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ORIGINAL PAPER

Assembling the prenylneoflavone system through a Pechmann condensation/Mitsunobu reaction/Claisen rearrangement/olefin cross-metathesis sequence

Oleg A. Lozinski[1,2,3] · J. Bistodeau[2] · C. Bennetau-Pelissero[4] · Vladimir P. Khilya[1] · S. Shinkaruk[2]

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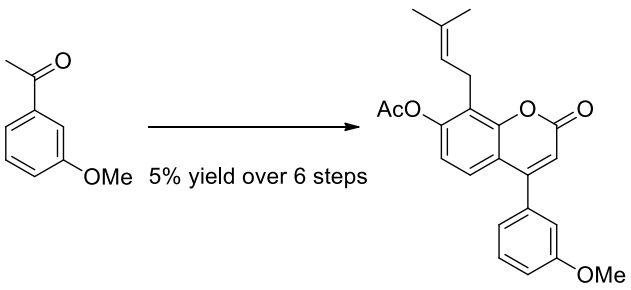
Abstract

The multistep synthesis of a prenylneoflavone through a sequence of the Mitsunobu reaction/Claisen rearrangement/olefin cross-metathesis reaction has been accomplished in 5% yield over six steps starting from commercially available 3-methoxyacetophenone. The sequence is shown to be compatible with a Pechmann condensation which proved to be a robust and cost-effective method for the assembling of the α-pyrone core. The results open doors to a general approach to the prenylneoflavone system starting from phenol and acetophenone derivatives.

Graphic abstract



Keywords Prenyl · Flavonoids · Alkenes · Heterocycles · Metathesis

Introduction

Prenyl group plays an important role in the enhancement of bioactivity [1] being responsible for protein–protein binding through the specific attachment to the prenyl binding domains [2]. For a range of oxygen-containing heterocycles, the presence of prenyl group is linked to the increased potency of estrogenic activity profile [3]. Notably, 8-prenylnaringenin (8PN, **1**, Fig. 1) is considered to be the most potent estrogenic flavonoid known [4].

In addition, targeting proteases is an effective antiviral strategy in suppressing viral genome replication to cure CoV infection [5]. Angiotensin-converting enzyme (ACE) inhibitors are blockbusters among protease inhibitors on the market [6]. Zhou et al. confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin-converting enzyme II

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✉ Oleg A. Lozinski
lozinskioleg@gmail.com

[1] Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

[2] University of Bordeaux, ISM, UMR 5255, CNRS, Bordeaux, France

[3] University of Bordeaux, Neurocentre Magendie, UMR 1215, INSERM, Bordeaux, France

[4] University of Bordeaux, ARNA, UMR 1212, INSERM/CNRS, Bordeaux, France

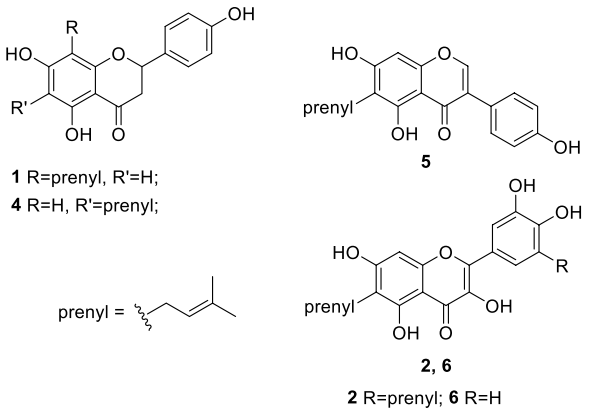


Fig. 1 Compounds **1**, **2**, and **4**–**6**

(ACE2)—as SARS-CoV [7]. This represents protease inhibitors as attractive targets in search for the treatment of 2019-nCoV. Interestingly, the prenylated derivative of quercetin **2** (Fig. 1) exhibited the highest inhibitory effects on the papain-like protease [PL^{pro}] in SARS-CoV (IC_{50} = 3.7 μM) [5].

A set of prenylation methods have been reported up to date [8]. The prenylneoflavone system assembling is of particular interest due to the fact that neoflavones represent one of the most ubiquitous classes of naturally occurring oxygen-containing heterocycles that still remain poorly investigated.

Results and discussion

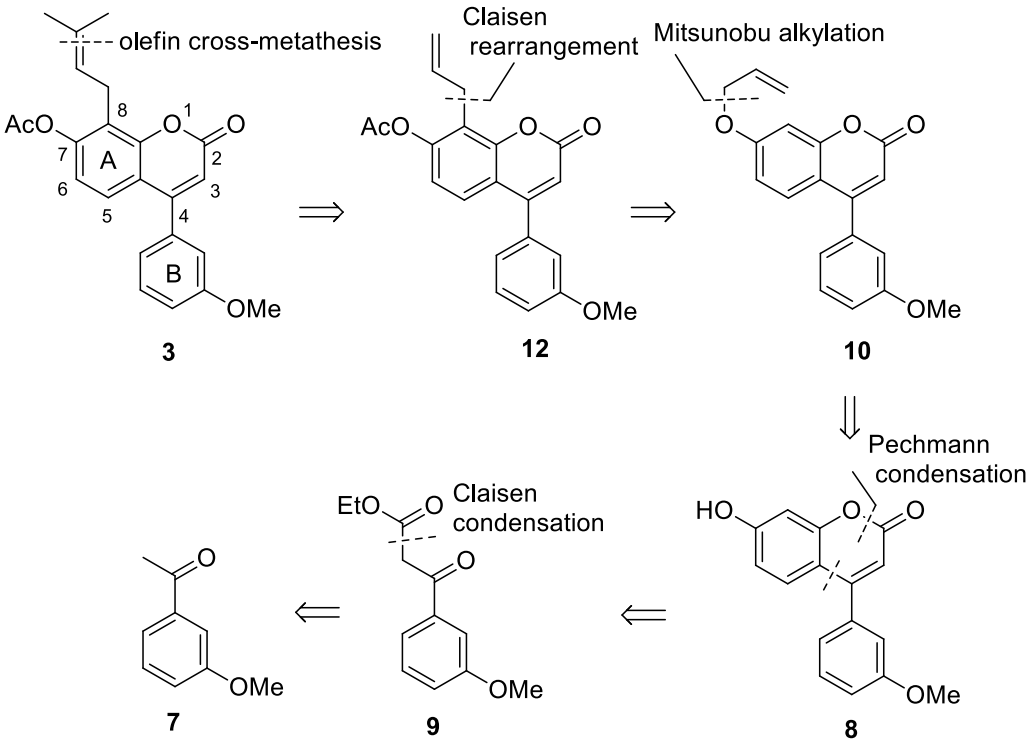
Our studies in the requisite 4-(3-methoxyphenyl)-8-(3-methylbut-2-en-1-yl)-2-oxo-2*H*-chromen-7-yl acetate (**3**) synthesis (Scheme 1) commenced with close examination of the strategy and the means of the synthesis that should meet the criteria required in terms of cost-effective and feasible design. The synthetic task falls into two groups of questions: the prenyl group installment and the α-pyrone ring assembling, respectively.

Two approaches towards the prenylcoumarin motif are distinguished: (1) starting from salicylic aldehydes and cinnamates through the tandem Claisen rearrangement/Wittig olefination/cyclization sequence [9] and (2) using preformed coumarin skeleton via the Mitsunobu reaction/Claisen rearrangement/olefin cross-metathesis reaction sequence [10]. The latter was used by Tischer and Metz for the synthesis of the naturally occurring 8-prenylnaringenin (**1**), 6-prenylnaringenin (**4**), 6-prenylgenistein (**5**), and 6-prenylquercetin (**6**) (Fig. 1).

It has drawn our attention as the excellent example of the synergy of up-to-date olefin cross-metathesis reaction and conventionally used the Claisen rearrangement in a single synthetic sequence through which prenyl group can be readily installed.

However, to extend the substrate scope of this approach it may be advantageous to start from aromatic compounds

Scheme 1



such as phenols. As part of our ongoing research program in the field of the chemistry of oxygen-containing heterocycles [11] we aimed to build a bridge between the conventionally used and the most state-of-the art methods. Thus, we chose the Pechmann condensation to study its compatibility with the Mitsunobu reaction/Claisen rearrangement/olefin cross-metathesis reaction sequence to access prenylneoflavones starting from aromatic compounds such as 3-methoxyacetophenone (**7**) (Scheme 1).

In view of the presence of multiple reaction centers in two aromatic rings of a neoflavone, its *ortho*-functionalization must be effectively achieved through the Claisen rearrangement. A series of groups has been reported in the literature as prenyl synthons, namely 2-methylbut-3-en-2-yl, prenyl, and allyl [8].

Nevertheless, the selective Claisen rearrangement is a challenging task because of the isomer formation in the competent Claisen–Cope rearrangement [8]. At the same time, allyl group has been reported to be the versatile synthon of prenyl group in the Mitsunobu reaction/Claisen rearrangement/olefin cross-metathesis reaction sequence [8].

This approach relies upon the Mitsunobu alkylation which is not water sensitive and, therefore, takes an advantage of time-saving benefits compared to a classical alkylation using alkyl halides and bases in a dry solvent. It enables proceeding on the next step without further purification of the coumarin obtained via the Pechmann condensation.

Therefore, the Pechmann condensation/Mitsunobu alkylation/Claisen rearrangement/olefin cross-metathesis reaction sequence represents the approach through which the prenylneoflavone synthesis can be readily achieved in a cheap manner employing the idea of the synergy of cost-effective and powerful means to organic synthesis.

The foregoing synthetic blueprint demonstrates the key scissions in the retrosynthesis of the prenylneoflavone **3** via the synthetic strategy shown in the Scheme 1.

To assemble the pivotal neoflavone system, the two-step conversion of 3-methoxyacetophenone (**7**) into 7-hydroxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (**8**) was effected via the Claisen condensation of **7** into ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (**9**) in 40% yield, followed by the Pechmann condensation of **9** with resorcinol in the presence of sulfuric acid to obtain neoflavone **8** in 52% yield (Scheme 2) [12].

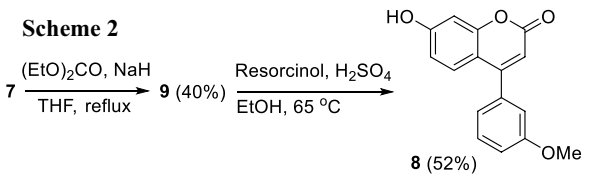
With neoflavone **8** in hand, our attention turned to prenyl group installment in the neoflavone core. The prenyl group installment strategy relied upon the sequence of the Mitsunobu reaction and the Claisen rearrangement with the following olefin cross-metathesis reaction. Therefore, subsequent treatment of **8** with DIAD, PPh_3 in THF at 0 °C resulted in 7-allyloxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (**10**) formation in 78% yield (Scheme 3).

In the ^{1}H NMR spectrum of *O*-allyl product **10** recorded in $CDCl_3$ the doublet at 4.61 ppm, the doublet of doublet of triplets at 5.34–5.45 ppm and at 6.05 ppm are consistent with OH substitution with allyl moiety.

The Claisen rearrangement proved to be the most challenging step required extensive troubleshooting for reaction conditions optimization. Thermal and Lewis acid catalysis factors are considered [8]. It has been reported that in contrast to the boron trichloride catalyst, upon treatment with Et_2AlCl, a range of substituted allylchlorophenyl ethers bearing electron-withdrawing groups on the aromatic ring undertook the Claisen rearrangement to afford allylchlorophenols in quantitative yields [13].

However, the attempted reaction of 7-allyloxyneoflavone **10** with Et_2AlCl at the same conditions resulted in dealkylation of 7-allyloxyneoflavone **10** (Scheme 3, Table 1) to give neoflavone **8** in 87% yield. Therefore, we chose to proceed

Scheme 2



Scheme 3

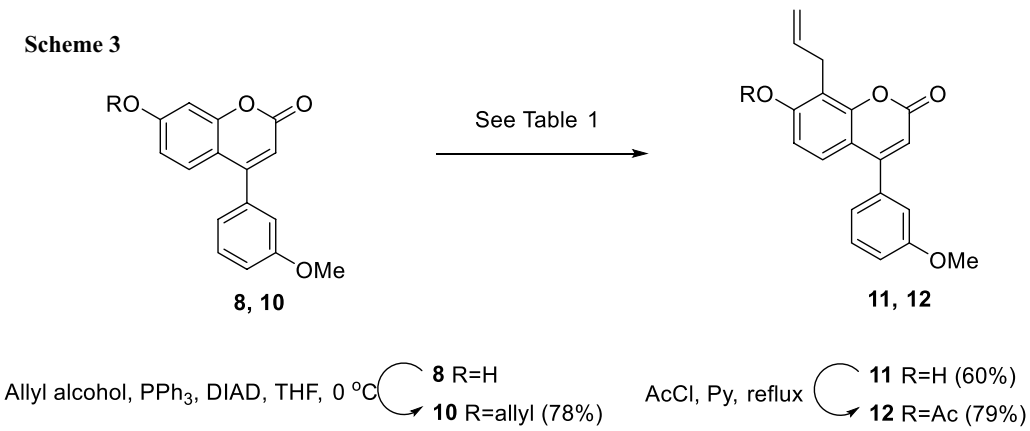


Table 1 The optimization of the reaction conditions of the Claisen rearrangement of *O*-allyl product **10**

Entry	*T*/°C	Time/h	Solvent	*W*	Catalyst	**11** Yield/%
1	r.t	24	Toluene	–	Et_2AlCl	13
2	70	20	DCM	300	–	–
3	160	2	DMF	300	–	–
4	230	7	DMF	300	–	–
5	230	20	DMF	300	–	–
6	230	20	DMF	300	$Eu(fod)_3$[a]	60

[a]Fod refers to 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate

on the Claisen rearrangement with thermal conditions in the microwave-assisted synthesis of the compound **11** [14]. Interestingly, $Eu(fod)_3$ had a marked effect upon 8-allyl-7-hydroxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (**11**) formation. Thus, heating in microwaves 7-allyloxyneoflavone **10** at 230 °C in DMF for 20 h recovered starting material only, while the addition of $Eu(fod)_3$ (9 mol%) gave rise to 60% yield of C-allylated product **11** (Table 1), set for the further step in the olefin cross-metathesis reaction.

^{1}H NMR spectrum of 8-allyl-7-hydroxyneoflavone **11** shows the signal at 8.12 ppm assigned to OH, while the absence of H8, the doublet at 3.63 ppm, the multiplets at 5.00–5.12 ppm and 5.95–6.11 ppm indicate the CO-bond cleavage and the substitution of C-8 with allyl group.

Acetylation of **11** with acetyl chloride was then undertaken to facilitate the product solubility in the olefin cross-metathesis reaction conditions (Scheme 3). It furnished the acetylated product **12** in 79% yield. The singlet at 2.35 ppm in the ^{1}H NMR spectrum (acetone-d_6) of **12** and the absence of the singlet at 8.12 ppm assigned to OH in the ^{1}H NMR spectrum (acetone-d_6) of 8-allyl-7-hydroxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (**11**) are associated with the OH substitution with acetyl group.

With 7-acetoxyneoflavone **12** in hand, its further elaboration to the 3,3′-dimethylallyl derivative **3** was pursued through the olefin cross-metathesis reaction with the second-generation Grubbs catalyst (Scheme 4).

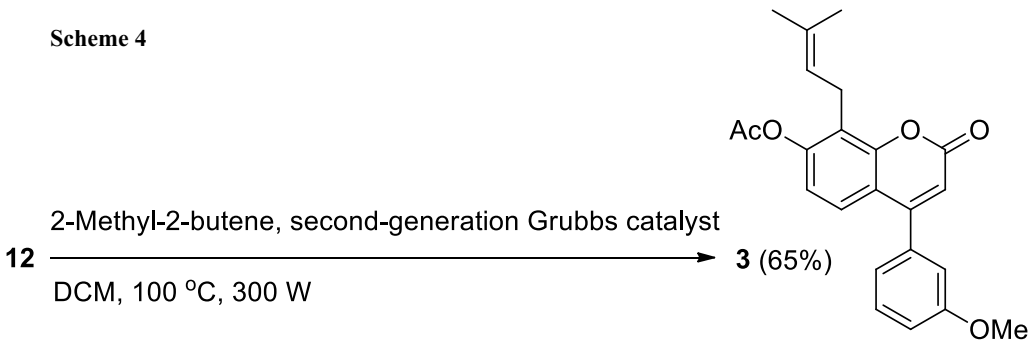
Notably, Pahari et al. reported that attempted the olefin cross-metathesis reaction in the presence of the second-generation Grubbs catalyst failed in the conditions identical to those reported by Hastings et al. [15, 16]. We envisaged that the olefin cross-metathesis reaction with 8-allylneoflavone **12** would proceed in relatively low yield of the target 3,3′-dimethylallyl product **3** in view of the steric hindrance factor that requires a higher temperature for this reaction. Therefore, in contrast with the approach reported by Tischer and Metz (2-methyl-2-butene, the second-generation Grubbs catalyst (1 mol%), benzene, room temperature, overnight, 73% yield for a mixture) the suggested rapid heating in microwaves (100 °C, 300 W) of the 8-allylneoflavone **12**, 2-methyl-2-butene, the second-generation Grubbs catalyst (5 mol%) in DCM under argon allowed us to overcome this problem successively to isolate the pivotal product **3** in 65% yield. The demonstrated 6 steps synthesis of the target compound **3** proceeded in an overall yield of 5%.

The ^{1}H NMR spectrum (acetone-d_6) of 3,3′-dimethylallyl product **3** reveals two singlets at 1.69 ppm and 1.87 ppm assigned to two CH_3 groups in addition to the absence of the corresponding multiplet at 5.01–5.14 ppm assigned to the olefinic $=CH_2$ moiety in the ^{1}H NMR spectrum (acetone-d_6) of the compound **12**.

Conclusion

The prenylneoflavone system assembling has been achieved in six steps in 5% overall yield using the Pechmann condensation with the sequence of the Mitsunobu reaction/Claisen

Scheme 4



rearrangement/olefin cross-metathesis reaction. It allowed extending the substrate scope for abovementioned prenylation approach with regard to the prenylneoflavone system assembling starting from phenols. The present approach will be useful in medicinal chemistry to modulate the bioactivity of drug candidates through the structural modification of oxygen-containing heterocycles with the lipophilic prenyl group. It is of particular interest for the creation of protease inhibitors against the CoV infection.

Experimental

Reaction progress and identity of obtained compounds were monitored by TLC on Merck 60 F254 silica gel plates. NMR spectra were recorded on Bruker Avance 300 (spectrometer frequency for ^{1}H: 300 MHz) spectrometer at 298 K in DMSO-d_6, $CDCl_3$, and acetone-d_6. The TMS signal was used as an internal standard. The results of elemental analyses for C, H, and N were found to be in good agreement (0.2%) with the calculated values. Compound **8** was synthesized according to a procedure published in the literature [12]. All reagents and solvents used were of commercial quality without further purification.

Ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (9) Diethyl carbonate (4.94 g, 41.85 mmol, 1.03 equiv) was added dropwise to the solution of 5.07 g sodium hydride (211.28 mmol, 5.2 equiv) and 6.02 g 3-methoxyacetophenone (**7**, 40.63 mmol, 1 equiv) in 50 cm^3 distilled THF under argon. The reaction mixture was then stirred at reflux for 6 h. The resulting mixture was cooled down to the room temperature, a beige precipitate was observed. It was then filtered out and the filtrate was acidified with HCl (15% aq) and extracted with EtOAc (3 × 50 cm^3). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (cyclohexane/EtOAc, 8:2) to give **9**. Brown oil; yield: 3.72 g (40%); b.p.: 123 °C/0.3 Torr) (Ref. [17]. 123 °C/0.3 Torr); ^{1}H NMR of keto form: ($CDCl_3$, 300 MHz): $\delta = 1.24$ (t, 3H, $J = 6$ Hz, CH_3CH_2), 3.84 (s, 3H, CH_3O), 3.96 (s, 2H, CH_2), 4.20 (q, 2H, $J = 9$ Hz, CH_3CH_2), 7.10–7.14 (m, 1H, H2′); 7.34–7.39 (m, 1H, H5′), 7.46–7.50 (m, 2H, H4′, H6′) ppm; ^{1}H NMR of enol form ($CDCl_3$, 300 MHz): $\delta = 1.32$ (t, 3H, $J = 6$ Hz, CH_3CH_2), 3.82 (s, 3H, CH_3O), 4.25 (q, 2H, $J = 9$ Hz, CH_3CH_2), 5.64 (s, 1H, =CH–), 6.97–7.01 (m, 1H, H2′), 7.30–7.33 (m, 3H, H4′, H5′, H6′), 12.57 (s, 1H, OH) ppm [18].

7-Hydroxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (8) To a stirred solution of 0.803 g **9** (3.62 mmol, 1 equiv) and 0.52 g resorcinol (4.71 mmol, 1.3 equiv) in 8 cm^3 EtOH was added dropwise 5 cm^3 sulfuric acid over 30 min, followed by the heating of the reaction mixture at 65 °C for 7 h. The reaction mixture was then cooled down to the room temperature and poured into 50 cm^3 of distilled water and then extracted with chloroform (3 × 50 cm^3). The solvent was removed under reduced pressure; the viscous brown oil was dissolved in the 0.5 M solution of potassium hydroxide (100 cm^3) and extracted with DCM (3 × 50 cm^3). The aqueous layer was acidified with HCl (15% aq) until pH 1 and then extracted with chloroform (3 × 50 cm^3). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The oil residue was recrystallized from MeOH to give **8**. White solid; yield: 0.50 g (52%); m.p.: 242 °C (Ref. [12]. 241–243 °C).

7-Allyloxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (10, $C_{19}H_{16}O_4$) To a stirred solution of 0.88 g **8** (1 equiv, 3.28 mmol), 1.07 g triphenylphosphine (1.24 equiv, 4.07 mmol) and 0.4 cm^3 allyl alcohol (1.79 equivalents, 5.87 mmol) in 20 cm^3 distilled THF was added dropwise a solution of 1.10 cm^3 diisopropyl azodicarboxylate (1.71 equiv, 5.61 mmol) in 20 cm^3 distilled THF under argon at 0 °C over 10 min. The reaction was stirred at room temperature overnight. Then it was quenched with brine and washed with it several times until no precipitate formed. The aqueous layer was extracted with Et_2O (3 × 50 cm^3) and the layers were separated. The combined organics were dried over anhydrous $MgSO_4$ and the volatiles were removed under reduced pressure. The crude product was purified by silica gel column chromatography (cyclohexane/Et_2O, from 8:2 to 7:3) to give **10**. White solid; yield: 0.79 g (78%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.86$ (s, 3H, CH_3O), 4.61 (d, 2H, $J = 5.7$ Hz, OCH_2), 5.34–5.45 (ddt, 2H, $J = 44.5$, 17.2, 1.7 Hz, $=CH_2$), 6.05 (ddt, 1H, $J = 17.3$, 10.5, 5.3 Hz, =CH–), 6.23 (s, 1H, H3), 6.81 (dd, 1H, $J = 8.9$, 2.6 Hz, H8), 6.90 (d, 1H, $J = 2.5$ Hz, H6′), 6.95 (t, 1H, $J = 2.1$ Hz, H2′), 7.03 (td, 2H, $J = 11.5$, 2.7 Hz, H6, H5′), 7.42 (dd, 2H, $J = 11.5$, 2.7 Hz, H4′, H5) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 53.58$, 69.82, 101.98, 111.83, 112.57, 112.82, 114.08, 114.99, 118.58, 120.70, 128.05, 129.97, 132.17, 137.35, 155.67, 156.67, 160.31, 161.22, 162.24 ppm.

8-Allyl-7-hydroxy-4-(3-methoxyphenyl)-2*H*-chromen-2-one (11, $C_{19}H_{16}O_4$) To a solution of 0.65 g **10** (1 equiv, 2.11 mmol) in 12 cm^3 DMF was added 0.22 g Eu(fod)$_3$ (9 mol%). The vial was sealed and heated at 230 °C under microwaves for 20 h (START SYNTH Microwave synthesis labstation, 300 W). The reaction mixture was then washed with the aqueous HCl (15% aq) (3 × 50 cm^3) and extracted with EtOAc (3 × 40 cm^3) and the layers were separated. The combined organics were dried over anhydrous $MgSO_4$ and the volatiles were removed under reduced pressure. The viscous brown oil was dissolved in the 0.5 M solution of

potassium hydroxide (100 cm^3) and extracted with DCM (6×30 cm^3). The aqueous layer was acidified with HCl (15% aq) and extracted with chloroform (5×40 cm^3). The organic layer was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure to give. The crude product was purified by silica gel column chromatography (cyclohexane/Et_2O, from 8:2 to 7:3) to give **11**. Light yellow solid; yield: 0.39 g (60%); ^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 3.63$ (d, 2H, $J = 6.3$ Hz, –CH_2–), 3.89 (s, 3H, CH_3O), 5.00–5.12 (dd, 2H, $J = 10.0$, 17.1 Hz, =CH_2), 5.95–6.11 (m, 1H, =CH–), 6.12 (s, 1H, H3), 6.92 (d, 1H, $J = 8.9$ Hz, H6′), 7.01–7.16 (m, 3H, H2′, H6, H5), 7.25 (d, 1H, $J = 8.8$ Hz, H4′), 7.47 (t, 1H, $J = 8.1$ Hz, H5′), 8.12 (s, 1H, OH) ppm; ^{13}C NMR (acetone-d_6, 76 MHz): $\delta = 26.84$, 55.46, 102.49, 110.52, 111.63, 112.58, 113.65, 114.69, 114.97, 121.78, 125.84, 129.84, 135.39, 137.31, 153.79, 156.00, 158.81, 159.94, 160.20 ppm.

8-Allyl-4-(3-methoxyphenyl)-2-oxo-2*H*-chromen-7-yl acetate (12, $C_{21}H_{18}O_5$) To a stirred solution of the crude product of **11** (1 equiv, 0.33 g, 1.08 mmol) in 1 cm^3 pyridine was added 0.46 cm^3 acetyl chloride (6 equiv). The reaction mixture was stirred at reflux for 6 h. The mixture was poured into distilled water and then extracted with DCM. The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The brown oil was purified by silica gel column chromatography (cyclohexane/EtOAc, 8:2) to give **12**. Brown solid; yield: 0.3 g (79%); ^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 2.35$ (s, 3H, CH_3CO), 3.57 (dt, 2H, $J = 6.3$, 1.6 Hz, –CH_2–), 3.88 (s, 3H, CH_3O), 5.01–5.14 (qq, 2H, $J = 6.3$, 1.5 Hz, =CH_2), 5.83–6.04 (m, 1H, =CH-), 6.33 (s, 1H, H3), 7.07–7.15 (m, 4H, H2′, H6′, H6, H5), 7.36–7.59 (m, 2H, H4′, H5′) ppm; ^{13}C NMR (acetone-d_6, 76 MHz): $\delta = 20.55$, 27.72, 55.46, 113.88, 114.01, 115.27, 115.60, 117.36, 118.98, 120.64, 121.27, 125.45, 129.99, 134.55, 137.76, 151.86, 153.40, 155.31, 159.29, 160.60, 169.05 ppm.

4-(3-Methoxyphenyl)-8-(3-methylbut-2-en-1-yl)-2-oxo-2*H*-chromen-7-yl acetate (3, $C_{23}H_{22}O_5$) To a solution of 0.08 g **12** (1 equiv, 0.24 mmol) and 0.26 cm^3 2-methyl-2-butene (2.44 mmol) was added 0.12 g of the second-generation Grubbs catalyst (5 mol%) in distilled DCM under argon. The mixture was placed into START SYNTH Microwave synthesis labstation for 30 min (100 °C, 300 W). The solvent was removed under reduced pressure, and the product purified by silica gel column chromatography (cyclohexane/EtOAc 9:1) to give **3**. Brown oil; yield: 0.06 g (65%); ^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 1.69$ (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.38 (s, 3H, CH_3CO), 3.52 (d, 2H, $J = 7.1$ Hz, –CH_2–), 3.89 (s, 3H, CH_3O), 5.19 (t, 1H, $J = 7.1$ Hz, –CH–), 6.33 (s, 1H, H3), 7.02–7.20 (m, 4H, 2′, H6′, H6, H5), 7.40 (dd, 1H, $J = 8.8$, 5.8 Hz, H4′), 7.44–7.57 (m, 1H, H5′) ppm; ^{13}C NMR (acetone-d_6, 76 MHz): $\delta = 17.06$, 20.51, 26.61, 54.09, 54.90, 113.87, 115.25, 116.77, 118.698, 120.63, 121.55, 125.21, 126.53, 127.00, 130.63, 132.79, 136.76, 151.61, 152.82, 155.35, 159.34, 160.02, 168.97 ppm.

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