An Efficient Synthesis of Neoflavonoid Antioxidants Based on Montmorillonite K-10 Catalysis

Jian-Ming Lee,[a] Tsui-Hwa Tseng,[b] Yean-Jang Lee*[a]

[a] Department of Chemistry, National Changhua University of Education, Changhua, Taiwan, Republic of China
Fax +886(4)7211190; E-mail: leeyj@cc.ncue.edu.tw

[b] Institute of Biochemistry, Chung Shan Medical and Dental College, Taiwan, Republic of China

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Abstract: A new approach to synthesis of neoflavonoids, based on a high yielding Montmorillonite K-10 catalyzed lactone ring forming cyclization process, is described. The utility of this methodology is exemplified by its employment in the preparation of the substituted 4-phenylneoflavonoids **1**–**8**. The free radical scavenging properties of these substances were evaluated. The neoflavonoids **1** and **5**, which mimic esculetin-type antioxidants, were observed to quench hydrazyl free radicals.

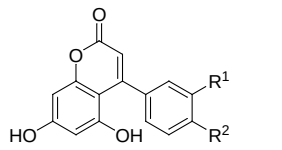
Key words: montmorillonite K-10, 4-phenylneoflavonoids, Fries rearrangement

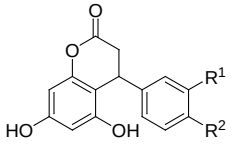
As part of a recent search[1] to prepare new biologically active substances, we were attracted to the coumarin family whose members are widely distributed in biologically important natural products and pharmaceutical agents.[2] Coumarins exist in free or glycoside-conjugated forms in a wide variety of plants.[3] Indirect analgesic effects (abolition of oedema and inflammation) of coumarin in rabbit have been observed.[4] Coumarin and 7-hydroxycoumarin also inhibit the biosynthesis of prostaglandins and leucotrienes to about the same degree as acetylsalicylic acid.[5] Moreover, this substance has anti-oedematous, lymphokinetic and haemorheological properties.[6] Naturally occurring neoflavonoid glycosides are known to serve as inhibitors of energy transfer in spinach chloroplasts.[7] Inspite of these effects, Zobel and Brown[8] have concluded that the biologcal roles of coumarins are not well understood.

In our previous studies, we have demonstrated that esculetin (6,7-dihydroxycoumarin) possesses potent antioxidant and antitumor promotion properties.[9] The data indicate that this compound induces apoptosis in human leukemia cells by increasing cytosolic translocation of cytochrome c and activating the cysteine protease 32 kDa proenzyme (CPP32). 4-Phenylcoumarins are also of synthetic interest owing to the fact that this ring system is present in a number of naturally occurring compounds, such as serratin,[10a] dalbergin,[10b–10d] calophyllolide,[10e] calomelanols B and C[11] and vismiaguianones D and E.[3d]

As a consequence of the biological and structural interest in these substances, we initiated a study aimed at developing a general and high yielding method to prepare coumarins. The commercial availability of cinnamic acids and phloroglucinol prompted us to probe a route to the neoflavonoids, which is based on an esterification-cyclization sequence. It is known that regioselective esterification of the α,β-unsaturated carboxylic acids with polyphenols often is problematic due to competition between cyclization by Friedel–Crafts acylation and Fries rearrangement of the initially formed ester intermediate.[12] Although the synthesis of some coumarins has been successfully approached by using this strategy,[13] harsh condition and high substrate concentrations are commonly required. In addition, Shamsuddin has reported a one-pot procedure for the synthesis of 4-phenylcoumarins.[14] However, the scope of this process appears to be limited. For instance, by following Shamsuddin's procedure, we were unable to efficiently prepare 5,7-dihydroxy-4-phenylcoumarin from phloroglucinol and the appropriate cinnamate.

To overcome the difficulties associated with this approach to coumarin synthesis, we explored the use of Montmorillonite K-10 to catalyze the esterification-cyclization reactions of phloroglucinol and cinnamates.[15] Applications of clays to catalyze organic reactions have increased in number in recent years.[16] One clay, K-10, has been employed as an effective catalyst in several organic transformations,[17] including the per-O-acetylation of sugars,[16a] dehydrative cyclization of *o*-hydroxydibenzoylmethanes,[16b] and intramolecular Ferrier reactions.[18] In addition, Hoz et al.[19] reported the synthesis of coumarin derivatives using Montmorillonite KSF and cation-exchange resins in conjunction with microwave irradiation, however, the choosing of appropriate catalysts and microwave irradiation were required. In the current study, we demonstrate that Montmorillonite K-10 serves as an ideal catalyst for the esterification-cyclization sequence, affording neoflavonoids in high yields.





1 $R^1=R^2$=OH **3** R^1=H,R^2=OH **5** $R^1=R^2$=OH **7** R^1=H,R^2=OH
2 $R^1=R^2$=OMe **4** R^1=H,R^2=OMe **6** $R^1=R^2$=OMe **8** R^1=H,R^2=OMe

Figure 1

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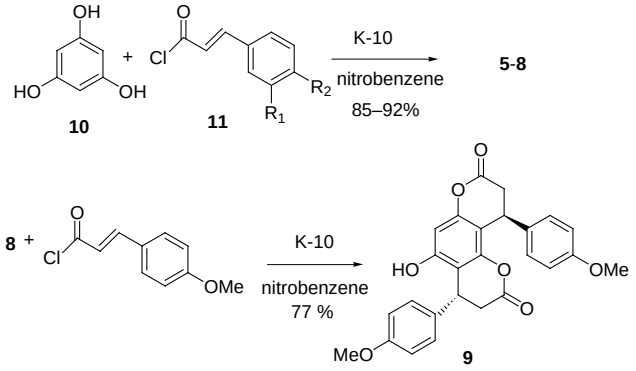
In the current effort, we probed a new method to construct the 4-phenylchroman-2-one ring system by use of an esterification-cyclization methodology. Accordingly, reaction of appropriate cinnamoyl chlorides with phloroglucinol in nitrobenzene containing K-10 clay at 25 °C for 12 h gives the phenylchromanones **5**–**8** in high yields (Scheme 1). ^{1}H and ^{13}C NMR spectroscopic analysis of these substances showed that they contained the desired lactone ring system but the data were not sufficient to enable unambiguous assignments of the structures. Thus, **8** was subjected to X-ray crystallographic analysis,[20] which provided the structure.

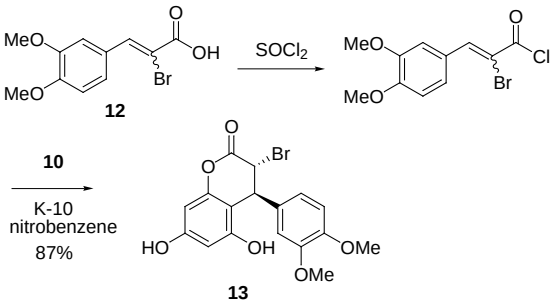


Scheme 1

It is worth noting that reaction of 1.5 equivalents of 4-methoxycinnamoyl chloride with phloroglucinol under the conditions presented above and a reaction time of 3 d instead of 12 h led to isolation of the chromanone **8** (65%) along with the 2:1-adduct **9** (14%). The trans-4,4'-stereochemistry of **9** was assigned by use of X-ray crystallographic methods.[20] The origin of the 2:1-adduct is revealed by the observation that K-10 clay catalyzed reaction of chromanone **8** with 4-methoxycinnamoyl yields **9** in a 77% yield.

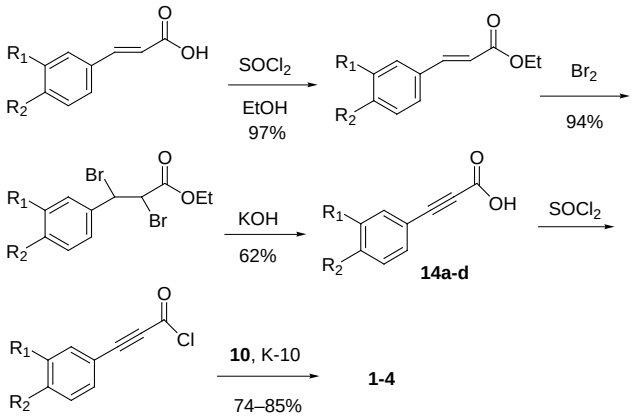
We next attempted to transform the chromanones, formed in this way, to the corresponding coumarins **1**–**4**. 4-Phenylchroman-2-ones **5**–**8** were each treated with DDQ or I_2/pyridine, to introduce unsaturation into the lactone ring system. However, coumarins (**1**–**4**) were not formed under these conditions.

Since oxidative dehydrogenation of the chroman-2-ones was not successful, other approaches to synthesize coumarin **1**–**4** were investigated. First, we subjected the known[21] bromocinnamic acid **12** to K-10 catalyzed reaction with phloroglucinol to produce the corresponding bromo-chromanone as the *cis*-diastereomer **13** in an 87% yield (Scheme 2). The structure of **13** was assigned based on its ^{1}H, ^{13}C NMR and mass spectroscopic properties. Characteristic in this regard are the ^{1}H NMR chemical shifts of the bromomethine and benzylic protons of **13** at 4.73 and 4.88 ppm (J = 2.2 Hz). In addition, the bromomethine and benzylic carbons are deshielded by the inductive effect of bromine and occur in the ^{13}C NMR spectrum of **13** at 42 and 44 ppm as compared to the resonances of the corresponding carbons of **6**, which occur at 30 and 34 ppm. The *trans*-3,4-stereochemistry of **13** was assigned by use of X-ray crystallographic methods.[20] With **13** in hand, we attempted to promote dehydrobromination by using KOH, pyridine, or LHMDS. However, these reactions did not produce the desired coumarin.



Scheme 2

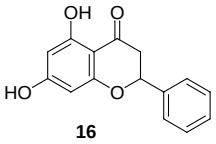
An alternate strategy for coumarin synthesis, involving esterification-cyclization of aryl-propiolic acid chlorides, proved to be successful. Accordingly, K-10 catalyzed reaction of the propioloyl chlorides obtained from propargyl acids **14a**–**d** (prepared by the route shown in Scheme 3)[22] with phloroglucinol gives the corresponding coumarins **1**–**4** in high yields. An advantageous feature of this method is that the esterification-cyclization reaction is performed under relatively moderate conditions and provides the desired coumarin exclusively.



Scheme 3

To investigate the scope of the selective K-10 catalyzed esterification-cyclization process, we investigated reactions of various starting materials, including simple phenols, resorcinols and several cinnamoyl chlorides. The results are summarized in Table 1. Chromanones, bearing substituents in the 3,4-positions (entries 1 and 2), are prepared by use of this method in high yields. Both resorcinol (entry 5) and phenol (entry 6) are reactive partners in this process, although higher reaction temperatures are required to drive these reactions to completion. Unsubstituted cinnamic acid chlorides also react under these conditions to afford the desired products (entries 3 and 7).

However, the esterification-cyclization of phenol and cinnamoyl chloride, catalyzed by K-10, requires high temperature and leads to only the regioisomeric product **16** in 57% yield (entry 4).



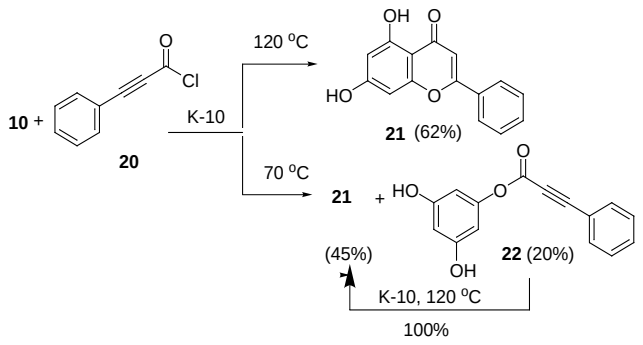
16

Figure 2

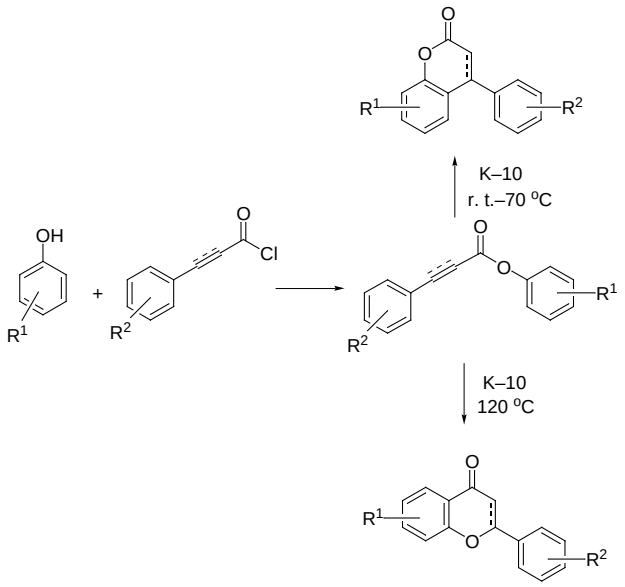
Interesting results have come from an investigation with phenylpropioloyl chloride **20**. K-10 catalyzed reaction of **20** with phloroglucinol, carried out at 120 °C, yields the product **21**, resulting from Fries rearrangement of the intermediate ester, in 62% yield (Scheme 4). When this reaction is conducted at lower temperature, the intermediate ester **22**, along with flavone **21** are formed in respective yields of 20% and 45%. In addition, we observed that **22** undergoes quantitative, K-10 catalyzed conversion to the Fries rearrangement product **21**. On the basis of these observations, we propose that the mechanistic route for formation of **21** at high temperature involves (1) esterification of the phenol by the acid chloride (2) *ortho*-Fries rearrangement of the intermediate ester **22**, and (3) cyclization by Micheal addition of the *ortho*-hydroxyl group to the unsaturated ketone. On the other hand, coumarin formation dominates in reactions conducted at low temperatures. This is a consequence of preferential Friedel–Crafts cyclization of the initially formed ester (Scheme 5).

To evaluate the capability of the synthetic neoflavonoids as free radical inhibitors, we employed the 1,1-diphenyl-2-picrylhydrazyl (DPPH).[9] This test judges free radical-quenching by the ability to bleach the stable free radical DPPH. The results (Table 2) show that **1** and **5** at 0.1 mM bleach 92% and 95% of DPPH, respectively and therefore these substances are potent radical inhibitors. These observations suggest that **1** and **5** might exhibit in vitro antioxidant bioactivity to the same extent as esculetin.

We have developed a practical and high yielding method to synthesize neoflavonoids starting with commercially available cinnamic acids by using a K-10 catalyzed ester-



Scheme 4



Scheme 5

ification-cyclization process. We also have shown that products resulting from Fries rearrangement of initially formed esters becomes dominant in reactions conducted at high temperatures. The mechanistic issues uncovered in this effort as well as the scope and generality of this new synthetic method will be probed in detail in our continuing studies in this area. Finally, the DPPH test demonstrates that **1** and **5** are effective free radical quenchers. Further biological assays are currently underway to evaluate the efficacy of these compounds as chemotherapeutic agents against HIV integrase or tumors.

Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker-200 spectrometer. Chemical shifts are reported in parts per million (δ, ppm) using $CHCl_3$ (δ_H 7.26) as an internal standard. HPLC analyses were performed using a Waters system with UV detector, on Nava-Pak® C_{18} column. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a JEOL JMS-HX 110 mass spectrometer from National Tsing-Hua University, Hsinchu. X-ray single crystal analyses were performed on a R3m/V diffractometer in the Hsinchu Instrumentation Center, National Science Council. Solvents were freshly distilled prior to use from phosphorus pentoxide or CaH_2. THF was from sodium diphenyl ketyl. All reactions were carried out under N_2 atmosphere unless otherwise stated. Silica gel (silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous $MgSO_4$.

5,7-Dihydroxy-4-(3,4-dihydroxyphenyl)-chromen-2-one (1)
A mixture of propargyl acid **14a** (0.9 g, 2.8 mmol) and $SOCl_2$ (0.3 mL, 1.6 equiv) in dioxane (20 mL, anhyd) was heated to reflux for 2 h and followed by removal of the solvent in vacuo. To the residue was added phloroglucinol (0.5 g, 3.2 mmol), K-10 (1.0 g) in nitrobenzene (15 mL, anhyd) at r.t. and the solution was stirred for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica, EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to obtain the crude product, which was recrystallized from CH_2Cl_2–hexane to afford **1** (0.6 g, 76%) as a pale yellow solid; mp 214–216 °C (lit.[23] mp 217–220 °C).

Table 1 Synthesis of Neoflavonoids via Esterification-Cyclization with K-10 Catalysis

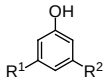
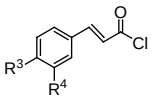
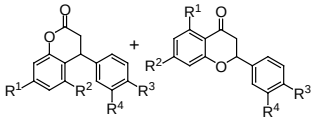
Entry	Phenol		Acyl Chloride		Solvent	Temp. (°C)	Product(s)	Isolated Yield (%)
								
	R^1	R^2	R^3	R^4				
1	OH	OH	OH	OH	nitrobenzene	r.t.	**5**	90
2	OH	OH	OH	OH	dioxane	r.t.	**5**	88
3	OH	OH	H	H	nitrobenzene	70	**15**	80
4	OH	OH	H	H	nitrobenzene	120	**16**	57
5	OH	H	OH	OH	dioxane–nitrobenzene	45	**17**	82
6	H	H	OMe	OMe	nitrobenzene	45	**18**	75
7	H	H	H	H	nitrobenzene	70	**19**	45

Table 2 Quenching Effect of 4-Phenylcoumarins on 1,1-Diphenyl-2-picrylhydrazyl (DPPH) Test

Treatment[a]	% of DPPH Bleaching[b]		EC_{50} (mM)
	0.01 mM	0.1 mM	
Esculetin	71.04 ± 1.08	86.19 ± 0.46	0.040
1	65.08 ± 0.91	91.82 ± 0.68	0.038
2	1.94 ± 0.23	24.18 ± 2.16	0.764
4	8.18 ± 0.90	18.95 ± 0.73	0.781
5	84.67 ± 2.77	95.22 ± 0.14	0.030
6	8.18 ± 0.43	14.84 ± 1.21	0.982
7	1.82 ± 0.33	14.81 ± 0.43	0.985
8	2.28 ± 0.63	11.95 ± 0.45	1.257

[a] The reaction mixture contained, in 3 mL of MeOH, 10 mM DPPH and 30 μL of 4-phenylcoumarins in DMSO. After 30 min at r.t., 1 mL of redistilled water and 3 mL of toluene were added and samples were mixed and centrifuged. The absorbance of the upper phase was read at 517 nm against a blank without drugs.
[b] Percentages of DPPH bleaching=[(absorbance of DMSO–absorbance of test)/ absorbance of DMSO]×100%; Data represent the mean ± SD from three independent experiments.

^{1}H NMR [$(CD_3)_2CO$]: δ = 5.98 (s, 1 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.98 (d, *J* = 9.5 Hz, 1 H), 7.09 (d, *J* = 9.5 Hz, 1 H), 7.11 (s, 1 H), 8.25 (s, OH, 1 H), 8.35 (s, OH, 1 H), 8.80 (s, OH, 1 H), 9.57 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 95.7, 96.6, 100.7, 112.1, 115.9, 116.4, 120.6, 132.2, 145.6, 146.9, 157.0, 158.1, 158.6, 161.2, 162.6.

HR-FABMS (*m/z*): calcd for $C_{15}H_{11}O_6$, 287.0556; found, 287.0564.

5,7-Dihydroxy-4-(3,4-dimethoxyphenyl)-chromen-2-one (2)
To a solution of **14b** (1.0 g, 4.9 mmol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (0.5 mL, 1.5 equiv) dropwise at r.t. and the solution was then refluxed for 3 h. The solvent was removed and to the residue was added phloroglucinol (0.9 g, 5.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) at r.t. and the solution was stirred for12 h. The suspension was directly filtered and the solvent was removed in vacuo. The solid was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide the crude product, which was recrystallized from acetone to obtain **2** (1.3 g, 85%) as a pale yellow solid; mp 270 °C.

^{1}H NMR (d_6-DMSO): δ = 3.83 (s, 3 H) 3.88 (s, 3 H), 5.87 (s, 1 H), 6.28 (s, 1 H), 6.35 (s, 1 H), 6.98–7.03 (m, 3 H), 10.20 (s, OH, 2 H), 10.51(s, OH, 2 H).

^{13}C NMR (d_6-DMSO): δ = 55.6, 55.6, 94.7, 99.4, 100.8, 110.1, 110.7, 112.1, 120.1, 132.0, 147.6, 148.8, 156.0, 157.0, 157.2, 160.1, 161.6.

HPLC: R_t = 2.28 min (97%), 3.23 min (2%).

HR-FABMS (*m/z*): calcd for $C_{17}H_{15}O_6$, 315.0869; found, 315.0876.

5,7-Dihydroxy-4-(4-hydoxyphenyl)-chromen-2-one (3)
To a solution of **14c** (1.2 g, 7.4 mmol) in dioxane (25 mL) was added $SOCl_2$ (0.7 mL, 1.3 equiv) dropwise at r.t. and the solution was refluxed for 3 h. The solvent was removed and to the residue was added phloroglucinol (1.4 g, 8.6 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) at r.t. and the solution was stirred for12 h. The residue was directly filtered and the solvent was removed in vacuo. The solid was subjected to column chromatography (silica, EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to give **3** (1.5 g, 74%) as pale yellow solid; mp 290–291 °C (lit.[24] mp 293–294 °C).

5,7-Dihydroxy-4-(4-methoxyphenyl)-chromen-2-one (4)
To a mixture of **14d** (1.8 g, 10.2 mmol) in CH_2Cl_2 (80 mL) was introduced $SOCl_2$ (1.0 mL, 1.3 equiv) into the solution dropwise at r.t. and the solution was refluxed for 2 h. The resulting solution was cooled and the solvent removed in vacuo. To the solid was added phloroglucinol (1.8 g, 11.3 mmol), K-10 (5.0 g) in nitrobenzene (20 mL, anhyd) and the solution was stirred at r.t. for 12 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo. The

crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to give **4** (2.4 g, 84%) as a light brown solid; mp 259–260 °C (lit.[24] mp 256–258 °C).

^{1}H NMR [$(CD_3)_2CO$–DMSO]: δ = 4.03 (s, 3 H), 5.84 (s, 1 H), 6.48 (s, OH, 2 H). 6.49 (d, *J* = 2.3 Hz, 2 H), 7.13 (d, *J* = 8.7 Hz, 2 H), 7.50 (d, *J* = 8.7 Hz, 2 H).

5,7-Dihydroxy-4-(3,4-dihydroxyphenyl)-chroman-2-one (5)
A mixture of 3,4-dihydroxycinnamic acid (1.5 g, 8.3 mmol) and $SOCl_2$ (1.0 mL, 1.6 equiv) in dioxane (30 mL, anhyd) was heated to reflux for 2 h followed by removal of the solvent in vacuo. To the residue was added phloroglucinol (1.2 g, 9.5 mmol), K-10 (5.0 g) in nitrobenzene (15 mL, anhyd) at r.t. and the solution was stirred 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica, EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to obtain the crude product, which was recrystallized with EtOAc–hexane to afford **5** (2.2 g, 90%) as white solid; mp 74–75 °C.

^{1}H NMR [$(CD_3)_2CO$]: δ = 2.84 (dd, *J* = 15.7, 2.0 Hz, 1 H), 3.05 (dd, *J* = 15.7, 6.6 Hz, 1 H), 4.43 (dd, *J* = 6.6, 2.0 Hz, 1 H), 6.11 (d, *J* = 2.3 Hz, 1 H), 6.25 (d, *J* = 2.3 Hz, 1 H), 6.48 (dd, *J* = 8.1, 2.3 Hz, 1 H), 6.58 (d, *J* = 2.3 Hz, 1 H), 6.69 (d, *J* = 8.1 Hz, 1 H), 7.78 (s, OH, 1 H), 7.83 (s, OH, 1 H), 8.63 (s, OH, 1H), 8.77 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 35.0, 38.6, 96.5, 100.0, 105.7, 115.2, 116.5, 119.4, 135.4, 145.1, 146.3, 154.8, 156.7, 159.2, 168.6.

HPLC: R_t = 10.59 min (100%).

HRMS (*m/z*): calcd for $C_{15}H_{12}O_6$, 288.0634; found, 288.0625.

5,7-Dihydroxy-4-(3,4-dimethoxyphenyl)-chroman-2-one (6)
To a solution of 3,4-dimethoxycinnamic acid (3.0 g, 14.4 mmol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (1.4 mL, 1.3 equiv) dropwise at r.t. and the solution was refluxed for 2 h. The solvent was removed and to the residue was added phloroglucinol (2.6 g, 15.9 mmol), K-10 (5.0 g) in nitrobenzene (25 mL, anhyd) at r.t. and the solution was stirred for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The solid was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide the crude product, which was recrystallized with CH_2Cl_2–hexane to obtain **6** (4.2 g, 92%) as a white solid; mp 183–184 °C.

^{1}H NMR [$(CD_3)_2CO$]: δ = 2.86 (dd, *J* = 15.7, 2.0 Hz, 1 H), 3.04 (dd, *J* = 15.7, 6.6 Hz, 1 H), 3.73 (s, 6 H), 4.44 (dd, *J* = 6.6, 2.0 Hz, 1 H), 6.15 (d, *J* = 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1 H), 6.47 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.77 (d, *J* = 2.0 Hz, 1 H), 6.78 (d, *J* = 8.3 Hz, 1 H), 7.16 (s, OH, 1 H), 7.28 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$–$CDCl_3$]: δ = 33.6, 36.9, 55.0, 55.2, 95.6, 99.0, 103.8, 110.1, 111.0, 118.2, 134.1, 147.5, 148.6, 152.7, 154.5, 157.1, 168.2.

HPLC: R_t = 2.19 min (94%), 3.17 min (5%).

HRMS (*m/z*): calcd for $C_{17}H_{16}O_6$, 316.0947; found, 316.0950.

5,7-Dihydroxy-4-(4-hydroxyphenyl)-chroman-2-one (7)
A mixture of 4-hydroxycinnamic acid (1.5 g, 9.1 mmol) and $SOCl_2$ (1.1 mL, 1.6 equiv) in dioxane (20 mL, anhyd) was refluxed for 3 h, followed by removal of the solvent in vacuo. To the residue was added phloroglucinol (1.7 g, 10.5 mmol), K-10 (3.0 g) in nitrobenzene (20 mL, anhyd) at r.t. and the solution was stirred for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to obtain the crude product, which was recrystallized with CH_2Cl_2–hexane to afford **7** (2.1 g, 85%) as pale yellow solid; mp 275–276 °C (lit.[13] mp 270 °C).

^{1}H NMR [$(CD_3)_2CO$]: δ = 2.78 (dd, *J* = 15.8, 2.0 Hz, 1 H), 3.23 (dd, *J* = 15.8, 6.9 Hz, 1 H), 4.50 (dd, *J* = 6.9, 2.0 Hz, 1 H), 6.11 (d, *J* = 2.4 Hz, 1 H), 6.25 (d, *J* = 2.4 Hz, 1 H), 6.72 (d, *J* = 8.5 Hz, 2 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 8.19 (s, OH, 1 H), 8.53 (s, OH, 1 H), 8.67 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 33.3, 37.0, 95.0, 98.4, 104.1, 115.0, 127.5, 132.9, 153.3, 155.0, 155.9, 157.7, 167.0.

5,7-Dihydroxy-4-(4-methoxyphenyl)-chroman-2-one (8)
To a mixture of 4-methoxycinnamic acid (2.5 g, 14.0 mmol) in CH_2Cl_2 (50 mL) was introduced $SOCl_2$ (1.2 mL, 1.2 equiv) into the solution dropwise at r.t. and the reaction mixture was refluxed for 2 h. The resulting solution was cooled, followed by removal of the solvent in vacuo. To the solid was added phloroglucinol (2.6 g, 16.0 mmol), K-10 (5.0 g) in nitrobenzene (20 mL, anhyd) and the solution was stirred at r.t. for 12 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to give **8** (3.6 g, 89%) as a white solid; mp 150–151 °C (lit.[13] mp 147–148 °C).

^{1}H NMR [$(CD_3)_2CO$]: δ = 2.87 (dd, *J* = 15.7, 1.9 Hz, 1 H), 3.10 (dd, *J* = 15.7, 6.7 Hz, 1 H), 3.72 (s, 3 H), 4.53 (dd, *J* = 6.7, 1.9 Hz, 1 H), 6.12 (d, *J* = 2.2 Hz, 1 H), 6.23 (d, *J* = 2.2 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 8.57 (s, OH, 1 H), 8.71 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 32.3, 36.0, 64.0, 94.1, 97.6, 103.0, 112.6, 126.5, 133.0, 152.3, 154.0, 156.7, 157.3, 166.2.

9-Hydroxy-4,8-(4-methoxyphenyl)-dichroman-2,6-dione (9)
To a solution of 4-methoxycinnamic acid (1.0 g, 5.6 mmol) in CH_2Cl_2 (50 mL) was introduced $SOCl_2$ (0.5 mL, 1.2 equiv) into the solution dropwise at r.t. and the reaction mixture was refluxed for 2 h. The resulting solution was cooled, followed by removal of the solvent in vacuo. To the residue was added **8** (1.6 g, 5.6 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) and the solution was stirred at r.t. for 12 h. The resulting suspension was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to afford **9** (1.9 g, 77%) as pale yellow solid; mp 265–266 °C.

^{1}H NMR [$(CD_3)_2CO$]: δ = 3.06–3.29 (m, 4 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 4.65 (d, *J* = 5.2 Hz, 1 H), 4.67 (d, *J* = 5.3 Hz, 1 H), 6.52 (s, 1 H), 6.83 (d, *J* = 8.6 Hz, 4 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 7.12 (d, *J* = 8.6 Hz, 2 H), 9.46 (s, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 33.3, 33.4, 36.3, 36.5, 54.2, 54.2, 99.0, 105.1, 109.2, 113.6, 113.8, 127.3, 127.5, 133.2, 149.3, 151.8,154.1, 158.4, 165.9, 166.3.

HPLC: R_t = 2.27 min (96%), 3.19 min (3%).

HRMS (*m/z*): calcd for $C_{26}H_{22}O_7$, 446.1366; found, 446.1361.

5,7-Dihydroxy-4-(3,4-dimethoxyphenyl)-3-bromochroman-2-one (13)
To a mixture of the known[21] bromocinnamic acid **12** (1.0 g, 3.5 mmol) in $CHCl_3$ (50 mL) was added $SOCl_2$ (0.4 mL, 1.6 equiv) dropwise at r.t. and then the solution was refluxed for 2 h. The solvent was removed and to the residue was added phloroglucinol (0.6 g, 3.7 mmol), K-10 (3.0 g) in nitrobenzene (20 mL, anhyd) and the solution was stirred at r.t. for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to obtain **13** (1.2 g, 87%) as a white solid; mp 129–130 °C.

^{1}H NMR [$(CD_3)_2CO$]: δ = 3.71 (s, 3 H), 3.74 (s, 3 H), 4.73 (d, *J* = 2.2 Hz, 1 H), 4.88 (d, *J* = 2.2 Hz, 1 H), 6.22 (d, *J* = 2.2 Hz, 1 H), 6.34 (d, *J* = 2.2 Hz, 1 H), 6.51 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 6.99 (d, *J* = 2.1 Hz, 1 H), 8.76 (s, 1 H), 8.91 (s, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 42.4, 43.4, 54.7, 54.7, 94.6, 98.9, 100.3, 111.4, 111.4, 118.5, 130.2, 148.8, 149.3, 152.4, 155.9, 158.1, 162.5.

^{13}C NMR ($CDCl_3$): δ = 41.8, 44.1, 55.7, 55.7, 96.2, 100.1, 101.2, 110.5, 111.7, 119.3, 130.4, 148.6, 149.1, 152.2, 155.3, 157.2, 164.1.

HRMS (*m/z*): calcd for $C_{17}H_{15}Br\,O_6$, 394.0052; found, 394.0052.

General procedure for propargyl acids from cinnamic acids
The propargyl acids **14a–d** were prepared according to a literature procedure (Scheme 3).[22]

3-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-propynoic acid (14a)
A mixture of 3,4-dihydroxycinnamic acid (2.0 g, 11.1 mmol) and $SOCl_2$ (1.2 mL, 1.5 equiv) in EtOH (50 mL) were refluxed for 4 h, followed by removal of the solvent in vacuo. The solid was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide ester (2.2 g, 97%). The ester (2.2 g, 10.6 mmol) was treated with dichlorodiphenylmethane (10 mL) at 175 °C for 5 min. The brown solution was subjected to short column chromatography (silica, CH_2Cl_2) to obtain the protected ester (2.2 g, 56%).

^{1}H NMR ($CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 6.25 (d, *J* = 15.9 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.10 (d, *J* = 1.5 Hz, 1 H), 7.35–7.60 (m, 10 H), 7.59 (d, *J* = 15.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.3, 60.4, 106.6, 108.6, 116.0, 117.6, 124.4, 126.2, 128.3, 128.9, 129.3, 139.8, 144.4, 147.9, 149.1, 167.2.

To a solution of the ester (2.2 g, 5.9 mmol) in CH_2Cl_2 (50 mL) was introduced Br_2 (0.3 mL, 6.5 mmol) dropwise into the solution at 0 °C for 20 min. The brown solution was extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was concentrated in vacuo and afforded dibromo ester (3.0 g, 94%).

^{1}H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 6.3 Hz, 3 H), 4.31 (q, *J* = 6.3 Hz, 2 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 5.30 (d, *J* = 11.6 Hz, 1 H), 6.84 (d, *J* = 6.1 Hz, 1 H), 6.93 (s, 1 H), 7.34–7.55 (m, 10 H), 7.79 (d, *J* = 6.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.8, 47.2, 51.4, 62.5, 107.8, 108.2, 117.6, 121.8, 122.3, 126.1, 128.2, 129.1, 130.0, 131.1, 132.3, 137.4, 139.8, 147.6, 147.9, 167.7.

A mixture of dibromide (3.0 g, 5.5 mmol) and KOH (3 equiv) in EtOH (50 mL) was heated to reflux for 4 h, followed by removal of the solvent in vacuo. The residue was treated with 2 N HCl and extracted with Et_2O (3 × 150 mL) to provide **14a** (1.2 g, 62%). ^{1}H NMR ($CDCl_3$): δ = 6.85–7.20 (m, 3 H), 7.37–7.64 (m, 10 H).

^{13}C NMR ($CDCl_3$): δ = 79.3, 89.4, 108.4, 108.7, 112.1, 112.8, 117.6, 124.4, 126.2, 128.3, 129.2, 139.7, 142.5, 147.3, 148.2, 149.8, 158.1, 168.3.

3,4-Dimethoxypropynoic acid (14b)
^{1}H NMR ($CDCl_3$–DMSO): δ = 3.73 (s, 3 H), 3.76 (s, 3 H), 6.71 (d, *J* = 8.3 Hz, 1 H), 6.93 (d, *J* = 1.7 Hz, 1 H), 7.07 (dd, *J* = 8.3, 1.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$–DMSO): δ = 55.6, 55.6, 80.2, 85.8, 110.7, 111.3, 114.9, 126.7, 148.3, 150.9, 155.4.

4-Methoxypropynoic acid (14d)
^{1}H NMR [$CDCl_3$–$(CD_3)_2CO$]: δ = 3.83 (s, 3 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR [$CDCl_3$–$(CD_3)_2CO$]: δ = 55.1, 80.0, 86.9, 111.1, 114.0, 134.6, 155.3, 161.2.

5,7-Dihydroxy-4-phenyl-chroman-2-one (15)
To a solution of cinnamic acid (1.2 g, 8.3 mmol) in CH_2Cl_2 (30 mL) was added $SOCl_2$ (0.9 mL, 1.6 equiv) dropwise at r.t. and the reaction mixture was refluxed for 2 h. The solvent was removed in vacuo and to the residue was added phloroglucinol (1.5 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, dried) at r.t. and the solution was heated to 70 °C for 12 h. The resulting suspension was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide **15** (1.7 g, 80%) as a white solid; mp 206–207 °C (lit.[25] mp 210–211 °C).

^{1}H NMR [$(CD_3)_2CO$]: δ = 3.13 (dd, *J* = 15.8, 1.9 Hz, 1 H), 3.38 (dd, *J* = 15.8, 7.0 Hz, 1 H), 4.82 (dd, *J* = 7.0, 1.9 Hz, 1 H), 6.37 (d, *J* = 2.2 Hz, 1 H), 6.50 (d, *J* = 2.2 Hz, 1 H), 7.44 (m, 5 H), 8.80 (s, OH, 1 H), 8.97 (s, OH, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 34.0, 36.6, 94.9, 98.3, 103.4, 126.3, 126.4, 128.1, 142.1, 153.3, 155.0, 157.7, 166.7.

5,7-Dihydroxy-2-phenyl-chroman-4-one (16)
A mixture of cinnamic acid (1.2 g, 8.3 mmol) and $SOCl_2$ (0.9 mL, 1.5 equiv) in CH_2Cl_2 (30 mL) was heated to reflux for 2 h, followed by removal of the solvent in vacuo. The residue was added phloroglucinol (1.5 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) at r.t. and the solution was heated to 120 °C for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to obtain **16** (1.2 g, 57%) as a white solid; mp 185–186 °C (lit.[26] mp 193–194 °C).

7-Hydroxy-4-(dihydroxyphenyl)-chroman-2-one (17)
To a mixture of 3,4-dihydroxycinnamic acid (1.5 g, 8.3 mmol) in dioxane (30 mL, anhyd) was introduced $SOCl_2$ (0.9 mL, 1.6 equiv) into the solution dropwise at r.t. and the reaction mixture was refluxed for 2 h. The resulting solution was cooled, followed by removal of the solvent in vacuo. The residue was added resorcinol (1.4 g, 9.5 mmol), K-10 (3.0 g) in dioxane (15 mL, anhyd) and the solution was heated to 45 °C for 12 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to give **17** (1.9 g, 82%) as an oil.

^{1}H NMR [$(CD_3)_2CO$]: δ = 3.13 (dd, *J* = 15.7, 6.3 Hz, 1 H), 3.26 (dd, *J* = 15.7, 5.9 Hz, 1 H), 4.44 (dd, *J* = 6.3, 5.9 Hz, 1 H), 6.74 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.76 (d, *J* = 2.1 Hz, 1 H), 6.82 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 7.12 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 38.4, 40.4, 104.6, 112.7, 115.5, 116.7, 118.6, 120.0, 130.4, 134.8, 145.4, 146.5, 153.8, 158.9, 168.4.

HPLC: R_t =1.79 min (1%), 2.19 min (91%), 3.17 min (6%).

4-(Dimethoxyphenyl)-chroman-2-one (18)
To a solution of 3,4-dimethoxycinnamic acid (1.7 g, 8.3 mmol) in CH_2Cl_2 (30 mL) was added $SOCl_2$ (0.9 mL, 1.6 equiv) dropwise at r.t. and the solution was refluxed for 2 h. The solvent was removed and to the residue was added phenol (1.2 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) and the solution was heated to 45 °C for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The solid was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide **18** (1.8 g, 75%) as an oil.

^{1}H NMR ($CDCl_3$): δ = 3.01 (dd, *J* = 15.7, 11.0 Hz, 1 H), 3.06 (dd, *J* = 15.7, 3.9 Hz, 1 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 4.28 (dd, *J* = 11.0, 3.9 Hz, 1 H), 6.67–7.30 (m, 7 H).

^{13}C NMR ($CDCl_3$): δ = 37.8, 41.0, 56.6, 56.6, 111.2, 112.2, 117.8, 120.4, 125.3, 126.8, 128.9, 129.4, 133.3, 149.2, 150.1, 152.3, 168.5.

HPLC: R_t = 1.92 min (1%), 2.38 min (94%), 3.07 min (1%), 3.24 min (4%).

HR-FABMS (*m/z*): calcd for $C_{17}H_{16}O_4$, 284.1049; found, 284.1057.

4-phenyl-chroman-2-one (19)

A mixture of 3,4-dihydroxycinnamic acid (1.5 g, 8.3 mmol) and $SOCl_2$ (0.9 mL, 1.5 equiv) in dioxane (30 mL, anhyd) was heated to reflux for 2 h, followed by removal of the solvent in vacuo. To the residue was added phenol (1.2 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) and the solution was heated to 70 °C for 12 h. The suspension was directly filtered and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica EtOAc–Et_2O–CH_2Cl_2, 1:1:1) to obtain the crude product, which was recrystallized from EtOAc–hexane to afford **19** (0.8 g, 45%) as yellow solid; mp 82–83 °C (lit.[27] mp 78 °C).

^{1}H NMR [$(CD_3)_2CO$]: δ = 3.24 (dd, *J* = 15.8, 6.4 Hz, 1 H), 3.39 (dd, *J* = 15.8, 6.1 Hz, 1 H), 4.74 (dd, *J* = 6.4, 6.1 Hz, 1 H), 7.31–7.61 (m, 9 H).

5,7-Dihydroxy-2-phenyl-chromen-4-one (21)

Method A: To a solution of phenylpropargyl acid (1.2 g, 8.3 mmol) in CH_2Cl_2 (30 mL) was added $SOCl_2$ (0.9 mL, 1.5 equiv) dropwise at r.t. and the solution was refluxed for 2 h. The solvent was removed in vacuo, to the residue was added phloroglucinol (1.5 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) and heated to 120 °C for 12 h. The resulting suspension was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide **21** (1.3 g, 62%) as yellow solid; mp 294–295 °C (lit.[28] mp 297–300 °C).

^{1}H NMR [$(CD_3)_2CO$–DMSO]: δ = 6.45 (d, *J* = 2.0 Hz, 1 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 7.14 (s, 1 H), 7.81 (m, 3 H), 8.28 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR [$(CD_3)_2CO$–DMSO]: δ = 94.7, 99.7, 104.7, 105.8, 127.0, 129.8, 131.5, 132.6, 158.3, 162.4, 164.0, 165.3, 182.6.

Method B: A mixture of **22** (0.4 g, 1.6 mmol) and K-10 (1.0 g) in nitrobenzene (10 mL, dried) was heated to 120 °C for 12 h, followed by removal of the solvent in vacuo. The solid was subjected to column chromatography (silica Et_2O–CH_2Cl_2, 1:1) to provide **21** (0.4 g, 100%).

3,5-Dihydroxyphenyl-3-phenylpropynoate (22)

To a solution of phenylpropargyl acid (1.2 g, 8.3 mmol) in CH_2Cl_2 (30 mL) was added $SOCl_2$ (0.9 mL, 1.5 equiv) dropwise at r.t. and the reaction mixture was refluxed for 2 h. The solvent was removed in vacuo, to the residue was added phloroglucinol (1.5 g, 9.5 mmol), K-10 (3.0 g) in nitrobenzene (15 mL, anhyd) and the solution was heated to 70 °C for 12 h. The resulting suspension was filtered and the filtrate was concentrated in vacuo. The crude product was subjected to column chromatography (silica, Et_2O–CH_2Cl_2, 1:1) to provide **22** (0.4 g, 20%) as pale yellow solid; mp 115 °C.

^{1}H NMR [$(CD_3)_2CO$]: δ = 6.45, 6.53 (dd, *J* = 2.2 Hz, 3 H), 7.68–7.79 (m, 3H), 7.90 (d, *J* = 7.9 Hz, 2 H), 8.88 (s, OH, 2 H).

^{13}C NMR [$(CD_3)_2CO$]: δ = 80.9, 88.8, 101.6, 102.0, 120.2, 130.3, 132.6, 134.2, 152.7, 153.1, 160.3.

HPLC: R_t = 2.25 min (97%), 3.22 min (2%).

HR-FABMS (*m/z*): calcd for $C_{15}H_{11}O_4$, 255.0657; found, 255.0659.

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References

(1) (a) Chen, W. K.; Tsai, C. F.; Liao, P. H.; Lee, Y. J. *Chin. Pharmacol. J.* **1999**, *51*, 271. (b) Lee, Y. J.; Liao, P. H.; Chen, W. K.; Yang, C. C. *Cancer Lett.* **2000**, *153*, 51. (c) Tseng, T. H.; Tsheng, Y. M.; Lee, Y. J.; Hsu, H. L. *J. Chin. Chem. Soc.* **2000**, *47*, 1165. (d) Tseng, T. H.; Tsheng, Y. M.; Lee, Y. J. *Toxicology* **2001**, *161*, 179.

(2) (a) Zhao, H.; Neamati, N.; Hong, H.; Mazumder, A.; Wang, S.; Sunder, S.; Milne, G. W. A.; Pommier, Y.; Burke, T. R. Jr. *J. Med. Chem.* **1997**, *40*, 242. (b) Fuller, R. W.; Westergaard, C. K.; Collins, J. W.; Cardellina, J. H. II.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 67. (c) Sardari, S.; Mori, Y.; Horita, K.; Micetich, R. G.; Nishibe, S.; Daneshtalab, M. *Bioorg. Med. Chem.* **1999**, *7*, 1933. (d) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H. II.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W. Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735. (e) Currens, M. J.; Gulakowski, R. J.; Mariner, J. M.; Moran, R. A.; Buckheit, R. W.; Gustafson, K. R.; McMahon, J. B.; Boyd, M. R. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 645. (f) Wang, S.; Milne, G. W. A.; Yan, X.; Posey, I. J.; Nicklaus, M. C.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1996**, *39*, 2047. (g) Mazumder, A.; Wang, S.; Neamati, N.; Nicklaus, M. C.; Sunder, S.; Chen, J.; Milne, G. W. A.; Rice, W. G.; Burke, T. R. Jr.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 2472. (h) Chang, W. S.; Chiang, H. C. *Anticancer Res.* **1995**, *15*, 1969.

(3) (a) da Gramacho, R. S.; Nagem, T. J.; de Oliveira, T. T.; Eliana, M.; de Queiroz, L. R.; Neves, A. A.; Saddi, N. *Phytochemistry* **1999**, *51*, 579. (b) Bordoloi, M.; Mohan, S.; Barua, N. C.; Dutta, S. C.; Mathur, R. K.; Ghosh, A. C. *Phytochemistry* **1997**, *44*, 939. (c) Currens, M. J.; Mariner, J. M.; McMahon, J. B.; Boyd, M. R. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 652. (d) Seo, E. K.; Wani, M. C.; Wall, M. E.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *Phytochemistry* **2000**, *55*, 35. (e) Mata, R.; Calzada, F.; del Garcia, M. R.; Reguero, M. T. *J. Nat. Prod.* **1987**, *50*, 866. (f) O' Kennedy, R.; Thornes, R. D. *Comarins: Biology, Applications and Mode of Action*; John Wiley & Sons: New York, **1997**. (g) Ulubelen, A.; Kerr, R. R.; Mabry, T. J. *Phytochemistry* **1982**, *21*, 1145.

(4) (a) Hopf, G.; Kaeβmann, H. J.; Pekker, I.; Schafer, E. A.; Weber, H. G. *Arzneim-Forsch Drug Res.* **1971**, *21*, 5. (b) Casley-Smith, J. R.; Clodius, L.; Piller, N. B.; Foldi, M. *Chirurgia Plastica* **1977**, *4*, 5.

(5) Lee, R. E.; Bykadi, G.; Ritschel, W. A. *Arzneim-Forsch Drug Res.* **1981**, *31*, 640.

(6) (a) Foldi, M. *Diagnostik* **1978**, *11*, 411. (b) Casley-Smith, J. R. *Vasomed* **1994**, *6*, 232. (c) Gaffney, R. M.; Casley-Smith, J. R. *J. Pathol.* **1981**, *133*, 229. (d) Piller, N. B.; Clodius, L. *Br. J. Exp. Pathol.* **1978**, *59*, 319. (e) Knight, K. R.; Khazanchi, R. K.; Pederson, W. C. H.; McCann, J. J.; Coe, S. A.; O' Brien, B. *Clin. Sci.* **1989**, *77*, 69.

(7) Calera, M. R.; Mata, R.; Lotina-Hennsen, B.; Anaya, A. L. *J. Agric. Food Chem.* **1996**, *44*, 2966.

(8) Zobel, A. M.; Brown, S. A. *Allelopathy J.* **1995**, *2*, 9.

(9) (a) Lin, W. L.; Wang, C. J.; Tsai, Y. Y.; Liu, C. L.; Hwang, J. M.; Tseng, T. H. *Arch. Toxicol.* **2000**, *74*, 467. (b) Chu, C. Y.; Tsai, Y. Y.; Wang, C. J.; Lin, W. L.; Tseng, T. H. *Eur. J. Pharmacol.* **2001**, *416*, 25.

(10) (a) Mohindra, C. H.; Mittal, R. S. *Phytochemistry* **1983**, *22*, 2625. (b) Chan, S.-C.; Chang, Y.-S.; Wang, J.-P.; Chen, S.-C.; Kuo, S.-C. *Planta Med.* **1998**, *64*, 153. (c) Chan, S.-C.; Chang, Y.-S.; Kuo, S.-C. *Phytochemistry* **1997**, *46*, 947. (d) Donnelly, D. M. X. In *The Flavonoids*; Harborne, J. B.; Mabry, T. J.; Mabry, H., Eds.; Academic Press: New York, **1975**, 802. (e) Polonsky, J. *Bull. Chem. Soc. Fr.* **1957**, 1079.

(11) Asi, F.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1991**, *30*, 3091.
(12) (a) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990**, *55*, 4349. (b) Johnson, J. R. *Org. React.* **1942**, *1*, 210. (c) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1. (d) Awasthi, A. K.; Tewari, R. S. *Synthesis* **1986**, 1061. (e) An, Z. W.; Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1989**, *371*, C51. (f) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5919. (g) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5923. (h) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305.
(13) Speranza, G.; Meo, A. D.; Zanzola, S.; Fontana, G.; Manitto, P. *Synthesis* **1997**, 931.
(14) Shamsuddin, K. M.; Siddiqui, M. J. A. *J. Chem. Res.*; **1998**, 392.
(15) (a) Speranza, G.; Morelli, C. F.; Manitto, P. *Synthesis* **2000**, 123. (b) Li, T. S.; Zhang, Z. H.; Yang, F.; Fu, C. G. *J. Chem. Res. (S)* **1998**, 38. (c) Singh, J.; Kaur, J.; Nayyar, S.; Kad, G. L. *J. Chem. Res. (S)* **1998**, 280.
(16) (a) Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215; and references cited therein. (b) Varma, R. S.; Saini, R. K.; Kumar, D. *J. Chem. Res. (S)* **1998**, 348.
(17) Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer Verlag: New York, **1993**.
(18) Sharma, G. V. M.; Ramanaiah, K. C. V.; Krishnudu, K. R. *Tetrahedron: Asymmetry* **1994**, *5*, 1905.
(19) Hoz, A. D. L.; Moreno, A.; Vazquez, E. *Synlett* **1999**, 608.
(20) The X-ray data for **8**, **9**, **13** are deposited at CCDC as numbers 170003, 170002 and 170001, respectively.
(21) Reimer, M.; Tobin, E.; Schaffner, M. *J. Am. Chem. Soc.* **1935**, *57*, 211.
(22) (a) Abbott, T. W. *Org. Synth. Coll. Vol. II*; Wiley & Sons: New York, **1943**, 515. (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.
(23) Mata, R.; Camacho, M. R. del.; Mendoza, S.; Cruz, M. C. C. del. *Phytochemistry* **1992**, *31*, 3199.
(24) Parmar, V. S.; Jain, R.; Singh, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2277.
(25) Nair, V. *Synth. Commun.* **1987**, *17*, 723.
(26) Hsieh, Y. L.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1998**, *47*, 845.
(27) Shukla, M. R.; Patil, P. N.; Wadgaonkar, P. P.; Joshi, P. N.; Salunkhe, M. M. *Synth. Commun.* **2000**, *30*, 39.
(28) Yang, F.; Li, X. C.; Wang, H. Q.; Yang, C. R. *Phytochemistry* **1996**, *42*, 867.