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An efficient synthesis of the potent phytoestrogens 8-prenylnaringenin and 6-(1,1-dimethylallyl)naringenin by europium(III)-catalyzed Claisen rearrangement

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Dedicated to Professor Günter Domschke on the occasion of his 70th birthday

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Abstract—Starting from commercially available naringenin (**3**), the flavanoids 8-prenylnaringenin (**1**) and 6-(1,1-dimethylallyl)naringenin (**2**) have been prepared in racemic form using prenyl ether **5** as a general intermediate. While a domino Claisen–Cope rearrangement of **5** was the key step in the synthesis of **1**, the cytotoxic compound **2** was additionally secured via a europium(III)-catalyzed Claisen rearrangement of **5** at low temperature. Both **1** and **2** display strong estrogenic activities. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

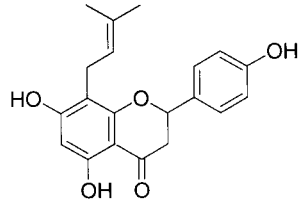
The flavanoid[1] 8-prenylnaringenin (**1**) (Fig. 1) isolated from the plants *Marshallia grandiflora*,[2] *Sophora tomentosa*[3,4] and *Humulus lupulus*[4] has recently been shown to be an extremely potent phytoestrogen.[5,6] Moreover, **1** displays a strong antifungal activity as well.[4,7] In order to further investigate these interesting properties, an efficient access to this compound was desired that would supply sufficient amounts of **1** for biological studies. So far, **1** has been prepared either by unselective direct *C*-prenylations[4,7–10] of the commercially available citrus flavanoid naringenin (**3**) or by an equally low yielding route starting from phloroacetophenone.[11]

Here we report a convenient four-step sequence from racemic **3** to **1** via a domino Claisen–Cope rearrangement[12,13] that delivers **1** in 42–45% overall yield. We have also used this novel route for the first synthesis of 6-(1,1-dimethylallyl)naringenin (**2**), which has recently been isolated from the leaves of *Monotes engleri* and found to exhibit a significant cytotoxic activity against several human tumor cell lines.[14]

2. Results and discussion

The conversion of naringenin (**3**) to **1** and **2** along these lines is depicted in Scheme 1. Chemoselective acetylation[15] of the C(7) and C(4′) phenolic hydroxyl groups of **3** set the stage for installation of the requisite prenyl ether moiety at C(5). Whereas attempts to *O*-alkylate diacetate **4** with prenyl bromide in the presence of potassium carbonate[16] or under phase transfer catalysis conditions[17] met with failure, Mitsunobu reaction[18] of **4** with prenyl alcohol smoothly delivered the desired substrate **5** for the key sigmatropic event[19] in good yield.

For the uncatalyzed thermal rearrangement of **5**, reflux in decalin turned out to effect the cleanest transformation to **6** (Table 1), whereas no conversion of **5** was noted after 2 d of



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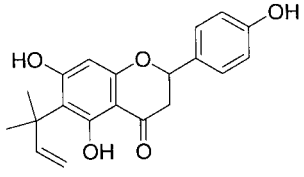

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Figure 1.

Keywords: physiologically active compounds; flavanoids and isoflavanoids; rearrangements; catalysis; Mitsunobu reactions.

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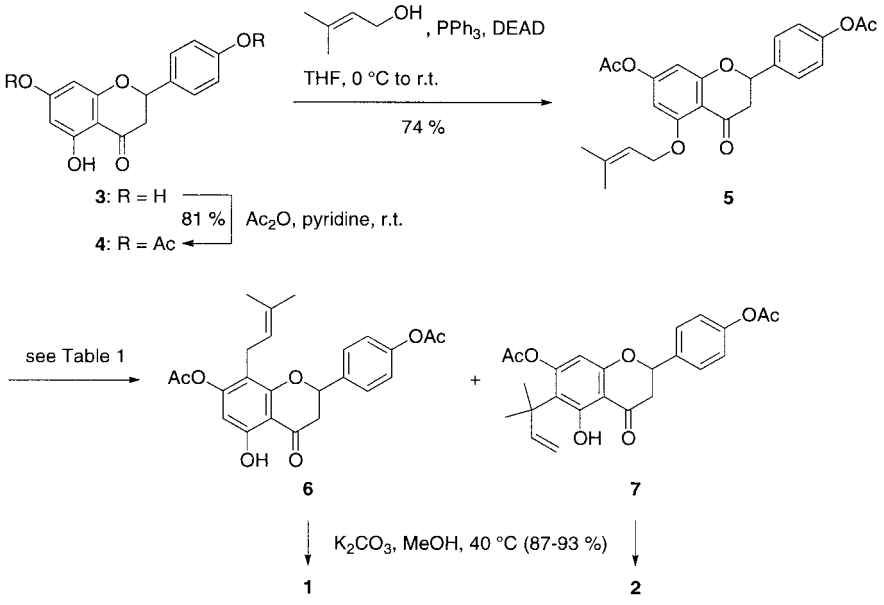

Scheme 1.

reflux in toluene, and complete consumption of **5** to give an intractable product mixture was observed after 4 h reflux in DMF. After 2 h at reflux in decalin, **5** was nearly completely consumed to give a 3:1 mixture of **6** and **7**. Upon extending the reaction time to 2 d, only the Claisen–Cope product **6** was observed. With the aim of enhancing the proportion of **7**, catalysis[20,21] of the Claisen rearrangement was investigated. To this end, prenyl ether **5** was treated with catalytic amounts of $Eu(fod)_3$ in chloroform[21] at different temperatures (Table 1). While the Eu(III)-complex did not cause any conversion at room temperature, heating for 6 h at 40°C allowed the isolation of a 1.2:1 mixture of **6** and **7** in high yield. Remarkably, after 12 h at 60°C **6** and **7** were formed in a 7.0:1 ratio, which points to a Eu(III)-catalysis of the Cope rearrangement step as well.[20] Thus, with proper temperature control, the $Eu(fod)_3$ accelerated reaction is preferable to the purely thermal process for the production of both **6** or **7** in terms of overall yield. Since no preparative separation of **6** and **7** was achieved, the mixture of these diacetates was subjected to a potassium carbonate catalyzed solvolysis,[22] whereupon 8-prenylnaringenin (**1**) and 6-(1,1-dimethylallyl)naringenin (**2**) could be easily isolated as pure isomers.

With sufficient amounts of **1** and **2** in our hands, in vitro testing of their estrogenic potency was performed. For the assessment of the estrogenicity we applied the widely used estrogen inducible yeast screen estrogen receptor assay.[23,24] The yeast strain used contained both a stably transfected estrogen receptor-α construct and an expression plasmid carrying estrogen-responsive sequences controlling the reporter gene lac-Z encoding the enzyme β-galactosidase. Estrogenic activity could directly be read in a colorimetric assay from the enzymatic hydrolysis of chlorophenol red β-D-galactopyranoside by monitoring the absorbance at 540 nm.[23] In a concentration-dependent analysis of reporter gene activity, halfmaximal induction of β-galactosidase activity is a direct measure for the affinity of the compound to the estrogen receptor-α and therefore for estrogenic activity.

Table 1. Rearrangement of prenyl ether **5**

Method[a]	T (°C)	t (h)	Ratio **6**:**7**[b]	Yield **6**+**7** (%)[c]
A	188	2	3.0:1	73
A	188	48	>20:1[d]	62
B	40	6	1.2:1	81
B	60	12	7.0:1	92

[a] A: Decalin, reflux; B: $CHCl_3$, 10 mol% $Eu(fod)_3$.
[b] By preparative separation after solvolysis to **1**+**2**.
[c] Isolated yield.
[d] Only **6** observed.

Applying these criteria it becomes apparent that **1** and **2** exhibit a clearcut estrogenic activity, whereas the parent compound **3** is void of this activity (Fig. 2). Further it is apparent that the relative activity of **1** and **2** is 2–3 orders of magnitude less potent than the natural female sex hormone estradiol. Nevertheless, with a halfmaximal activity at a concentration of **1** slightly lower than 10^{-7} M we confirm previous observations[6] that **1** represents at least in vitro the most potent phytoestrogen identified so far.

3. Experimental

3.1. General experimental information

For general experimental information see Ref. 25.

3.1.1. 2-(4-Acetoxy-phenyl)-5-hydroxy-4-oxo-chroman-7-yl acetate (4). To a solution of **3** (1.361 g, 5.00 mmol) in dry pyridine (5 mL) is added dropwise at room temperature acetic anhydride (0.94 mL, 10.0 mmol). After stirring the mixture for 24 h at room temperature, it is poured into ice-cold water (30 mL). The ocher precipitate is separated by filtration, washed twice with a small amount of ice-cold water and recrystallized from methanol (50 mL). The

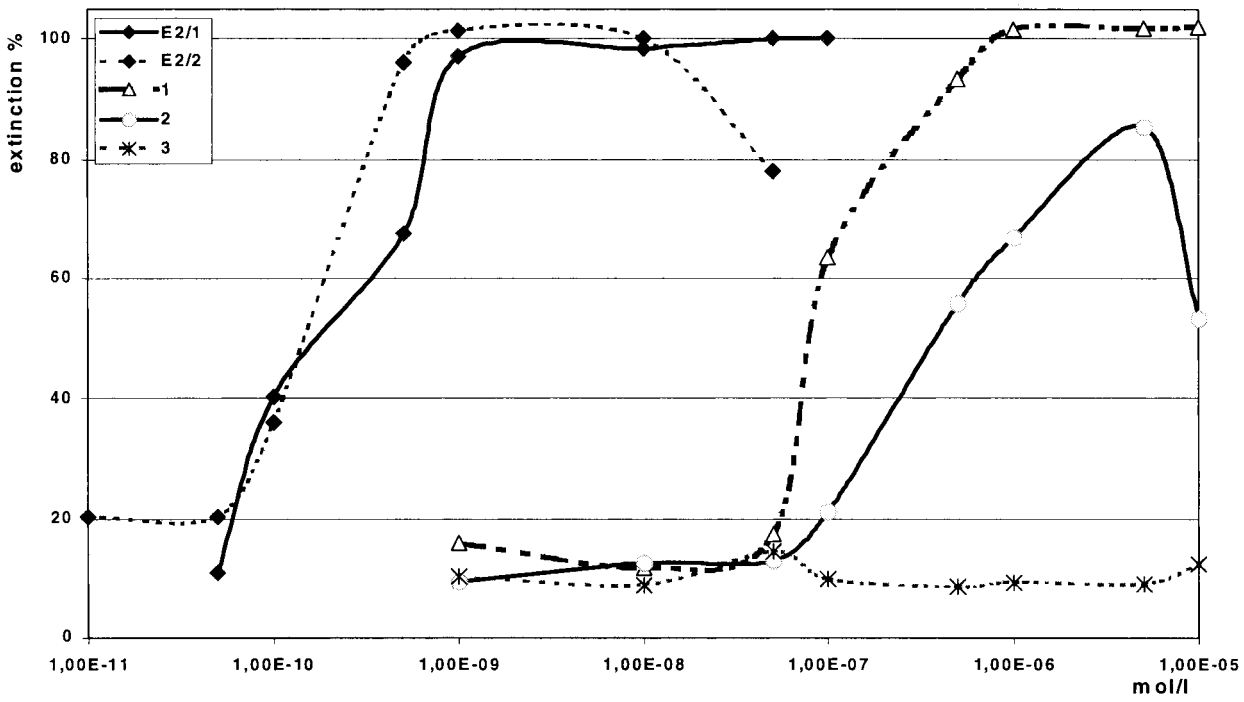

Figure 2. Estrogenic activity of 8-prenylnaringenin (**1**) and 6-(1,1-dimethylallyl)naringenin (**2**). **1** and **2** like the corresponding positive control estradiol (**E2/1**) activate β-galactosidase reporter activity, whereas naringenin (**3**) in contrast to the corresponding positive control estradiol (**E2/2**) does not. Note, **1** and **2** have been measured in the same assay, whereas **3** has been measured separately. Therefore, two reference curves were included. For the sake of comparability, data have additionally been normalized by setting absorbance units measured at 10^{-8}M estradiol in each experimental set at 100% and calculating all other data points accordingly.

resultant material is washed with a small amount of ice-cold methanol and dried at 60°C to yield **4** (1.452 g, 82%) as a slightly sandy solid. R_f 0.69 (ethyl acetate/pentane, 1:2); m.p. 141–142°C (MeOH); IR (KBr): 1747, 1657, 1629, 1587, 1373, 1217, 1183, 1128, 1085, 1021 cm^{-1}; ^1H NMR (d_6-DMSO, 300 MHz): δ 2.26 (s, 3H), 2.28 (s, 3H), 2.90 (dd, 1H, J=17.2 Hz, J=2.8 Hz), 3.46 (dd, 1H, J=17.2 Hz, J=13.2 Hz), 5.73 (dd, 1H, J=13.2 Hz, J=2.8 Hz), 6.37 (d, 1H, J=2.2 Hz), 6.38 (d, 1H, J=2.2 Hz), 7.21 (d, 2H, J=8.5 Hz), 7.59 (d, 2H, J=8.5 Hz), 11.93 (s, 1H); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 20.88 (q), 20.96 (q), 42.31 (t), 78.30 (d), 101.80 (d), 102.95 (d), 105.90 (s), 122.10 (d, intense), 128.09 (d, intense), 135.78 (s), 150.72 (s), 158.06 (s), 162.03 (s), 162.22 (s), 168.29 (s), 169.23 (s), 197.79 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 356 (43) [M^+], 314 (33) [M^+—CH_2CO], 313 (26) [M^+—CH_3CO], 273 (9), 272 (51) [M^+—CH_2CO—CH_2CO], 271 (65) [M^+—CH_2CO—CH_3CO], 43 (100) [CH_3CO^+]. Anal. calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53. Found C, 64.18; H, 4.55.

3.1.2. 2-(4-Acetoxy-phenyl)-5-(3-methyl-but-2-enyloxy)-4-oxo-chroman-7-yl acetate (5). To a solution of diacetate **4** (1.160 g, 3.26 mmol), triphenylphosphine (1.041 g, 3.97 mmol) and 3-methyl-2-buten-1-ol (0.48 mL, 4.84 mmol) in dry THF (40 mL) cooled to 0°C is added dropwise over 45 min under argon a solution of diethyl azodicarboxylate (0.82 mL, 5.25 mmol) in dry THF (10 mL). The resultant yellow solution is allowed to warm to room temperature and stirred for 2 h. After removal of the solvent in vacuo, the brownish residue is dissolved in a small amount of ethyl acetate and subjected to flash chromatography (ethyl acetate/pentane, 1:2) followed by recrystallization of the major product (R_f 0.41) from a diethyl ether/pentane mixture to give **5** (1.027 g, 74%) as a white solid. R_f 0.41 (ethyl acetate/pentane, 1:2); m.p. 121–122°C (diethyl ether/pentane); IR (KBr): 1768, 1683, 1608, 1510, 1437, 1371, 1198, 1137, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.71 (s, 3H), 1.77 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.79 (dd, 1H, J=16.5 Hz, J=2.8 Hz), 2.99 (dd, 1H, J=16.5 Hz, J=13.2 Hz), 4.59 (d, 2H, J=6.3 Hz), 5.41 (dd, 1H, J=13.2 Hz, J=2.8 Hz), 5.51 (t, 1H, J=6.3 Hz), 6.29 (d, 1H, J=2.2 Hz), 6.40 (d, 1H, J=2.2 Hz), 7.12 (d, 2H, J=8.6 Hz), 7.44 (d, 2H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.32 (q), 21.05 (q), 21.14 (q), 25.74 (q), 45.69 (t), 66.32 (t), 78.55 (d), 99.82 (d), 103.11 (d), 109.52 (s), 118.82 (d), 121.88 (d, intense), 127.23 (d, intense), 136.05 (s), 138.17 (s), 150.71 (s), 156.29 (s), 161.04 (s), 163.63 (s), 168.36 (s), 169.28 (s), 189.00 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 424 (44) [M^+], 382 (41) [M^+—CH_2CO], 381 (100) [M^+—CH_3CO]. Anal. calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found C, 68.14; H, 5.89.

3.2. General procedure for Claisen rearrangement of prenyl ether (5) to 2-(4-acetoxy-phenyl)-5-hydroxy-8-(3-methyl-but-2-enyl)-4-oxo-chroman-7-yl acetate (6) and 2-(4-acetoxy-phenyl)-6-(1,1-dimethyl-allyl)-5-hydroxy-4-oxo-chroman-7-yl acetate (7)

Thermal reaction: A solution of **5** (200 mg, 0.471 mmol) in dry decalin (10 mL) is heated to reflux for the time indicated in Table 1. The solvent is removed in vacuo, and the residue is subjected to flash chromatography (ethyl acetate/pentane, 1:3) to give a mixture of **6** and **7** (R_f 0.54 for both components) in the yield listed in Table 1.

Europium(III)-catalyzed reaction: A solution of **5** (500 mg, 1.18 mmol) in dry $CHCl_3$ (0.2 mL) is treated with $Eu(fod)_3$ (124 mg, 0.118 mmol). After stirring the mixture for the time and at the temperature listed in Table 1, it is directly subjected to flash chromatography (ethyl acetate/pentane, 1:3) to give a mixture of **6** and **7** (R_f 0.54 for both components) in the yield listed in Table 1.

3.3. Solvolysis of 6 and 7 to 8-prenylnaringenin (1) and 6-(1,1-dimethylallyl)naringenin (2)—typical procedure

The mixture of **6** and **7** (407 mg, 0.96 mmol) obtained from a Eu(III)-catalyzed run (6 h 40°C, 81%) is treated with methanol (10 mL) and a drop of water. K_2CO_3 (20 mg) is added, and the resultant yellow solution is stirred for 1 h at 40°C. After removal of the solvent in vacuo, addition of saturated aqueous $NaHCO_3$ (10 mL) and extraction with CH_2Cl_2 (3×15 mL), the combined organic layers are dried over Na_2SO_4, and the solvent is removed in vacuo. The crude product is subjected to flash chromatography (CH_2Cl_2/methanol, 20:1) and the separated components **1** and **2** are recrystallized from $CHCl_3$ to give pure **1** (157 mg, 48%) and **2** (128 mg, 39%) as white solids.

3.3.1. 8-Prenylnaringenin (1). R_f 0.19 (CH_2Cl_2/MeOH, 20:1); m.p. 193°C; IR (KBr): 3317, 1640, 1603, 1519, 1442, 1378, 1344, 1267, 1229, 1171, 1074, 834 cm^{-1}; ^1H NMR (d_6-DMSO, 500 MHz): δ 1.53 (s, 3H), 1.58 (s, 3H), 2.71 (dd, 1H, J=17.1 Hz, J=3.0 Hz), 3.07 (d, 2H, J=7.2 Hz), 3.20 (dd, 1H, J=17.1 Hz, J=12.6 Hz), 5.08 (t, 1H, J=7.2 Hz), 5.42 (dd, 1H, J=12.6 Hz, J=3.0 Hz), 5.96 (s, 1H), 6.79 (d, 2H, J=8.5 Hz), 7.31 (d, 2H, J=8.5 Hz), 9.57 (s, 1H), 10.77 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (d_6-DMSO, 125 MHz): δ 17.62 (q), 21.30 (t), 25.58 (q), 41.95 (t), 78.24 (d), 95.31 (d), 101.81 (s), 106.94 (s), 115.17 (d, intense), 122.71 (d), 128.10 (d, intense), 129.26 (s), 130.23 (s), 157.60 (s), 159.73 (s), 161.20 (s), 164.41 (s), 196.76 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 340 (66) [M^+], 285 (18) [M^+—C_4H_7], 247 (16) [M^+—C_6H_5OH], 165 (100). Anal. calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found C, 70.23; H, 5.88.

3.3.2. 6-(1,1-Dimethylallyl)naringenin (2). R_f 0.35 (CH_2Cl_2/MeOH, 20:1); m.p. 163°C; IR (KBr): 3361, 1638, 1594, 1447, 1346, 1156, 1101, 838 cm^{-1}; ^1H NMR (d_6-DMSO, 500 MHz): δ 1.49 (s, 6H), 2.66 (dd, 1H, J=17.1 Hz, J=2.9 Hz), 3.25 (dd, 1H, J=17.1 Hz, J=12.9 Hz), 4.75 (dd, 1H, J=10.6 Hz, J=1.2 Hz), 4.80 (dd, 1H, J=17.3 Hz, J=1.2 Hz), 5.39 (dd, 1H, J=12.9 Hz, J=2.9 Hz), 5.92 (s, 1H), 6.22 (dd, 1H, J=17.3 Hz, J=10.6 Hz), 6.79 (d, 2H, J=8.5 Hz), 7.30 (d, 2H, J=8.5 Hz), 9.58 (s, 1H), 10.64 (s, 1H), 13.18 (s, 1H); ^{13}C NMR (d_6-DMSO, 125 MHz): δ 28.92 (q), 28.95 (q), 40.16 (s), 42.14 (t), 78.07 (d), 95.45 (d), 101.75 (s), 107.38 (t), 112.29 (s), 115.21 (d, intense), 128.35 (d, intense), 128.98 (s), 149.99 (d), 157.77 (s), 160.41 (s), 162.90 (s), 165.84 (s), 196.74 (s).

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