp 165 °C) identical with a synthetic sample. Subsequently (Okogun, J. I.; Enyenihi, V. U.; Ekong, D. E. U. *Tetrahedron* **1978**, *34*, 1221), from the same synthetic process, it was reported as melting at 139–141 °C. The latter is the melting point (138–139 °C) we find for 2-hydroxy-3-methoxy-β-methylcinnamic acid (**32**).