

An Efficient and Concise Synthesis of Biologically Interesting Natural Flemichapparin A, Flemingins A, Flemingins D, and Their Non-natural Analogues

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The efficient and concise synthesis of natural and non-natural pyranochalcones was achieved from readily available 2,4,5-trihydroxyacetophenone. The key steps in the synthetic strategy were ethylenediamine diacetate-catalyzed benzopyran formation and aldol reactions.

Key Words : Ethylenediamine diacetate, Pyranochalcone, Flemichapparin A, Flemingins A and D

Introduction

Pyranochalcones are an abundant subclass of the flavonoids and are widely distributed in nature.¹ Members of the pyranochalcones have been associated with a wide variety of biological activities² and some plants are used in traditional medicines in China and in Europe.³ This wide range of biological properties has stimulated interest in the synthesis of naturally occurring pyranochalcones (Figure 1). Among these, flemichapparin A (**1**) was isolated from *Flemingia chappar* along with other chalcones.⁴ This plant has shown to possess a potent antifungal activity.⁵ Flemingins A (**5**), B (**6**), and C (**7**) were isolated from "Wars", which is a drug prepared in East Africa by scraping the seed pods of *Flemingia rhodocarpa*.⁶ It is widely used as a

medication, cosmetic, and dye in East Africa. A very similar drug prepared from *Flemingia* species is also known in India.⁷ Flemingins D (**8**) was isolated from *Flemingia congesta*.⁸ Although a few synthetic methods to flemichapparin A (**1**) and flemingin A derivatives have been reported, these synthetic approaches have been limited due to many reaction steps, harsh reaction conditions, and low yield involving side reactions.⁹ In particular, no convergent total syntheses of flemingin A (**5**) and D (**8**) are unknown.

Recently, we have developed a new and facile methodology for preparing benzopyrans by ethylenediamine diacetate-catalyzed reactions of resorcinols to α,β -unsaturated aldehydes.¹⁰ These reactions involve a formal [3+3]-cycloaddition *via* a 6π -electrocyclization (Scheme 1). As part of an ongoing examination of the synthetic efficacy of this methodology, we investigated ethylenediamine diacetate-catalyzed condensation of 2,4,5-trihydroxyacetophenone with 3-methyl-2-butenal and citral to yield benzopyrans. Using synthesized benzopyrans as a key step, we report herein an efficient and rapid synthetic routes to biologically interesting natural flemichapparin A (**1**), flemingins A (**5**) and D (**8**), and their non-natural analogues **2-4**.

Results and Discussion

The retrosynthetic strategy of products **1-8** is shown in Scheme 2. Pyranochalcones **1-8** could be prepared from base-catalyzed aldol reactions of benzopyrans **15** and **23** with the corresponding benzaldehydes **17-19** and **25-26**. The crucial intermediates **15** and **23** could be generated from the readily available materials 2,4,5-trihydroxyacetophenone

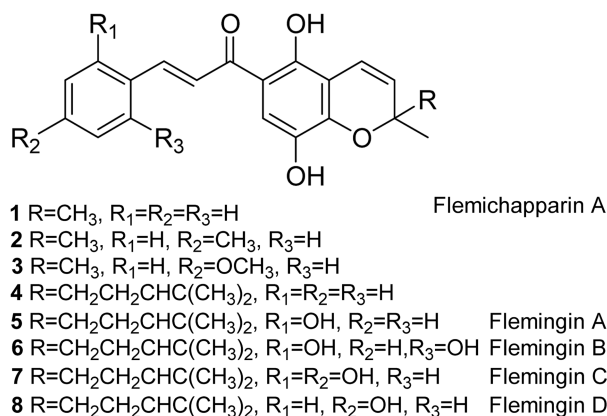
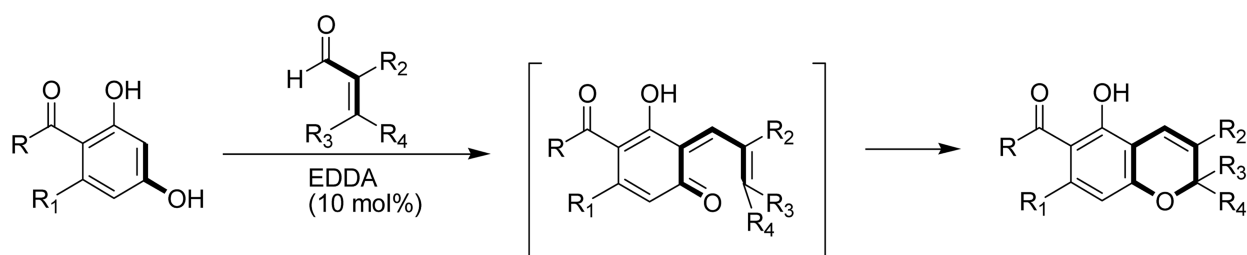
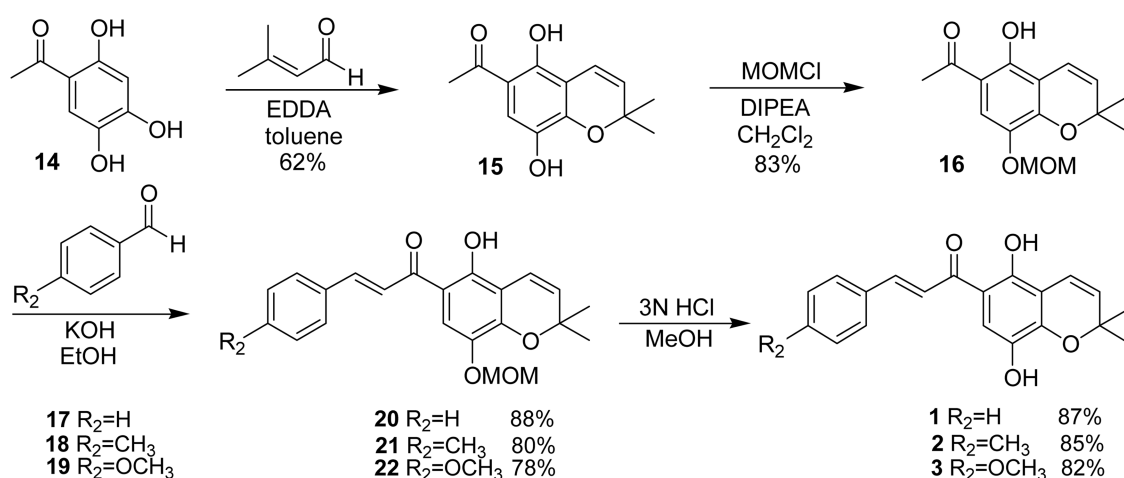
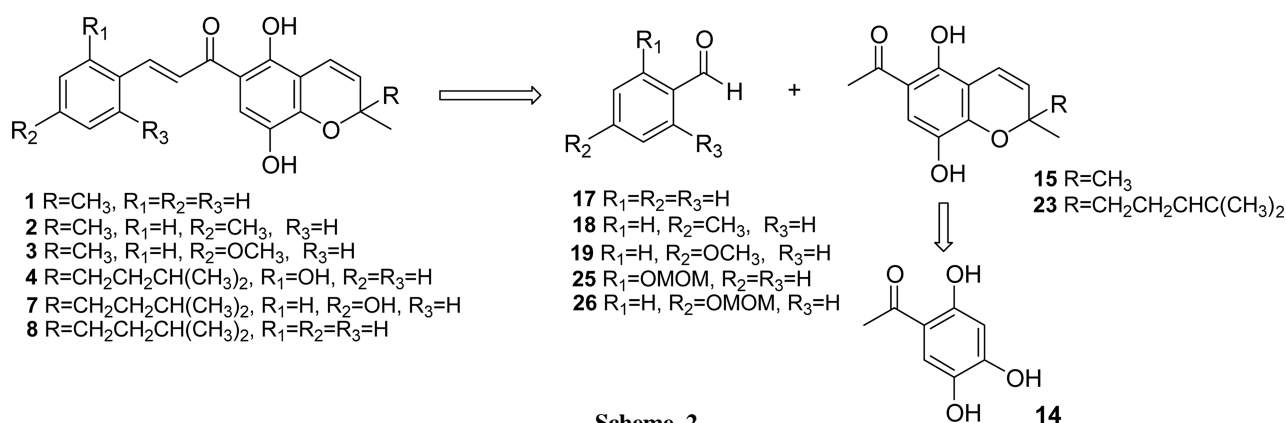


Figure 1. Naturally occurring pyranochalcones and their unnatural analogues.



Scheme 1



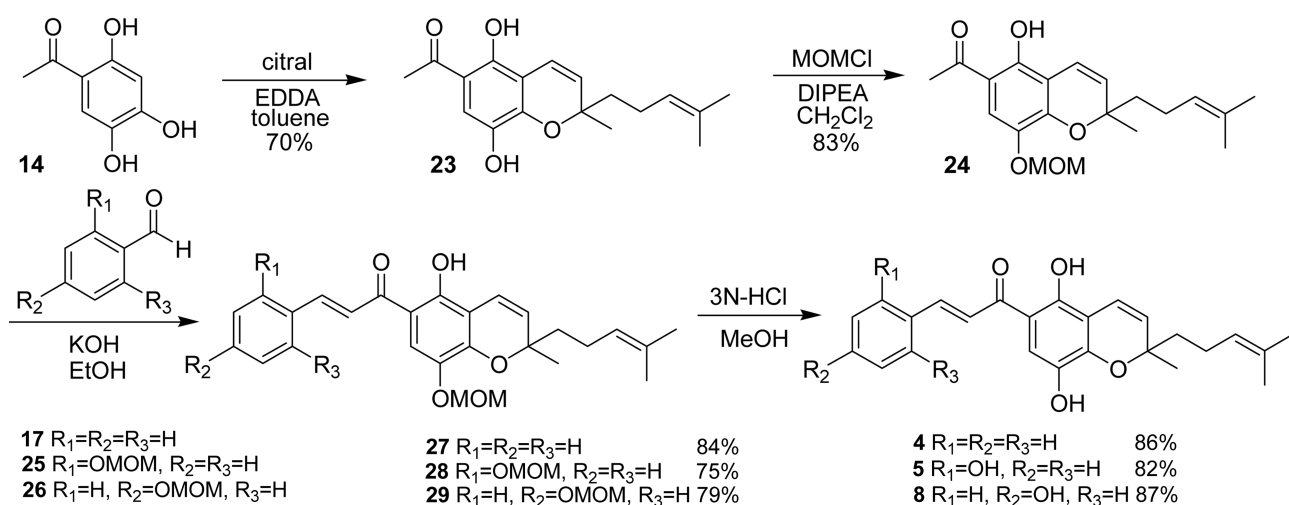
14 using ethylenediamine diacetate-catalyzed benzopyran formation reactions.

The benzopyran **15** was first achieved starting from 2,4,5-trihydroxyacetophenone (**14**) as shown in Scheme 3. A reaction of **14** with 3-methyl-2-butanone in the presence of 10 mol % of ethylenediamine diacetate in refluxing toluene for 12 h gave product **15** in 62% yield. To complete the synthesis of natural products, aldol reactions were next tried. Attempts to directly condense compound **15** to benzaldehyde using KOH in ethanol were unsuccessful due to two phenolic groups. Fortunately, we were able to introduce chalcone structures through the protection of acidic phenolic groups. Treatment of **15** with 1 equiv of MOMCl in the presence of diisopropylethylamine in methylene chloride at room temperature for 10 h gave a monoprotected product **16** in 83% yield. Reaction of **16** with benzaldehyde **17** using KOH in ethanol at room temperature for 48 h gave compound **20** in 88% yield. Similarly, treatment of **16** with 4-methylbenzaldehyde (**18**) in ethanolic KOH solution at room temperature for 48 h provided product **21** in 80% yield, whereas that of **16** with 4-methoxybenzaldehyde (**19**) afforded compound **22** in 78% yield. Deprotection of MOM ether of compound **20** with 3 N HCl in refluxing methanol for 1 h gave flemichapparin A (**1**) in 87% yield.

The spectral data of synthetic compound **1** was in good agreement with that of the natural product reported in the literature.¹¹ Similarly, compounds **21** and **22** afforded non-natural products **2** and **3** in 85 and 82% yields, respectively.

The total synthesis of flemingins A (**5**) and D (**8**) was investigated starting from 2,4,5-trihydroxyacetophenone (**14**) as shown in Scheme 4. Treatment of **14** with citral in the presence of 10 mol % of ethylenediamine diacetate in refluxing toluene for 12 h gave product **23** in 70% yield. Treatment of **23** with 1 equiv of MOMCl in the presence of diisopropylethylamine in methylene chloride gave compound **24** in 83% yield. Condensation of compound **24** with benzaldehyde **17** in ethanolic KOH at room temperature for 48 h afforded product **27** in 84% yield, which was deprotected with 3 N HCl in refluxing methanol for 1 h to give unnatural product **4** in 86% yield. Similarly, reactions of **24** with aldehydes **25** and **26** afforded products **28** and **29** in 75 and 79% yields, respectively. Deprotection of **28** and **29** with 3 N HCl afforded flemingins A (**5**) and D (**8**) in 82 and 87% yields. The spectral data of our synthetic materials **5** and **8** are the same as values reported in the literature.^{6,8}

In conclusion, the efficient and concise total synthesis of biologically interesting pyranochalcone natural products flemichapparin A (**1**), flemingins A (**5**) and D (**8**), and their



Scheme 4

non-natural analogues **2-4**. The key strategy in the synthetic procedures involves the ethylenediamine diacetate-catalyzed benzopyran formation and the aldol reactions.

Experimental

All the experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in CDCl_3 using $\delta = 77.0$ ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. MS spectra were carried out at the Korea Basic Science Institute.

1-(5,8-Dihydroxy-2,2-dimethyl-2H-chromen-6-yl)ethone (15). To a solution of 2,4,5-trihydroxyacetophenone (**14**) (336 mg, 2.0 mmol) and 3-methyl-2-butenal (336 mg, 4.0 mmol) in toluene (30 mL) was added ethylenediamine diacetate (36 mg, 0.2 mmol) at room temperature. The reaction mixture was refluxed for 12 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **15** (290 mg, 62%) as a solid: mp 154–155 °C; ^1H NMR (300 MHz, CDCl_3) δ 12.62 (1H, s), 7.12 (1H, s), 6.70 (1H, d, $J = 10.1$ Hz), 5.58 (1H, d, $J = 10.1$ Hz), 5.13 (1H, s), 2.50 (3H, s), 1.47 (6H, s); IR (KBr) 2964, 1622, 1472, 1377, 1329, 1294, 1250, 1198, 1169, 1125, 1080, 1051, 895, 862, 812, 725 cm^{-1} ; EIMS m/z 234 (M^+ , 28), 220 (13), 219 (100), 191 (5), 91 (4), 77 (4).

1-(5-Hydroxy-8-methoxymethoxy-2,2-dimethyl-2H-chromen-6-yl)ethanone (16). Methoxymethyl chloride (81 mg, 1.0 mmol) was added to a solution of **15** (234 mg, 1.0 mmol) and diisopropylethylamine (646 mg, 5.0 mmol) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h, and then water (30 mL) was added. The reaction mixture

was extracted with methylene chloride (3×20 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried (MgSO_4), and evaporated in vacuo. Flash chromatography on silica gel afforded **16** (231 mg, 83%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 12.60 (1H, s), 7.32 (1H, s), 6.69 (1H, d, $J = 10.1$ Hz), 5.58 (1H, d, $J = 10.1$ Hz), 5.09 (2H, s), 3.53 (3H, s), 2.51 (3H, s), 1.48 (6H, s); IR (neat) 2976, 1622, 1474, 1377, 1331, 1290, 1196, 1157, 1127, 1076, 1049, 963, 895, 729 cm^{-1} ; EIMS m/z 278 (M^+ , 50), 264 (15), 263 (100), 233 (37), 231 (11), 219 (37), 218 (12).

(E)-1-(5-Hydroxy-8-methoxymethoxy-2,2-dimethyl-2H-chromen-6-yl)-3-phenylpropenone (20). To a solution of **16** (83 mg, 0.3 mmol) in ethanol (10 mL) was added potassium hydroxide (84 mg, 1.5 mmol) and benzaldehyde (**17**) (48 mg, 0.45 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N-HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **20** (97 mg, 88%) as a solid: mp 92–93 °C; ^1H NMR (300 MHz, CDCl_3) δ 13.47 (1H, s), 7.87 (1H, d, $J = 15.4$ Hz), 7.65–7.62 (2H, m), 7.51 (1H, s), 7.50–7.40 (4H, m), 6.74 (1H, d, $J = 10.1$ Hz), 5.60 (1H, d, $J = 10.1$ Hz), 5.13 (2H, s), 3.57 (3H, s), 1.47 (6H, s); IR (KBr) 2928, 1641, 1574, 1362, 1289, 1155, 1125, 1046, 965, 889, 768, 727 cm^{-1} ; EIMS m/z 366 (M^+ , 100), 352 (20), 351 (91), 321 (39), 247 (28), 217 (31), 189 (27), 149 (40), 131 (60), 105 (20), 103 (24).

(E)-1-(5-Hydroxy-8-methoxymethoxy-2,2-dimethyl-2H-chromen-6-yl)-3-*p*-tolylpropenone (21). To a solution of **16** (83 mg, 0.3 mmol) in ethanol (10 mL) was added potassium hydroxide (84 mg, 1.5 mmol) and 4-methylbenzaldehyde (**18**) (54 mg, 0.45 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N-HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **21** (91 mg, 80%)

as a solid: mp 110-111 °C; ^1H NMR (300 MHz, CDCl_3) δ 15.53 (1H, s), 7.85 (1H, d, $J = 15.4$ Hz), 7.53 (2H, d, $J = 8.1$ Hz), 7.70 (1H, s), 7.43 (1H, d, $J = 15.4$ Hz), 7.22 (2H, d, $J = 8.1$ Hz), 6.74 (1H, d, $J = 10.1$ Hz), 5.60 (1H, d, $J = 10.1$ Hz), 5.10 (2H, s), 3.54 (3H, s), 2.38 (3H, s), 1.47 (6H, s); IR (KBr) 3456, 2982, 2953, 1642, 1591, 1568, 1480, 1375, 1283, 1182, 1152, 1128, 1057, 966, 844, 808, 751 cm^{-1} ; EIMS m/z 380 (M^+ , 100), 366 (17), 365 (72), 335 (38), 289 (15), 247 (34), 231 (10), 230 (11), 217 (41), 203 (18), 202 (14), 189 (29), 174 (12), 145 (55), 117 (16), 115 (16), 105 (11), 91 (13), 57 (13).

(E)-1-(5-Hydroxy-8-methoxymethoxy-2,2-dimethyl-2H-chromen-6-yl)-3-(4-methoxyphenyl)propenone (22). To a solution of **16** (83 mg, 0.3 mmol) in ethanol (10 mL) was added potassium hydroxide (84 mg, 1.5 mmol) and 4-methoxybenzaldehyde (**19**) (61 mg, 0.45 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N-HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **22** (93 mg, 78%) as a solid: mp 128-129 °C; ^1H NMR (300 MHz, CDCl_3) δ 13.59 (1H, s), 7.84 (1H, d, $J = 15.4$ Hz), 7.59 (2H, d, $J = 8.8$ Hz), 7.54 (1H, s), 7.35 (1H, d, $J = 15.4$ Hz), 6.90 (2H, d, $J = 8.8$ Hz), 6.74 (1H, d, $J = 10.1$ Hz), 5.59 (1H, d, $J = 10.1$ Hz), 5.13 (2H, s), 3.84 (3H, s), 3.57 (3H, s), 1.49 (6H, s); IR (KBr) 3453, 2986, 1640, 1607, 1562, 1514, 1474, 1377, 1292, 1254, 1177, 1152, 1121, 1028, 963, 824, 783 cm^{-1} ; EIMS m/z 396 (M^+ , 14), 368 (15), 217 (11), 161 (13), 147 (10), 29 (40), 125 (13), 123 (11), 113 (15), 112 (16), 111 (24), 110 (10), 109 (17), 99 (14), 97 (41), 96 (17), 95 (26), 85 (36), 84 (18), 83 (51), 82 (19), 81 (29), 73 (28), 71 (61), 70 (30), 69 (62), 57 (100), 55 (67).

Flemichapparin A (1). To a solution of **20** (73 mg, 0.2 mmol) in methanol (10 mL) was added 3 N HCl (10 drops) and the reaction mixture was heated at 50 °C for 1 h. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3×30 mL). The combined organic phases were washed with saturated NaHCO_3 solution, water (30 mL), and dried over MgSO_4 . Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **1** (56 mg, 87%) as a solid: mp 190-191 °C; ^1H NMR (300 MHz, CDCl_3) δ 13.34 (1H, s), 7.86 (1H, d, $J = 15.5$ Hz), 7.64-7.61 (2H, m), 7.51 (1H, d, $J = 15.5$ Hz), 7.42-7.40 (3H, m), 7.34 (1H, s), 6.74 (1H, d, $J = 10.1$ Hz), 5.60 (1H, d, $J = 10.1$ Hz), 5.12 (1H, s), 1.49 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 192.0, 155.2, 147.0, 144.3, 136.9, 134.7, 130.6, 129.0, 128.5, 128.1, 120.3, 116.1, 113.5, 112.8, 109.5, 79.1, 28.4; IR (KBr) 3449, 2973, 1636, 1591, 1476, 1396, 1362, 1300, 1165, 1121, 1046, 978, 891, 842, 766, 716 cm^{-1} ; EIMS m/z 322 (M^+ , 69), 308 (16), 307 (78), 218 (14), 204 (12), 203 (100), 191 (10), 190 (16), 153 (11), 131 (16), 103 (14), 77 (11).

(E)-1-(5,8-Dihydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-*p*-tolylpropenone (2). To a solution of **21** (76 mg, 0.2 mmol) in methanol (10 mL) was added 3 N HCl (10 drops)

and the reaction mixture was heated at 50 °C for 1 h. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3×30 mL). The combined organic phases were washed with saturated NaHCO_3 solution, water (30 mL), and dried over MgSO_4 . Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **2** (57 mg, 85%) as a solid: mp 168-169 °C; ^1H NMR (300 MHz, CDCl_3) δ 13.59 (1H, s), 7.84 (1H, d, $J = 15.4$ Hz), 7.52 (2H, d, $J = 8.0$ Hz), 7.46 (1H, d, $J = 15.4$ Hz), 7.34 (1H, s), 7.21 (2H, d, $J = 8.0$ Hz), 6.74 (1H, d, $J = 10.1$ Hz), 5.56 (1H, d, $J = 10.1$ Hz), 5.11 (1H, s), 2.38 (3H, s), 1.49 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 192.1, 155.1, 146.9, 144.5, 141.3, 136.9, 132.0, 129.7, 128.6, 128.1, 119.3, 116.2, 113.5, 112.8, 109.5, 79.1, 28.4, 21.6; IR (KBr) 3347, 2973, 1638, 1589, 1561, 1478, 1393, 1358, 1292, 1242, 1184, 1154, 1121, 1036, 1036, 972, 928, 928, 887, 812, 725 cm^{-1} ; EIMS m/z 336 (M^+ , 84), 322 (11), 321 (53), 293 (12), 218 (22), 204 (12), 203 (100), 190 (22), 153 (12), 149 (39), 145 (15), 115 (12), 91 (12), 71 (14), 69 (14), 57 (16), 55 (11).

(E)-1-(5,8-Dihydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-(4-methoxyphenyl)propenone (3). To a solution of **22** (59 mg, 0.15 mmol) in methanol (10 mL) was added 3 N HCl (10 drops) and the reaction mixture was heated at 50 °C for 1 h. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3×30 mL). The combined organic phases were washed with saturated NaHCO_3 solution, water (30 mL), and dried over MgSO_4 . Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **3** (43 mg, 82%) as a solid: mp 195-196 °C; ^1H NMR (300 MHz, CDCl_3) δ 13.45 (1H, s), 7.83 (1H, d, $J = 15.4$ Hz), 7.59 (2H, d, $J = 8.7$ Hz), 7.38 (1H, d, $J = 15.4$ Hz), 7.34 (1H, s), 6.92 (2H, d, $J = 8.7$ Hz), 6.74 (1H, d, $J = 10.1$ Hz), 5.59 (1H, d, $J = 10.1$ Hz), 5.12 (1H, s), 3.84 (3H, s), 1.49 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 192.0, 161.8, 155.1, 144.2, 136.8, 130.4, 128.0, 127.5, 117.9, 116.2, 114.4, 113.5, 112.9, 109.5, 79.1, 55.4, 28.4; IR (KBr) 3441, 2973, 2936, 1642, 1601, 1570, 1512, 1480, 1424, 1395, 1379, 1292, 1240, 1175, 1152, 1123, 1038, 889, 835, 783, 720 cm^{-1} ; EIMS m/z 352 (M^+ , 78), 337 (26), 218 (33), 204 (12), 203 (100), 190 (26), 161 (17), 134 (30), 133 (10), 91 (10), 69 (10), 57 (16), 55 (11).

1-[5,8-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]ethone (23). To a solution of 2,4,5-trihydroxyacetophenone (**14**) (336 mg, 2.0 mmol) and citral (608 mg, 4.0 mmol) in toluene (30 mL) was added ethylenediamine diacetate (36 mg, 0.2 mmol) at room temperature. The reaction mixture was refluxed for 12 h and then cooled to room temperature. Water was added and the solution was extracted with ethyl acetate. Evaporation of solvent and purification by column chromatography on silica gel gave **23** (423 mg, 70%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 12.61 (1H, s), 7.11 (1H, s), 6.72 (1H, d, $J = 10.2$ Hz), 5.51 (1H, d, $J = 10.2$ Hz), 5.21 (1H, s), 5.04 (1H, t, $J = 7.0$ Hz), 2.48 (3H, s), 2.10-2.02 (2H, m), 1.85-1.65 (2H, m), 1.62 (3H, s), 1.52 (3H, s), 1.42 (3H, s); IR (neat) 3420, 2924,

1622, 1478, 1393, 1329, 1294, 1221, 1082, 1047, 974, 904, 864, 727 cm^{-1} ; EIMS m/z 302 (M^+ , 25) (12), 220 (13), 219 (100), 210 (11), 69 (32).

1-[5-Hydroxy-8-methoxymethoxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]ethone (24). Methoxy-methyl chloride (81 mg, 1.0 mmol) was added to a solution of **23** (302 mg, 1.0 mmol) and diisopropylethylamine (646 mg, 5.0 mmol) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 h, and then water (30 mL) was added. The reaction mixture was extracted with methylene chloride (3×20 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried (MgSO_4), and evaporated *in vacuo*. Flash chromatography on silica gel afforded **24** (288 mg, 83%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 12.75 (1H, s), 7.29 (1H, s), 6.72 (1H, d, $J = 10.2$ Hz), 5.54 (1H, d, $J = 10.2$ Hz), 5.04 (2H, s), 5.02 (1H, t, $J = 7.0$ Hz), 3.53 (3H, s), 2.50 (3H, s), 2.11-2.04 (2H, m), 1.86-1.78 (1H, m), 1.69-1.63 (1H, m), 1.62 (3H, s), 1.53 (3H, s), 1.43 (3H, s); IR (neat) 2926, 1622, 1474, 1372, 1331, 1287, 1221, 1186, 1155, 1090, 1047, 962, 907, 826, 729 cm^{-1} ; EIMS m/z 346 (M^+ , 22), 302 (6), 264 (15), 263 (100), 259 (7), 220 (5), 219 (38), 218 (6), 201 (5), 181 (5), 69 (22), 55 (6).

(E)-1-[5-Hydroxy-8-methoxymethoxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]-3-phenylpropenone (27). To a solution of **24** (69 mg, 0.2 mmol) in ethanol (10 mL) was added potassium hydroxide (56 mg, 1.0 mmol) and benzaldehyde (**17**) (32 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **27** (73 mg, 84%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 13.50 (1H, s), 7.86 (1H, d, $J = 15.5$ Hz), 7.65-7.61 (2H, m), 7.50 (1H, s), 7.45-7.40 (3H, m), 6.78 (1H, d, $J = 10.1$ Hz), 5.56 (1H, d, $J = 10.1$ Hz), 5.10 (2H, s), 5.70 (1H, t, $J = 7.0$ Hz), 3.56 (3H, s), 2.15-2.06 (2H, m), 1.86-1.79 (1H, m), 1.71-1.61 (1H, m), 1.63 (3H, s), 1.55 (3H, s), 1.46 (3H, s); IR (neat) 2963, 2926, 1640, 1574, 1474, 1362, 1287, 1167, 1046, 965, 926, 845, 768, 729 cm^{-1} ; EIMS m/z 434 (M^+ , 20), 351 (98), 236 (38), 111 (40), 98 (31), 97 (82), 96 (46), 95 (40), 85 (51), 84 (36), 83 (100), 82 (48), 73 (57), 71 (82), 70 (40), 67 (50), 60 (47), 57 (53), 56 (49), 55 (88).

(E)-1-[5-Hydroxy-8-methoxymethoxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]-3-(2-methoxymethoxyphenyl)propenone (28). To a solution of **24** (69 mg, 0.2 mmol) in ethanol (10 mL) was added potassium hydroxide (56 mg, 1.0 mmol) and **25** (50 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **28** (74 mg, 75%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 13.56 (1H, s), 8.18 (1H, d, $J = 15.4$ Hz), 7.64-7.59

(2H, m), 7.52 (1H, s), 7.34 (1H, t, $J = 7.6$ Hz), 7.17 (1H, d, $J = 7.6$ Hz), 7.03 (1H, t, $J = 8.2$ Hz), 6.79 (1H, d, $J = 10.1$ Hz), 5.55 (1H, d, $J = 10.1$ Hz), 5.29 (2H, s), 5.12 (2H, s), 5.09 (1H, t, $J = 7.0$ Hz), 3.55 (3H, s), 3.50 (3H, s), 2.15-2.06 (2H, m), 1.89-1.78 (1H, m), 1.71-1.61 (1H, m), 1.65 (3H, s), 1.55 (3H, s), 1.45 (3H, s); IR (neat) 2928, 1634, 1568, 1476, 1362, 1283, 1157, 1082, 1046, 988, 926, 756 cm^{-1} ; EIMS m/z 494 (M^+ , 29), 412 (25), 411 (100), 349 (10), 247 (29), 203 (10), 69 (18).

(E)-1-[5-Hydroxy-8-methoxymethoxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]-3-(4-methoxymethoxyphenyl)propenone (29). To a solution of **24** (69 mg, 0.2 mmol) in ethanol (10 mL) was added potassium hydroxide (56 mg, 1.0 mmol) and **26** (50 mg, 0.3 mmol) at room temperature. The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol and extraction with ethyl acetate (3×50 mL), washing with 2 N HCl solution and brine, drying over MgSO_4 and removal of the solvent followed by flash column chromatography on silica gel gave **29** (78 mg, 79%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 13.56 (1H, s), 7.83 (1H, d, $J = 15.4$ Hz), 7.59 (2H, d, $J = 8.8$ Hz), 7.48 (1H, s), 7.36 (1H, d, $J = 15.4$ Hz), 7.07 (2H, d, $J = 8.8$ Hz), 6.75 (1H, d, $J = 10.1$ Hz), 5.55 (1H, d, $J = 10.1$ Hz), 5.21 (2H, s), 5.09 (2H, s), 5.07 (1H, t, $J = 7.0$ Hz), 3.54 (3H, s), 3.47 (3H, s), 2.15-2.06 (2H, m), 1.88-1.78 (1H, m), 1.71-1.55 (1H, m), 1.63 (3H, s), 1.55 (3H, s), 1.45 (3H, s); IR (neat) 2928, 1636, 1568, 1510, 1474, 1372, 1289, 1242, 1155, 1082, 1046, 995, 926, 831, 731 cm^{-1} ; EIMS m/z 494 (M^+ , 30), 412 (25), 411 (100), 346 (11), 263 (10), 247 (47), 203 (11), 97 (10), 71 (15), 69 (20), 57 (19), 55 (11).

(E)-1-[5,8-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-6-yl]-3-phenylpropenone (4). To a solution of **27** (56 mg, 0.13 mmol) in methanol (10 mL) was added 3 N HCl (10 drops) and the reaction mixture was heated at 50 $^\circ\text{C}$ for 1 h. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3×30 mL). The combined organic phases were washed with saturated NaHCO_3 solution, water (30 mL), and dried over MgSO_4 . Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **4** (44 mg, 86%) as a solid: mp 190-191 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 13.35 (1H, s), 7.85 (1H, d, $J = 15.4$ Hz), 7.64-7.60 (2H, m), 7.50 (1H, d, $J = 15.4$ Hz), 7.41-7.38 (3H, m), 7.33 (1H, s), 6.77 (1H, d, $J = 10.1$ Hz), 5.54 (1H, d, $J = 10.1$ Hz), 5.19 (1H, s), 5.06 (1H, t, $J = 7.0$ Hz), 2.16-2.07 (2H, m), 1.85-1.67 (2H, m), 1.63 (3H, s), 1.54 (3H, s), 1.45 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 191.9, 155.2, 147.2, 144.3, 136.7, 134.8, 132.2, 130.6, 129.0, 128.9, 128.5, 128.4, 127.0, 123.5, 120.4, 116.6, 113.5, 112.7, 109.3, 81.7, 41.5, 27.2, 25.6, 22.7, 17.6; IR (KBr) 3418, 2971, 2926, 1644, 1576, 1478, 1394, 1296, 1169, 978, 766, 721 cm^{-1} ; EIMS m/z 390 (M^+ , 58), 347 (26), 308 (22), 307 (100), 203 (75), 147 (21), 131 (27), 129 (92), 112 (26), 83 (23), 71 (40), 70 (30), 69 (34), 57 (54), 55 (29).

Fleming A (5). To a solution of **28** (54 mg, 0.11 mmol) in methanol (10 mL) was added 3 N HCl (10 drops) and the reaction mixture was heated at 50 $^\circ\text{C}$ for 1 h. The mixture

was cooled, diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated NaHCO₃ solution, water (30 mL), and dried over MgSO₄. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **5** (37 mg, 82%) as a solid: mp 149-150 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.44 (1H, s), 8.15 (1H, d, *J* = 15.4 Hz), 7.70 (1H, d, *J* = 15.4 Hz), 7.56 (1H, d, *J* = 7.7 Hz), 7.37 (1H, s), 7.24 (1H, t, *J* = 7.7 Hz), 6.94 (1H, t, *J* = 7.5 Hz), 6.84 (1H, d, *J* = 7.5 Hz), 6.79 (1H, d, *J* = 10.1 Hz), 5.55 (1H, d, *J* = 10.1 Hz), 5.21 (1H, s), 5.07 (1H, t, *J* = 7.0 Hz), 2.14-2.04 (2H, m), 1.86-1.67 (2H, m), 1.64 (3H, s), 1.55 (3H, s), 1.46 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.9, 156.0, 155.2, 147.4, 140.5, 136.6, 132.1, 131.8, 130.0, 126.9, 123.5, 122.1, 121.0, 120.8, 116.6, 116.5, 113.9, 112.8, 109.3, 81.7, 41.5, 27.2, 25.6, 22.7, 17.6; IR (KBr) 3385, 2972, 1626, m 1479, 1395, 1296, 1167, 1094, 1044, 986, 932, 900, 864, 752 cm⁻¹; EIMS *m/z* 406 (M⁺, 59), 388 (54), 368 (20), 345 (45), 323 (73), 306 (25), 305 (100), 266 (22), 203 (89), 91 (29), 83 (24), 71 (25), 69 (53), 57 (42), 55 (35).

Fleming D (8). To a solution of **29** (59 mg, 0.12 mmol) in methanol (10 mL) was added 3 N HCl (10 drops) and the reaction mixture was heated at 50 °C for 1 h. The mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated NaHCO₃ solution, water (30 mL), and dried over MgSO₄. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel to give **8** (42 mg, 87%) as a solid: mp 164-165 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.45 (1H, s), 7.80 (1H, d, *J* = 15.4 Hz), 7.53 (2H, d, *J* = 8.6 Hz), 7.37 (1H, d, *J* = 15.4 Hz), 7.32 (1H, s), 6.87 (2H, d, *J* = 8.6 Hz), 6.79 (1H, d, *J* = 10.1 Hz), 6.70 (1H, s), 5.53 (1H, d, *J* = 10.1 Hz), 5.12 (1H, s), 5.06 (1H, t, *J* = 7.0 Hz), 2.17-2.03 (2H, m), 1.85-1.65 (2H, m), 1.64 (3H, s), 1.54 (3H, s), 1.45 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.0, 158.2, 155.1, 147.2, 144.2, 136.6, 132.2, 130.6, 127.6, 126.9, 123.5, 117.8, 116.7, 116.2, 116.0, 113.5, 112.7, 109.3, 81.6, 41.5, 27.2, 25.6, 22.7, 17.6; IR (KBr) 3385, 1630, 1605, 1514, 1478, 1395, 1292, 1165, 1042, 980, 930, 829, 760 cm⁻¹; EIMS *m/z* 406 (M⁺, 83), 363 (27), 324 (21), 323 (90), 286 (12), 243 (14), 217 (11), 204 (13), 203 (100), 165 (12), 147 (29), 120 (16), 119 (11), 91 (12), 69 (19).

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