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Selective C-6 Prenylation of Flavonoids *via* Europium(III)-Catalyzed Claisen Rearrangement and Cross-Metathesis

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Dedicated to Professor Jürgen Fabian on the occasion of his 70th birthday

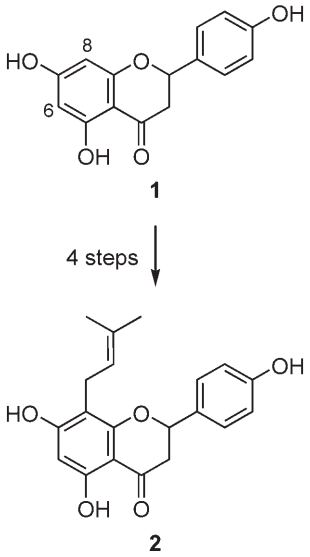
Abstract: Starting from the readily available parent flavonoids, the flavanone 6-prenylnaringenin, the isoflavone 6-prenylgenistein (wighteone, erythrinin B) and a protected derivative of the flavonol 6-prenylquercetin (gancaonin P) have been synthesized in short reaction sequences featuring the title processes as key steps.

Keywords: Claisen rearrangement; cross-metathesis; flavonoids; homogeneous catalysis; natural products; prenylation

Flavonoids constitute a large class of plant metabolites, many of which have been shown to display useful physiological properties.[1] Among this group of phytochemicals, especially prenylated flavonoids have attracted considerable interest in the field of nutrition, health and medicine.[2] We have recently reported an efficient four-step synthesis of the potent phytoestrogen 8-prenylnaringenin (**2**) from commercially available naringenin (**1**) consisting of chemoselective diacetylation of the C-7 and C-4′ phenolic hydroxy groups, prenyl ether formation at C-5−OH, domino Claisen–Cope rearrangement and deprotection (Scheme 1).[3]

Here we disclose a related route that allows a completely regioselective C-6 prenylation of flavonoids belonging to different subgroups of these natural products *via* europium(III)-catalyzed Claisen rearrangement[4] followed by cross-metathesis (CM)[5,6] as the key events.[7] Using this approach, the flavanone 6-prenylnaringenin (**3**) first isolated from *Humulus lupulus*,[8] the isoflavone 6-prenylgenistein (wighteone, erythrinin B) (**4**) first isolated from *Glycine wightii*[9] and *Erythrina variegata*[10] as well as a protected derivative of the flavonol 6-prenylquercetin (gancaonin P) (**5**) first isolated from *Glycyrrhiza uralensis*[11] have been synthesized in short reaction sequences (Figure 1).

Previous preparations of the antifungal[8] and antibacterial[12] compound 6-prenylnaringenin (**3**) that also exhibits a weak estrogenic activity[13] relied on unselective nuclear prenylations of naringenin (**1**),[8,14–17] a similarly unselective cyclization of the corresponding chalcone demethylxanthohumol[18] or multi-tep total synthesis.[19] Our novel access to **3** is depicted in Scheme 2. Chemoselective diacetylation[3,20] of **1** and subsequent Mitsunobu reaction[3,21] of **6** with allyl alcohol gave rise to allyl ether **7**, which in turn was subjected to a europium(III)-catalyzed Claisen rearrangement at relatively low temperature to provide the C-6 allylated intermediate **8** without competing domino Claisen–Cope reaction. CM of **8** with isobutylene[5] was conveniently achieved at room temperature using the CM partner and benzene as a mixed solvent system with a 1 mol% loading of catalyst **10** to give the C-6 prenylated product **9** in good yield. Finally, potassium carbonate-catalyzed solvolysis[22] smoothly afforded the natural product **3**.



Scheme 1.

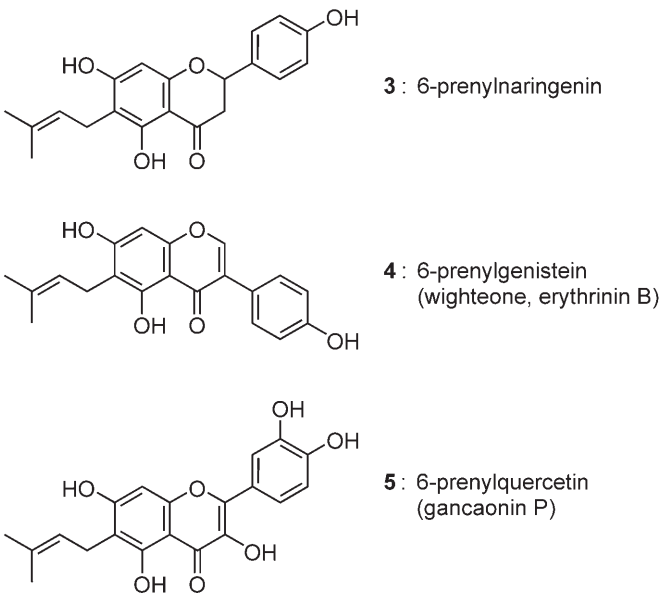
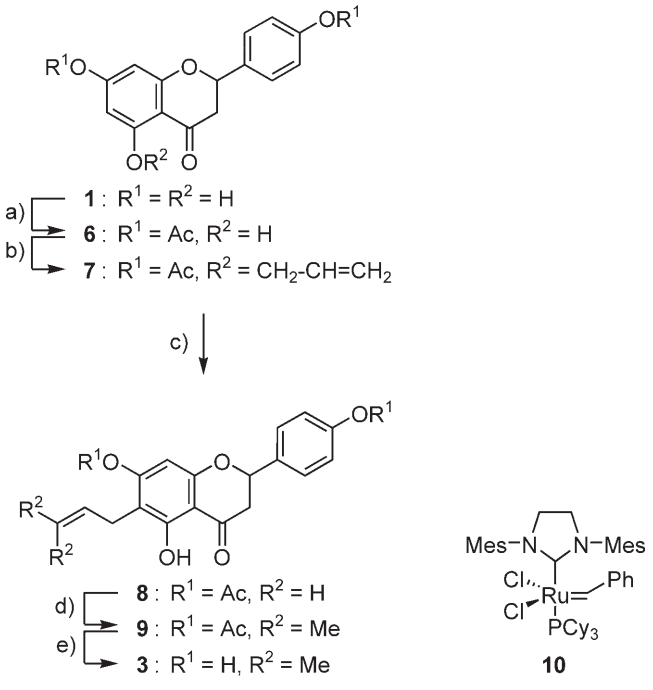
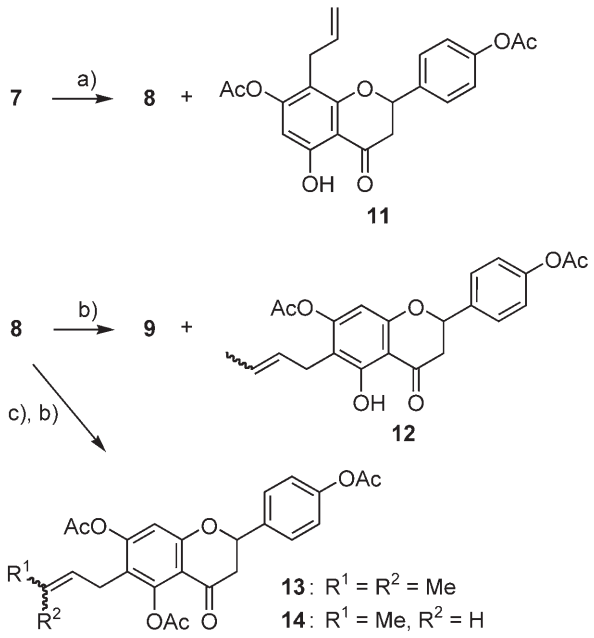


Figure 1.



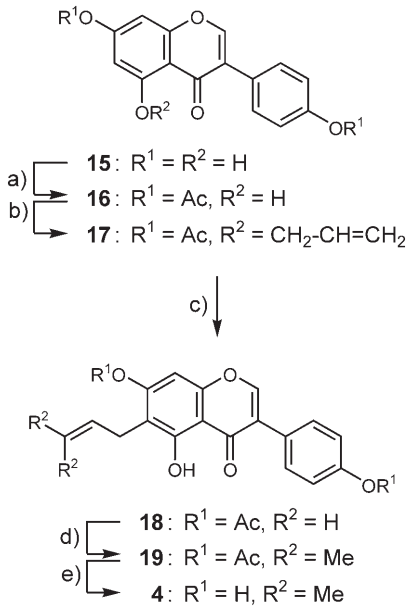
Scheme 2. *Reagents and conditions*: a) 2 equivs. Ac_2O, pyridine, room temperature, 89%; b) allyl alcohol, PPh_3, DEAD, THF, 0°C to room temperature, 73%; c) 10 mol% $Eu(fod)_3$, $CHCl_3$, 70°C (sealed tube), 16.5 h, 74%; d) isobutylene, 1 mol% **10**, benzene, room temperature (sealed tube), 2 d, 78%; e) MeOH, 0.3 equivs. K_2CO_3, 40°C, 2 h, 88%. DEAD = diethyl azodicarboxylate.

Some important observations made during the development of the route discussed above are illustrated in Scheme 3. Thus, europium(III) catalysis of the Claisen step was essential in order to stop the rearrangement of allyl ether **7** at the C-6 allyl stage, since purely thermal activation afforded a 1:1 mixture of the desired product **8** and the C-8 allylated diacetate **11** resulting from a domino Claisen–Cope process.[23] Furthermore, CM of **8** using 2-methyl-2-butene[5] led to a mixture of the required prenyl derivative **9** and the methyl-substituted olefins (*E*)- and (*Z*)-**12**, from which pure **9** could not be separated chromatographically. Likewise, CM of the corresponding triacetate derived from **8** resulted in a mixture of dimethyl- and methyl-substituted products **13** and **14** under these conditions as well, whereas CM of **8** with isobutylene avoids such a severe purification problem.

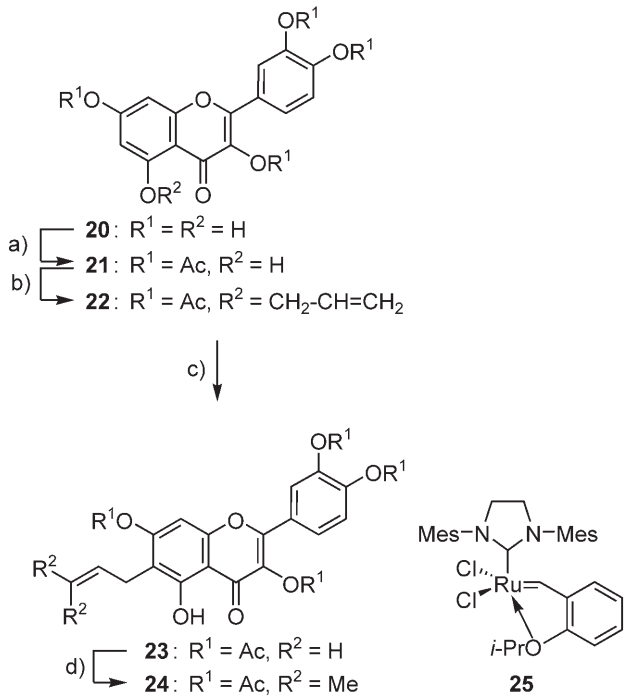


Scheme 3. *Reagents and conditions*: a) decalin, 200°C, 1 d, 41% **8** + **11** (1:1); b) 2-methyl-2-butene, 1 mol% **10**, benzene, room temperature, overnight, 73% **9** + **12** (8.5:1), 71% **13** + **14** (5.6:1); c) Ac_2O, pyridine, room temperature, 90%.

The reaction sequence used for the preparation of flavanone **3** (Scheme 2) could be readily applied to the synthesis of the antifungal[24] phytoalexin 6-prenylgenistein (**4**), too (Scheme 4). This isoflavone additionally displays considerable antibacterial activity[25] against diverse microbes including vancomycin-resistant *Enterococcus* species and methicillin-resistant *Staphylococcus aureus*,[25b] significantly inhibits the Na^+/H^+ exchange system of arterial smooth muscle cells,[26] acts as a hepatoprotective agent[27] and shows a potent cytotoxic activity[28] against human solid tumor (KB) cells.[28a] So far, **4** has been prepared by unselective nuclear prenylation of the isoflavone genistein (**15**),[29] small-scale enzymatic C-6 prenylation of **15** using prenyltransferases[30] or multistep synthesis *via* prenylation of a 6-iodotrialkoxyisoflavone intermediate through an alkynylation/hydrogenation/dehy-



Scheme 4. *Reagents and conditions*: a) 2 equivs. Ac_2O, pyridine, room temperature, 81%; b) allyl alcohol, PPh_3, DEAD, THF, 0°C to room temperature, 53%; c) 10 mol% $Eu(fod)_3$, $CHCl_3$, 85°C (sealed tube), 18 h, 57%; d) isobutylene, 1 mol% **10**, benzene, room temperature (sealed tube), 3 d, 86%; e) MeOH, 0.3 equivs. K_2CO_3, 40°C, 2 h, 91%.



Scheme 5. *Reagents and conditions*: a) 4 equivs. Ac_2O, pyridine, room temperature, 7 min, 59%; b) allyl alcohol, PPh_3, DEAD, THF, 0°C to room temperature, 72%; c) 10 mol% $Eu(fod)_3$, $CHCl_3$, 80°C (sealed tube), 15 h, 73%; d) isobutylene, 3 mol% **25**, CH_2Cl_2, room temperature (sealed tube), 3 d, 51%.

dration sequence.[31] Our novel route to 6-prenylgenistein (**4**) commenced with a chemoselective diacetylation[32] of commercially available genistein (**15**) that can also easily be prepared from inexpensive building blocks.[33] Allyl ether formation from **16** under Mitsunobu conditions followed by europium(III)-catalyzed Claisen rearrangement of **17** provided the substrate **18** for the CM event without interference by a domino Claisen–Cope process. After CM of **18** with isobutylene using a 1 mol% loading of catalyst **10**, the prenylated diacetate **19** was isolated in high yield and efficiently deblocked to give the natural product **4**.

The Claisen rearrangement/CM strategy could be employed for a concise preparation of the tetraacetate **24** of the flavonol 6-prenylquercetin (**5**) that shows cytotoxic activity against human oral tumor cell lines[34] as well (Scheme 5). During the previous synthesis of **5**,[35] reaction of the tetra-MOM ether of quercetin (**20**) with prenyl bromide and potassium carbonate afforded only a 2% yield of the desired C-6 prenylated product. In our novel approach to **5**, commercially available quercetin (**20**) was first chemoselectively converted to the tetraacetate **21**,[36] which in turn was *O*-allylated using the Mitsunobu methodology to provide **22**. A subsequent europium(III)-catalyzed Claisen rearrangement of **22** cleanly gave rise to the C-6 allyl derivative **23** without competing C-8 allylation. While the 1 mol% loading of catalyst **10** used before only led to low levels of conversion in the CM of **23** with isobutylene, which might be due to the higher number of Lewis basic donor groups within this substrate, application of the ruthenium carbene complex **25**[37] in dichloromethane and increasing the catalyst loading to 3 mol% accomplished the formation of the desired prenylated flavonol tetraacetate **24** in a satisfactory 51% isolated yield. Unfortunately, the solvolysis conditions successfully utilized for deacylation of acetates **9** and **19** did not effect complete deblocking of **24** to give the natural product **5**, and alternative methodologies are currently being investigated.

In summary, we have developed an efficient strategy for regioselective C-6 prenylation of flavanones, isoflavones and flavonols starting from the readily available parent flavonoids. This technology should be helpful for medicinal chemists in providing substantial amounts of prenyl flavonoids for further biological evaluation.

Experimental Section

General Procedure for Europium(III)-Catalyzed Claisen Rearrangement

To a stirred suspension of a flavonoid C-5-*O*-allyl ether (2.0 mmol) in dry $CHCl_3$ (3 mL) was added $Eu(fod)_3$

(0.2 mmol, 10 mol%) under an argon atmosphere. After refluxing in a sealed tube at the temperature and for the time listed in the Schemes, the solvent was removed under vacuum, and the crude product was purified by flash chromatography on silica gel.

23: R_f=0.66 (pentane/ethyl acetate, 1:1); mp 187–188°C; IR (neat): $\tilde{\nu}$=3082 (w), 2936 (w), 2853 (w), 1771 (s, C=O), 1646 (m), 1619 (s), 1454 (m), 1370 (s), 1251 (w), 1189 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.33 (s, 3H), 2.36 (s, 9H), 3.38 (d, ^3J=6.2 Hz, 2H, CH_2-CH), 4.99–5.03 (m, 2H, CH_2=CH), 5.84–5.89 (m, 1H, CH$_2$=C*H*), 6.83 (s, 1H, 8-H), 7.35 (d, ^3J=8.4 Hz, 1H, 5′-H), 7.72 (d, ^4J=2.0 Hz, 1H, 2′-H), 7.74 (dd, ^4J=2.0 Hz, ^3J=8.4 Hz, 1H, 6′-H), 12.40 (s, 1H, 5-O*H*); ^{1}H ^{1}H NOESY ($CDCl_3$, 500 MHz): crosspeak for 8-H with 2′-H and 6′-H, crosspeak for 5-O*H* with CH_2-CH and CH$_2$=C*H* and CH_2=CH; ^{13}C NMR ($CDCl_3$, 126 MHz): δ=20.43 (q), 20.67 (q, intense), 20.98 (q), 27.25 (t, *C*H$_2$-CH), 101.67 (d, C-8), 108.58 (s, C-4a), 115.44 (t, *C*H$_2$=CH), 115.78 (s, C-6), 123.98 (d), 124.01 (d), 126.54 (d, C-6′), 127.65 (s, C-1′), 132.05 (s, C-3), 134.59 (d, CH$_2$=*C*H), 142.21 (s, C-4′), 144.56 (s, C-3′), 153.99 (s, C-7), 154.76 (s, C-8a), 155.43 (s, C-2), 159.43 (s, C-5), 167.74 (s), 167.81 (s), 167.85 (s), 168.28 (s), 176.41 (s, C-4); MS (LC/MS, ESI): *m/z* (%)= 511.1 (100) [M+H$^+$]; anal. calcd. for $C_{26}H_{22}O_{11}$: C 61.18, H 4.34; found: C 61.17, H 4.44.

General Procedure for Cross-Metathesis with Isobutylene

To a stirred solution of the C-6 allylated flavonoid derivative (0.126 mmol) in dry benzene (4 mL) or dry CH_2Cl_2 (4 mL) was added **10** (0.0013 mmol, 1 mol%) or **25** (0.0038 mmol, 3 mol%) as indicated in the Schemes under an argon atmosphere. The mixture was cooled to −78°C followed by the addition of isobutylene (3 mL). After stirring the mixture in a sealed tube at room temperature for 2–3 d, it was filtered through a plug of silica gel, the solvent was removed under vacuum, and the crude product was purified by flash chromatography.

24: R_f=0.35 (pentane/ethyl acetate, 3:2); mp 157–158°C; IR (neat): $\tilde{\nu}$=2927 (w), 1773 (s), 1647 (m), 1618 (s), 1455 (m), 1370 (s), 1250 (w), 1187 (s), 1153 (s), 1119 (m), 1082 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.67 (s, 3H, *E* CH_3-C=CH), 1.75 (s, 3H, *Z* CH_3-C=CH), 2.32 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 3.31 (d, ^3J=7.0 Hz, 2H, CH_2-CH), 5.11 (t, ^3J=7.0 Hz, 1H, CH$_2$-C*H*), 6.80 (s, 1H, 8-H), 7.34 (d, ^3J=8.4 Hz, 1H, 5′-H), 7.71 (d, ^4J=2.0 Hz, 1H, 2′-H), 7.73 (dd, ^4J=2.0 Hz, ^3J=8.4 Hz, 1H, 6′-H), 12.37 (s, 1H, 5-O*H*); ^{1}H ^{1}H NOESY ($CDCl_3$, 500 MHz): crosspeak for 8-H with 2′-H and 6′-H, crosspeak for 5-O*H* with CH_2-CH and CH$_2$-C*H*; ^{13}C NMR ($CDCl_3$, 126 MHz): δ=17.84 (q, *Z* *C*H$_3$-C=CH), 20.43 (q), 20.67 (q, intense), 20.96 (q), 22.26 (t, *C*H$_2$-CH), 25.68 (q, *E* *C*H$_3$-C=CH), 101.51 (d, C-8), 108.60 (s, C-4a), 117.71 (s, C-6), 120.80 (d, prenyl *C*H), 123.96 (d), 123.99 (d), 126.54 (d, C-6′), 127.71 (s, C-1′), 132.01 (s, C-3), 132.67 (s, prenyl *C*), 142.19 (s, C-3′), 144.53 (s, C-4′), 153.69 (s, C-8a), 154.55 (s, C-7), 155.33 (s, C-2), 159.35 (s, C-5), 167.75 (s), 167.82 (s), 167.85 (s), 168.38 (s), 176.43 (s, C-4); MS (LC/MS, ESI): *m/z* (%)=539.1 (100) [M+H$^+$]; anal. calcd. for $C_{28}H_{26}O_{11}$: C 62.45, H 4.87; found: C 62.54, H 4.98.

General Procedure for Cross-Metathesis with 2-Methyl-2-butene

To a stirred solution of **10** (0.0025 mmol, 1 mol%) in dry benzene (0.5 mL) was added the C-6 allylated flavonoid derivative (0.252 mmol) in dry benzene (1.5 mL) and 2-methyl-2-butene (0.5 mL) under an argon atmosphere. After stirring the mixture at room temperature overnight, it was filtered through a plug of silica gel. Following removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel.

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