# Concise Total Synthesis of Biologically Interesting Prenylated Chalcone Natural Products: 4'-*O*-Methylxanthohumol, Xanthohumol E, and Sericone

**Yong Rok Lee,* Xin Li, Seung Woo Lee, Chul Soon Yong,* Ma-Ro Hwang,† and Won Seok Lyoo‡**

*School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea. *E-mail: yrlee@yu.ac.kr*
*†College of Pharmacy, Yeungnam University, Gyeongsan 712-749, Korea*
*‡School of Textiles, Yeungnam University, Gyeongsan 712-749, Korea*
*Received April 2, 2008*

A new and efficient synthetic approach is reported for biologically interesting prenylated chalcones, 4'-*O*-methylxanthohumol (**3**), xanthohumol E (**4**), and sericone (**5**) from 2,4,6-trihydroxyacetophenone. The strategies involve the introduction of a prenyl group onto an aryl ring, benzopyran formation, and base-catalyzed aldol reactions.

**Key Words :** Prenylated chalcone, Xanthohumol, 4'-*O*-Methylxanthohumol, Xanthohumol E, Sericone

## Introduction

Prenylated chalcones are an abundant subclass of flavonoids that are widely distributed in nature.[1] Members of prenylated chalcones are associated with a wide variety of biological activities such as antimalarial,[2] antidiabetic,[3] antifungal,[4] antibacterial,[5] antitumor,[6] antimetastatic,[7] antioxidative,[8] anti-inflammatory,[9] and NF-κB inhibitory activities.[10] This wide range of biological activity has stimulated interest in the synthesis of naturally occurring prenylated chalcones. Among these, xanthohumol (**1**), desmethylxanthohumol (**2**), 4'-*O*-methylxanthohumol (**3**), and xanthohumol E (**4**) were isolated from *Humulus lupulus* (hop plant), which are cultivated in virtually all temperate zones in the world (Figure 1).[11] This plant is widely used in the brewing industry to add bitterness and aroma to beer.[12] These compounds have been found to have a variety of interesting biological activities. In particular, they have been shown to be potential anti-proliferative[13] and cancer chemopreventive agents[14] with broad-spectrum for the treatment of both breast and prostate cancers. They have been also shown to possess therapeutic utility, including hormonal activity for the treatment of osteoporosis,[15] an antioxidant for the treatment of atherosclerosis.[16] and inhibitory activity against HIV-I.[17] In addition, these compounds have also significant anti-inflammatory[18] and antimutagenic activities.[14a] Synthetic approaches to xanthohumol (**1**),[19] desmethylxanthohumol (**2**),[20] and 4'-*O*-methylxanthohumol (**3**)[21] have been already reported by other groups. However, the total synthesis of xanthohumol E (**4**) has not been reported thus far. Sericone (**5**), a regioisomer of xanthohumol E (**4**), was isolated from another plant, *Mundulea sericea*.[22] One synthetic approach to sericone (**5**) was reported by Diller, but this synthetic method suffers from the disadvantages of having many reaction steps.[22] This range of important biological properties and activities has stimulated research into the synthesis of naturally occurring 4'-*O*-methylxanthohumol (**3**), xanthohumol E (**4**), and sericone (**5**).

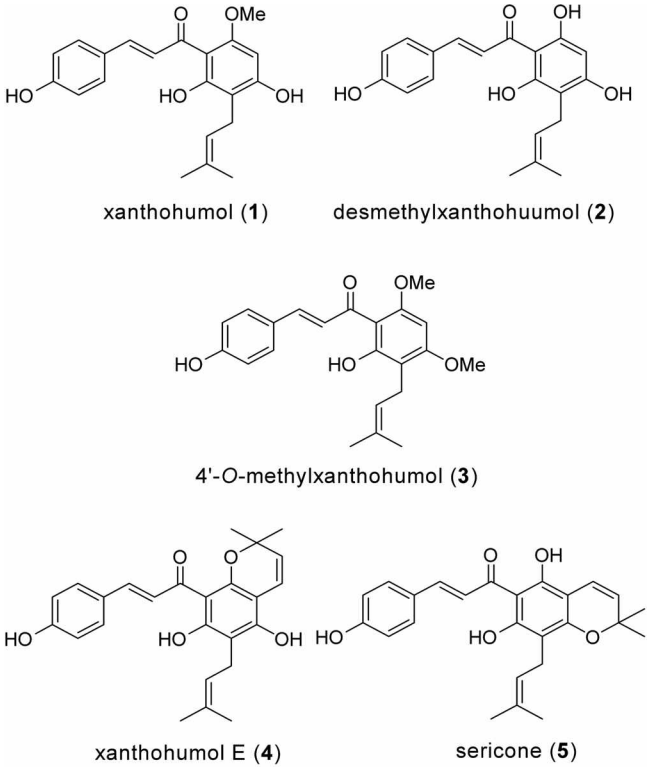
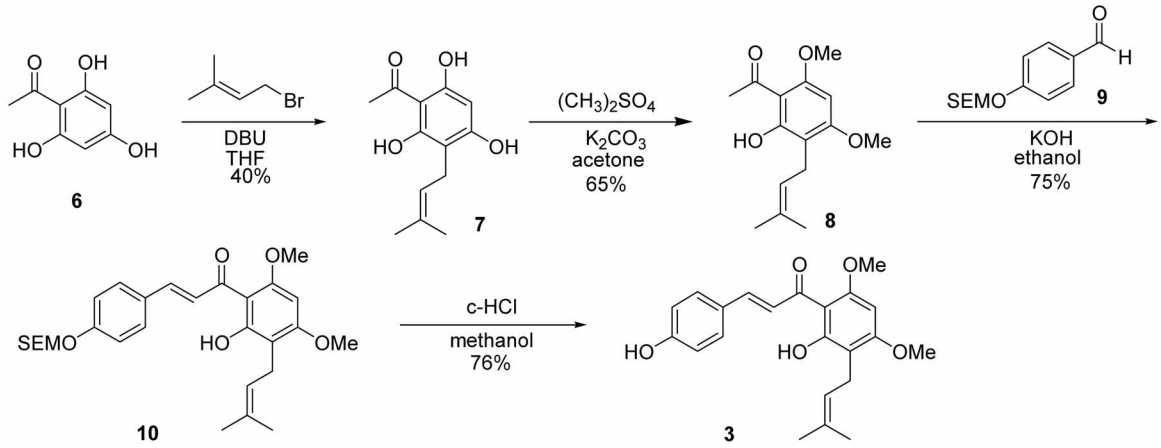



**Figure 1**. Selected naturally occurring prenylated chalcones

## Results and Discussion

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate-catalyzed reactions of resorcinols or naphthols to $\alpha,\beta$-unsaturated aldehydes.[23] Using this methodology as a key step, convergent synthetic routes have also been developed to provide biologically interesting natural products with benzopyran moiety.[24] As part an of ongoing study into the synthetic efficacy of these two methodologies, this paper reports a new synthetic route for biologically interesting prenylated chalcone natural products, 4'-*O*-methylxanthohumol (**3**), xanthohumol E (**4**), and sericone (**5**).

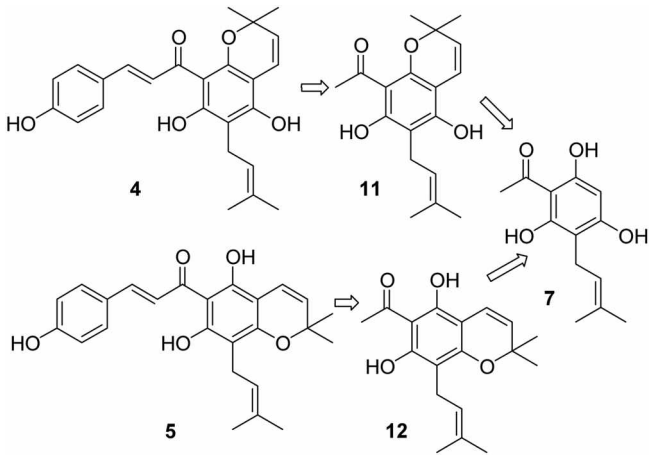



**Scheme 1**

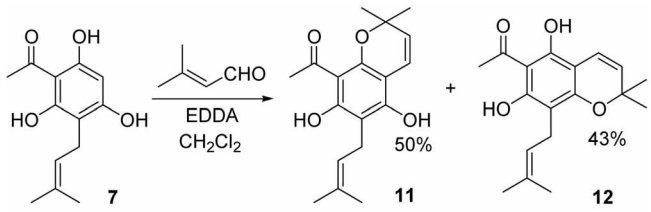
The synthesis of natural 4'-*O*-methylxanthohumol (**3**) was first attempted starting from 2,4,6-trihydroxyacetophenone (**6**), as shown in Scheme 1. Previous studies reported that *C*-prenylation can be achieved with prenyl bromide in the presence of either potassium hydroxide[22] or potassium carbonate.[25] Under these conditions, the desired product **7** was obtained in 30-34% yield. A better yield was obtained with DBU. A reaction of compound **6** with prenyl bromide in the presence of 1.1 equiv of DBU in THF at room temperature for 48 h gave compound **7** in 40% yield. Treatment of compound **7** with 2 equiv of dimethyl sulfate in the presence of potassium carbonate in acetone at room temperature for 4 h gave product **8** in 65% yield. An aldol reaction was next attempted to complete the synthesis of natural 4'-*O*-methylxanthohumol (**3**). The condensation of compound **8** with benzaldehyde **9** protected as a SEM ether in an ethanolic KOH solution at room temperature for 48 h afforded product **10** in 75% yield. Deprotection of compound **10** through a treatment with c-HCl in methanol at room temperature for 1 h gave the natural product **3** in 76% yield. The spectral data of the synthetic material **3** were in agreement with those reported in the literature.[26]

Next, the total synthesis of xanthohumol E (**4**) and sericone (**5**) was attempted. The strategy is depicted in Scheme 2. Xanthohumol E (**4**) and sericone (**5**) can be prepared from the base-catalyzed aldol reactions of the corresponding compounds **11** and **12** with the benzaldehyde **9** protected as a SEM ether. The crucial intermediates **11** and **12** could be generated from prenylated phloroacetophenone **7** through ethylenediamine diacetate-catalyzed benzopyran formation reactions.

Schemes 3-5 show the reaction pathway for the synthesis of natural xanthohumol E (**4**) and sericone (**5**). The cycloadditon reaction of prenylated compound **7** described above was first attempted (Scheme 3). A reaction of compound **7** with 3-methyl-2-butenal in the presence of 20 mol% of ethylenediamine diacetate (EDDA) in methylene chloride at room temperature for 12 h provided the products **11** and **12** in 50 and 43% yield, respectively. These two compounds were readily separated by column chromatography and assigned by a comparison with other compounds including



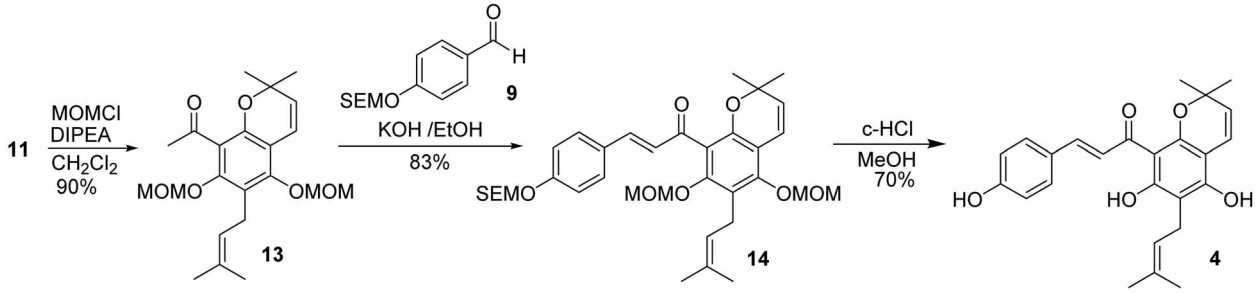

**Scheme 2**



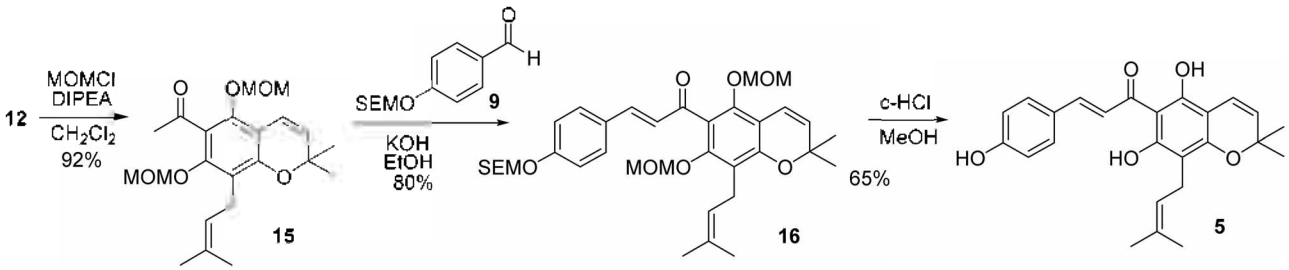

**Scheme 3**

these types of benzopyran skeletons as an angular and linear form.[27] The chemical shifts of the two vinylic protons on the pyranyl ring of compound **11** were more upfield than those of compound **12**. The $^1$H NMR spectrum of compound **11** showed two vinylic protons on the pyranyl ring at $\delta$ 6.52 ($J$ = 9.9 Hz) and 5.41 ($J$ = 9.9 Hz), whereas compound **12** showed two vinylic protons at $\delta$ 6.60 ($J$ = 9.9 Hz) and 5.43 ($J$ = 9.9 Hz).

Next, further reactions shown in Scheme 4 were carried out to complete the synthesis of xanthohumol E (**4**). Protection of compound **11** with 2.5 equiv of MOMCl in the presence of diisopropylethylamine in methylene chloride at room temperature for 12 h provided compound **13** in 90% yield. Compound **13** was then condensed with the corresponding aldehyde **9** in ethanolic KOH solution at room temperature for 48 h to give pyranochalcone **14** in 83%




**Scheme 4**




**Scheme 5**

yield. Attempts to deprotect compound **14** with TBAF or magnesium bromide diethyl etherate[28] did not give the desired natural product **4**. Fortunately, all the protecting groups were easily removed by a treatment with c-HCl in methanol at room temperature for 1 h to yield xanthohumol E (**4**) in 70% yield. The spectroscopic data of synthetic material **4** were in agreement with those reported in the literature.[29]

Additional reactions were carried out to synthesize sericone (**5**) as shown in Scheme 5. A reaction of compound **12** with 2.5 equiv of MOMCl gave product **15** in 92% yield. Condensation of compound **15** with benzaldehyde **9** in KOH at room temperature for 48 h followed by cleavage of the MOM and SEM ethers with c-HCl in methanol at room temperature for 1 h afforded sericone (**5**) in 52% yield (2-steps).

In conclusion, a new and concise synthetic route for biologically interesting prenylated pyranochalcone natural products, 4'-*O*-methylxanthohumol (**3**), xanthohumol E (**4**), and sericone (**5**) was developed starting from 2,4,6-trihydroxyacetophenone (**6**). The key strategies for 4'-*O*-methylxanthohumol (**3**) involve the insertion of a preyl group onto the aryl ring and base-catalyzed aldol reactions. The key strategies for xanthohumol E (**4**) and sericone (**5**) involve benzopyran formation reactions and base-catalyzed aldol reactions.

## Experimental

All the experiments were carried out in 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 $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ and benzene $d_6$ as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS and MS spectra were carried out at the Korea Basic Science Institute.

**2,4,6-Trihydroxy-3-prenylacetophenone (7).** A mixture of phloracetophenone (**6**) (2.02 g, 12.0 mmol), prenyl bromide (1.79 g, 12.0 mmol), and DBU (2.01 g, 13.2 mmol) in dry THF (50 mL) was stirred at room temperature for 48 h. Addition of 2 N HCl solution (50 mL), and extraction with ethyl acetate (3 × 50 mL), washing with brine (50 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (5:1) gave **7** (1.13 g, 40%) as a solid: mp 166-167 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.82 (1H, s), 5.22 (1H, t, $J$ = 7.0 Hz), 3.33 (2H, d, $J$ = 7.0 Hz), 2.64 (3H, s), 1.80 (3H, s), 1.75 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 203.6, 163.5, 162.1, 160.5, 132.4, 122.9, 106.5, 104.9, 94.7, 32.8, 25.9, 21.4, 17.9; IR (KBr) 3418, 1634, 1402, 1370, 1285, 1235, 1150, 1073, 986, 818 cm$^{-1}$; EIMS $m/z$ (%) 236 ($M^+$, 60), 221 (29), 193 (29), 181 (100), 165 (40), 153 (17), 69 (24); HRMS $m/z$ ($M^+$) calcd for $C_{13}H_{16}O_4$: 236.1049. Found: 236.1050.

**2-Hydroxy-4,6-dimethoxy-3-prenylacetophenone (8).** $K_2CO_3$ (1.87 g, 13.50 mmol) was added to a solution of **7** (0.64 g, 2.7 mmol) in acetone (10 mL) at room temperature. Dimethyl sulfate (0.68 g, 5.4 mmol) was then added dropwise, and the mixture was stirred at room temperature for 4 h. A saturated $NH_4Cl$ solution (50 mL) was added and the mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave an oily residue. The residue was then purified by column chromatography on silica gel using hexane/ethyl acetate (15:1) to give the product **8** (0.46 g, 65%) as a solid: mp 107-108 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 13.95 (1H, s), 5.89 (1H, s), 5.15 (1H, t,

$J$ = 6.9 Hz), 3.84 (6H, s), 3.22 (2H, d, $J$ = 6.9 Hz), 2.55 (3H, s), 1.74 (3H, s), 1.63 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 203.2, 163.3, 163.1, 161.6, 131.1, 122.6, 109.4, 105.7, 85.7, 55.3, 55.2, 33.0, 25.7, 21.1, 17.6; IR (KBr) 3454, 2909, 1624, 1595, 1460, 1420, 1275, 1211, 1123, 893, 791 cm$^{-1}$; EIMS *m/z* (%) 264 ($M^+$, 90), 250 (16), 249 (100), 221 (70), 209 (85), 193 (40), 191 (16), 181 (22), 69 (15).

**Compound 10.** To a solution of **8** (0.13 g, 0.5 mmol) in ethanol (10 mL) was added potassim hydroxide (0.14 g, 2.5 mmol) and aldehyde **9** (0.15 g, 0.6 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2 N HCl solution (30 mL) and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (20:1) gave **10** (0.19 g, 75%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 14.15 (1H, s), 7.77 (1H, d, $J$ = 15.8 Hz), 7.72 (1H, d, $J$ = 15.8 Hz), 7.52 (2H, d, $J$ = 8.7 Hz), 7.01 (2H, d, $J$ = 8.7 Hz), 5.93 (1H, s), 5.24 (2H, s), 5.19 (1H, t, $J$ = 7.0 Hz), 3.91 (3H, s), 3.87 (3H, s), 3.78 (2H, t, $J$ = 8.6 Hz), 3.27 (2H, d, $J$ = 7.0 Hz), 1.76 (3H, s), 1.66 (3H, s), 0.94 (2H, t, $J$ = 8.6 Hz), −0.01 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 192.9, 164.0, 163.1, 161.1, 159.0, 141.8, 131.3, 129.8, 129.1, 125.8, 122.7, 116.3, 109.9, 106.3, 92.6, 86.3, 66.4, 55.7, 55.4, 25.8, 21.3, 18.0, 17.7, −1.5; IR (neat) 2938, 1607, 1514, 1169, 1116 cm$^{-1}$; EIMS *m/z* (%) 498 ($M^+$, 34), 400 (16), 397 (27), 372 (50), 371 (52), 233 (22), 207 924), 193 (47), 192 (28), 181 (36), 180 (15), 179 (53), 73 (100).

**4'-*O*-Methylxanthohumol (3).** To a solution of **10** (0.16 g, 0.31 mmol) in methanol (10 mL) was added c-HCl (5 drops) and the reaction mixture was stirred at room temperature for 1 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 $NaHCO_3$ solution (30 mL), 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 using hexane/ethyl acetate (2:1) to give **3** (0.08 g, 76%) as a solid: mp 152-153 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.75 (1H, d, $J$ = 15.8 Hz), 7.70 (1H, d, $J$ = 15.8 Hz), 7.45 (2H, d, $J$ = 8.7 Hz), 6.84 (2H, d, $J$ = 8.7 Hz), 5.97 (1H, s), 5.18 (1H, t, $J$ = 6.9 Hz), 3.91 (3H, s), 3.87 (3H, s), 3.27 (2H, d, $J$ = 6.9 Hz), 1.76 (3H, s), 1.65 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.1, 163.9, 163.3, 162.3, 161.3, 157.7, 131.5, 130.3, 128.1, 125.2, 122.6, 115.9, 109.9, 106.4, 86.4, 55.8, 55.5, 25.8, 21.4, 14.1; IR (KBr) 3368, 1607, 1512, 1416, 1329, 1227, 1169, 1138, 1117, 978, 831, 733 cm$^{-1}$; EIMS *m/z* (%) 368 ($M^+$, 80), 358 (25), 325 (73), 313 (27), 261 (16), 248 (15), 233 (77), 219 (17), 205 (45), 193 (100), 181 915), 147 (22), 119 (24), 107 (24), 91 (44), 77 (21), 65 (26); HRMS *m/z* ($M^+$) calcd for $C_{22}H_{24}O_5$: 368.4230. Found: 368.4232.

**1-(5,7-Dihydroxy-2,2-dimethyl-6-prenyl-2*H*-chromen-8-yl)ethanone (11) and 1-(5,7-dihydroxy-2,2-dimethyl-8-prenyl-2*H*-chromen-6-yl)ethanone (12).** To a solution of **7** (0.66 g, 2.8 mmol) and 3-methyl-2-butenal (0.47 g, 5.6 mmol) in methylene chloride (20 mL) was added ethylenediamine diacetate (0.10 g, 0.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. Water (50 mL) was added and the solution was extracted with methylene chloride (3 × 50 mL). Evaporation of solvent and purification by column chromatography on silica gel using hexane/ethyl acetate (10:1) gave **11** (0.42 g, 50%) and **12** (0.36 g, 43%). Compound **11**: mp 80-81 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 14.10 (1H, s), 6.52 (1H, d, $J$ = 9.9 Hz), 6.36 (1H, br s), 5.41 (1H, d, $J$ = 9.9 Hz), 5.23 (1H, t, $J$ = 7.0 Hz), 3.35 (2H, d, $J$ = 7.0 Hz), 2.65 (3H, s), 1.81 (3H, s), 1.75 (3H, s), 1.46 (6H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 203.3, 160.5, 156.7, 154.9, 125.4, 124.7, 116.4, 116.1, 105.5, 102.3, 102.1, 78.2, 33.2, 28.3, 28.0; IR (KBr) 2976, 1601, 1464, 1364, 1283, 1196, 1140, 1003, 883, 729 cm$^{-1}$; EIMS m/z (%) 302 ($M^+$, 42), 288 (9), 287 (48), 247 (10), 232 (15), 231 (100), 213 (17). Compound **12**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 12.69 (1H, s), 7.79 (1H, br s), 6.60 (1H, d, $J$ = 9.9 Hz), 5.43 (1H, d, $J$ = 9.9 Hz), 5.15 (1H, t, $J$ = 7.0 Hz), 3.29 (2H, d, $J$ = 7.0 Hz), 2.61 (3H, s), 1.80 (3H, s), 1.73 (3H, s), 1.38 (6H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 203.3, 159.1, 157.6, 156.8, 134.9, 125.0, 121.1, 115.6, 105.2, 104.6, 101.8, 77.2, 32.4, 27.6, 25.3, 20.8, 17.4; IR (neat) 2921, 1613, 1453, 1126, 802 cm$^{-1}$; EIMS *m/z* (%) 302 ($M^+$, 29), 288 (10), 287 (52), 247 (15), 232 (14), 231 (100), 213 (13).

**1-(5,7-Bismethoxymethoxy-2,2-dimethyl-6-prenyl-2*H*-chromen-8-yl)ethanone (13).** Methoxymethyl chloride (0.20 g, 2.5 mmol) was added to a solution of **11** (0.30 g, 1.0 mmol) and *N,N*-diisopropylethylamine (0.65 g, 5.0 mmol) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then water (40 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 30 mL) and the combined organic extracts were washed with saturated $NH_4Cl$ solution (30 mL), water (30 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (7:1) afforded **13** (0.35 g, 90%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.48 (1H, d, $J$ = 9.9 Hz), 5.57 (1H, d, $J$ = 9.9 Hz), 5.11 (1H, t, $J$ = 7.0 Hz), 4.87 (2H, s), 4.86 (2H, s), 3.44 (6H, s), 3.24 (2H, d, $J$ = 7.0 Hz), 2.50 (3H, s), 1.72 (3H, s), 1.63 (3H, s); 1.37 (6H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.8, 153.3, 152.7, 148.5, 131.2, 129.6, 122.5, 120.0, 116.8, 111.9, 101.2, 100.0, 76.4, 57.6, 32.7, 27.7, 25.7, 22.8, 17.9; IR (neat) 2975, 2928, 1697, 1642, 1588, 1452, 1373, 1238, 1213, 1124, 1059, 1023, 991, 932, 894, 800, 753 cm$^{-1}$; EIMS *m/z* (%) 390 ($M^+$, 22), 346 (34), 331 (18), 302 (11), 301 (52), 299 (18), 247 (15), 246 (16), 245 (12), 232 (14), 231 (100), 213 (11).

**Compound 14.** To a solution of **13** (0.26 g, 0.7 mmol) in ethanol (10 mL) was added potassium hydroxide (0.19 g, 3.3 mmol) and aldehyde **9** (0.25 g, 1.0 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2 N HCl solution (30 mL), water (30 mL), and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate

(10:1) gave **14** (0.34 g, 83%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.47 (2H, d, $J$ = 8.8 Hz), 7.39 (1H, d, $J$ = 16.0 Hz), 7.00 (2H, d, $J$ = 8.8 Hz), 6.92 (1H, d, $J$ = 16.0 Hz), 6.54 (1H, d, $J$ = 9.9 Hz), 5.59 (1H, d, $J$ = 9.9 Hz), 5.21 (2H, s), 5.15 (1H, t, $J$ = 7.0 Hz), 4.88 (2H, s), 4.87 (2H, s), 3.81 (2H, t, $J$ = 8.4 Hz), 3.41 (3H, s), 3.40 (3H, s), 3.30 (2H, d, $J$ = 7.0 Hz), 1.75 (3H, s), 1.66 (3H, s), 1.40 (6H, s), 0.92 (2H, t, $J$ = 8.4 Hz), −0.03 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 194.0, 159.8, 153.9, 149.8, 144.6, 131.6, 130.5, 129.9, 128.7, 127.2, 123.2, 122.9, 120.5, 117.5, 116.8, 112.5, 101.4, 101.2, 93.0, 76.9, 66.9, 58.1, 58.0, 28.3, 26.2, 23.4, 18.4, -1.0; IR (neat) 2955, 1641, 1595, 1510, 1236, 1161, 1092, 993, 837 cm$^{-1}$; EIMS $m/z$ (%) 624 ($M^+$, 38), 609 (21), 580 (18), 579 (15), 577 (17), 519 (10), 419 (8), 330 (29), 315 (25), 301 (22), 286 (19), 285 (100), 271 (60), 269 (27), 243 (16), 231 (15), 219 (54), 215 (33), 201 (15), 73 (74).

**Xanthohumol E (4).** To a solution of **14** (0.21 g, 0.3 mmol) in methanol (10 mL) was added c-HCl (5 drops) and the reaction mixture was stirred at room temperature for 1 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 $NaHCO_3$ 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 using hexane/ethyl acetate (2:1) to give **4** (0.09 g, 70%) as an oil; $^1$H NMR (300 MHz, benzene-$d_6$) $\delta$ 14.56 (1H, br s), 7.98 (1H, d, $J$ = 15.6 Hz), 7.71 (1H, d, $J$ = 15.6 Hz), 7.46 (2H, d, $J$ = 8.6 Hz), 6.86 (2H, d, $J$ = 8.6 Hz), 6.55 (1H, d, $J$ = 9.9 Hz), 6.42 (1H, br s), 5.45 (1H, d, $J$ = 9.9 Hz), 5.27 (1H, t, $J$ = 7.0 Hz), 3.38 (2H, d, $J$ = 7.0 Hz), 1.81 (3H, s), 1.76 (3H, s), 1.51 (6H, s); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 191.8, 163.3, 160.1, 157.2, 153.6, 142.5, 130.3, 130.2, 125.9, 125.0, 123.5, 122.8, 117.1, 116.0, 108.3, 105.0, 102.5, 77.1, 27.2, 25.4, 21.1, 17.7; IR (neat) 3395, 1604, 1512, 1443, 1346, 1167, 831 cm$^{-1}$; EIMS $m/z$ (%) 406 ($M^-$, 81), 405 (19), 392 (24), 391 (93), 368 (24), 351 (16), 286 (15), 285 (36), 271 (46), 243 (25), 231 (28), 230 (15), 229 (16), 215 (100), 147 (17), 97 (15), 91 (17), 83 (17), 81 (15), 71 (16), 69 (19); HRMS $m/z$ ($M^+$) calcd for $C_{25}H_{26}O_5$: 406.4709. Found: 406.4707.

**1-(5,7-Bismethoxymethoxy-2,2-dimethyl-8-prenyl-2*H*-chromen-6-yl)ethanone (15).** Methoxymethyl chloride (0.17 g, 2.1 mmol) was added to a solution of **12** (0.26 g, 0.8 mmol) and *N,N*-diisopropylethylamine (0.54 g, 4.2 mmol) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then water (40 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 30 mL) and the combined organic extracts were washed with saturated $NH_4Cl$ solution (30 mL), water (30 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (7:1) afforded **15** (0.30 g, 92%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.46 (1H, d, $J$ = 9.9 Hz), 5.52 (1H, d, $J$ = 9.9 Hz), 5.11 (1H, t, $J$ = 7.0 Hz), 4.87 (2H, s), 4.82 (2H, s), 3.49 (3H, s), 3.39 (3H, s), 3.24 (2H, d, $J$ = 7.0 Hz), 2.44 (3H, s), 1.66 (3H, s), 1.56 (3H, s); 1.35 (6H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.7, 154.1, 153.5, 149.6, 131.6, 129.8, 123.8, 123.0, 122.1, 117.7, 112.4, 101.3, 100.8, 76.9, 58.0, 57.6, 35.0, 28.0, 25.6, 23.9, 18.3; IR (neat) 2973, 2928, 1698, 1638, 1586, 1428, 1351, 1281, 1214, 1161, 1072, 1039, 962, 801, 753 cm$^{-1}$; EIMS $m/z$ (%) 390 ($M^-$, 28), 346 (57), 331 (27), 302 (14), 301 (67), 299 (23), 285 (13), 247 (15), 246 (16), 245 (12), 232 (14), 231 (100), 213 (11).

**Compound 16.** To a solution of **15** (0.22 g, 0.6 mmol) in ethanol (10 mL) was added potassium hydroxide (0.16 g, 2.9 mmol) and aldehyde **9** (0.22 g, 0.9 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2 N HCl solution (30 mL), water (30 mL), and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (10:1) gave **16** (0.29 g, 80%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43 (2H, d, $J$ = 8.7 Hz), 7.32 (1H, d, $J$ = 16.0 Hz), 6.97 (2H, d, $J$ = 8.7 Hz), 6.86 (1H, d, $J$ = 16.0 Hz), 6.52 (1H, d, $J$ = 9.9 Hz), 5.52 (1H, d, $J$ = 9.9 Hz), 5.18 (2H, s), 5.18 (1H, t, $J$ = 7.0 Hz), 4.94 (2H, s), 4.87 (2H, s), 3.69 (2H, t, $J$ = 8.4 Hz), 3.54 (3H, s), 3.33 (3H, s), 3.32 (2H, d, $J$ = 7.0 Hz), 1.69 (3H, s), 1.64 (3H, s), 1.29 (6H, s), 0.90 (2H, t, $J$ = 8.4 Hz), −0.06 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 193.5, 159.1, 153.5, 149.5, 144.1, 131.0, 129.7, 129.3, 128.1, 126.7, 123.3, 121.5, 120.4, 117.2, 116.2, 111.9, 100.5, 100.2, 92.4, 76.1, 66.2, 57.4, 57.1, 27.5, 25.5, 23.4, 17.8, −1.6; IR (neat) 2955, 1645, 1599, 1510, 1314, 1236, 1159, 1130, 1092, 1033, 982, 860, 835 cm$^{-1}$; EIMS $m/z$ (%) 624 ($M^-$, 54), 609 (15), 579 (14), 551 (15), 548 (15), 533 (15), 521 (33), 475 (19), 330 (14), 285 (29), 283 (22), 271 (16), 269 (19), 223 (19), 220 (14), 219 (77), 215 (32), 179 (15), 73 (100).

**Sericone (5).** To a solution of **16** (0.21 g, 0.3 mmol) in methanol (10 mL) was added c-HCl (5 drops) and the reaction mixture was stirred at room temperature for 1 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 $NaHCO_3$ solution (30 mL), 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 using hexane/ethyl acetate (2:1) to give **5** (0.09 g, 65%) as an oil: $^1$H NMR (300 MHz, benzene-$d_6$) $\delta$ 13.17 (1H, br s), 7.82 (1H, d, $J$ = 15.5 Hz), 7.73 (1H, d, $J$ = 15.5 Hz), 7.50 (2H, d, $J$ = 8.6 Hz), 7.28 (1H, br s), 6.83 (2H, d, $J$ = 8.6 Hz), 6.66 (1H, d, $J$ = 9.9 Hz), 5.46 (1H, d, $J$ = 9.9 Hz), 5.19 (1H, t, $J$ = 7.0 Hz), 3.34 (2H, d, $J$ = 7.0 Hz), 1.83 (3H, s), 1.77 (3H, s), 1.42 (6H, s); IR (neat) 3387, 1605, 1514, 1443, 1169, 833 cm$^{-1}$; EIMS $m/z$ (%) 406 ($M^-$, 67), 404 (14), 403 (15), 392 (27), 391 (100), 369 (18), 368 (36), 351 (16), 285 (26), 271 (38), 269 (22), 243 (24), 236 (16), 231 (26), 230 (15), 229 (20), 215 (85), 151 (29), 149 (51), 147 (33), 129 (17), 122 (15), 121 (27), 120 (20), 119 (20), 111 (23), 109 (23), 107 (21), 98 (22), 97 (38), 91 (29), 83 (42), 81 (35), 71 (43), 69 (52); HRMS $m/z$ ($M^+$) calcd for $C_{25}H_{26}O_5$: 406.4709. Found: 406.4710.

**Acknowledgments.** This research was supported by the Yeungnam University research grants in 208-A-235-021.

## References


1. (a) Shimizu, K.; Kondo, R.; Sakai, K.; Buabarn, S.; Dilokkunanant, U. *Phytochemistry* **2000**, *54*, 737. (b) Jayasinghe, L.; Rupasinghe, G. K.; Hara, N.; Fujimoto, Y. *Phytochemistry* **2006**, *67*, 1353. (c) Nishimura, R.; Tabata, K.; Motoki, A.; Ito, Y.; Kimura, Y.; Akihisa, T.; Nagai, H.; Sakuma, A.; Kohno, H.; Suzuki, T. *Biol. Pharm. Bull.* **2007**, *30*, 1878. (d) Rodriguez, R. J.; Miranda, C. L.; Stevens, J. F.; Deinzer, M. L.; Buhler, D. R. *Food Chemical. Toxicol.* **2001**, *39*, 437.
2. Narender, T.; Shweta; Tanvir, K.; Rao, M. S.; Srivastava, K.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2453.
3. Enoki, T.; Ohnogi, H.; Nagamine, K.; Kudo, Y.; Sugiyama, K.; Tanabe, M.; Kobayashi, E.; Sagawa, H.; Kato, I. *J. Agric. Food Chem.* **2007**, *55*, 6013.
4. Jayasinghe, L.; Balasooriya, B. A. I. S.; Padmini, W. C.; Hara, N.; Fujimoto, Y. *Phytochemistry* **2004**, *65*, 1287.
5. Yin, S.; Fan, C.-Q.; Wang, Y.; Dong, L.; Yue, J.-M. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 4387.
6. (a) Akihisa, T.; Tokuda, H.; Hasegawa, D.; Ukiya, M.; Kimura, Y.; Enjo, F.; Suzuki, T.; Nishino, H. *J. Nat. Prod.* **2006**, *69*, 38. (b) Akihisa, T.; Tokuda, H.; Ukiya, M.; Iizuka, M.; Schneider, S.; Ogasawara, K.; Mukainaka, T.; Iwatsuki, K.; Suzuki, T.; Nishino, H. *Cancer Lett.* **2003**, *201*, 133. (c) Tabata, K.; Motani, K.; Takayanagi, N.; Nishimura, R.; Asami, S.; Kimura, Y.; Ukiya, M.; Hasegawa, D.; Akihisa, T.; Suzuki, T. *Biol. Pharm. Bull.* **2005**, *28*, 1404.
7. Kimura, Y.; Baba, K. *Int. J. Cancer* **2003**, *106*, 429.
8. Haraguchi, H.; Ishikawa, H.; Mizutani, K.; Tamura, Y.; Kinoshita, T. *Bioorg. Med. Chem.* **1998**, *6*, 339.
9. Hsieh, H.-K.; Lee, T. H.; Wang, J.-P.; Wang, J.-J.; Lin, C.-N. *Pharm. Res.* **1998**, *15*, 39.
10. Sugil, M.; Ohkita, M.; Taniguchi, M.; Baba, K.; Kawai, Y.; Tahara, C.; Takaoka, M.; Matsumura, Y. *Bio. Pharm. Bull.* **2005**, *28*, 607.
11. Stevens, J. F.; Ivancic, M.; Hsu, V.; Deinzer, M. L. *Phytochemistry* **1997**, *44*, 1575.
12. Stevens, J. F.; Page, J. E. *Phytochemistry* **2004**, *65*, 1317.
13. Miranda, C. L.; Stevens, J. F.; Helmrich, A.; Henderson, M. C.; Rodriguez, R. J.; Yang, Y.-H.; Deinzer, M. L.; Barnes, D. W.; Buhler, D. R. *Food Chemical. Toxicol.* **1999**, *37*, 271.
14. (a) Miranda, C. L.; Aponso, G. L. M.; Stevens, J. F.; Deinzer, M. L.; Buhler, D. R. *Cancer Lett.* **2000**, *149*, 21. (b) Miranda, C. L.; Yang, Y.-H.; Henderson, M. C.; Stevens, J. F.; Santana-Rios, G.; Deinzer, M. L.; Buhler, D. R. *Drug Metab. Dispos.* **2000**, *28*, 1297. (c) Henderson, M. C.; Miranda, C. L.; Stevens, J. F.; Deinzer, M. L.; Buhler, D. R. *Xenobiotica* **2000**, *30*, 235.
15. (a) Overk, C. R.; Yao, P.; Chadwick, L. R.; Nikolic, D.; Sun, Y.; Cuendet, M. A.; Deng, Y.; Hedayat, A. S.; Pauli, G. F.; Farnsworth, N. R.; van Breemen, R. B.; Bolton, J. L. *J. Agric. Food Chem.* **2005**, *53*, 6246. (b) Miranda, C. L.; Stevens, J. F.; Ivanov, V.; McCall, M.; Frei, B.; Deinzer, M. L.; Buhler, D. R. *J. Agric. Food Chem.* **2000**, *48*, 3876.
16. Stevens, J. F.; Miranda, C. L.; Frei, B.; Buhler, D. R. *Chem. Res. Toxicol.* **2003**, *16*, 1277.
17. Wang, Q.; Ding, Z.-H.; Liu, J.-K.; Zheng, Y.-T. *Antiviral Res.* **2004**, *64*, 189.
18. Gerhäuser, C.; Alt, A.; Heiss, E.; Gamal-Eldeen, A.; Klimo, K.; Knauft, J.; Neumann, I.; Scherf, H.-R.; Frank, N.; Bartsch, H.; Becker, H. *Mol. Cancer Ther.* **2002**, *1*, 959
19. Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2007**, *70*, 1507.
20. Diller, R. A.; Riepl, H. M.; Rose, O.; Frias, C.; Henze, G.; Prokop, A. *Chem. Biodivers.* **2005**, *2*, 1331.
21. Jain, A. C.; Sinha, S. P. *Indian J. Chem. Sec. B* **1994**, *33*, 317.
22. Zyl, J. J. V.; Rall, G. J. H.; Roux, D. G. *J. Chem. Research (S)* **1979**, 97.
23. a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539. (b) Wang, X.; Lee, Y. R. *Tetrahedron Lett.* **2007**, *48*, 6275. (c) Lee, Y. R.; Kim, Y. M. *Helv. Chim. Acta* **2007**, *90*, 2401. (d) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232.
24. (a) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044. (a) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240. (c) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853. (d) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603. (e) Lee, Y. R.; Xia, L. *Bull. Korean Chem. Soc.* **2007**, *28*, 1579. (f) Lee, Y. R.; Wang, X.; Kim, Y. M.; Shim, J. J.; Kim, B. N.; Han, D. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 1735. (g) Lee, Y. R.; Li, X. *Bull. Korean Chem. Soc.* **2007**, *28*, 1739. (h) Lee, Y. R.; Wang, X. *Bull. Korean Chem. Soc.* **2007**, *28*, 2061. (i) Lee, Y. R.; Xia, L. *Tetrahedron Lett.* **2008**, *49*, 3283. (j) Lee, Y. R.; Li, X.; Kim, J. H. *J. Org. Chem.* in press. (k) Lee, Y. R.; Xia, L. *Synlett.* in press.
25. Yang, Y.-G.; Zhang, Y.; Cao, X.-P. *Huaxue Xuebao* **2005**, *63*, 1901.
26. Sun, S.; Watanabe, S.; Saito, T. *Phytochemistry* **1989**, *28*, 1776.
27. (a) Daikonya, A.; Katsuki, S.; Kitanaka, S. *Chem. Pharm. Bull.* **2004**, *52*, 1326. (b) Daikonya, A.; Katsuki, S.; Wu, J.-B.; Kitanaka, S. *Chem. Pharm. Bull.* **2002**, *50*, 1566. (c) Su, C.-R.; Kuo, P.-C.; Wang, M.-L.; Liou, M.-J.; Damu, A. G.; Wu, T.-S. *J. Nat. Prod.* **2003**, *66*, 990
28. Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 2185.
29. Stevens, J. F.; Taylor, A. W.; Nickerson, G. B.; Ivancic, M.; Henning, J.; Haunold, A.; Deinzer, M. L. *Phytochemistry* **2000**, *53*, 759.