

New Synthetic Routes to Biologically Interesting Geranylated Acetophenones from *Melicope semecarpifolia* and Their Unnatural Prenylated and Farnesylated Derivatives[†]

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This paper describes a new synthetic approach for biologically interesting geranylated acetophenones. The first total syntheses of 1-(5-geranyloxy-7-hydroxy-2,2-dimethyl-2H-chromen-8-yl)ethanone and 1-[5-geranyloxy-7-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone, isolated from *Melicope semecarpifolia*, were carried out starting from commercially available 2,4,6-trihydroxyacetophenone.

Key Words: Geranylated acetophenone, *Melicope semecarpifolia*, Chalcone

Introduction

Prenylated and geranylated acetophenones are widely distributed in nature.¹ Interestingly, it was reported that the presence of the prenyl and geranyl group leads to remarkable increases in certain bioactivities.² These groups have shown to possess many physiological properties, including anti-convulsive,³ antifungal,⁴ antiproliferative,⁵ and antioxidant activities.⁶ Among these, two acetophenones, 4-(1'-geranyloxy)-2,6-dihydroxyacetophenone (**1**) and 4-(1'-geranyloxy)-2,6-dihydroxy-3-prenylacetophenone (**2**), with geranyl groups, were isolated from the fruits of *Evodia merrillii*, a small folk medicinal tree distributed throughout Taiwan (Fig. 1).^{1a,7} Two other geranylated acetophenones bearing pyranyl rings, 1-(5-geranyloxy-7-hydroxy-2,2-dimethyl-2H-chromen-8-yl)ethanone (**3**) and 1-[5-geranyloxy-7-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone (**4**), were isolated from *Melicope semecarpifolia*, a small- to medium-sized evergreen tree found at low altitude in Taiwan and the Philippines (Fig. 1).⁸ The roots of this plant have been used as a carminative in folk medicines.⁹ Isolated compounds from this plant have demonstrated antiplatelet aggregation¹⁰ and cytotoxic¹¹ activities that have stimulated interest in the synthesis of naturally occurring acetophenones with geranyloxy groups on the benzene ring. Although synthetic schemes for 4-(1'-geranyloxy)-2,6-dihydroxyacetophenone (**1**) have been reported, starting from 2,4,6-trihydroxyacetophenone through 5-steps,¹² no syntheses of naturally occurring geranylated acetophenones **2-4** have been reported thus far.

Recently, we reported the synthesis of biologically interesting natural products with benzopyran skeletons.¹³ In this lab's continuous efforts to synthesize biologically active molecules, we investigated a new route for the synthesis of biologically interesting acetophenones with geranyloxy groups on the benzene rings. Reported herein are the first total syntheses of naturally occurring geranylated acetophenones **3-4**. We also report the synthesis of their unnatural prenylated and farnesylated derivatives.

Results and Discussion

Scheme 1 shows the retrosynthetic strategy for naturally occurring geranylated acetophenones **3** and **4** through regioselective *O*-geranylation reactions of key intermediates, chromenes **9** and **11**. These intermediates could be prepared by EDDA-catalyzed benzopyran formation reactions of compound **7**, generated from commercially available 2,4,6-trihydroxyacetophenone (**5**) using selective protection and deprotection reactions.

The synthesis of naturally occurring geranylated acetophenone **3** bearing the pyranyl ring was first carried out as shown in Scheme 2. Treatment of 2,4,6-trihydroxyacetophenone (**5**) with 2.2 eq of methoxymethyl chloride (MOMCl) and *N,N*-diisopropylethylamine in methylene chloride at room temperature for 12 h afforded **6** in 85% yield.¹⁴ Selective dimethoxymethylation of **5** was confirmed by ¹H-NMR spectral analysis of the obtained compound **6**. The signal for the proton of hydroxyl group of **6** was observed as a singlet associated with a hydrogen bond to a carbonyl group at δ 13.68 ppm. Two methoxy signals

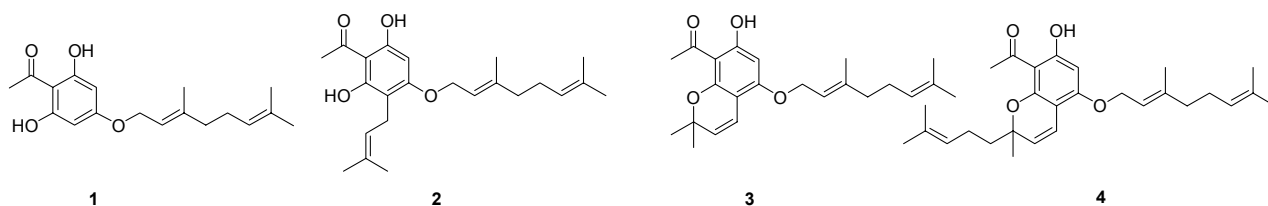
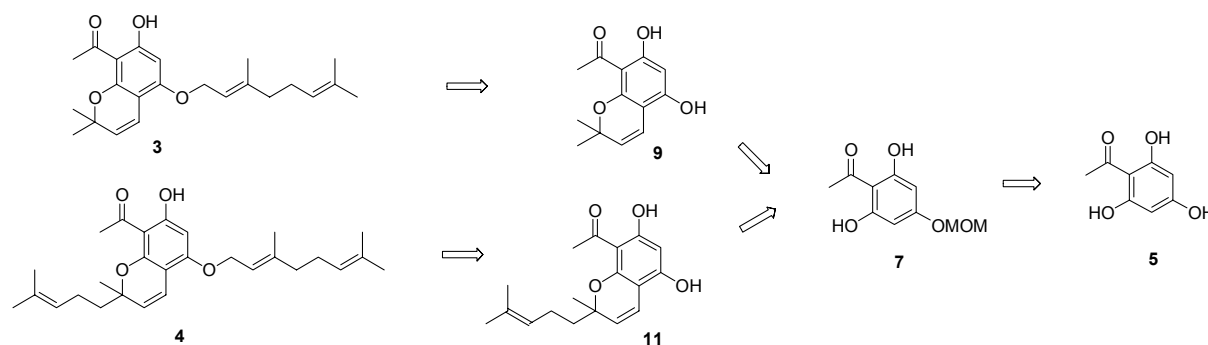
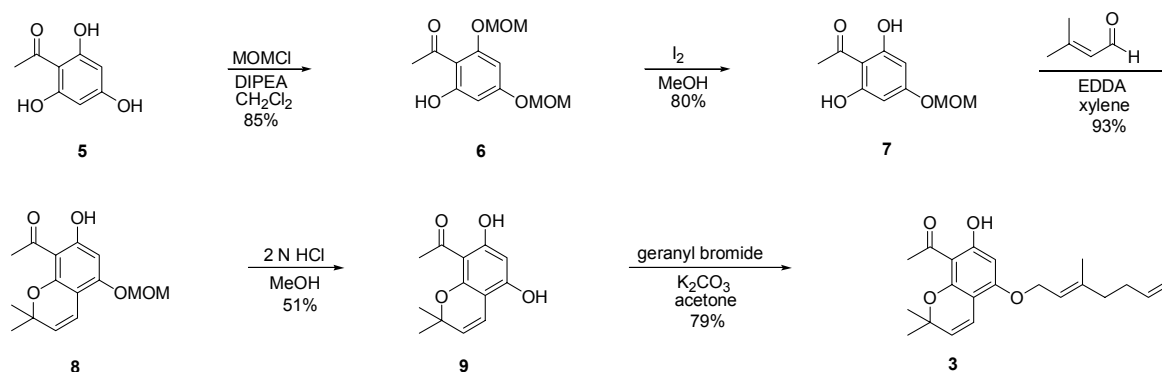


Figure 1. Naturally occurring geranylated acetophenones.

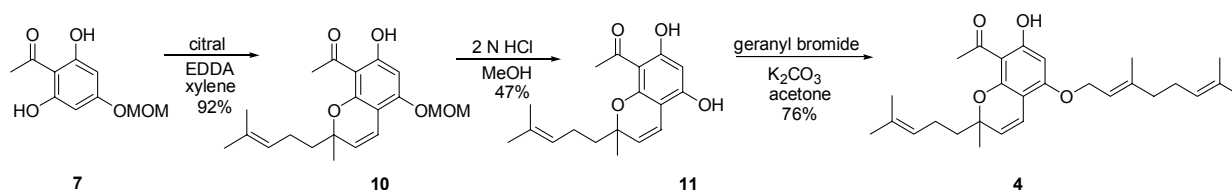
[†]This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



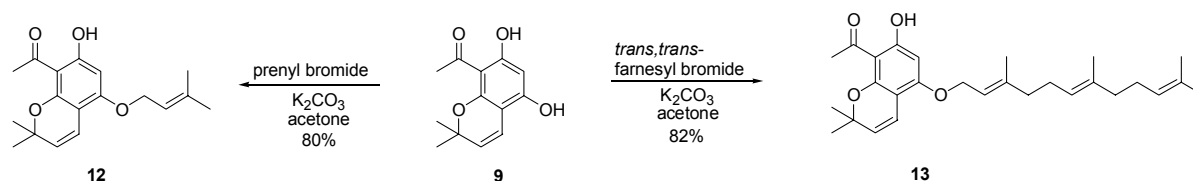
Scheme 1



Scheme 2



Scheme 3



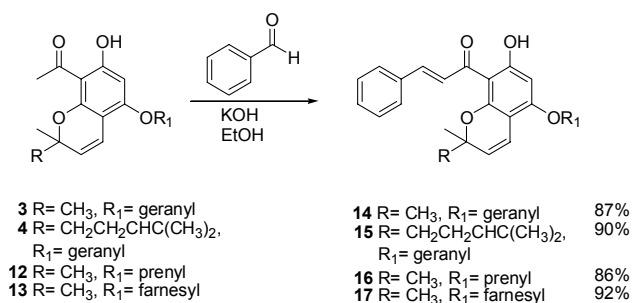
Scheme 4

of the MOM ethers were observed as two singlets at δ 3.48 and 3.44 ppm. Using known reaction conditions,^{14,15} selective *ortho*-cleavage of the methoxymethyl ether of **6** to give **7** was achieved in 80% yield by treatment with iodine in methanol at room temperature for 10 h. Reaction of **7** with 3-methyl-2-butenal in the presence of 20 mol % ethylenediamine diacetate in refluxing xylene for 10 h provided the desired chromene **8** in 93% yield. Deprotection of **8** with 2N HCl in methanol at room temperature for 10 h gave **9** in 51% yield. Regioselective *O*-geranylation of **9** with 1.1 eq of geranyl bromide and K_2CO_3 in acetone at room temperature for 10 h gave **3** in 79%. The spectral data of synthetic **3** were in agreement with those reported in the literature.⁸

Next, the synthesis of naturally occurring geranylated aceto-

phenone **4** was initiated with compound **7** as shown in Scheme 3. Reaction of **7** with citral in the presence of 20 mol % ethylenediamine diacetate in refluxing xylene for 10 h gave cycloadduct **10** in 92% yield. The MOM group of **10** was removed by hydrolysis with 2N HCl in methanol at room temperature for 10 h to afford **11** in 47% yield. Treatment of **11** with 1.1 eq of geranyl bromide in the presence of K_2CO_3 provided the desired product **4** in 76% yield. The spectral data of compound **4** were in agreement with those reported in the literature.⁸

As an application of this synthetic approach, the synthesis of the unnatural acetophenones **12** and **13** with the prenyl and farnesyl groups was carried out as shown in Scheme 4. Treatment of **9** with 1.1 eq of prenyl bromide in the presence of K_2CO_3 in



Scheme 5

acetone at room temperature for 12 h afforded **12** in 80% yield, whereas reaction with *trans,trans*-farnesyl bromide at room temperature for 12 h afforded **13** in 82% yield.

As other application, the synthesis of chalcones with prenyl, geranyl, and farnesyl group was next attempted by aldol condensation (Scheme 5). Chalcones with prenyl and geranyl groups are subclass of the flavonoids and are widely found in nature.¹⁶ They have been shown to have a range of biological activities.¹⁷ These important biological properties led to the synthesis of chalcones with prenyl, geranyl, and farnesyl group. Reactions of **3** and **4** with benzaldehyde in ethanolic KOH at room temperature for 48 h afforded chalcones **14** and **15** in 87 and 90% yields, respectively, whereas those of **12** and **13** gave **16** and **17** in 86 and 92% yields, respectively. These reactions present a rapid route for the synthesis of pyranoacetophenones and pyranochalcones with the prenyl, geranyl, and farnesyl groups.

In conclusion, an efficient synthetic route for biologically interesting geranylated acetophenones is described. The total syntheses of geranylated acetophenones bearing the pyran ring, 1-(5-geranyloxy-7-hydroxy-2,2-dimethyl-2H-chromen-8-yl) ethanone and 1-[5-geranyloxy-7-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone, were accomplished starting from commercially available 2,4,6-trihydroxyacetophenone through selective protection and deprotection, benzopyran formation, and *O*-geranylation. This synthetic approach was applied successfully to the syntheses of unnatural prenylated, geranylated, and farnesylated acetophenones and chalcones bearing the pyran ring.

Experimental

All experiments were carried out in a nitrogen atmosphere. Merck, pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ¹H and ¹³C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in CDCl₃ as the solvent chemical shift. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer.

2-Hydroxy-4,6-bis-methoxymethoxyacetophenone (6). Methoxymethyl chloride (0.354 g, 4.40 mmol) was added to a solution of **5** (0.336 g, 2.0 mmol) and diisopropylethylamine (1.292 g, 10.0 mmol) in dry CH₂Cl₂ (30 mL). The reaction mixture was stirred at room temperature for 12 h and then water (30 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were wash-

ed with saturated NH₄Cl solution (30 mL) and evaporated in vacuo. Flash chromatography on silica gel with hexane/EtOAc (7:1) afforded **6** (0.436 g, 85%) as a solid: mp 42–43 °C; ¹H NMR (300 MHz, CDCl₃) δ 13.68 (1H, s), 6.22 (1H, s), 6.21 (1H, s), 5.22 (2H, s), 5.14 (2H, s), 3.48 (3H, s), 3.44 (3H, s), 2.62 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.3, 167.0, 163.6, 160.5, 107.1, 97.3, 94.7, 94.2, 56.8, 56.6, 33.1; IR (KBr) 2959, 2933, 1624, 1434, 1366, 1273, 1224, 1156, 1066, 1023, 928, 831 cm⁻¹.

2,6-Dihydroxy-4-methoxymethoxyacetophenone (7). Iodine (152 mg, 0.60 mmol) was added to a solution of compound **6** (384 mg, 1.50 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was quenched with aqueous Na₂S₂O₃ (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with saturated NaHCO₃ (30 mL) and brine (30 mL), dried over MgSO₄, filtered, and evaporated to give the residue. Flash chromatography on silica gel with hexane/EtOAc (4:1) afforded **7** (0.255 g, 80%) as a solid: mp 108–109 °C; ¹H NMR (300 MHz, acetone-*d*₆) δ 11.71 (2H, s), 6.07 (2H, s), 5.18 (2H, s), 3.41 (3H, s), 2.62 (3H, s); ¹³C NMR (75 MHz, acetone-*d*₆) δ 204.3, 165.2, 164.7, 106.6, 96.1, 94.8, 56.5, 33.0; IR (KBr) 3278, 1628, 1598, 1422, 1378, 1310, 1278, 1231, 1156, 1074, 1022, 935, 818 cm⁻¹.

1-(7-Hydroxy-5-methoxymethoxy-2,2-dimethyl-2H-chromen-8-yl)ethanone (8). To a solution of **7** (233 mg, 1.10 mmol) and 3-methyl-2-butenal (110 mg, 1.32 mmol) in xylene (20 mL) was added ethylenediamine diacetate (40 mg, 0.22 mmol) at room temperature. The reaction mixture was refluxed for 10 h and cooled to room temperature. Evaporation of solvent and purification by column chromatography on silica gel using hexane/ethyl acetate (15:1) gave **8** (285 mg, 93%) as an oil; ¹H NMR (300 MHz, CDCl₃) δ 13.62 (1H, s), 6.53 (1H, d, *J* = 9.9 Hz), 6.15 (1H, s), 5.39 (1H, d, *J* = 9.9 Hz), 5.16 (3H, s), 3.43 (3H, s), 2.62 (3H, s), 1.45 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.3, 165.8, 158.4, 156.3, 124.8, 116.5, 106.5, 103.2, 94.8, 94.1, 77.9, 56.4, 33.2, 27.8; IR (neat) 2972, 1612, 1485, 1426, 1366, 1279, 1158, 1079, 954, 877, 825 cm⁻¹.

1-(5,7-Dihydroxy-2,2-dimethyl-2H-chromen-8-yl)ethanone (9). To a solution of **8** (250 mg, 0.90 mmol) in methanol (10 mL) was added 2N HCl (10 drops) and the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was 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 using hexane/ethyl acetate (7:1) to give **9** (105 mg, 51%) as an oil; ¹H NMR (300 MHz, acetone-*d*₆) δ 13.67 (1H, s), 9.60 (1H, s), 6.58 (1H, d, *J* = 9.9 Hz), 5.95 (1H, s), 5.52 (1H, d, *J* = 9.9 Hz), 2.62 (3H, s), 1.51 (6H, s); ¹³C NMR (75 MHz, acetone-*d*₆) δ 203.7, 166.9, 160.6, 158.0, 125.4, 117.4, 106.2, 103.0, 96.5, 78.9, 32.3, 28.0; IR (neat) 23330, 2976, 1606, 1503, 1425, 1367, 1273, 1176, 1086, 961, 881, 819 cm⁻¹.

1-(5-Geranyloxy-7-hydroxy-2,2-dimethyl-2H-chromen-8-yl)ethanone (3). Geranyl bromide (96 mg, 0.44 mmol) in acetone (1 mL) was added to a solution of compound **9** (94 mg, 0.40 mmol) and K₂CO₃ (276 mg, 2.0 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 10 h.

The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a 1N HCl solution, and extracted with ethyl acetate (50 mL \times 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with hexane/EtOAc (20:1) to give compound **3** (117 mg, 79%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 13.82 (1H, s), 6.58 (1H, d, J = 9.9 Hz), 6.00 (1H, s), 5.45 (1H, t, J = 6.3 Hz), 5.40 (1H, d, J = 9.9 Hz), 5.11 (1H, t, J = 6.6 Hz), 4.56 (2H, d, J = 6.3 Hz), 2.66 (3H, s), 2.18-2.04 (4H, m), 1.72 (3H, s), 1.68 (3H, s), 1.61 (3H, s), 1.48 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 166.3, 160.4, 156.2, 141.7, 131.9, 124.3, 123.7, 118.7, 116.8, 105.8, 103.0, 93.2, 77.9, 65.5, 39.5, 33.1, 27.8, 26.3, 25.7, 17.7, 16.7; IR (neat) 3495, 2970, 2923, 1610, 1424, 1366, 1274, 1168, 1116, 961, 878, 817 cm⁻¹.

1-[7-Hydroxy-5-methoxymethoxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone (10). To a solution of **7** (170 mg, 0.80 mmol) and citral (146 mg, 0.96 mmol) in xylene (20 mL) was added ethylenediamine diacetate (29 mg, 0.16 mmol) at room temperature. The reaction mixture was refluxed for 10 h and cooled to room temperature. Evaporation of solvent and purification by column chromatography on silica gel using hexane/ethyl acetate (15:1) gave **10** (255 mg, 92%) as an oil: ¹H NMR (300 MHz, acetone-*d*₆) δ 13.68 (1H, s), 6.65 (1H, d, J = 9.9 Hz), 6.17 (1H, s), 5.55 (1H, d, J = 9.9 Hz), 5.29 (2H, s), 5.14 (1H, t, J = 6.3 Hz), 3.46 (3H, s), 2.67 (3H, s), 2.30-1.78 (4H, m) 1.64 (3H, s), 1.57 (s, 3H), 1.48 (s, 3H); ¹³C NMR (75 MHz, acetone-*d*₆) δ 203.2, 166.0, 158.5, 156.6, 131.3, 124.0, 123.8, 116.8, 106.0, 102.9, 94.6, 94.3, 80.8, 55.8, 41.2, 32.6, 26.0, 24.9, 23.0, 16.8; IR (neat) 3728, 2967, 2920, 2862, 1612, 1590, 1483, 1427, 1367, 1279, 1216, 1160, 1110, 1059, 955, 888, 826 cm⁻¹.

1-[5,7-Dihydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone (11). To a solution of **10** (208 mg, 0.60 mmol) in methanol (10 mL) was added 2N HCl (10 drops) and the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with water (20 mL), and extracted with EtOAc (3 \times 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 using hexane/ethyl acetate (7:1) to give **11** (85 mg, 47%) as an oil: ¹H NMR (300 MHz, acetone-*d*₆) δ 13.80 (1H, s), 9.71 (1H, s), 6.72 (1H, d, J = 9.9 Hz), 6.04 (1H, s), 5.58 (1H, d, J = 9.9 Hz), 5.22 (1H, t, J = 6.3 Hz), 2.72 (3H, s), 2.30-1.78 (4H, m), 1.72 (3H, s), 1.65 (3H, s), 1.56 (3H, s); ¹³C NMR (75 MHz, acetone-*d*₆) δ 203.2, 166.5, 160.1, 157.8, 131.8, 124.5, 123.5, 117.5, 105.6, 102.2, 95.9, 81.3, 41.8, 33.0, 26.5, 25.4, 23.5, 17.3; IR (neat) 3728, 3303, 2971, 2928, 1609, 1501, 1429, 1368, 1275, 1174, 1085, 962, 891, 824 cm⁻¹.

1-[5-Geranyloxy-7-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]ethanone (4). Geranyl bromide (48 mg, 0.22 mmol) in acetone (1 mL) was added to a solution of compound **11** (60 mg, 0.20 mmol) and K₂CO₃ (138 mg, 1.0 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 10 h. The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a 1N

HCl solution, and extracted with ethyl acetate (50 mL \times 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with hexane/EtOAc (20:1) to give compound **4** (67 mg, 76%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 13.83 (1H, s), 6.62 (1H, d, J = 9.9 Hz), 5.99 (1H, s), 5.43 (1H, t, J = 6.6 Hz), 5.35 (1H, d, J = 9.9 Hz), 5.16-5.04 (2H, m), 4.57 (2H, d, J = 6.6 Hz), 2.66 (3H, s), 2.20-1.78 (8H, m), 1.72 (3H, s), 1.68 (3H, s), 1.65 (3H, s), 1.61 (3H, s), 1.57 (3H, s), 1.43 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 166.5, 160.6, 156.7, 141.9, 132.2, 132.1, 123.9, 123.9, 123.1, 118.9, 117.5, 105.9, 102.8, 93.2, 80.8, 65.6, 41.7, 39.7, 33.3, 26.7, 26.5, 25.8, 23.3, 17.9, 17.8, 16.9; IR (neat) 2969, 2921, 1610, 1425, 1368, 1277, 1175, 1106, 961, 875, 818 cm⁻¹.

1-[7-Hydroxy-2,2-dimethyl-5-prenyloxy)-2H-chromen-8-yl]ethanone (12). Prenyl bromide (82 mg, 0.55 mmol) in acetone (1 mL) was added to a solution of compound **9** (117 mg, 0.50 mmol) and K₂CO₃ (345 mg, 2.5 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a 1N HCl solution, and extracted with ethyl acetate (50 mL \times 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with hexane/EtOAc (15:1) to give compound **12** (121 mg, 80%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 13.80 (1H, s), 6.56 (1H, d, J = 9.9 Hz), 5.98 (1H, s), 5.44 (1H, t, J = 6.3 Hz), 5.38 (1H, d, J = 9.9 Hz), 4.50 (2H, d, J = 6.3 Hz), 2.64 (3H, s), 1.77 (3H, s), 1.71 (3H, s), 1.46 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 166.2, 160.3, 156.2, 138.5, 124.3, 118.8, 116.8, 105.8, 102.9, 93.1, 77.8, 65.4, 33.1, 27.8, 27.7, 25.8, 18.2; IR (neat) 2928, 2923, 1605, 1421, 1374, 1275, 1176, 1107, 961, 872, 822 cm⁻¹.

1-[7-Hydroxy-2,2-dimethyl-5-(*E*), (*E*)-farnesyloxy)-2H-chromen-8-yl]ethanone (13). *Trans, trans*-farnesyl bromide (94 mg, 0.33 mmol) in acetone (1 mL) was added to a solution of compound **9** (70 mg, 0.30 mmol) and K₂CO₃ (207 mg, 1.50 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a 1N HCl solution, and extracted with ethyl acetate (50 mL \times 3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel with hexane/EtOAc (20:1) to give compound **13** (108 mg, 82%) as a light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 13.80 (1H, s), 6.55 (1H, d, J = 9.9 Hz), 5.98 (1H, s), 5.44 (1H, t, J = 6.3 Hz), 5.39 (1H, d, J = 9.9 Hz), 5.16-5.02 (2H, m), 4.54 (2H, d, J = 6.3 Hz), 2.64 (3H, s), 2.16-1.95 (8H, m), 1.71 (3H, s), 1.65 (3H, s), 1.58 (6H, s), 1.46 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 203.1, 166.2, 160.3, 156.2, 141.6, 135.4, 131.2, 124.3, 123.7, 123.5, 118.6, 116.8, 105.8, 102.9, 93.1, 77.8, 65.4, 39.6, 39.6, 39.4, 33.0, 27.8, 26.6, 26.1, 25.7, 17.6, 16.7, 16.0; IR (neat) 2969, 2920, 2857, 1700, 1610, 1428, 1366, 1276, 1168, 1117, 961, 879, 817, 775, 689, 630, 582, 476 cm⁻¹.

1-(5-Geranyloxy-7-hydroxy-2,2-dimethyl-2H-chromen-8-

yl)-3-(E)-phenylpropenone (14). To a solution of **3** (33 mg, 0.09 mmol) in ethanol (10 mL) was added KOH (50 mg, 0.9 mmol) and benzaldehyde (11 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of NH₄Cl solution (40 mL), extraction with EtOAc (3 × 30 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (20:1) gave **14** (36 mg, 87%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 14.21 (1H, s), 8.12 (1H, d, *J* = 15.6 Hz), 7.75 (1H, d, *J* = 15.6 Hz), 7.61-7.58 (2H, m), 7.42-7.37 (3H, m), 6.60 (1H, d, *J* = 9.9 Hz), 6.04 (1H, s), 5.43 (1H, d, *J* = 9.9 Hz), 5.47-5.40 (1H, m), 5.08 (1H, t, *J* = 6.6 Hz), 4.57 (2H, d, *J* = 6.6 Hz), 2.15-1.98 (4H, m), 1.71 (3H, s), 1.66 (3H, s), 1.59 (3H, s), 1.53 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.7, 167.3, 160.7, 155.7, 142.1, 141.8, 135.6, 131.9, 130.0, 128.9, 128.2, 127.5, 124.4, 123.6, 118.6, 117.0, 107.0, 103.3, 93.5, 77.9, 65.5, 39.5, 27.9, 27.8, 26.2, 25.7, 17.7, 16.7; IR (neat) 2969, 2923, 2357, 1729, 1637, 1598, 1553, 1450, 1417, 1344, 1258, 1218, 1159, 1116, 1039, 980, 881, 817 cm⁻¹.

1-[5-Geranyloxy-7-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2H-chromen-8-yl]-3-(E)-phenylpropenone (15). To a solution of **4** (48 mg, 0.11 mmol) in ethanol (10 mL) was added KOH (62 mg, 1.10 mmol) and benzaldehyde (13 mg, 0.12 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of NH₄Cl solution (40 mL), extraction with EtOAc (3 × 30 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (20:1) gave **15** (52 mg, 90%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 14.23 (1H, s), 8.10 (1H, d, *J* = 15.6 Hz), 7.75 (1H, d, *J* = 15.6 Hz), 7.59-7.49 (2H, m), 7.38-7.30 (3H, m), 6.64 (1H, d, *J* = 9.9 Hz), 6.03 (1H, s), 5.45 (1H, t, *J* = 6.3 Hz), 5.39 (1H, d, *J* = 9.9 Hz), 5.25-5.08 (2H, m), 4.57 (2H, d, *J* = 6.3 Hz), 2.20-1.78 (8H, m), 1.72 (3H, s), 1.67 (3H, s), 1.62 (3H, s), 1.60 (3H, s), 1.47 (3H, s), 1.46 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.7, 167.3, 160.6, 156.0, 142.1, 141.7, 135.6, 132.1, 131.9, 130.0, 128.9, 128.3, 127.5, 123.6, 123.1, 118.6, 117.4, 106.0, 103.0, 94.0, 93.3, 80.5, 65.5, 41.4, 39.5, 26.6, 26.2, 25.7, 25.6, 23.0, 17.7, 17.5, 16.7; IR (neat) 2965, 2922, 2858, 1729, 1633, 1597, 1553, 1449, 1416, 1343, 1280, 1228, 1159, 1104, 980, 893, 818 cm⁻¹.

1-[7-Hydroxy-2,2-dimethyl-5-prenyloxy)-2H-chromen-8-yl]-3-(E)-phenylpropenone (16). To a solution of **12** (48 mg, 0.16 mmol) in ethanol (10 mL) was added KOH (90 mg, 1.60 mmol) and benzaldehyde (19 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of NH₄Cl solution (40 mL), extraction with EtOAc (3 × 30 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (20:1) gave **16** (54 mg, 86%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 13.80 (1H, s), 8.12 (1H, d, *J* = 15.6 Hz), 7.76 (1H, d, *J* = 15.6 Hz), 7.60 (2H, d, *J* = 7.8 Hz), 7.42-7.34 (3H, m), 6.59 (1H, d, *J* = 9.9 Hz), 6.04 (1H, s), 5.45 (1H, t, *J* = 6.6 Hz), 5.43 (1H, d, *J* = 9.9 Hz), 4.55 (2H, d, *J* = 6.6 Hz), 1.79 (3H, s), 1.73 (3H, s), 1.53 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.8, 170.9, 167.3, 160.6, 142.1, 138.6, 135.9, 130.0, 128.9, 128.3, 127.5, 124.4, 118.8, 117.0, 106.7, 103.3, 93.5, 77.9, 66.3, 27.9, 25.8, 21.0, 18.3; IR (neat) 3034, 2929, 1739, 1605, 1447, 1355, 1235, 1169, 1113, 1031, 980, 882, 823, 747,

701, 635, 575, 491 cm⁻¹.

1-[7-Hydroxy-2,2-dimethyl-5-(E), (E)-famesyloxy)-2H-chromen-8-yl]-3-(E)-phenylpropenone (17). To a solution of **13** (70 mg, 0.16 mmol) in ethanol (10 mL) was added KOH (90 mg, 1.60 mmol) and benzaldehyde (19 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of NH₄Cl solution (40 mL), extraction with EtOAc (3 × 30 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (50:1) gave **17** (77 mg, 92%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 13.87 (1H, s), 8.12 (1H, d, *J* = 15.6 Hz), 7.76 (1H, d, *J* = 15.6 Hz), 7.60 (2H, d, *J* = 7.8 Hz), 7.42-7.30 (3H, m), 6.60 (1H, d, *J* = 9.9 Hz), 6.04 (1H, s), 5.44 (1H, t, *J* = 6.6 Hz), 5.43 (1H, d, *J* = 9.9 Hz), 5.18-5.02 (2H, m), 4.57 (2H, d, *J* = 6.6 Hz), 2.64 (3H, s), 2.16-1.90 (8H, m), 1.72 (3H, s), 1.66 (3H, s), 1.59 (6H, s), 1.53 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 192.7, 167.3, 160.6, 155.7, 142.1, 141.8, 135.6, 135.5, 131.3, 130.0, 128.9, 128.2, 127.5, 124.4, 127.3, 123.5, 118.6, 117.0, 106.2, 103.3, 93.5, 77.9, 65.5, 61.4, 39.7, 39.5, 27.9, 26.7, 26.1, 25.7, 17.7, 16.7, 16.0; IR (neat) 2956, 2920, 1735, 1591, 1444, 1346, 1224, 1157, 1114, 978, 880, 819, 769, 696, 643, 576, 483 cm⁻¹.

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