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Microwave-Assisted Rate-Enhanced Method for the Synthesis of 2,2-Dimethyl-2*H*-chromenes

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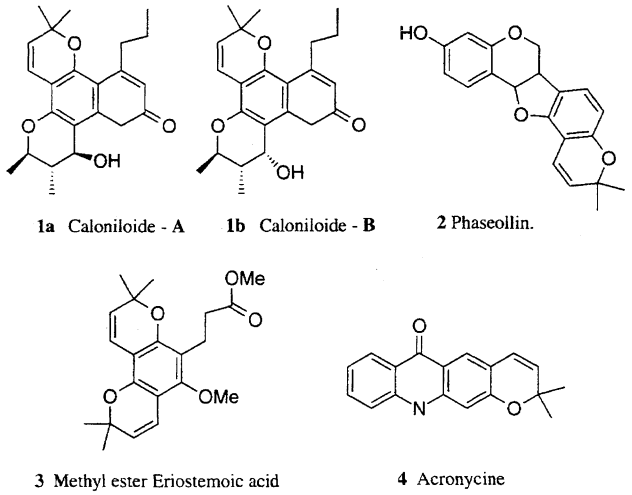
Herein we describe a simple and facile method for the synthesis of chromenes by base catalyzed condensation of phenols with 3-methyl-2-butenal under microwave irradiation.

The 2,2-dimethyl-2*H*-chromene ring system constitutes the basic frame work of a large number of natural phytoalexins and coumarins, having potent biological activities. For example, caloniloide A and B (**1**), dihydropyranocoumarins from the leaves and twigs of the tropical rain-forest tree Calophyllum lanigerum Var. austrocoriaceum, have recently been identified as being a potent representative of a pharmacologically distinct subclass of non-nucleosidal human immunodeficiency virus-1 (HIV-1) specific reverse transcriptase inhibitors (Scheme 1).[1] These compounds are also reported to have activity against the azidothymine-resistant HIV-1 strain G-9106 and the pyridinone-resistant HIV-1 strain A17. Phaseollin (**2**), a naturally occurring phytoalexin, is of great interest because of its reputed pathological activity (Scheme 1).[2] Methyl ester of eriostemoic acid (**3**), a dihydrocinnamic acid derivative having 2,2-dimethyl-2*H*-pyranochromene, was isolated along with coumarin glycosides from the aerial parts of Eriostemon wonganensis.[3] Acronycine (**4**), isolated from Acronycia baueri, is a promising anti-tumor agent (Scheme 1).[4]

Construction of the 2,2-dimethyl-2*H*-chromene ring system, due to its wide presence in many natural products, has received considerable interest in recent years. Synthetic approaches, such as the base-catalyzed thermal condensation of reactive phenols with α,β-unsaturated aldehydes or its acetals,[5] the acid-catalyzed cyclisation of 7-(3,3-dialkoxypropoxy)-2,2-dimethyl-2*H*-benzopyran,[6] reduction followed by dehydration of the 4-chromanones,[7] and a thermal rearrangement of aryl propargyl ethers[8] are reported in the literature. Recently, Sartori et al. have reported on the zeolite-induced regioselective synthesis of 2*H*-chromenes from phenol and α-alkynols.[9] Frequently used base-catalyzed reactions suffer from some drawbacks, such as prolonged heating and low yields.[5,10] Furthermore, even acid-catalyzed reactions were found to be low yielding.



1a Caloniloide - A **1b** Caloniloide - B **2** Phaseollin.

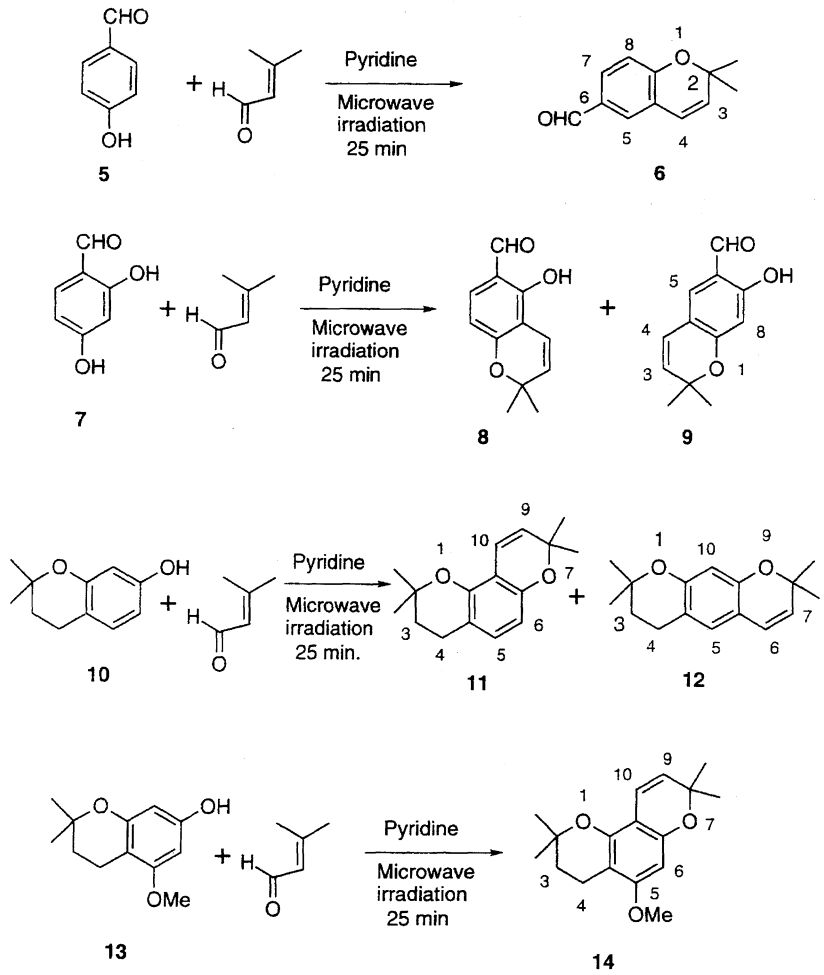
3 Methyl ester Eriostemoic acid **4** Acronycine

Scheme 1. Biologically active compounds having 2,2-dimethyl-2*H*-chromene ring system.

The use of microwave irradiation to bring about organic transformations has taken new dimensions in the recent years.[11] It has been successfully employed for numerous functional-group transformations in organic synthesis,[12] such as Diels–Alder, Ene, Claisen, Henry and Heck reactions, the selective oxidation of alcohols and the synthesis of short-lived pharmaceuticals. Very recently, microwave irradiation has been used to carry out solid-phase as well as solvent-free synthesis.[13] The reported rate accelerations and cleaner reactions, with or without solvents, prompted us to reinvestigate base-catalyzed thermal reactions under microwave conditions. Herein we report on the synthesis of chromenes **6**, **8**, **9**, **11**, **12**, **14**, **16**, and **17** in good yields employing these conditions.

Results and Discussion

It is well known that under thermal conditions, reactive phenols undergo cyclisation with α,β-unsaturated aldehydes in the presence of a base.[5,10] 4-Hydroxybenzaldehyde (**5**) (122.0 mg, 1.0 mmol), 3-methyl-2-butenal (0.192 mL, 2 mmol), and pyridine (0.1 mL, 1.2 mmol) were therefore placed in a sealed glass tube and subjected to microwave irradiation for various durations (Scheme 2). The best results were obtained in 25 min and yielded chromene **6** in 68% (Table 1, Entry 1).[14] The formation of compound **6** was confirmed by the appearance of two one-proton doublets with



Scheme 2. Synthesis of 2*H*-chromenes.

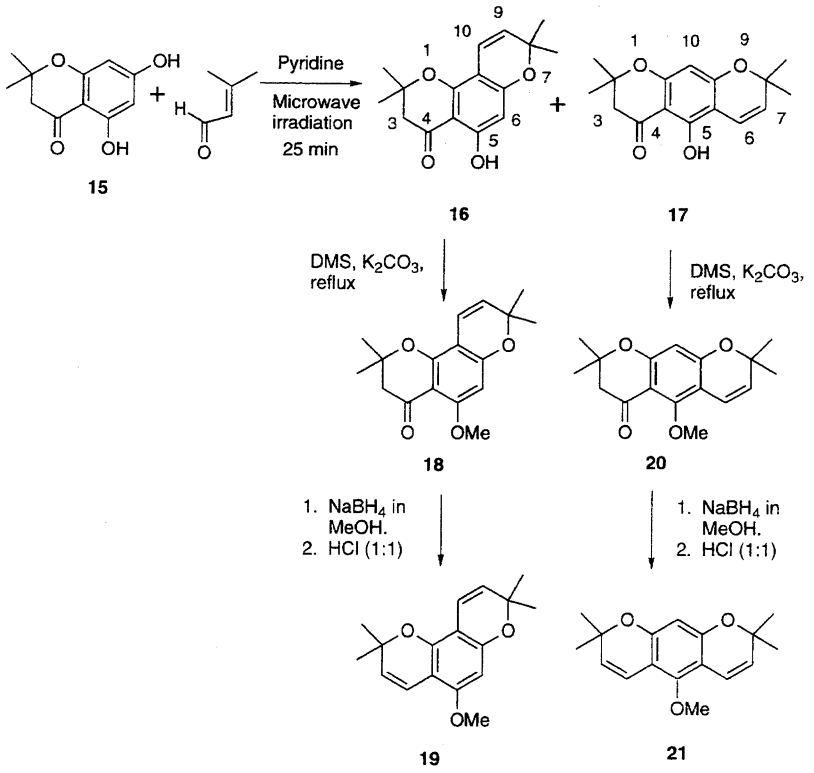
Table 1. Microwave Assisted Cyclization of Substituted Phenols with 3-Methyl-2-butenal[a)]

Entry	Phenol	Thermal condition		Microwave condition	
		Time (h)	Products (yield)	Time (min)	Products (yield)
1	**5**	—	—	25	**6** (68)
2	**7**	9	**8** (52), **9** (6)	25	**8** (49), **9** (12)
3	**10**	—	—	25	**11** (21), **12** (28)
4	**13**	48	**14** (68)	25	**14** (73)
5	**15**	12	**16** (46), **17** (19)	25	**16** (45), **17** (23)

a) All reactions were carried out in 1 mmol scale except Entry 5.

J = 9.8 Hz centered at δ = 5.69 and 6.37 for C_3 and C_4-H in the ^{1}H NMR spectrum and the disappearance of the hydroxyl function in its IR spectrum. In light of this result, we carried out the condensation of substituted phenols **7**, **10**, **13**, and **15** with 3-methyl-2-butenal in the presence of pyridine. Similar results were obtained in all cases, and are summarized in Table 1. The condensation of 2,4-dihydroxybenzaldehyde (**7**) with 3-methyl-2-butenal was carried out in the presence of pyridine as well as in triethylamine. The formation of chromenes **8** and **9** was observed only in pyridine;[15)] triethylamine led to polymerization. Linear and angular fusion of the chromenes was ascertained by the appearance of two aromatic protons as two doublets (at δ = 6.42 and 7.28) and two singlets (at δ = 6.33 and 7.11) in their respective ^{1}H NMR spectrum. Under thermal conditions, this reaction took 9 h at 140 °C (bath temperature) to give a comparable yield (Entry 2).

2,2-Dimethyl-7-chromanol (**10**) upon a reaction with 3-methyl-2-butenal in the presence of pyridine gave chromenes **11** and **12** in 49% yield (Entry 3). The appearance of two aromatic protons as two doublets with J = 8.1 Hz at δ = 6.31 and 6.79, and two singlets at δ = 6.22 and 6.64 in its ^{1}H NMR spectrum confirms the formation of compounds **11** and **12**, respectively. Under similar conditions, chroman **13** upon a reaction with 3-methyl-2-butenal gave chromene **14** in 73% yield. It was noted that, the formation of **14** took nearly



Scheme 3. Synthesis of 2*H*-chromenes.

48 h under thermal conditions at 140 °C (bath temperature) (Entry 4).[10b] The formation of a possible linear isomer was not observed in both cases.

Chromene **19**, the key intermediate for the synthesis of methyl ester of eriostemoic acid (**3**),[3] and its isomer **21** were synthesized, as shown in Scheme 3. The reaction of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**15**) with 3-methyl-2-butenal was carried out under thermal as well as microwave conditions in the presence of pyridine. The formation of compounds **16** and **17** was observed in both cases, but completion of the reaction took 12 h in the former case (Entry 5). In order to differentiate the two isomers, compounds **16** and **17** were derivatised to their corresponding methyl ethers, **18** and **20**, respectively. NOE studies on **18** and **20** were carried out. The irradiation of the methoxy proton signal (δ = 3.87) of chromene **18** led to an enhancement of the aromatic proton singlet at δ = 5.99. This indicated that the unsubstituted and methoxy-bearing aromatic carbons are adjacent. This implies that **16** is the angular one.

This was further confirmed by NOE studies on chromenes **19** and **21**, which were obtained by $NaBH_4$ reduction, followed by the acid catalyzed dehydration of the 4-chromanones **18** and **20**, respectively. Irradiation of the methoxy proton signals of **19** and **21** led to a signal enhancement of the aromatic proton singlet at δ = 5.95 in the case of **19** and olefinic proton signals at δ = 6.48 in the case of **21**. These studies unequivocally confirmed compound **16** to be angular and **17** to be linearly fused. The observed acceleration of the reaction rates may perhaps be due to a rapid achievement of high temperature and the buildup of high pressure in the sealed tube during microwave heating.[11c] The condensation of 3,5-dimethylphenol and 2,4-di-*t*-butylphenol were also attempted under similar conditions without much success. The starting materials were recovered in both cases.

Experimental

3-Methyl-2-butenal was purchased from Aldrich Chemical Company and a commercial oven Microwin MX1000 was used for microwave irradiation. The melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 688 spectrometer. NMR spectra were recorded either on a Varian VXR 300S or Bruker-200 instruments using $CDCl_3$ as a solvent containing TMS as an internal standard with chemical shifts (δ) expressed as ppm down field with respect to TMS. The *J* values are given in Hz. Elemental analyses were performed on a CEST elemental analyzer. Mass spectra were recorded either on a Hewlett Packard MS Engine 5989-A mass spectrometer or Hitachi M-2000 spectrometer at 70 eV.

General Procedure. A mixture of phenol (1.0 mmol), 3-methyl-2-butenal (2.0 mmol), and pyridine (1.2 mmol) was placed in a sealed glass tube and subjected to microwave irradiation for 25 min at microwave power 9. Hydrochloric acid (10 mL, 20% v/v) was added to the reaction mixture at 0 °C and extracted with dichloromethane, washed with water, brine and then dried (Na_2SO_4). After removing the solvent, the resultant product was subjected to silica-gel column chromatography using pet. ether/ethyl acetate as eluents.

2,2-Dimethyl-2*H*-chromene-6-carbaldehyde (6). 4-Hydroxybenzaldehyde (**5**) (122 mg, 1.0 mmol), 3-methyl-2-butenal (0.192 mL, 2.0 mmol), and pyridine (0.1 mL, 1.2 mmol) gave compound **6** as a colorless oil; 127 mg, 68%; IR ($CHCl_3$) 3000, 2900, 1680, 1630, 1590, 1480, 1270, 1210, 1110, 750 cm^{-1}; ^1HNMR (300 MHz) δ = 1.47 (6H, s, $C_2(CH_3)_2$), 5.69 (1H, d, *J* = 9.8 Hz, C_3-

H), 6.37 (1H, d, J = 9.8 Hz, C_4-H), 6.86 (1H, d, J = 8.4 Hz, C_8-H), 7.52 (1H, d, J = 2.01 Hz, C_5-H), 7.64 (1H, dd, J = 2.01, 8.4 Hz, C_7-H), 9.93 (1H, s, –CHO). MS m/z M^+ 188 (23%), 172 (100), 151 (8), 144 (8), 115 (13). Found: C, 76.52; H, 6.49%. Calcd for $C_{12}H_{12}O_2$: C, 76.59; H, 6.38%.

5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (8) and 7-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (9). 2,4-Dihydroxybenzaldehyde (**7**) (138 mg, 1.0 mmol), 3-methyl-2-butenal (0.192 mL, 2.0 mmol), and pyridine (0.1 mL, 1.2 mmol) gave compounds **8** and **9** as colorless solids.

Compound 8: 100 mg, 49%; mp 110—112 °C; IR (Nujol) 1640, 1620, 1490, 1380, 1370 cm^{-1}; ^1H NMR (300 MHz) δ = 1.46 (6H, s, $C_2(CH_3)_2$), 5.61 (1H, d, J = 10.2 Hz, C_3-H), 6.42 (1H, d, J = 8.6 Hz, C_8-H), 6.68 (1H, d, J = 10.2 Hz, C_4-H), 7.28 (1H, d, J = 8.6 Hz, C_7-H), 9.66 (1H, s, CHO), 11.65 (1H, s, –OH). MS m/z M^+ 204 (24%), 189 (100), 173 (2), 160 (4), 116 (4). Found: C, 70.52; H, 5.92%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88%.

Compound 9: 25 mg, 12%; mp 91—92 °C; IR ($CHCl_3$) 1634, 1621, 1492, 1376, 1370 cm^{-1}; ^1H NMR (300 MHz) δ = 1.45 (6H, s, $C_2(CH_3)_2$), 5.59 (1H, d, J = 9.8 Hz, C_3-H), 6.29 (1H, d, J = 9.8 Hz, C_4-H), 6.33 (1H, s, C_8-H), 7.11 (1H, s, C_5-H), 9.66 (1H, s, CHO), 11.4 (1H, s, –OH). MS m/z M^+ 204 (19%), 189 (100), 116 (2). Found: C, 70.45; H, 5.81%. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88%.

3,4-Dihydro-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromene (11) and 3,4-Dihydro-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[3,2-*g*]chromene (12). 7-Chromanol (**10**) (178 mg, 1.0 mmol), 3-methyl-2-butenal (0.192 mL, 2.0 mmol) and pyridine (0.1 mL, 1.2 mmol) gave compounds **11** and **12**.

Compound 11: Colorless viscous oil; 52 mg, 21%; IR (neat) 2950, 2901, 2825, 1624, 1600, 1575, 1472, 1430, 1274, 1200, 1060, 962, 878 cm^{-1}; ^1H NMR (300 MHz) δ = 1.32 (6H, s, $C_2(CH_3)_2$), 1.40 (6H, s, $C_8(CH_3)_2$), 1.76 (2H, t, J = 6.8 Hz, C_3-H), 2.67 (2H, t, J = 6.8 Hz, C_4-H), 5.51 (1H, d, J = 9.9 Hz, C_9-H), 6.31 (1H, d, J = 8.1 Hz, C_6-H), 6.66 (1H, d, J = 9.9 Hz, C_{10}-H), 6.79 (1H, d, J = 8.1 Hz, C_5-H). MS m/z M^+ 244 (58%), 229 (100), 190 (9), 174 (74).

Compound 12: Colorless cubes; 67 mg, 28%; mp 69—70 °C; IR (Nujol) 1620, 1550, 1480, 1450, 1370, 1350 cm^{-1}; ^1H NMR (300 MHz) δ = 1.30 (6H, s, $C_8(CH_3)_2$), 1.38 (6H, s, $C_2(CH_3)_2$), 1.75 (2H, t, J = 6.6 Hz, C_7-H), 2.65 (2H, t, J = 6.6 Hz, C_6-H), 5.44 (1H, d, J = 9.4 Hz, C_3-H), 6.22 (1H, s, C_{10}-H), 6.23 (1H, d, J = 9.4 Hz, C_4-H), 6.64 (1H, s, C_5-H). MS m/z M^+ 244 (74%), 229 (100), 189 (10), 173 (80). Found: C, 78.60; H, 8.16%. Calcd for $C_{16}H_{20}O_2$: C, 78.68; H, 8.19%.

3,4-Dihydro-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromene (14). 5-Methoxy-2,2-dimethyl-7-chromanol (**13**) (208 mg, 1.0 mmol), 3-methyl-2-butenal (0.192 mL, 2.0 mmol) and pyridine (0.1 mL, 1.2 mmol) gave compound **14** as a colorless oil; 201 mg, 73%; IR (neat) 3024, 2974, 2935, 1622, 1587, 1479, 1221, 1149 cm^{-1}; ^1H NMR (300 MHz) δ = 1.30 (6H, s, $C_2(CH_3)_2$), 1.40 (6H, s, $C_8(CH_3)_2$), 1.73 (2H, t, J = 6.8 Hz, C_3-H), 2.54 (2H, t, J = 6.8 Hz, C_4-H), 3.76 (3H, s, OCH_3), 5.37 (1H, d, J = 9.9 Hz, C_9-H), 5.97 (1H, s, C_6-H), 6.59 (1H, d, J = 9.9 Hz, C_{10}-H); ^{13}C NMR (50 MHz) δ = 16.75, 26.73, 27.78, 32.34, 55.35, 74.23, 75.87, 91.36, 102.05, 103.71, 117.17, 125.17, 150.11, 152.44, 158.04. MS m/z M^+ 274 (56%), 259 (100), 203 (85), 181 (49). Found: C, 74.61; H, 8.16%. Calcd for $C_{17}H_{22}O_3$: C, 74.45; H, 8.03%.

3,4-Dihydro-5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-4-one (16) and 3,4-Dihydro-5-hydroxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[3,2-*g*]chromen-4-one (17). 5,7-Dihydroxy-2,2-dimethylchroman-4-one (**15**) (1040 mg, 5.0 mmol), 3-methyl-2-butenal (0.96 mL, 10.0 mmol), and pyridine (0.5 mL, 6.0 mmol) gave compounds **16** and **17** as colorless solids.

Compound 16: 610 mg, 45%; mp 68—69 °C; IR ($CHCl_3$) 3250, 3030, 2985, 1645, 1570, 1478, 1460, 1422, 1390, 1274, 1218, 1090, 755 cm^{-1}; ^1H NMR (300 MHz) δ = 1.44 (12H, s, C_2, $C_8(CH_3)_2$), 2.66 (2H, s, C_3-H), 5.47 (1H, d, J = 10.0 Hz, C_9-H), 5.84 (1H, s, C_6-H), 6.59 (1H, d, J = 10.0 Hz, C_{10}-H), 12.3 (1H, s, –OH). MS m/z M^+ 274 (47%), 259 (100), 203 (92), 122 (17). Found: C, 70.01; H, 6.61%. Calcd for $C_{16}H_{28}O_4$: C, 70.07; H, 6.56%.

Compound 17: 315 mg, 23%; mp 63—65 °C; IR ($CHCl_3$) 3350, 2994, 2950, 1660, 1630, 1594, 1565, 1475, 1315, 1205, 1118, 750 cm^{-1}; ^1H NMR (300 MHz) δ = 1.43 (6H, s, $C_8(CH_3)_2$), 1.46 (6H, s, $C_2(CH_3)_2$), 2.68 (2H, s, C_7-H), 5.47 (1H, d, J = 10.2 Hz, C_3-H), 5.93 (1H, s, C_{10}-H), 6.53 (1H, d, J = 10.2 Hz, C_4-H), 12.0 (1H, s, –OH). MS m/z M^+ 274 (33%), 259 (100), 217 (42), 203 (72). Found: C, 70.22; H, 6.49%. Calcd for $C_{16}H_{18}O_4$: C, 70.07; H, 6.56%.

3,4-Dihydro-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-4-one (18) and 3,4-Dihydro-5-methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[3,2-*g*]-chromen-4-one (20). A 100 mL round-bottom flask fitted with a stirrer, reflux condenser and guard tube was charged with K_2CO_3 (414 mg, 3.0 mmol), dry acetone (20 mL), and chromen-4-one **16** or **17** (274 mg, 1.0 mmol) under a nitrogen atmosphere. To this well-stirred, ice-cooled mixture (0—5 °C), dimethyl sulfate (0.189 mL, 2.0 mmol) was gradually added. The mixture was allowed to come to room temperature and then heated to reflux for 3 h. After completion of the reaction, a solid material was filtered off and the filtrate was concentrated under vacuum. Water (20 mL) was added to the product, which was then extracted with ether, washed with water, brine and finally dried (Na_2SO_4). The crude product, after removing the solvent, was chromatographed over silica gel using petroleum ether/ethyl acetate (95 : 5) as an eluent to afford methyl ether **18** or **20**, respectively.

Compound 18: Colorless solid; 240 mg, 83%; mp 68—70 °C; IR ($CHCl_3$) 2996, 2950, 1668, 1630, 1596, 1570, 1205, 1145, 1080, 750 cm^{-1}; ^1H NMR (300 MHz) δ = 1.44 (6H, s, $C_2(CH_3)_2$), 1.45 (6H, s, $C_8(CH_3)_2$), 2.64 (2H, s, C_3-H), 3.87 (3H, s, $-OCH_3$), 5.46 (1H, d, J = 10.2 Hz, C_9-H), 5.99 (1H, s, C_6-H), 6.57 (1H, d, J = 10.2 Hz, C_{10}-H). MS m/z M^+ 288 (89%), 273 (99), 217 (100), 201 (15). Found: C, 70.71; H, 6.93%. Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94%.

Compound 20: Colorless solid; 221 mg, 77%; mp 99—100 °C; IR ($CHCl_3$) 2990, 2950, 1660, 1630, 1595, 1560, 1360, 1120, 740 cm^{-1}; ^1H NMR (300 MHz) δ = 1.43 (12H, s, C_2–$C_8(CH_3)_2$), 2.63 (2H, s, C_7-H), 3.92 (3H, s, $-OCH_3$), 5.56 (1H, d, J = 10.0 Hz, C_3-H), 6.12 (1H, s, C_{10}-H), 6.59 (1H, d, J = 10.0 Hz, C_4-H). MS m/z M^+ 288 (26%), 273 (59), 257 (19), 217 (100), 201 (6). Found: C, 70.87; H, 6.87%. Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94%.

5-Methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[2,3-*f*]chromene (19) and 5-Methoxy-2,2,8,8-tetramethyl-2*H*,8*H*-pyrano[3,2-*g*]chromene (21). To a solution of methoxy-4-chromenone **18** and **20** (288.0 mg, 1.0 mmol) in dry methanol (15 mL) was added sodium borohydride (150 mg, 4.0 mmol); the mixture was refluxed on a boiling water bath for 3 h. Hydrochloric acid (1 : 1 v/v), precooled at ice-bath temperature, was added to the resultant product after removing the solvent and extracted with dichloromethane. The organic layer was washed with water, brine and then dried (Na_2SO_4). Evaporation of the solvent gave a colorless residue, which was then chromatographed over silica gel and eluted with petroleum ether/ethyl acetate (97 : 3) to give compound

19 and **21**, respectively.

Compound 19: Colorless solid; 140 mg, 51%; mp 84—85 °C; IR ($CHCl_3$) 2996, 2950, 1624, 1595, 1570, 1476, 1458, 1360, 1115, 750 cm^{-1}; ^1H NMR (300 MHz) δ = 1.40 (6H, s, $C_2(CH_3)_2$), 1.41 (6H, s, $C_8(CH_3)_2$), 3.77 (3H, s, OCH_3), 5.41 (1H, d, J = 9.9 Hz, C_3-H), 5.42 (1H, d, J = 9.8 Hz, C_9-H), 5.95 (1H, s, C_6-H), 6.56 (1H, d, J = 9.9 Hz, C_4-H), 6.59 (1H, d, J = 9.8 Hz, C_{10}-H). MS *m/z* M^+ 272 (77%), 257 (100), 241 (7), 120 (39). Found: C, 75.25; H, 7.43%. Calcd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35%.

Compound 21: Colorless solid; 161 mg, 59%; mp 102—104 °C; IR ($CHCl_3$) 2980, 2950, 1621, 1600, 1558, 1570, 1460, 1458, 1357, 1209, 1124, 1076, 750 cm^{-1}; ^1H NMR (300 MHz) δ = 1.40 (12H, s, C_2, $C_8(CH_3)_2$), 3.74 (3H, s, OCH_3), 5.48 (2H, d, J = 10.2 Hz, C_3, C_7-H), 6.1 (1H, s, C_{10}-H), 6.48 (2H, d, J = 10.2 Hz, C_4, C_6-H). MS *m/z* M^+ 272 (97%), 257 (100), 241 (14), 227 (66), 120 (38). Found: C, 75.18; H, 7.31%. Calcd for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35%.

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