

## Total Synthesis of Xanthohumol

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The total synthesis of xanthohumol (**1**) was accomplished in 10% overall yield from phloracetophenone after six steps. Insertion of a prenyl group onto the aryl ring was achieved by a para-Claisen rearrangement after using a Mitsunobu reaction to establish the key prenyl ether precursor. A Claisen–Schmidt condensation was deployed to construct the chalcone scaffold followed by removal of MOM protecting groups under acidic conditions that were optimized to prevent concomitant cyclization to the flavone.

Xanthohumol (**1**) is the principal prenylated chalcone present in the female inflorescences of the hop plant *Humulus lupulus* L. (Cannabaceae).<sup>1</sup> The latter are commonly used to add a bitter flavor to beer wherein **1** readily undergoes cyclization to the flavone isoxanthohumol (**2**) during the brewing process.<sup>1,2</sup> Xanthohumol has been found to have a range of interesting biological properties in vitro that may have therapeutic utility including hormonal (for relief of “hot flashes” and treatment of osteoporosis),<sup>3</sup> antioxidant (for treating atherosclerosis),<sup>4</sup> and inhibition of HIV-1,<sup>5</sup> as well as its multimechanism classification as a potential “broad-spectrum” anticancer and cancer prevention agent (applicable to both breast and prostate cancers).<sup>6–10</sup> As a result, studies directed toward dietary supplements having increased xanthohumol content<sup>11–13</sup> and further biological characterization of purified **1** at the in vivo level are underway.<sup>14</sup> In vivo studies are limited, however, by the need to obtain pure material from natural sources using a multistep process that typically involves extraction, chromatography, precipitation, and crystallization.<sup>1,15,16</sup> An interest in the synthesis<sup>17,18</sup> and in vivo disposition of pterocarpanoid natural products having potential anticancer or cancer preventive properties<sup>19,20</sup> prompted our consideration of xanthohumol as conveyed herein.

Xanthohumol was first isolated by Power et al.<sup>21</sup> Its structure was initially elucidated by Verzele et al.<sup>22</sup> and later confirmed by two independent groups using partial synthesis and chemical degradation methods.<sup>23,24</sup> Although both a 4,4'-*O,O*-dimethylated analogue and a 6'-*O*-desmethyl analogue have subsequently been synthesized,<sup>25,26</sup> a formal construction of **1** has not been previously reported. Our overall synthesis is depicted in Scheme 1.

While the enlistment of robust protecting groups is advantageous for the Claisen–Schmidt condensation that would ultimately produce the polyhydroxylated chalcone,<sup>26</sup> we recognized that their removal would need to be accomplished under mild conditions lest we run the risk of prompting spontaneous ring-closure to the unwanted flavone.<sup>25</sup> On the basis of our work with other flavonoid and pterocarpanoid systems, we selected the methoxymethyl (MOM) group. It represents an ideal compromise of stability under basic conditions and facile cleavage under a range of acidic conditions.<sup>17,18</sup> Thus, the first step (“a”) involved partial MOM protection of 2',4',6'-trihydroxyacetophenone (phloracetophenone; **3**). Steps “b” and “c” were then used to insert a prenyl group. While direct alkylation of systems related to **3** and **4** often runs the risk of giving poor yields,<sup>26,27</sup> the use of a Claisen rearrangement on a variety of related systems has typically been very efficient even though two steps are required.<sup>28,29</sup> Intending to take advantage of the free phenolic hydroxyl group in **4**, we first attempted to form the prenyl ether by refluxing in acetone with prenyl bromide and potassium carbonate.<sup>29</sup>

Although we were not able to observe significant formation of the desired product by this approach, a Mitsunobu reaction with prenyl alcohol delivered **5** in 80% yield.<sup>30</sup> Returning to the closest literature procedure for step “c”, however, again met with difficulty. For example, although there was an observable loss of the prenyl ether, no desired product was obtained after heating **5** neat at 200 °C.<sup>29</sup> Refluxing in decalin produced an intractable mixture, while no reaction was observed after refluxing in chloroform for up to two days even when Eu(fod)<sub>3</sub> was added as a catalyst.<sup>30</sup> Finally, when **5** was heated at 200 °C in *N,N*-dimethylaniline,<sup>28</sup> the desired para-*C*-prenylated product **6** was obtained in ca. 65% yield after conveniently removing the high-boiling solvent by adding ethyl acetate and washing with aqueous acid followed by column chromatography to obtain pure material.

Step “d” involved introducing the desired methyl functionality onto the re-exposed ortho-hydroxy group in **6**. This was accomplished by using dimethylsulfate in the presence of potassium carbonate to produce ketone **7** as the first partner for the Claisen–Schmidt condensation. The MOM-protected aldehyde partner **9** was obtained uneventfully from 4-hydroxybenzaldehyde (**8**) in step “e” by using standard conditions.<sup>31</sup> Refluxing these partners in methanol and 10% aqueous sodium hydroxide (step “f”) gave the fully protected chalcone **10** in 60% yield.<sup>17,18</sup>

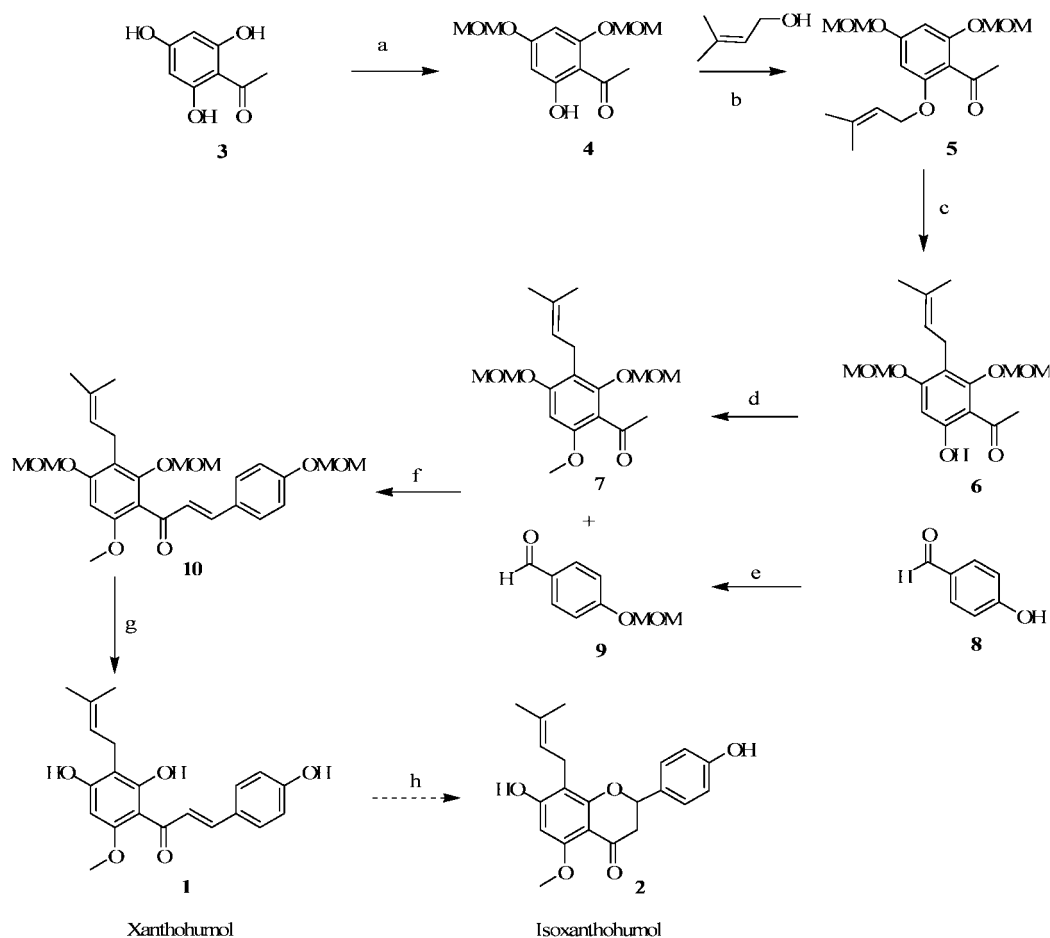
In the final step “g”, which involved MOM deprotection, we needed to carefully avoid concomitant cyclization to isoxanthohumol **2** (dotted line “h”). Indeed, heating **10** at pH 5–6 largely resulted in the cyclized product, as did subsequent heating at pH 4–5 and pH 3–4 for shorter times.<sup>32</sup> Alternatively, lowering the pH to slightly less than 1 and avoiding elevated temperature<sup>1,2</sup> by stirring at room temperature for 12 h allowed gradual removal of the MOM groups without cyclization. The optimized yield for this final step was 72%, and the overall yield for the entire six-step synthesis became about 10%.<sup>35</sup> This synthetic process should be able to be used to prepare larger quantities of xanthohumol needed for in vivo efficacy and toxicity studies. It should also be amenable to instillation of stable and radio isotopes for in vivo disposition, metabolism, and pharmacokinetic (PK) studies.

### Experimental Section

**General Description.** All chemical reactions were conducted under nitrogen in anhydrous solvents unless stated otherwise. Reagents obtained from commercial suppliers were used without further purification. Acetone was dried over 4 Å molecular sieves. THF was distilled under nitrogen over sodium-benzophenone. Thin-layer chromatography (TLC) was done on 250 μm fluorescent plates and visualized by using UV light or iodine vapor. Normal-phase flash column chromatography was performed using silica gel (200–425 mesh 60 Å pore size) and ACS grade solvents. Melting points (mps) are uncorrected. NMR spectra were recorded on either a 600 or 400 MHz instrument and were referenced using either tetramethylsilane (TMS) or residual nondeuterated solvent as an internal standard. Proton coupling constants are

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Scheme 1<sup>a</sup>

<sup>a</sup> (a) MOMCl (3 equiv), diisopropyl ethyl amine (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT (60%); (b) 3-methyl-2-butene-1-ol (1.5 equiv), diethylazodicarboxylate (1.6 equiv), PPh<sub>3</sub> (1.2 equiv), toluene/THF, RT (80%); (c) *N,N*-dimethylaniline, reflux, 200 °C (64%); (d) (CH<sub>3</sub>O)SO<sub>2</sub> (2 equiv), K<sub>2</sub>CO<sub>3</sub> (2 equiv), acetone, reflux (82%); (e) MOMCl (3 equiv), diisopropyl ethyl amine (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT (90%); (f) aqueous NaOH, MeOH, reflux (60%); (g) concentrated HCl (pH 1), MeOH/H<sub>2</sub>O, RT (72%); (h) can occur spontaneously upon heating and by acid or base catalysis.

expressed in hertz, and in some cases overlapping signals occurred in the <sup>13</sup>C NMR spectra. Spectroscopic data are in agreement with all known compounds. Abbreviations: DCM = dichloromethane; EtOAc = ethyl acetate; MeOH = methanol; MOM = methoxymethyl; DEAD = diethylazodicarboxylate; RT = room temperature (ambient).

**2'-Hydroxy-4',6'-dimethoxymethylacetophenone (4).** To an ice-cooled suspension of 2',4',6'-trihydroxyacetophenone monohydrate (1.86 g, 10 mmol) in 20 mL of DCM was added *N,N*-diisopropylethylamine (5.3 mL, 30 mmol). MOMCl (2.3 mL, 30 mmol) was added dropwise, and the reaction was gradually allowed to reach RT. The reaction was stirred for 6 h. After disappearance of most of the starting material (TLC), the reaction was quenched with aqueous saturated ammonium chloride solution (20 mL). The resulting mixture was extracted with DCM/water [2 × 40 mL (1:1)]. The organic layers were combined, dried over sodium sulfate, filtered, and evaporated. The brownish residue was chromatographed over silica using hexanes/EtOAc (5:1) to obtain 1.53 g (60%) of known **4**<sup>33</sup> as a colorless oil, which on standing at room temperature produced a white solid; mp 49–52 °C [lit.33 42 °C]; TLC *R*<sub>f</sub> 0.46 in hexanes/EtOAc (5:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.27 (d, 1H, *J* = 2.4 Hz, Ar-H), 6.24 (d, 1H, *J* = 2.4 Hz, Ar-H), 5.26 (s, 2H, O-CH<sub>2</sub>-O), 5.17 (s, 2H, O-CH<sub>2</sub>-O), 3.52 (s, 3H, OCH<sub>3</sub>), 3.47 (s, 3H, OCH<sub>3</sub>), 2.66 (s, 3H, COCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.5, 167.1, 163.7, 160.6, 107.1, 97.3, 94.7, 94.2, 56.9, 56.7, 33.3; HRMS calc [M<sup>+</sup> + Na] 279.0845, found 279.0839.

**4',6'-Dimethoxymethyl-2'-(3-methylbut-2-en-1-yloxy)acetophenone (5).** To an ice-cooled solution of **4** (0.512 g, 2 mmol) in 10 mL of THF was added triphenyl phosphine (0.628 g, 2.4 mmol) and 3-methyl-2-buten-1-ol (0.3 mL, 3 mmol). Diethyl azodicarboxylate, i.e., DEAD (1.5 mL of 40% solution in toluene, 3.2 mmol), was added dropwise and the resulting yellow solution warmed to RT and stirred for 12 h. The solvent was evaporated and the residue suspended in

ether. A solid precipitated and was filtered. The filtrate was evaporated and the residue chromatographed over silica using hexanes/EtOAc (2:1). Evaporation of the organic fractions provided 0.518 g (80%) of known **5**<sup>29</sup> as a clear oil; *R*<sub>f</sub> 0.29 in hexanes/EtOAc (5:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.44 (d, 1H, *J* = 1.8 Hz, Ar-H), 6.31 (d, 1H, *J* = 1.8 Hz, Ar-H), 5.4 (t, 1H, *J* = 5.4 Hz, CH=), 5.16 (s, 2H, O-CH<sub>2</sub>-O), 5.13 (s, 2H, O-CH<sub>2</sub>-O), 4.49 (d, 2H, *J* = 5.4 Hz, CH<sub>2</sub>), 3.48 (s, 3H, OCH<sub>3</sub>), 3.45 (s, 3H, OCH<sub>3</sub>), 2.47 (s, 3H, COCH<sub>3</sub>), 1.76 (s, 3H, CH<sub>3</sub>), 1.71 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 202.0, 159.7, 157.5, 155.4, 138.2, 119.6, 116.5, 96.2, 95.2, 94.9, 94.7, 65.8, 56.5, 32.8, 26, 18.5, 18.0; HRMS calc [M<sup>+</sup> + Na] 347.1471, found 347.1481.

**2',4'-Dimethoxymethyl-6'-hydroxy-3'-(3-methylbut-2-en-1-yloxy)acetophenone (6).** Intermediate **5** (0.324 g, 1 mmol) was dissolved in 10 mL of dimethylaniline and heated at 200 °C for 4 h. Ethyl acetate (50 mL) was added and the mixture washed with 1 N HCl (2 × 50 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed over silica using hexanes/EtOAc (20:1 gradient to 5:1). Evaporation of the organic fractions provided 0.207 g (64%) of known **6**<sup>29</sup> as a yellowish oil; TLC *R*<sub>f</sub> 0.55 in hexanes/EtOAc (5:1); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.47 (s, 1H, Ar-H), 5.21 (s, 2H, O-CH<sub>2</sub>-O), 5.14 (t, 1H, *J* = 6.6 Hz, CH=), 4.95 (s, 2H, O-CH<sub>2</sub>-O), 3.51 (s, 3H, OCH<sub>3</sub>), 3.45 (s, 3H, OCH<sub>3</sub>), 3.31 (d, 2H, *J* = 6.6 Hz, CH<sub>2</sub>), 2.69 (s, 3H, COCH<sub>3</sub>), 1.76 (s, 3H, CH<sub>3</sub>), 1.56 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 204.2, 163.7, 161.8, 160.7, 131.9, 123.2, 116.4, 111.2, 101.6, 99.1, 94.1, 58.6, 56.6, 31.7, 25.9, 23.3, 18.1; HRMS calc [M<sup>+</sup> + Na] 347.1471, found 347.1470.

**2',4'-Dimethoxymethyl-6'-methoxy-3'-(3-methylbut-2-en-1-yloxy)acetophenone (7).** To a stirred solution of **6** (0.162 g, 0.5 mmol) in 10 mL of acetone was slowly added oven-dried potassium carbonate (0.138 g, 1 mmol) and dimethyl sulfate (0.1 mL, 1 mmol). The reaction

mixture was refluxed for 6 h, allowed to cool to RT, and quenched with 10 mL of ammonium hydroxide. It was then extracted with DCM/water [3 × 20 mL (1:1)] The organic layers were combined, dried over sodium sulfate, and evaporated. The residue was chromatographed over silica using hexane/EtOAc (3:1). Evaporation of the organic fractions provided 0.138 g (82%) of **7** as a yellow oil:  $R_f$  0.34 in hexanes/EtOAc (5:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.54 (s, 1H, Ar-H), 5.21 (s, 2H, O-CH<sub>2</sub>-O), 5.13 (t, 1H,  $J = 6.6$  Hz, CH=), 4.90 (s, 2H, O-CH<sub>2</sub>-O), 3.78 (s, 3H, OCH<sub>3</sub>), 3.47 (s, 6H, 2 × OCH<sub>3</sub>) 3.30 (d, 2 H,  $J = 6.6$  Hz, CH<sub>2</sub>), 2.49 (s, 3H, COCH<sub>3</sub>), 1.76 (s, 3H, CH<sub>3</sub>), 1.65 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  201.9, 157.5, 155.8, 153.5, 131.2, 123.1, 120.2, 117.1, 101.1, 94.7, 94.3, 57.4, 56.1, 32.6, 25.7, 23.3, 17.8; HRMS calc [ $\text{M}^+ + \text{Na}$ ] 361.1627, found 361.1628.

**4-Methoxymethylbenzaldehyde (9)**. To an ice-cooled suspension of 4-hydroxybenzaldehyde (1.22 g, 10 mmol) in 15 mL of DCM was added *N,N*-diisopropylethylamine (5.3 mL, 30 mmol). MOMCl (2.3 mL, 30 mmol) was added dropwise. The reaction was allowed to reach RT and stirred for 12 h. The reaction was quenched with aqueous saturated ammonium chloride solution, followed by extraction with DCM/water [50 mL (1:1)]. The organic layer was dried over sodium sulfate, filtered, and evaporated to give an oily residue. The residue was passed through a short silica column using hexanes/EtOAc (1:1) as eluant. Evaporation of the organic fractions provided 1.52 g (90%) of known **9**<sup>31</sup> as a brownish oil:  $R_f$  0.44 in hexanes/EtOAc (5:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  9.89 (s, 1H, CHO), 7.84 (d, 2H,  $J = 8.4$  Hz, Ar-H2/6) 7.14 (d, 2H,  $J = 8.4$  Hz, Ar-H3/5), 5.25 (s, 2H, O-CH<sub>2</sub>-O), 3.48 (s, 3H, OCH<sub>3</sub>);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  191.2, 162.4, 132.1, 130.9, 116.5, 94.3, 56.6; HRMS calc [ $\text{M}^+ + \text{Na}$ ] 189.0528, found 189.0531.

**2',4',4'-Trimethoxymethyl-6'-methoxy-3-(3-methylbut-2-en-1-yloxy)chalcone (10)**. To a stirred solution of **7** (0.170 g, 0.5 mmol) and **9** (0.082 g, 0.5 mmol) in 20 mL of methanol was added 1 mL of 10% aqueous NaOH solution, after which the reaction mixture was refluxed for 4 h. After completion of reaction (TLC), the solution was extracted with EtOAc/water [2 × 30 mL (1:1)]. The organic layers were combined, dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed over silica using hexanes/EtOAc (3:1). Evaporation of the organic fractions provided 0.145 g (60%) of **10** as a yellowish oil:  $R_f$  0.19 in hexanes/EtOAc (2:1);  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (d, 2H,  $J = 9$  Hz, Ar-H2/6), 7.37 (d, 1H,  $J = 15.6$ , CH=), 7.03 (d, 2H,  $J = 9$  Hz, Ar-H3/5), 6.90 (d, 1H,  $J = 15.6$  Hz, CH=), 6.58 (s, 1H, Ar-H4'), 5.23 (s, 2H, O-CH<sub>2</sub>), 5.19 (s, 3H, O-CH<sub>2</sub>/CH=), 4.90 (s, 2H, O-CH<sub>2</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.5 (s, 3H, OCH<sub>3</sub>), 3.47 (s, 3H, OCH<sub>3</sub>), 3.42 (s, 3H, OCH<sub>3</sub>), 3.35 (d, 2H, CH<sub>2</sub>), 1.76 (s, 3H, CH<sub>3</sub>), 1.67 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  194.4, 159.2, 157.8, 156.5, 154.3, 144.3, 131.5, 130.3, 128.9, 127.3, 123.4, 118.5, 117.4, 116.6, 100.9, 95.1, 94.6, 94.4, 57.7, 56.4, 25.9, 23.3, 18.1; HRMS calc [ $\text{M}^+ + \text{Na}$ ] 509.2151, found 509.2139.

**2',4',4'-Trihydroxy-6'-methoxy-3-(3-methylbut-2-en-1-yloxy)-chalcone (1; xanthohumol)**. To a stirred solution of **10** (0.148 g, 0.3 mmol) in methanol/water (18 mL:2 mL) was added concentrated HCl until the pH dropped to less than 1. The mixture was stirred at RT for ca. 12 h. A gradual removal of the MOM groups was observed by TLC. After 12 h, the reaction mixture was extracted with EtOAc/water [2 × 40 mL (1:1)]. The organic layers were combined, dried over sodium sulfate, filtered, and evaporated at 20 °C. The residue was chromatographed over silica using hexanes/EtOAc (2:1) as eluant. Evaporation of the organic fractions provided 0.076 g (72%) of xanthohumol as a yellow solid: mp 148–151 °C [lit. 34 157–159 °C, chloroform];  $R_f$  0.41 in hexanes/EtOAc (1:1);  $^1\text{H NMR}$  (600 MHz, methanol-*d*<sub>4</sub>)  $\delta$  7.78 (d, 1H,  $J = 15.6$ , CH=), 7.67 (d, 1H,  $J = 15.6$ , CH=), 7.49 (d, 2H,  $J = 8.4$  Hz, Ar-H2/6), 6.82 (d, 2H,  $J = 9$  Hz, Ar-H3/5), 6.0 (s, 1H, Ar-H4'), 5.19 (t, 1H, CH=), 4.9 (s, H<sub>2</sub>O), 3.89 (s, 3H, OCH<sub>3</sub>), 3.22 (d, 2H, CH<sub>2</sub>), 1.75 (s, 3H, CH<sub>3</sub>), 1.64 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  (100 MHz, methanol-*d*<sub>4</sub>)  $\delta$  194.2, 166.3, 163.9, 162.6, 161.3, 143.5, 131.5, 131.4, 128.6, 126.0, 124.4, 117.0, 109.5, 106.7, 91.7, 56.3, 26.1, 22.4, 18.0; *anal.*

calcd for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>•0.4H<sub>2</sub>O, C 69.75%, H 6.36%, found C 69.90%, H 6.32%; HRMS calc [ $\text{M}^+ + \text{Na}$ ] 377.1365, found 377.1354.

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**Supporting Information Available:** Copies of proton and carbon NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References and Notes

- (1) Stevens, J. F.; Page, J. E. *Phytochemistry* **2004**, *65*, 1317–1330.
- (2) Gerhaeuser, C.; Frank, N. *Mol. Nutr. Food Res.* **2005**, *49*, 821–823.
- (3) 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. *J. Agric. Food Chem.* **2005**, *53*, 6246–53.
- (4) Stevens, J. F.; Miranda, C. L.; Frei, B.; Buhler, D. R. *Chem. Res. Toxicol.* **2003**, *16*, 1277–1286.
- (5) Wang, Q.; Ding, Z.-H.; Liu, J.-K.; Zheng, Y.-T. *Antiviral Res.* **2004**, *64*, 189–194.
- (6) Gerhaeuser, C.; Alt, A.; Heiss, E.; Gamal-Eldeen, A.; Klimo, K.; Knauff, J.; Neumann, I.; Scherf, H.-R.; Frank, N.; Bartsch, H.; Becker, H. *Mol. Cancer Ther.* **2002**, *1*, 959–969.
- (7) Vervarcke, S. *Nutr. Cos., Biodyn. (Belg.)* **2005**, *4*, 14–16.
- (8) Vanhoecke, B.; Derycke, L.; Van Marck, V.; Depypere, H.; De Keukeleire, D.; Bracke, M. *Int. J. Cancer* **2005**, *117*, 889–895.
- (9) Guerreiro, S.; Monteiro, R.; Martins, M. J.; Calhau, C.; Azevedo, I.; Soares, R. *Clin. Biochem.* **2007**, *40*, 268–273.
- (10) Colgate, E. C.; Miranda, C. L.; Stevens, J. F.; Bray, T. M.; Ho, E. *Cancer Lett.* **2007**, *246*, 201–209.
- (11) Bourges-Sevenier, C. PCT Int. Appl. WO 2002085393, 2002.
- (12) Fuesser, H.; Tretzel, J.; Wydra, M. Eur. Pat. Appl. EP 1431385, 2004.
- (13) Hoepfner, F. G.; Wunsch, H.; Berg, K.; Buchner, P. Ger. Offen DE 10320250, 2004.
- (14) Nookandeh, A.; Frank, N.; Steiner, F.; Ellinger, R.; Schneider, B.; Gerhaeuser, C.; Becker, H. *Phytochemistry* **2004**, *65*, 561–570.
- (15) Stevens, J. F.; Ivancic, M.; Hsu, V. L.; Deinzer, M. L. *Phytochemistry* **1997**, *44*, 1575–1585.
- (16) Current prices of xanthohumol from common chemical suppliers are more than twice that of paclitaxel, which has typically been rather expensive as a research material.
- (17) Khupse R. S.; Erhardt, P. W. *Total Synthesis of the soybean flavonoids Glyceollin I and II Poster #30*, 6<sup>th</sup> Environmental Signaling Network Symposium, New Orleans, Oct. 2004.
- (18) Khupse R. S.; Erhardt, P. W. *Approaches towards the biomimetic total synthesis of the soybean flavonoids Glyceollin I and II, Poster #87*, 30<sup>th</sup> National Medicinal Chemistry Symposium, Seattle, June 2006.
- (19) Sarver, J. G.; Klis, W. A.; Byers, J. P.; Erhardt, P. W. *J. Biomol. Screening* **2002**, *7*, 29–34.
- (20) Salvo, V. A.; Boue, S. M.; Fonseca, J. P.; Elliott, S.; Corbitt, C.; Collins-Burrow, B. M.; Curriel, T. J.; Srivastav, S. K.; Shih, B. Y.; Carter-Wientjes, C.; Wood, C. E.; Erhardt, P. W.; Beckman, B. S.; McLachlan, J. A.; Cleveland, T. E.; Burrow, M. E. *Clin. Cancer Res.* **2006**, *12*, 7159–7164.
- (21) Power, F. B.; Tutin, F.; Rogerson, H. *J. Chem. Soc., Perkin Trans.* **1913**, *103*, 1267–92.
- (22) Verzele, M.; Stockx, J.; Fontijn, F.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1957**, *66*, 452–75.
- (23) Vanderwalle, M.; Verzele, M. *J. Chem. Soc.* **1961**, 1021–3.
- (24) Orth, W. A.; Riedl, W. *Ann. Chim.* **1963**, *663*, 74–82.
- (25) Vandewalle, M. *Bull. Soc. Chim. Belg.* **1961**, *70*, 163–7.
- (26) Diller, R. A.; Riepl, H. M.; Rose, O.; Frias, C.; Henze, G.; Prokop, A. *Chem. Biodiversity* **2005**, *2*, 1331–1337.
- (27) Roelens, F.; Heldring, N.; Dhooze, W.; Bengtsson, M.; Comhaire, F.; Gustafsson, J.-A.; Treuter, E.; De Keukeleire, D. *J. Med. Chem.* **2006**, *49*, 7357–7365.
- (28) Anjaneyulu, A. S. R.; Isaa, B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2089–94.
- (29) Bu, X. Y.; Zhao, L. Y.; Li, Y. L. *Synthesis* **1997**, 1246–1248.
- (30) Gester, S.; Metz, P.; Zierau, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015–1018.
- (31) Kagawa, H.; Shigematsu, A.; Ohta, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2005**, *53*, 547–554.
- (32) Miles, C. O.; Main, L. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1639–42.
- (33) Kumazawa, T.; Minatogawa, T.; Matsuba, S.; Sato, S.; Onodera, J. *Carbohydr. Res.* **2000**, *329*, 507–513.
- (34) Sun, S.; Watanabe, S.; Saito, T. *Phytochemistry* **1989**, *28*, 1776–7.
- (35) International patent application pending.