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An efficient synthesis of the phytoestrogen 8-prenylnaringenin from xanthohumol by a novel demethylation process

Heike Wilhelm and Ludger A. Wessjohann*

Department of Bio-organic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany

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Abstract—8-Prenylnaringenin, a flavonoid, is the strongest known phytoestrogen (plant derived estrogen mimic) used in phytomedicinal applications. Starting from xanthohumol a byproduct of hops-extraction, 8-prenylnaringenin can be synthesized via isoxanthohumol. Of various demethylation procedures tested, the best yield (92%) is obtained by treatment with scandium trifluoromethanesulfonate and potassium iodide without any need of protection. The demethylation with $AlBr_3$/collidine and of the TIPS protected isoxanthohumol provides good results too.

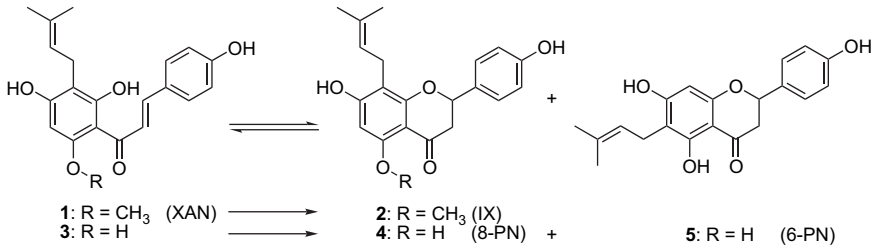
1. Introduction

Phytoestrogens are plant derived compounds with mild estrogenic activity and—compared to steroidal estrogens—often with improved pharmacokinetics and customer acceptance. They are used in treatment for menopause and other, mostly female, health problems. Most phytoestrogens are (iso-)flavonoids, e.g., genestein. The strongest one known is 8-prenylnaringenin, which naturally occurs in minor amounts in different *Wyethia* species[1] and hops.[2] The female inflorescences of the hop plant (*Humulus lupulus*) are used in the brewing industry as a flavoring and preservation agent, and for dietary preparations. Its principal prenylchalkone is xanthohumol (XAN, **1**) together with minor amounts of desmethylxanthohumol (**3**) and other prenylchalkones.[3,4] Both chalkones undergo thermal isomerization in the brew kettle (Scheme 1) to give the isomeric isoxanthohumol (IX, **2**), 8-prenylnaringenin (8-PN, **4**), and mostly 6-prenylnaringenin (6-PN, **5**). Of these compounds, only **4** possesses potent phytoestrogenic properties,[5–9] and recently has become of increasing commercial importance.

The first synthesis of **4** was achieved by direct C-prenylation of commercially available naringenin with prenyl bromide in very low yield.[10–15] The use of prenyl alcohol followed by an europium(III)-catalyzed Claisen rearrangement delivers **4** in four steps and 42–45% overall yield.[16] An alternative route starting from phloroacetophenone was much less successful.[17]

2. Results and discussion

Xanthohumol (**1**) is readily available from CO_2-extracted hops, and is a waste product of the hops industry. Its conversion into the 8-prenylnaringenin (**4**) requires a cyclization and subsequent demethylation. This course of events is crucial, since the reverse order, demethylation to **3** followed by cyclization will predominantly give the isomeric but inactive 6-PN (**5**). Substitution of the random brewing process by defined synthetic methodology thus should provide the high value target 8-PN (**4**) selectively, following the route **1**→**2**→**4**.



Scheme 1. Cyclization of hop chalcones xanthohumol (**1**) and its desmethyl derivative (**3**) in the brewing kettle.

Keywords: 8-Prenylnaringenin; Isoxanthohumol; Xanthohumol; Demethylathion; Phytoestrogen; Ether-cleavage.
* Corresponding author. Tel.: +49 345 5582 1301; fax: +49 345 5582 1309; e-mail: wessjohann@ipb-halle.de

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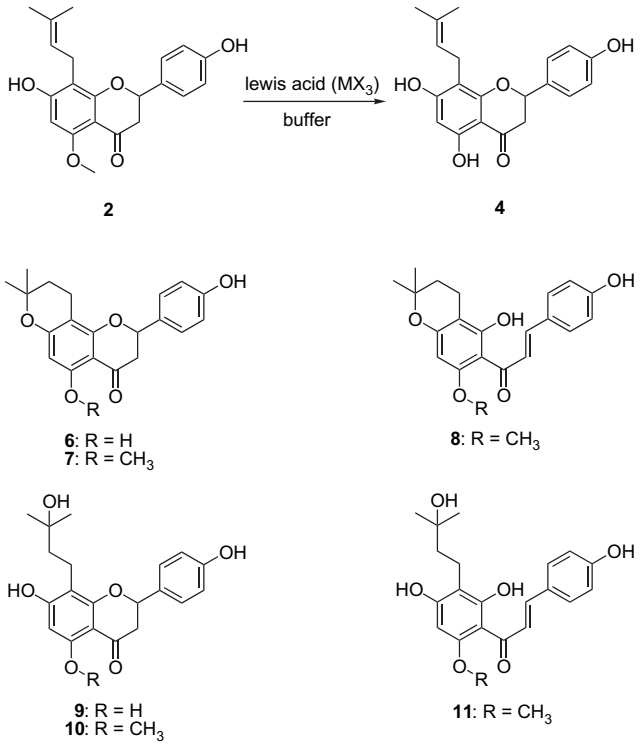
The first step, the isomerization of **1** to give isoxanthohumol (**2**) is known to proceed quantitatively under base catalysis.[18,19] Acid catalysis as well as catalysis with chiral bases is also possible, but is less efficient.[20] In principle, this intramolecular Michael-addition is reversible under the same conditions.

Crucial, however, is the second step, the demethylation of the 5-OMe group. Demethylation of 4′,7-dihydroxy-5-methoxy-6-(1″-geranyl)flavanone with BBr_3 to bonannione A was reported to proceed in high yield.[21] However, in our hands the reaction of isoxanthohumol (**2**) with BBr_3, $AlBr_3$,[22] or $AlCl_3$[23] was not useful and gave only products with cyclized side chain (**6**,[11] **7**,[24] and **8**[25,26]), and/or addition products to the double bond (**9**,[27] **10**,[26] and **11**;[25] Scheme 2). This cyclization reaction of the prenyl group with the neighboring OH-group under acidic conditions is well known.[24–26,28,29] The water addition products result from initial addition of the HBr (formed by reaction of phenol-OH with MBr_3) to the double bond with saponification under basic work-up (aqueous NaOH), or by direct acid catalyzed water addition upon work-up. Also, the application of MX_3-Lewis acids under neutral or basic conditions, or the intermittent protection of the reactive phenol group proved troublesome.



Scheme 2. Demethylation process **2**→**4** and main products of 'classical' demethylation procedures of **2** with MX_3.

The Lewis acid promoted demethylation in the presence of collidine as an acid scavenger[30] gives **4** in maximum 30% yield (Scheme 2, Table 1). Under these conditions **2** mostly remains unreacted. The principal byproduct is **1**, formed by a retro-opening of the chromanone B-ring. The increase of Lewis acid concentration leads to higher amounts of byproducts. The treatment of **2** with chlorotrimethylsilane for protection of the phenol groups and the use of methylaluminium dichloride acting as its own proton scavenger could not improve the yield of **4**.

Non-acidic, nucleophilic demethylation with $NaSCH_2CH_3$[31] in DMF failed. Instead, ringopening occurs to give 98% of **1**. In the reaction of **2** with LiI in pyridine[32] (Scheme 3a) only 8% of **4** could be isolated, accompanied by a new product of MW 486.16, compound **12**, the result of a retro-Friedel–Crafts reaction to split **1**, followed by annelation with **4** to give **12**.

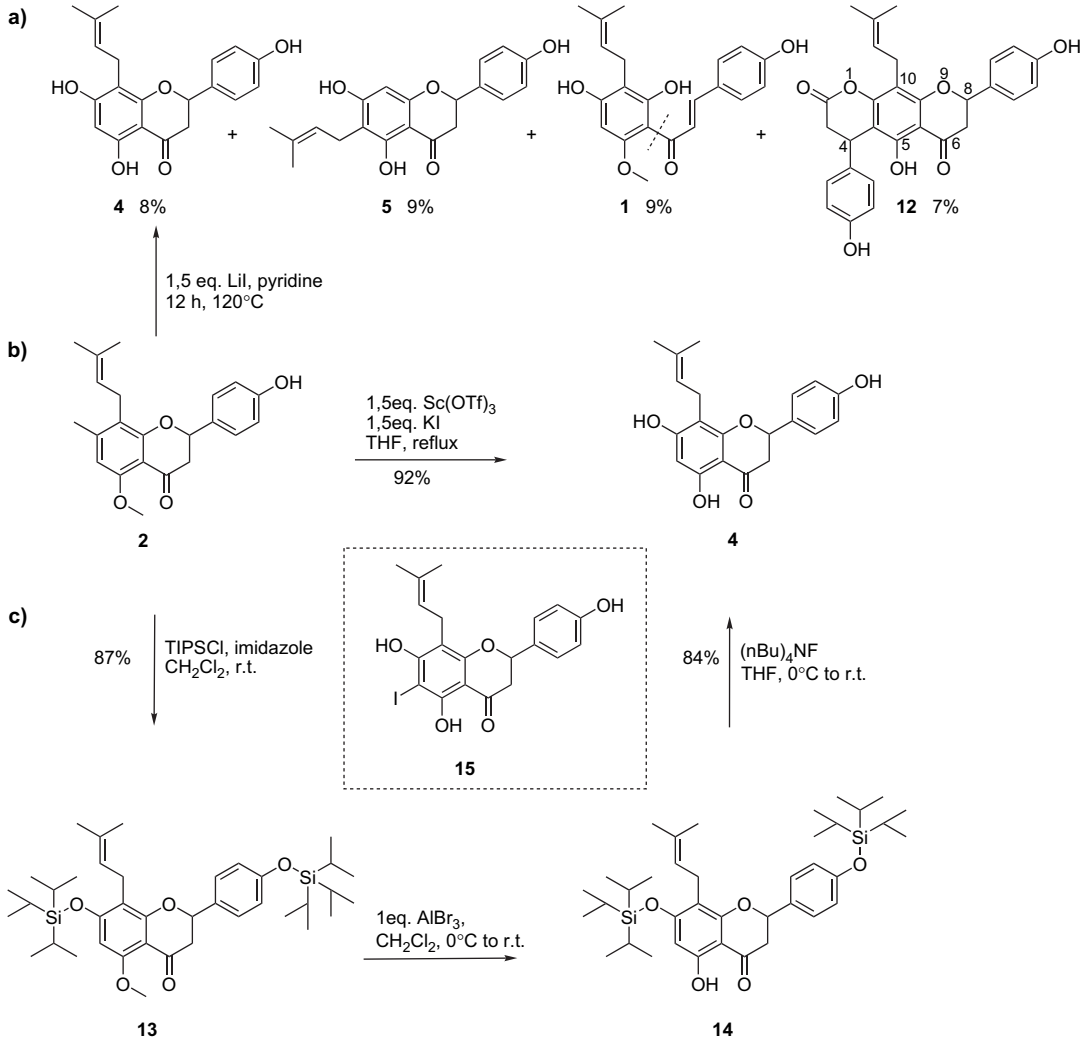
Because neither acidic nor non-acidic demethylation protocols were successful, we decided to protect the phenolic OH-groups with acetate[16] and triisopropylsilyl[33] (TIPS) groups. Acetate protection proved too labile under suitable demethylation conditions (Table 1, entry 1—with 1.2 equiv $AlBr_3$, 0.6 equiv collidine) and gives a mixture of demethylated products **4**, **6**, **9**, and the analogous 6-prenyl compounds. However, TIPS protected **13** reacts quantitatively to demethylation product **14** (Scheme 3c). The ^1H NMR does not show any signals of byproducts. Deprotection of crude **14** with *n*-Bu_4NF cleanly gives **4**. *n*-Bu_4N^+ and Silyl-compounds can be removed on short silica columns.

To improve the yield of **4** further, group IIIb Lewis acids including lanthanide salts were finally tested. They possess a high affinity to oxygen to activate the methyl–O bond for the attack of a nucleophile (e.g., iodide). At the same time, however, overactivation may promote retro-cleavage to the chalcone, which has to be avoided because of subsequent 6-PN formation. For this purpose **2** was treated with various reagent combinations in different solvents, some are shown in Table 2. Only scandium triflate in THF turned out to effect the conversion of **2** to **4** in high yield (Scheme 3b). The other reagents leave IX (**2**) almost unreacted in THF, whereas in $CHCl_3$ the cyclizations to **7** and **8** are favored. The use of pyridine as solvent increases retro-reaction to XAN (**1**). The attempt to reduce the amount of scandium triflate to catalytic quantities decreases the yield of **4** dramatically.

Table 1. Reaction of IX (**2**) with various Lewis acids in the presence of collidine in CH_2Cl_2

Entry	Lewis acid (equiv)	Collidine (equiv)	Conditions	Yield of **4** (%)	Yield of **1** (%)	Recycled **2** (%)	Byproducts (yield)
1	$AlBr_3$ (2)	5.5	5 h/rt	25	1	54	Traces of **8**, **3**, **5**
2[a,b]	$AlBr_3$ (1.5)	6.5	5 h/rt	30	5	35	**3**, **5**
3[b]	BBr_3 (3.5)	5.0	3 h/−80 °C	18	—	18	**6** (10%), **9** (6%), **8** (4%), **10**, **3**, **7**
4[b]	CH_3AlCl_2 (4.5)	4.5	4 h/reflux	~10[c]	~5[c]	~80[c]	**8**
5[b]	CH_3AlCl_2 (3.5)	0	1.5 h/0 °C	—	—	~10[c]	**8** (~70%),[c] **6** (~10%)[c]

[a] TMSCl (2.2 eqiuv).
[b] Longer work up in aqueous NaOH to convert **1** in **2**.
[c] Not isolated, detected by HPLC.



Scheme 3. Synthetic routes to 8-PN (**4**) and structure of 6-iodo-8-PN (**15**).

Table 2. Products formed by the treatment of isoxanthohumol (**2**) with Lewis acids and iodides in various solvents (detected by HPLC, byproducts in brackets)

Lewis acid	THF, 55 °C/24 h	$CHCl_3$, 55 °C/24 h	Pyridine, 80 °C/20 h	Sulfolane, 80 °C/20 h	CH_3OH/H_2O (5:1), 60 °C/6 h
$ZnBr_2$	**2** (**7**, **10**)	**7** (**2**)	**1**, **2** (**7**, **8**)	**8**, **7**, **5**	—
$ZnBr_2$/CuI	**2** (**7**, **10**, **8**, **4**)	**2**, **7** (**10**, **9**, **8**, **1**)	—	—	—
CuI	**2**	Many cpds	—	—	—
$Yb_2(SO_4)_3$/KI	**2** (**1**)	**2** (**7**, **8**)	**1**, **2** (**7**, **8**)	**2**, **1** (**8**, **7**, **5**, **4**)	—
$Yb_2(SO_4)_3$/CuI	**2** (**1**)	**2**, **7** (**8**, **1**)	—	**8** (**1**, **2**, **7**)	—
$Sc(OTf)_3$/KI	**4**	**7** (**8**, **1**)	**1**, **2** (**8**, **9**, **10**)	**1** (**8**)	**2** (**10**, **7**, **1**)
$Sm(OTf)_3$/KI	**2**	—	—	—	—
$CeCl_3$/LiI	**2**	—	—	—	—

But also proportional addition of further scandium triflate up to 1.2 equiv led to an incomplete reaction and higher amounts of byproducts, particularly the oxidation byproduct **15** with iodide in 6-position (Scheme 3—insert).

3. Experimental

3.1. General experimental information

All reactions were performed under an inert atmosphere of argon in dried solvents. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer in acetone-d_6 unless otherwise stated. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as an internal reference. ESI-MS spectra were taken with an API 150 EX spectrometer. High-resolution ESI mass spectra were recorded on a 7 T FT-ICR-MS—using nitrogen as drying gas at 150 °C. Analytical HPLC was carried out with diode array detector (DAD—was used for detection of UV spectra too) and a LiChrospher100 RP18 5 μm 4×125 mm column. For the preparative separation a HPLC device with a YMC-Pack ODS AA12S05-1520WT column and UV-detection at 210 nm was used. The eluent was acetonitrile/water. For

flash chromatography silica gel 60 (0.040–0.063 mm) was used. Xanthohumol was obtained from hop-industry (special thanks to Dr. Martin Biendl).

3.1.1. Isoxanthohumol (2). Xanthohumol (500 mg, 1.4 mmol) was dissolved in 500 ml 1% NaOH solution and stirred at 0 °C for 2 h. Acidification with 50% H_2SO_4 gives a light yellow precipitate. After filtration and careful washing with water the dried product (100%) can be used for most processes. If further purification is required the material is dissolved in methanol, filtered again, water is added to the solution for precipitation, and evaporated to further drive precipitation. Lyophylization of the filtered product gives **2** as a light yellow powder of at least 95% purity (usually >99.9%). **2**: UV: λ_{max} 288 nm; ^{1}H NMR: δ 1.60 (s, 3H), 1.61 (s, 3H), 2.62 (dd, 1H, J=16.3 Hz, J=2.9 Hz), 2.93 (dd, 1H, J=16.3 Hz, J=12.6 Hz), 3.26 (d, 1H, J=7.1 Hz), 3.73 (s, 3H), 5.20 (t, 1H, J=7.1 Hz), 5.36 (dd, 1H, J=12.6 Hz, J=2.9 Hz), 6.22 (s, 1H), 6.89 (d, 2H, J=8.6 Hz), 7.39 (d, 1H, J=8.6 Hz); ^{13}C NMR: δ 17.87, 22.50, 25.87, 46.12, 55.73, 79.37, 93.49, 106.04, 108.79, 115.85, 123.63, 128.45, 130.83, 131.31, 158.10, 160.84, 161.81, 162.57, 188.49; ESI-MS: 353.3 [M−H$^-$].

3.1.2. Demethylation of isoxanthohumol (2) with $AlBr_3$. To a stirred suspension of isoxanthohumol (**2**) (50 mg, 0.14 mmol) in 4 ml CH_2Cl_2 sym. collidine is slowly added until **2** is completely dissolved (ca. 100 mg, 0.83 mmol). $AlBr_3$ solution (0.28 ml, 1 M in CH_2Br_2) is added dropwise at rt. The mixture is stirred overnight and filtered. The orange precipitate is dried in vacuo and dissolved in 10 ml 0.5 M NaOH. After the solution is stirred for 1.5 h at 0 °C (to convert reformed **1** back to **2**) it is acidified with 50% H_2SO_4. The yellow precipitate is filtered off, washed carefully with water, and dried. The mixture is dissolved in methanol and separated by HPLC with a gradient of 40–70% acetonitrile in water within 20 min: **1**, t_R=21.1 min, **2**, t_R=9.6 min, **4**, t_R=14.4 min. Lyophylization gives **1** (0.5 mg, 1%) as yellow powder, **2** (27 mg, 54%), and **4** (12 mg, 25%, 60% based on recovered starting material) as white powders. 8-Prenylnaringenin (**4**): UV: λ_{max} 293, 335 nm; ^{1}H NMR: δ 1.60 (s, 3H), 1.61 (s, 3H), 2.76 (dd, 1H, J=17.2 Hz, J=3.1 Hz), 3.14 (dd, 1H, J=17.2 Hz, J=12.8 Hz), 3.22 (d, 2H, J=7.3 Hz), 5.19 (t, 1H, J=7.3 Hz), 5.45 (dd, 1H, J=12.8 Hz, J=3.1 Hz), 6.03 (s, 1H), 6.90 (d, 2H, J=8.6 Hz), 7.41 (d, 2H, J=8.6 Hz), 12.14 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 17.93, 21.88, 25.91, 43.17, 78.69, 96.80, 103.11, 106.01, 115.46, 121.42, 127.62, 130.78, 134.96, 155.72, 159.51, 162.03, 163.50, 196.19; ESI-MS: 339.3 [M−H$^-$].

3.1.3. Demethylation of isoxanthohumol (2) with BBr_3. To a stirred suspension of isoxanthohumol (**2**) (50 mg, 0.14 mmol) in 4 ml CH_2Cl_2 sym. collidine is slowly added until **2** is completely dissolved (ca. 100 mg, 0.83 mmol). BBr_3 solution (0.5 ml) (1 M in CH_2Cl_2) is added dropwise at −80 °C. The mixture is stirred for 3 h at −80 °C and filtered. For work up see above. Six fractions are separated by HPLC: **2**, t_R=9.8 min, 9 mg, 18%; **4**, t_R=14.6 min, 9 mg, 18%; 5,4′-dihydroxy-6″,6″-dimethyl-4″,5″-dihydropyrano-[2″,3″:7,8]flavanone (**6**),[11] t_R=20.7 min, 5 mg, 10% as white powder, UV: λ_{max} 218, 295 nm; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.35 (s, 3H), 1.76 (m, 2H), 2.58 (m, 2H), 2.78 (dd, 1H, J=17.0 Hz, J=3.1 Hz), 3.04 (dd, 1H, J=17.0 Hz, J=13.2 Hz), 5.32 (dd, 1H, J=13.2 Hz, J=3.1 Hz), 5.97 (s, 1H), 6.89 (d, 2H, J=8.6 Hz), 7.34 (d, 2H, J=8.2 Hz), 11.76 (s, 1H); ESI-MS: m/z 339.3 [M−H$^-$]; 4,2′-dihydroxy-6′-methoxy-6″,6″-dimethyl-4″,5″-dihydropyrano-[2″,3″:3′,4′]-chalkone (**8**),[27,28] t_R=26.3 min, 2 mg, 4% as yellow powder, UV: λ_{max} 371 nm; ^{1}H NMR: δ 1.36 (s, 6H), 1.81 (t, 2H, J=6.7 Hz), 2.63 (t, 2H, J=6.7 Hz), 3.88 (s, 3H), 5.88 (s, 1H), 6.86 (d, 2H, J=8.5 Hz), 7.51 (d, 2H, J=8.7 Hz), 7.74 (d, 1H, J=15.6 Hz), 7.83 (d, 1H, J=15.6 Hz), 14.79 (s, 1H); ESI-MS: m/z 353.3 [M−H$^-$]; 8-(3″-hydroxyisoamyl)-naringenin (**9**),[33] t_R=7.6 min, 3 mg, 6% as white powder, UV: λ_{max} 214, 293 nm; ^{1}H NMR: δ 1.18 (s, 6H), 1.64 (m, 2H), 2.64 (t, 2H, J=8.1 Hz), 2.80 (dd, 1H, J=17.0 Hz, J=3.1 Hz), 3.11 (dd, 1H, J=17.0 Hz, J=12.6 Hz), 5.47 (dd, 1H, J=12.6 Hz, J=3.1 Hz), 6.01 (s, 1H), 6.90 (d, 2H, J=8.6 Hz), 7.43 (d, 1H, J=8.4 Hz), 12.11 (s, 1H); ESI-MS: 357.3 [M−H$^-$]; 8-(3″-hydroxyisoamyl)-7,4′-dihydroxy-5-methoxyflavanone (**10**),[28] t_R=4.0 min, 0.5 mg, 1% as light yellow powder, UV: λ_{max} 287 nm; ^{1}H NMR: δ 1.18 (s, 6H), 1.66 (m, 2H), 2.64 (dd, 1H, J=16.3 Hz, J=2.9 Hz), 2.67 (t, 2H, J=8.1 Hz), 2.99 (dd, 1H, J=16.3 Hz, J=12.6 Hz), 3.74 (s, 3H), 5.37 (dd, 1H, J=12.6 Hz, J=2.9 Hz), 6.19 (s, 1H), 6.88 (d, 2H, J=8.6 Hz), 7.41 (d, 1H, J=8.4 Hz); ESI-MS: m/z 371.2 [M−H$^-$].

3.1.4. Demethylation of isoxanthohumol (2) with CH_3AlCl_2. This was conducted as described in procedure 3.1.2 with $AlBr_3$ exchanged for CH_3AlCl_2. Conditions were altered as given in Table 1, entries 4 and 5.

3.1.5. Demethylation of isoxanthohumol (2) with LiI. A solution of **2** (53 mg, 0.150 mmol) in 1.2 ml pyridine is added to LiI (30 mg, 0.224 mmol) and stirred for 12 h at 120 °C. After addition of 10 ml 0.5% HCl the solution is extracted with ethyl acetate (2×30 ml). The combined organic layers are washed with aqueous NH_4Cl solution and water and dried over Na_2SO_4. The solvent is evaporated, and the residue was dissolved in methanol and subjected to HPLC with a gradient of 40–70% acetonitrile in water within 20 min. Lyophylization gives **1**, t_R=20.1 min, 5 mg, 9%; **2**, t_R=9.5 min, 6 mg, 11%; **4**, t_R=14.1 min, 4 mg, 8%; 6-prenylnaringenin (**5**), t_R=18.3 min, 5 mg, 9% as off-white powder, UV: λ_{max} 292, 334 nm; ^{1}H NMR: δ 1.64 (s, 3H), 1.75 (s, 3H), 2.72 (dd, 1H, J=17.0 Hz, J=3.0 Hz), 3.17 (dd, 1H, J=17.0 Hz, J=12.9 Hz), 3.34 (d, 2H, J=7.3 Hz), 5.23 (t, 1H, J=1.4 Hz), 5.42 (dd, 1H, J=13.0 Hz, J=2.9 Hz), 6.03 (s, 1H), 6.89 (d, 2H, J=8.6 Hz), 7.39 (d, 1H, J=8.6 Hz), 12.47 (s, 1H); ESI-MS: m/z 339.3 [M−H$^-$]; 5-hydroxy-10-prenyl-4,8-di-(4-hydroxyphenyl)-3,4,7,8-tetrahydro-pyrano-[3,2-g]chromene-2,6-dione (**12**) mixture of diastereomers, t_R=17.6 min, 5 mg, 7% as off-white powder; ^{1}H NMR: δ 1.63, (s, 6H), 2.92 (m, 2H), 3.26 (m, 2H), 3.31 (dd, 2H), 4.60 (m, 1H), 5.19 (m, 1H), 5.58 (m, 1H), 6.76 (dd, 2H, J=8.6 Hz), 6.92 (d, 2H, J=8.4 Hz), 7.01 (dd, 2H, J=8.4 Hz), 7.44 (dd, 2H, J=8.6 Hz), 12.37 (s, 1H) (most peaks are doubled because of the two diastereomers); ^{13}C NMR (acetone-d_6): δ 17.89, 22.33, 22.36, 25.86, 33.92, 33.97, 37.25, 37.33, 43.31, 43.62, 80.06, 80.17, 105.52, 105.62, 106.99, 107.02, 109.40, 109.43, 116.18, 116.33, 122.61, 122.64, 128.62, 128.94, 128.98, 130.45, 130.52, 132.27, 132.29, 132.99, 133.06, 157.33, 157.35, 157.54, 157.58, 158.40, 158.45, 158.74, 159.88, 159.99, 166.92,

166.98, 199.18, 199.22; HRMS: FTICR: *m/z* 485.161, $C_{29}H_{25}O_7$ (error 9.22e−07) [M−H$^-$].

3.1.6. 7,4′-Di-triisopropylsilyloxy-isoxanthohumol (13). To a stirred suspension of **2** (302 mg, 0.85 mmol) in CH_2Cl_2 (10 ml) imidazole (290 mg, 4.26 mmol) is added, followed by chlorotriisopropylsilane (394 mg, 2.04 mmol) dropwise at 0 °C. The resultant suspension is allowed to warm to rt and stirred overnight. After removal of the solvent, pentane is added, the white precipitate is filtered off and washed with pentane. The organic filtrate solution is quickly washed with 5% HCl (2×10 ml) and H_2O (3×10 ml) and dried with Na_2SO_4. The solvent is removed in vacuo, the residue is dissolved in ethyl acetate, and subjected to flash chromatography (pentane/ethyl acetate = 5:1) to give **13** (495 mg, 87%) as a light yellow solid in the second fraction (R_f=0.16). ^{1}H NMR ($CDCl_3$): δ 1.12 (m, 36H), 1.29 (m, 6H), 1.49 (s, 3H), 1.62 (s, 3H), 2.75 (dd, 1H, *J*=16.5 Hz, *J*=2.9 Hz), 2.99 (dd, 2H, *J*=16.5 Hz, *J*=13.2 Hz), 3.26 (d, 2H, *J*=6.8 Hz), 3.84 (s, 3H), 5.12 (t, 1H, *J*=6.8 Hz), 5.28 (dd, 1H, *J*=13.2 Hz, *J*=2.9 Hz), 6.05 (s, 1H), 6.89 (d, 2H, *J*=8.6 Hz), 7.28 (d, 2H, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 12.74, 13.23, 17.91, 17.99, 18.09, 22.55, 25.86, 45.50, 55.95, 78.62, 95.75, 106.23, 112.53, 119.78, 122.58, 127.43, 130.97, 131.49, 156.02, 159.67, 160.28, 162.04, 190.18; ESI-MS: *m/z* 667.3 [M$^+$].

3.1.7. 7,4′-Di-triisopropylsilyloxy-8-prenylnaringenin (14). To a solution of **13** (100 mg, 0.15 mmol) in CH_2Cl_2 (10 ml) cooled to 0 °C is added dropwise a solution of $AlBr_3$ (0.15 ml of 1 M solution in CH_2Br_2). The resultant solution is stirred at 0 °C for 30 min and then allowed to warm to rt. After stirring overnight 0.1 M NaOH (10 ml) is added, and the mixture is stirred vigorously for 15 min. The organic layer is separated after acidification (50% H_2SO_4), washed with aqueous NH_4Cl (2×30 ml) and H_2O (1×30 ml), and dried (Na_2SO_4). Removal of the solvent in vacuo gives crude **14**, which is directly used for deprotection. ^{1}H NMR ($CDCl_3$): δ 1.12 (m, 36H), 1.29 (m, 6H), 1.50 (s, 3H), 1.62 (s, 3H), 2.76 (dd, 1H, *J*=17.1 Hz, *J*=3.0 Hz), 3.06 (dd, 1H, *J*=17.1 Hz, *J*=13.1 Hz), 3.22 (d, 2H, *J*=7.0 Hz), 5.11 (t, 1H, *J*=7.0 Hz), 5.31 (dd, 1H, *J*=13.1 Hz, *J*=3.0 Hz), 6.00 (s, 1H), 6.91 (d, 2H, *J*=8.6 Hz), 7.28 (d, 2H, *J*=8.4 Hz), 11.97 (s, 1H).

3.1.8. Deprotection of 14 to 8-PN (4). To a solution of crude **14** in THF (3 ml) cooled to 0 °C is added dropwise a solution of tetra-*n*-butyl-ammonium fluoride (0.36 ml of 1 M solution in THF). The solution is allowed to warm to rt and stirred for 1 h. After toluene (5 ml) is added, the solvent is removed in vacuo and the resultant residue is redissolved in $CHCl_3$ and subjected to flash chromatography ($CHCl_3$/methanol = 100:1) on a silica gel column to give **4** (42 mg, 84%) as a light yellow solid.

3.1.9. Direct demethylation of isoxanthohumol with scandium trifluoromethanesulfonate. A mixture of **2** (50 mg, 0.14 mmol), KI (36 mg, 0.23 mmol), and scandium triflate (104 mg, 0.21 mmol) is stirred in THF (10 ml) and refluxed for 2.5 h. After stirring overnight at rt the solution is concentrated in vacuo and subjected to filtration though a silica gel pad ($CHCl_3$/methanol = 100:1) to remove the scandium salt. Flash chromatography ($CHCl_3$/methanol = 100:1) on a silica gel column gives **4** (44 mg, 92%) as a light yellow solid.

3.1.10. 6-Iodo-8-prenylnaringenin (15). Another attempt with a smaller amount of scandium triflate (36 mg, 73 μmol, 1.3 equiv) added in three portions within 4 h to 20 mg **2** and 17 mg (0.11 mmol, 1.9 equiv) KI gave 9 mg **4** (47%) and 1.5 mg **15** (6%) as oxidation byproduct: t_R= 20.1, UV: λ_{max} 227, 295, 347 nm; ^{1}H NMR: δ 1.61 (s, 3H), 1.62 (s, 3H), 2.84 (dd, 1H, *J*=17.0 Hz, *J*=3.1 Hz), 3.24 (dd, 1H, *J*=17.0 Hz, *J*=12.6 Hz), 3.34 (d, 2H, *J*=7.3 Hz), 5.15 (t, 1H, *J*=7.3 Hz), 5.52 (dd, 1H, *J*=12.6 Hz, *J*= 3.1 Hz), 6.91 (d, 2H, *J*=8.6 Hz), 7.42 (d, 2H, *J*=8.4 Hz), 13.14 (s, 1H); ESI-MS: *m/z* 465.0 [M−H$^-$].

3.2. General procedure for the treatment isoxanthohumol (2) with Lewis acids and iodides (Table 2)

Isoxanthohumol (**2**) (10 mg, 0.03 mmol), the Lewis acid (1.5 equiv), and the iodide (1.5 equiv) are reacted in the given solvent in a closed glass tube at the temperature and for the time given in Table 2. The solvent is removed in vacuo (except for sulfolane, from which the product is extracted with ethyl acetate vs water). The residue is suspended in acetonitrile, filtered, and the solution is analyzed by HPLC.

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Supplementary data

HPLC-chromatograms and ^{1}H and ^{13}C NMR spectra of principal reactions and selected compounds, respectively. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.060.

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