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Tandem Claisen Rearrangement/6-*endo* Cyclization Approach to Allylated and Prenylated Chromones

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Allyl, dimethylallyl and prenyl ethers derived from *o*-acylphenols reacted upon microwave irradiation to form *C*-allylated or -prenylated chromone derivatives, depending on the substitution pattern of the arene and the allyl substituent. The reaction proceeds through a tandem Claisen rearrangement and 6-*endo*-*trig* or 6-*endo*-*dig* cyclization sequence. For prenyl ethers, the tandem sequence can be extended by a Cope rearrangement to furnish 6-prenylchromones. The method is potentially useful for the synthesis of natural products and drugs.

Introduction

Numerous secondary metabolites with a phenol or polyphenol structure are biochemically modified by prenyltransferase-mediated prenylation reactions.[1–4] It was recently demonstrated for tyrosine-containing cyclopeptides that *C*-prenylated phenols can arise through a sequence of enzymatic reverse *O*-prenylation and a subsequent Claisen rearrangement, which is facile under physiological conditions in this particular case.[5] This reaction sequence is complementary to an alternative biosynthetic mechanism that involves the formation of carbenium ions from prenyl diphosphate and a Friedel–Crafts-type alkylation of the aromatic core.[6] Among aromatic secondary metabolites, flavonoids[7,8] often occur as prenyl conjugates.[9] Interestingly, prenylation has been found on several occasions to modulate the bioactivity of natural products.[10] For example, the prenylated flavonoids licoflavone C and isobavachin (Figure 1) show notable cytotoxicities against C6 glioma cells, whereas their non-prenylated analogues were found to be inactive.[11] A series of geranylated chrysin analogues have been synthesized and tested for their ability to inhibit the proliferation of human tumour cell lines in comparison with chrysin itself. In this study it was found that in most assays the 6- and 8-geranylated chrysin derivatives were significantly more active than chrysin.[12] An example that has been particularly well studied is 8-prenylnaringenin (8-PN), a highly potent phytoestrogen isolated from hops.[13] 8-PN has been proposed as an alternative to hormone replacement therapy for menopausal women.[14] Several comparative studies have revealed that its estrogenic activity is by orders of magnitude higher than that observed for the parent compound naringenin[15–17] or its regioisomer 6-prenylnaringenin (Figure 1).[18] It has been reasoned that the increased bioactivity might originate from an increased lipophilicity and facilitated permeation through cell membranes.[19]

The synthesis of prenylated flavonoids can be accomplished by prenylation of an appropriately *O*-protected flavonoid. For example, Metz and co-workers obtained 8-prenylnaringenin from naringenin by Mitsunobu *O*-prenylation at C-5 and a sequential Claisen/Cope rearrangement. Depending on the conditions, 8-PN was obtained either as the sole product or as a 1.2:1 mixture of 8-PN and the initial Claisen rearrangement product, 6-(1,1-dimethylallyl)naringenin.[20] Very recently, Zhang and co-workers described the synthesis of the 8-prenylated flavonoid icariin from the 5-prenyl ether of kaempferol by a europium-catalysed Claisen/Cope rearrangement.[21] Nemoto and co-workers synthesized various 8-prenylated flavanones and flavanols from non-prenylated precursors through regioselective Pd-catalysed 1,1-dimethylallylation at 7-OH followed by thermal Claisen rearrangement.[22] Very recently, Wang and co-workers synthesized sophoflavescenol and two prenyl-cyclized natural products in high selectivity and yields by *O*-prenylation at 5-OH and microwave-promoted Claisen/Cope rearrangement.[23] An alternative route to prenylated flavonoids starts from appropriately prenylated aromatic precursors that are then cyclized, for example, by Allan–Robinson flavone synthesis or one of its variants.[24,25] This strategy has, for example, been applied to the synthesis of cannflavin B and its 8-prenyl isomer, isocannflavine B, by Appendino and co-workers.[26] Recently, approaches to *C*-prenylated or -allylated flavonoids and isoflavonoids have emerged that rely on a tandem (or domino) prenylation (or allylation) and cyclization sequence.[27–29] Examples are the syntheses of 3-allyl-substituted chromones[30,31] and isochromones[32] in which a metal-catalysed or electrophilic

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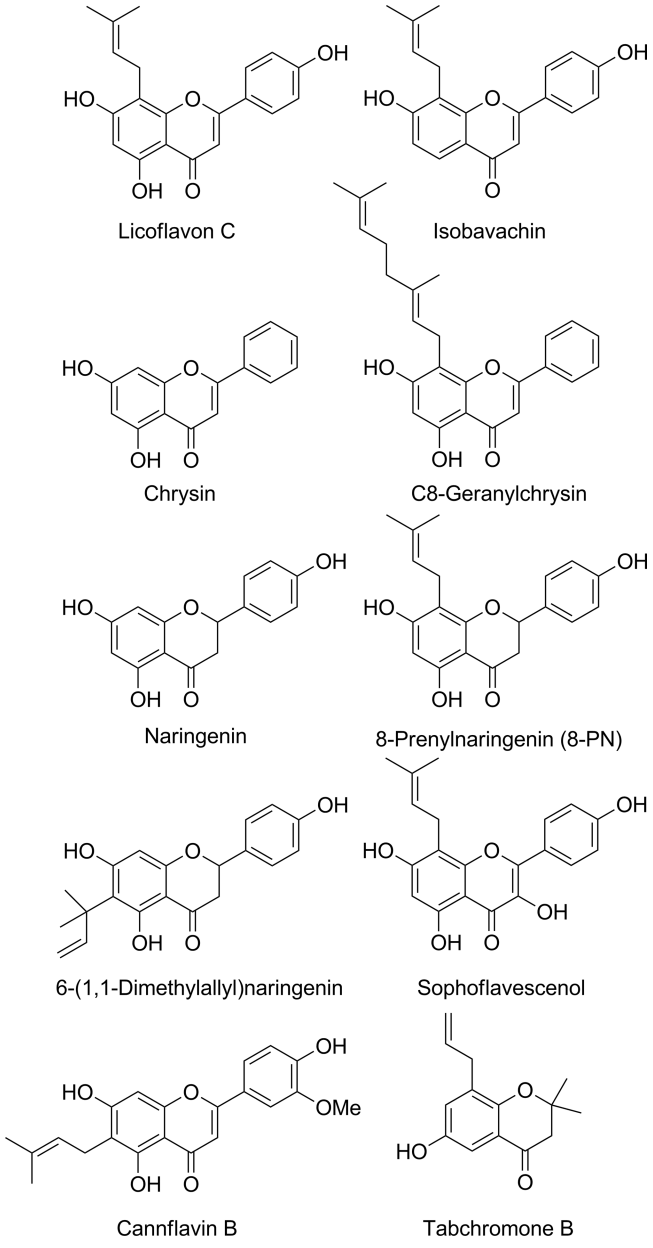
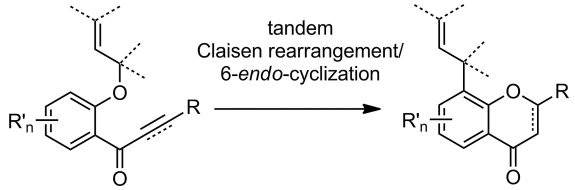


Figure 1. Structures of representative bioactive flavonoids.

alkynone cyclization and a concomitant allyl migration are combined. Motivated by the discovery of two new 8-substituted chroman-4-ones, tabchromones A and B, from the tobacco plant *nicotiana tabacum*,[33] we have very recently developed a synthesis[34] based on a microwave-promoted allyl aryl ether Claisen rearrangement and subsequent 6-*endo-trig* cyclization.

6-*endo*-Cyclization reactions[35–39] have previously been used for the synthesis of chromanones and chromones, but not in tandem with a Claisen rearrangement. This combination of synthetic steps offers the advantage that an allyl ether can be used as a protecting group during the preparation of the precursors, but that the protecting group becomes an essential part of the target structure upon its removal. Following our preliminary communication,[34] we report herein an extension of the tandem sequence to 6-*endo-trig* and 6-*endo-dig* cyclizations combined with 8- and 6-prenylations (Scheme 1).



Scheme 1. This work: tandem Claisen rearrangement and 6-*endo-dig* or 6-*endo-trig* cyclization sequence.

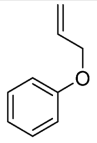
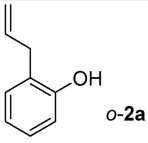
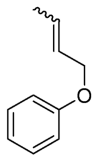
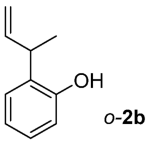
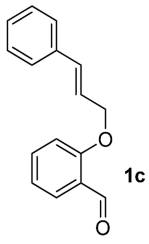
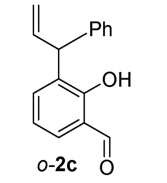
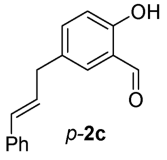
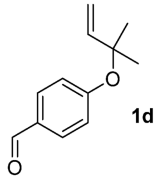
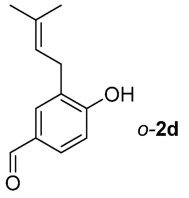
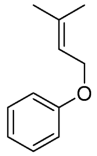
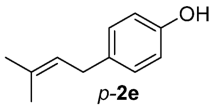
Results and Discussion

Microwave-Promoted Claisen Rearrangement

Claisen rearrangements of allyl phenyl ethers require high temperatures, which makes the use of high-boiling-point solvents and sometimes inconvenient heating sources such as sand baths necessary.[40–42] Controlling reaction temperatures higher than 200 °C over long periods of time is sometimes difficult to achieve, resulting in reproducibility problems.[34,43] Microwave irradiation[44–47] was early on discovered to be a suitable method of energy supply that avoids these obstacles in Claisen rearrangements,[48] and interest in the further development of microwave-promoted Claisen rearrangements continues, for example, with a view towards scale-up by using special microwave apparatus.[49] In our preliminary communication we identified microwave irradiation in the solvent *N*,*N*-diethylaniline as suitable conditions for the envisaged tandem Claisen rearrangement/6-*endo-trig* cyclization sequence.[34] With a view to generalizing these conditions for other substituted allyl groups, we synthesized a set of allyl ethers **1a**–**e** and subjected them to microwave irradiation in *N*,*N*-diethylaniline (Table 1). Microwave irradiation of a solution of **1a** in *N*,*N*-diethylaniline at 150 °C did not promote the Claisen rearrangement to *o*-allylphenol (**2a**). Increasing the temperature to 200 °C promoted the reaction, however, the conversion remained incomplete even after 1 hour. Irradiation at 250 °C for 1 hour resulted in full conversion to **2a**, which was isolated in quantitative yield (entries 1–3). Under the same conditions, the crotyl ether **1b** underwent a clean Claisen rearrangement to the expected 1-methylallyl-substituted phenol **2b**, which was isolated in 94% yield (entry 4). When the cinnamyl ether **1c** was subjected to microwave irradiation, the Claisen rearrangement product *o*-**2c** and the styrene *p*-**2c** were isolated as an inseparable 1.0:0.7 mixture in nearly quantitative yield (entry 5). The latter product results from a Cope rearrangement of the initially formed Claisen rearrangement product *o*-**2c**.[43] In an attempt to improve the selectivity towards *o*-**2c**, we reduced the reaction time to 5 min (entry 6), but to no avail: the isolated yield and product ratio were virtually identical. In the light of a report by Wang and co-workers, the observation of the Claisen rearrangement product *o*-**2c** was somewhat surprising.[50]

Wang and co-workers found for a closely related cinnamyl ether that the initial Claisen product could not be detected under conventional heating conditions, but that the tandem Claisen/Cope product analogous to *p*-**2c** was exclusively formed, regardless of the solvent and the reaction time. Next, the Claisen rearrangement of the 1,1-dimethylallyl ether **1d** was investigated under the standard conditions. This starting material was synthesized by Pd-catalysed allylation of *p*-hydroxybenzaldehyde with 1,1-dimethylallyl carbonate, in analogy to the procedure used by Nemoto and co-workers for the 7-OH dimethylallylation of chromones.[22] Thermal Claisen rearrangement of an aldol condensation product of **1d** had previously been exploited for the synthesis of prenylated carbazoles,[51] and a microwave-promoted Claisen rearrangement of **1d** in toluene at 190 °C was used more recently for the synthesis of abyssinones II and III.[52] Although the reaction temperature of our standard conditions is significantly higher and the solvent *N*,*N*-diethylaniline is basic and nucleophilic, we found that **1d** still selectively rearranged to **2d**. In particular, no decarbonylation products were detected although they had previously been observed when other *O*-allylated benzaldehydes were heated to temperatures of 200 °C[53] or when heteroaromatic aldehydes were exposed to microwave irradiation.[54]

Table 1. Microwave-promoted Claisen rearrangement of allyl aryl ethers.[a]

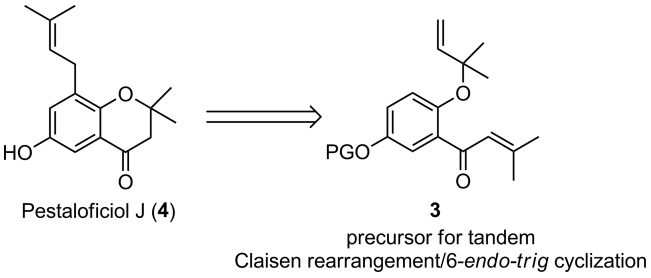
Entry	Substrate **1**	*T*/°C	Product(s)	Yield[b]
1	 **1a**	150	 *o*-**2a**	n.d.[c]
2		200		n.d.[d]
3		250		quant.
4	 **1b**	250	 *o*-**2b**	94%
5	 **1c**	250	 *o*-**2c**	96%[e]
6		250	 *p*-**2c**	95%[e,f]
7	 **1d**	250	 *o*-**2d**	80%
8	 **1e**	250	 *p*-**2e**	65%

[a] Reagents and conditions: **1** (0.2 M) in *N*,*N*-diethylaniline, microwave at temperature *T* for 1 h. [b] Yield of the isolated product; n.d.: not determined. [c] No conversion (NMR). [d] Incomplete conversion (NMR). [e] Ratio of *o*-**2c**/*p*-**2c** = 1.0:0.7. [f] Reaction time: 5 min.

Finally, we subjected the prenyl ether **1e** to microwave irradiation in *N*,*N*-diethylaniline. The *para*-substituted phenol *p*-**2e** was exclusively formed and could be isolated in 65% yield. This product results from a Claisen/Cope rearrangement sequence; in contrast to the rearrangement of cinnamyl ether **1c**, the intermediate Claisen product was not observed under our conditions. [3,3] Sigmatropic rearrangements of **1e** have been studied previously; Lewis acid catalysis at –20 °C led to mixtures of *o*- and *p*-prenylphenol (*p*-**2e**),[55] whereas conventional heating in *N*,*N*-diethylaniline for 90 h resulted in a mixture of *p*-**2e** and an "anomalous" product formed through a [1,5] sigmatropic shift following the first [3,3] sigmatropic rearrangement.[43] None of these byproducts were detected under microwave irradiation in *N*,*N*-diethylaniline.

Tandem Claisen *ortho*-Prenylation/6-*endo-trig* Cyclization – Synthesis of Pestaloficiol J

Pestaloficiol J (**4**) is an 8-prenylated chroman-4-one recently isolated from the endophytic fungus *Pestalotiopsis fici*.[56,57] Both the crude extracts of fermentation cultures and isolated pestaloficiol J display moderate inhibitory activity against HIV-1 cells.[58] This natural product has, to the best of our knowledge, not been synthesized previously. Following the general tandem approach outlined in Scheme 1 and taking into account the results presented in Table 1, its synthesis would require dimethylallyl ether **3**, appropriately protected at 6-OH (Scheme 2).



Scheme 2. Tandem precursor required for pestaloficiol J.

Our synthesis started from 5-hydroxysalicylaldehyde (**5**), which was first monoprotected as the MOM ether **6a**.[34] Dimethylallylation of the remaining OH group was accomplished by using allyl alkyl carbonate **7**[59] and $[Pd(PPh_3)_4]$ as pre-catalyst. Treatment of the resulting aldehyde **8a** with the 2-methylpropenyl Grignard reagent furnished allylic alcohol **9a**, which was oxidized to **3a** accord-

ing to the method of Ley et al.[60] Having in hand the precursor required for the tandem sequence, **3a** was subjected to microwave irradiation at 250 °C in *N*,*N*-diethylaniline. The MOM ether of pestaloficiol J (**10a**) was obtained in excellent yield, but deprotection turned out to be an insuperable problem. Under a variety of conditions and in the presence of various Lewis or Brønsted acids (e.g., $MgCl_2$, $ZnCl_2$, HCl, camphorsulfonic acid, *p*TsA or trifluoroacetic acid), either no conversion was observed or decomposition into multiple products occurred. The only identifiable product from these experiments was the tertiary alcohol **11**, which was in some cases isolated in minuscule amounts. Notably, even those conditions that had previously been described for the deprotection of phenolic MOM ethers in the presence of prenyl side-chains failed completely when applied to the deprotection of **10a**. This prompted us to replace the MOM protecting group by a TBS ether. The analogous precursor **3b** was obtained in four steps from the same dihydroxybenzaldehyde **5** in comparable yields and by using the same synthetic methods. The microwave-promoted tandem Claisen rearrangement/cyclization reaction gave TBS ether **10b** quantitatively, which was deprotected to pestaloficiol J (**4**) under non-acidic conditions with tetra-*n*-butylammonium fluoride (TBAF). In summary, this is the first synthesis of pestaloficiol J, which was obtained in a total yield of 38% over six steps (Scheme 3).

All the analytical data obtained by us for the synthetic pestaloficiol J match very well those reported for the natural product.[58] Although the natural product has been described as a colourless oil, we obtained pestaloficiol J (**4**) as a crystalline material. The structure of **4** was confirmed by single-crystal X-ray structure analysis (Figure 2); intermolecular hydrogen bonds contribute to the stabilization of the crystal packing (see the Supporting Information for details and graphic representation).[61]

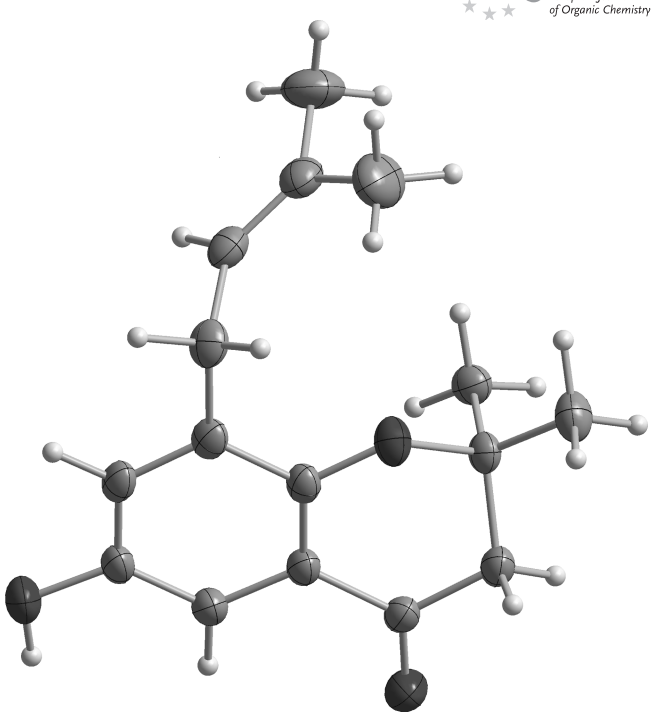
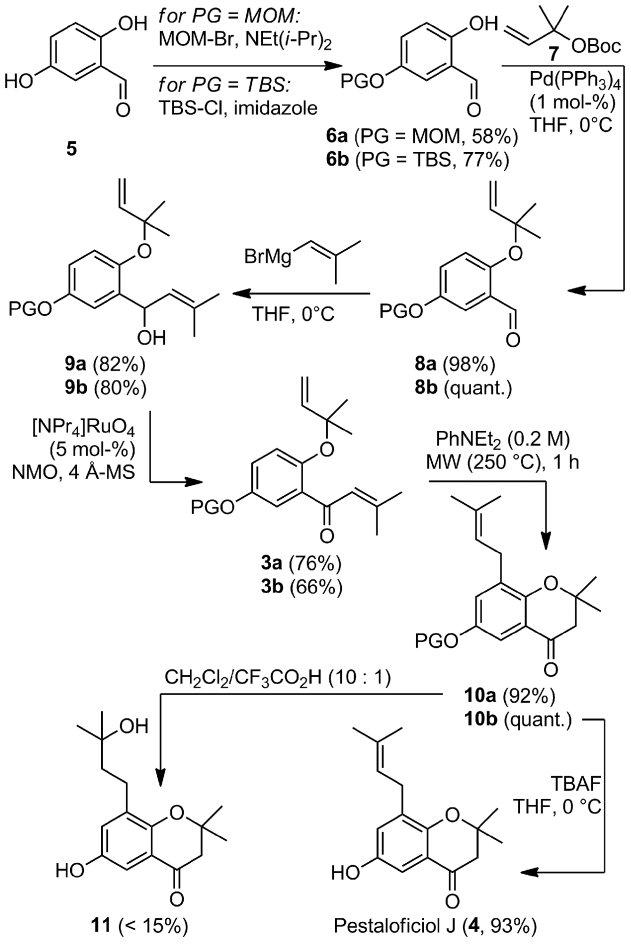


Figure 2. Single-crystal X-ray structure of **4**.

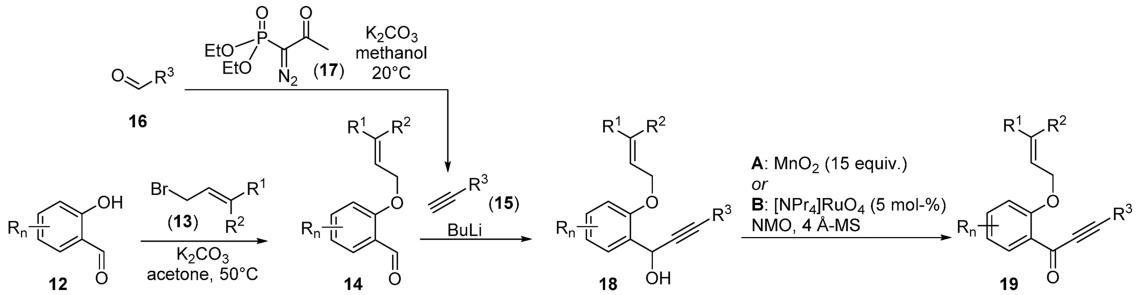
Synthesis of Precursors for Tandem Claisen Rearrangement/6-*endo-dig* Cyclization Sequences

The tandem Claisen rearrangement/6-*endo-dig* cyclization precursors can be obtained by a three-step synthesis starting from various salicylaldehydes **12** (Table 2). The aldehydes **12** were first treated with allyl, crotyl or prenyl bromide to furnish substituted *O*-allylated aldehydes **14**. These were treated with Li acetylides, obtained from alkynes **15** by metallation with butyllithium, to give the propargylic alcohols **18**. In some cases the Li acetylide was replaced by the analogous Grignard reagent. Lithium hexamethyldisilazane (LiHMDS) had to be used instead of BuLi for the metallation of **15f**, **15j** and **15k** to avoid nucleophilic attack (**15f**, **15j**) or halogen/metal exchange (**15k**). Alkynes **15h**–**o** were synthesized from the corresponding aldehydes **16** and the Bestmann–Ohira reagent **17**.[62,63] The propargylic alcohols **18** were then oxidized to the ketones **19** by using either MnO_2 (method A) or the method of Ley et al. (method B).[60]



Scheme 3. Synthesis of pestaloficiol J (**4**).

Table 2. Synthesis of Claisen rearrangement/6-*endo-dig* cyclization precursors.



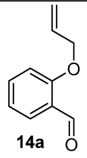
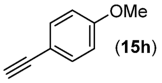
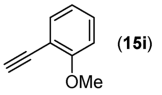
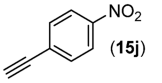
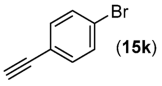
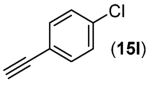
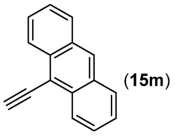
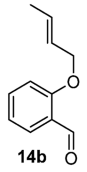
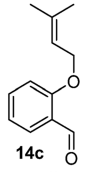
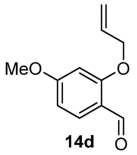
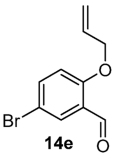
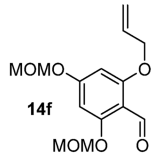
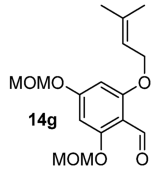
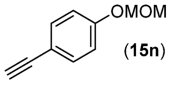
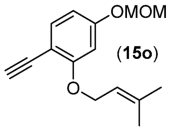
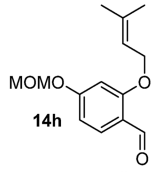
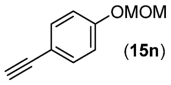
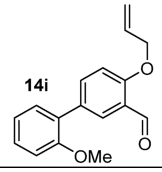
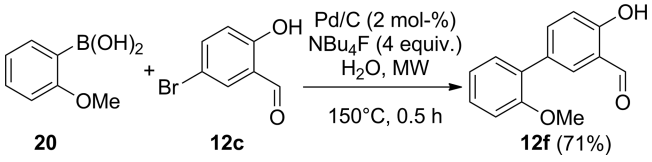
Entry	14	Yield	15	Yield	18	Yield	19	Method	Yield
1	 **14a**	88%	acetylene (**15a**)	–[a]	**18a**	93%[b]	**19a**	**A**	65%
2			propyne (**15b**)	–[a]	**18b**	95%[b]	**19b**	**A**	quant.
3			1-pentyne (**15c**)	–[a]	**18c**	94%	**19c**	**A**	78%
4			1-Octyne (**15d**)	–[a]	**18d**	85%	**19d**	**A**	quant.
5			$HCCSiMe_3$ (**15e**)	–[a]	**18e**	95%	**19e**	**A**	quant.
6			$HCCCO_2Et$ (**15f**)	–[a]	**18f**	72%[c]	**19f**	**A**	55%
7			HCCPh (**15g**)	–[a]	**18g**	91%	**19g**	**A**	87%
8			 (**15h**)	76%	**18h**	88%	**19h**	**A**	96%
9			 (**15i**)	71%	**18i**	79%	**19i**	**A**	quant.
10			 (**15j**)	quant.	**18j**	87%[c]	**19j**	**A**	96%
11			 (**15k**)	91%	**18k**	78%[c]	**19k**	**A**	95%
12			 (**15l**)	96%	**18l**	80%	**19l**	**A**	93%
13			 (**15m**)	38%	**18m**	95%	**19m**	**A**	81%
14	 **14b**	82%[d]	1-pentyne (**15c**)	–[a]	**18n**	quant.	**19n**	**A**	95%
15	 **14c**	70%	1-pentyne (**15c**)	–[a]	**18o**	97%	**19o**	**A**	quant.
16	 **14d**	79%	1-pentyne (**15c**)	–[a]	**18p**	94%	**19p**	**A**	98%
17	 **14e**	87%	1-pentyne (**15c**)	–[a]	**18q**	96%	**19q**	**A**	98%

Table 2. *(Continued)*.

18		92%	propyne (**15b**)	–[a]	**18r**	71%[b]	**19r**	**A**	96%
19		85%	propyne (**15b**)	–[a]	**18s**	84%[b]	**19s**	**A**	80%
20							**19s**	**B**	83%
21			1-pentyne (**15c**)	–[a]	**18t**	81%	**19t**	**A**	88%
22				89%	**18u**	85%	**19u**	**A**	82%
23				80%	**18v**	98%	**19v**	**A**	77%
24		84%		89%	**18w**	84%	**19w**	**A**	96%
							19w	**B**	86%
25		74%	HCCPh (**15g**)	–[a]	**18x**	78%	**19x**	**A**	quant.

[a] Purchased reagents. [b] Grignard reagent used instead of Li acetylide. [c] LiHMDS used instead of BuLi. [d] *E*/*Z*-ratio approx. 6:1, as determined by ^{1}H NMR spectroscopy.

For the synthesis of biaryl **19x**, aldehyde **12f** was required, which was synthesized by Suzuki–Miyaura coupling of **12c** and boronic acid **20** (Scheme 4) under conditions recently developed by us.[64] With a view to synthesizing dimeric chromones, precursors **19y**,**z** were synthesized by the reaction of the bis-acetylides **15p**,**q** with 2 equiv. of aldehyde **14a** followed by the oxidation of the resulting propargylic alcohols **18y**,**z** to the corresponding ketones **19y**,**z** (Scheme 5). 1,4-Diethynylbenzene (**15p**) was obtained from terephthaldehyde and 2 equiv. of the Bestmann–Ohira reagent **17**.

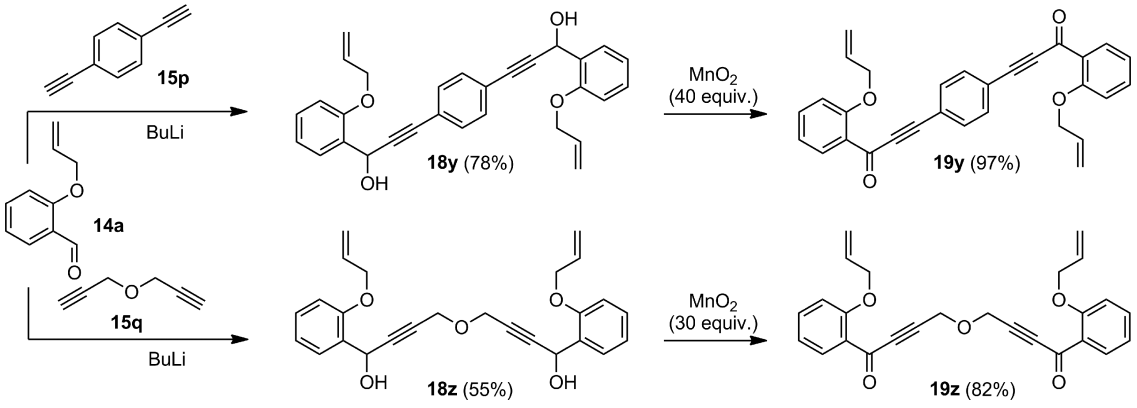


20 **12c** **12f** (71%)

Scheme 4. Synthesis of 5-arylsalicylic aldehyde **12f**.

Microwave-Promoted Sigmatropic Rearrangements/6-*endo*-*dig* Cyclization Sequences

Precursors **19a**–**z** were subjected to microwave irradiation using the optimized conditions (Table 3). The majority of

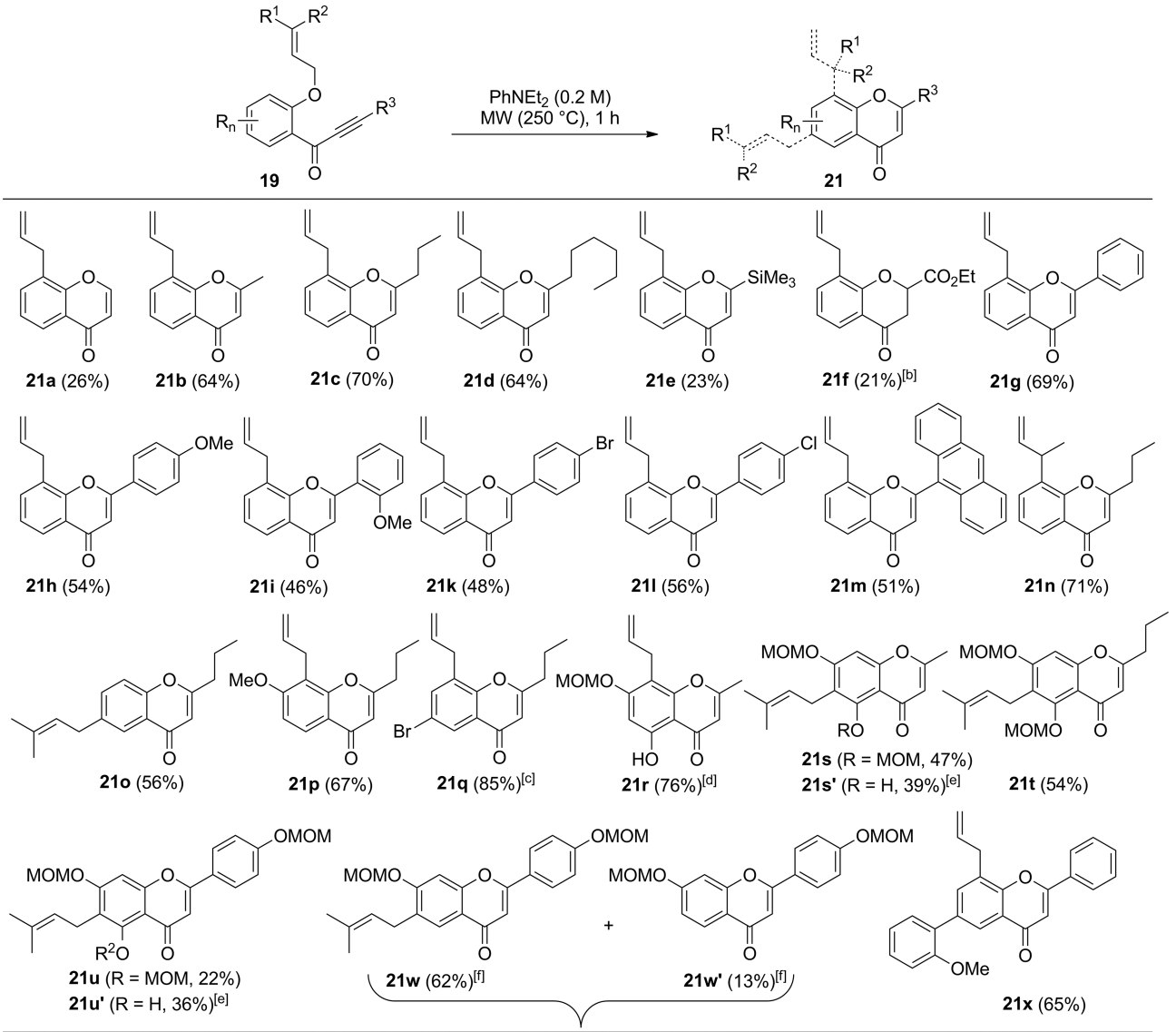


Scheme 5. Synthesis of precursors for an envisaged double-tandem Claisen rearrangement/6-*endo*-*dig* cyclization sequence.

alkynones **19** were successfully converted into chromones **21** in moderate-to-good yields. A notable exception was the *p*-nitrophenyl-substituted precursor **19j**, which reacted to give a complex mixture of highly polar compounds without a defined and isolable major product. Difficulties were also observed for all precursors with more than one allyl or alkynone moiety, that is, **19v**, **19y** and **19z**. Microwave irradiation of these precursors resulted in the formation of complex product mixtures. Defined products, albeit in low yields, were obtained from **19a**, **19e** and **19f**. The 2-unsubstituted chromone **21a**, which was obtained from a 6-*endo-dig* cyclization of a terminal alkyne, was isolated in a yield comparable to that observed for the analogous 6-*endo-trig* cyclization.[34] In the case of chromone **21e**, the cyclization is probably hampered by the steric demand of the $SiMe_3$ group. An interesting observation was made for the microwave-promoted Claisen rearrangement/cyclization of **19f**: in this case the saturated product **21f** was the only isolable product. We assume that the presence of two electron-withdrawing groups favours the transfer hydrogenation of the intermediate chromone. The solvent *N*,*N*-diethylaniline might be the hydrogen source.

The substitution patterns of chromones **21** reflect those observed upon microwave irradiation of the simple allyl and prenyl ethers **1** (Table 1). Thus, prenyl ethers **19o**, **19s**, **19t**, **19u** and **19w** underwent a dual [3,3] sigmatropic "Claisen-then-Cope" rearrangement cascade to the expected 6-prenylated chromones, whereas rearrangement of the crotyl ether **19n** stops at the Claisen stage to give an 8-(1′-methylallyl)-substituted chromone **21n**. A remarkable side-reac-

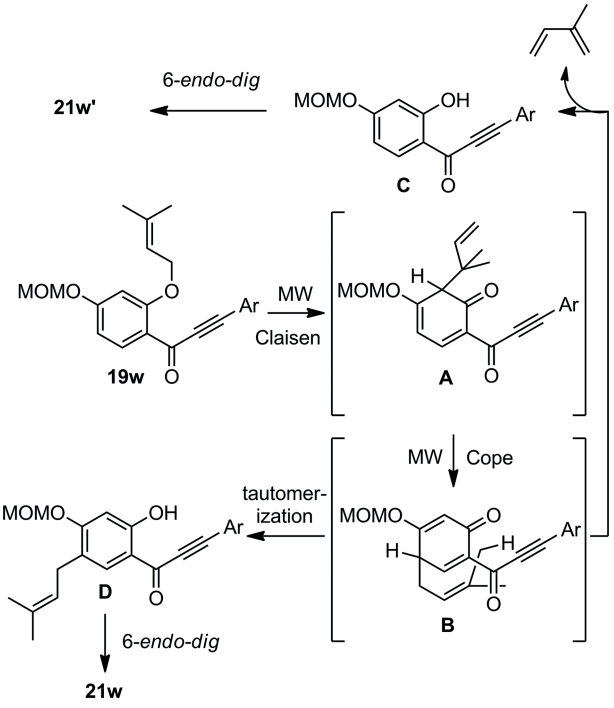
Table 3. Microwave-promoted Claisen/Cope rearrangement/6-*endo-dig* cyclization sequence of precursors **19**.[a]



[a] Only examples leading to defined products are shown. [b] **19f** yielded chroman-4-one **21f** rather than the expected chromone, see discussion. [c] In *N*,*N*-dimethylaniline; yield in *N*,*N*-diethylaniline 67%. [d] Quantitative cleavage of the MOM ether at C-5 occurred during microwave irradiation. [e] Partial cleavage of the MOM ether at C-5 occurred during microwave irradiation. [f] **21w** and **21w′** were obtained from **19w** as a separable mixture.

tion was observed for some samples bearing MOM ethers: upon microwave irradiation, selective partial or quantitative cleavage of the MOM ether at C-5 was observed for **21r**, **21s/21s′** and **21u/21u′**. The structures of these examples were elucidated by using 2D NMR methods. In particular, HMBC experiments were found to be useful for locating the prenyl or allyl substituent, and in the case of partially deprotected products, the remaining MOM group and the unprotected phenol.[65] Currently we cannot decide whether the partial MOM deprotection occurs during microwave irradiation (probably induced by trace amounts of water in the solvent) or upon work-up.

The formation of **21w**, which is unsubstituted at C-5, proceeded without notable cleavage of the MOM ethers at C-7 or C-4′, but was accompanied to a minor extent by deprenylation to yield **21w′**. Reports describing the traceless removal of a prenyl group[66] in the absence of acids or bases are scarce. We are aware of an example described by Lauer and Moe, who investigated the pyrolysis of the prenyl ether of *p*-hydroxybenzoate.[67] They found that heating this compound at temperatures above 200 °C for longer periods of time resulted in the formation of *p*-hydroxybenzoate and isoprene. More recently, Jun and co-workers discussed thermal deprenylation as a major obstacle in the synthesis of prenylated chalcones from prenyl ethers.[68] We assume that **21w′** also results from the cleavage of isoprene, either at the stage of the Claisen rearrangement or at the stage of the Cope rearrangement (Scheme 6). According to this mechanistic scenario, the prenyl group in **19w** would first undergo Claisen rearrangement to **A**, which would then rapidly isomerize to **B** by a Cope rearrangement. Tautomerization would then give phenol **D**, which cyclizes in a 6-*endo*-*dig* fashion to the major product **21w**. The minor pathway, leading to **21w′**, might involve transfer of an allylic hydrogen to the carbonyl oxygen, cleavage of the C–C-bond and formation of isoprene to give **C**, which eventually undergoes 6-*endo*-*dig* cyclization.



Scheme 6. Possible scenarios leading to **21w′**.

Conclusions

We have reported herein a microwave-promoted tandem sequence that combines one or two [3,3] sigmatropic rearrangements with a 6-*endo* cyclization. The starting materials are allyl or prenyl aryl ethers with an adjacent enone or alkynone moiety. During the synthesis of the precursors, the allyl or prenyl ether serves as a phenol protecting group, which becomes an essential part of the target structure upon cleavage, that is, an 8-allyl or 6-prenyl substituent, respectively. Allylated or prenylated chromones or chroman-4-ones are widespread in nature and can also be used as building blocks for the synthesis of other natural or non-natural chromone derivatives. The usefulness of the method is illustrated by the first synthesis of the fungal metabolite pestaloficiol J. In addition, several chromones synthesized in the course of this study have substitution and oxygenation patterns that are present in bioactive plant metabolites, for example, **21r** (eranthin[69]), **21s** (peucenin[70]), **21u** (6-prenylapigenin[71]) and **21w** (licoflavone A[72]). Investigations into the application of microwave-promoted tandem sigmatropic rearrangement/cyclization cascades for target molecule synthesis are currently underway in our laboratory.

Experimental Section

General: All experiments were conducted in dry reaction vessels under dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 or 500 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as internal standard. Chemical shifts are given in ppm and coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 or 125 MHz in $CDCl_3$, which also acted as internal standard (δ = 77.0 ppm). If the sample was insufficiently soluble in $CDCl_3$, [D_6]DMSO {[D_5]DMSO as internal standard for ^{1}H NMR spectroscopy (δ = 2.50 ppm), [D_6]DMSO as internal standard for ^{13}C NMR spectroscopy (δ = 39.5 ppm)} or [D_4]methanol [CD_2HOD as internal standard for ^{1}H NMR spectroscopy (δ = 3.31 ppm), CD_3OD as internal standard for ^{13}C NMR spectroscopy (δ = 49.2 ppm)] was used. IR spectra were recorded as ATR-FTIR spectra. The peak intensities are defined as strong (s), medium (m), or weak (w). Low- and high-resolution mass spectra were obtained by means of the EI-TOF or ESI-TOF technique.

General Procedure for the Microwave-Promoted Tandem Sigmatropic Rearrangement/6-*endo*-Cyclization Sequence: The appropriate precursor **3** or **19** (1.0 mmol) was dissolved in *N*,*N*-diethylaniline (5–10 mL) in a vessel suited for microwave irradiation. The vessel was sealed and irradiated in a dedicated microwave reactor at 250 °C for 1 h. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (50 mL) and extracted with aqueous HCl (1 M, 3 × 10 mL for each extraction) to remove the aniline. The organic extracts were dried with $MgSO_4$, filtered and the solvents

evaporated. The residue was purified by column chromatography on silica with hexane/MTBE mixtures of increasing polarity as eluent to furnish the chroman-4-ones **10** or chromones **21**.

6-[(*tert*-Butyldimethylsilyl)oxy]-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)chroman-4-one (10b): Following the general procedure, **3b** (89 mg, 0.24 mmol) was converted into **10b** (89 mg, 0.24 mmol, quant.). Colourless oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.73 (d, J = 3.1 Hz, 1 H), 7.11 (d, J = 3.1 Hz, 1 H), 5.42–5.31 (m, 1 H), 3.37 (d, J = 7.4 Hz, 2 H), 2.30 (s, 2 H), 1.65 (s, 3 H), 1.60 (s, 3 H), 1.05 (s, 6 H), 0.98 (s, 9 H), 0.15 (s, 6 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 191.5, 152.8, 149.5, 132.9, 132.7, 128.7, 122.6, 121.2, 113.4, 78.6, 48.7, 28.8, 26.4, 25.9, 25.8, 18.4, 17.9, –4.4 ppm. IR (ATR): $\tilde{\nu}$ = 1691 (m), 1610 (w), 1463 (s), 1253 (m), 1167 (m) cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{34}O_3Si$ [M]$^+$ 374.2277; found 374.2273.

8-Allyl-2-propyl-4*H*-chromen-4-one (21c): Following the general procedure, **19c** (158 mg, 0.69 mmol) was converted into **21c** (110 mg, 0.48 mmol, 70%). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (dd, J = 7.9, 1.2 Hz, 1 H), 7.43 (d, J = 7.3 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 6.13 (s, 1 H), 5.95 (ddd, J = 17.1, 10.3, 6.1 Hz, 1 H), 5.07 (d, J = 10.3 Hz, 1 H), 5.05 (d, J = 17.1 Hz, 1 H), 3.56 (d, J = 6.5 Hz, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 1.74 (qt, J = 7.5, 7.4 Hz, 2 H), 0.98 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6, 169.1, 154.5, 135.4, 133.7, 129.2, 124.6, 123.8, 123.8, 116.7, 109.8, 36.2, 33.8, 20.2, 13.5 ppm. IR (ATR): $\tilde{\nu}$ = 2964 (w), 1648 (s), 1586 (m), 1380 (m), 757 (m) cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}O_2$ [M]$^+$ 228.1150; found 228.1156.

6-(3-Methylbut-2-en-1-yl)-2-propyl-4*H*-chromen-4-one (21o): Following the general procedure, **19o** (147 mg, 0.57 mmol) was converted into **21o** (83 mg, 0.32 mmol, 56%). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.42 (dd, J = 8.6, 2.1 Hz, 1 H), 7.30 (dd, J = 8.6, 0.8 Hz, 1 H), 6.13 (s, 1 H), 5.29 (tm, J = 7.3 Hz, 1 H), 3.39 (d, J = 7.3 Hz, 2 H), 2.55 (t, J = 7.5 Hz, 2 H), 1.81–1.65 (m, 2 H), 1.72 (s, 3 H), 1.69 (s, 3 H), 0.98 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6, 169.4, 155.1, 138.9, 134.0, 133.4, 124.4, 123.5, 122.5, 117.8, 109.8, 36.2, 33.8, 25.8, 20.3, 17.9, 13.6 ppm. IR (ATR): $\tilde{\nu}$ = 2965 (w), 1648 (s), 1483 (m), 1447 (m), 1373 (m) cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{20}O_2$ [M]$^+$ 256.1463; found 256.1488.

8-Allyl-6-(2-methoxyphenyl)-2-phenyl-4*H*-chromen-4-one (21x): Following the general procedure, **19x** (141 mg, 0.38 mmol) was converted into **21x** (92 mg, 0.25 mmol, 65%). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.2 Hz, 1 H), 7.99–7.91 (m, 2 H), 7.81 (d, J = 2.2 Hz, 1 H), 7.57–7.53 (m, 3 H), 7.41 (dd, J = 7.2, 1.7 Hz, 1 H), 7.36 (dd, J = 8.1, 1.7 Hz, 1 H), 7.07 (td, J = 7.5, 1.0 Hz, 1 H), 7.03 (d, J = 8.2 Hz, 1 H), 6.89 (s, 1 H), 6.16 (ddt, J = 16.6, 10.1, 6.5 Hz, 1 H), 5.26 (dm, J = 16.8 Hz, 1 H), 5.22 (dm, J = 10.1 Hz, 1 H), 3.85 (s, 3 H), 3.83 (d, J = 6.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 162.9, 156.5, 153.4, 135.8, 135.6, 135.4, 132.1, 131.6, 130.9, 129.2, 129.1, 129.0, 128.9, 126.2, 124.3, 124.8, 121.0, 117.0, 111.3, 107.4, 55.6, 34.1 ppm. IR (ATR): $\tilde{\nu}$ = 1640 (s), 1463 (m), 1364 (s), 1244 (m), 1025 (m) cm^{-1}. HRMS (EI): calcd. for $C_{25}H_{20}O_3$ [M]$^+$ 368.1412; found 368.1409.

6-Hydroxy-2,2-dimethyl-8-(3-methylbut-2-en-1-yl)chroman-4-one (Pestaloficiol J, 4): TBAF·3H$_2$O (62 mg, 0.20 mmol) was added to a solution of **10b** (67 mg, 0.18 mmol) in THF (2 mL) at 0 °C. The solution was stirred for 0.5 h, all the volatiles were evaporated and the residue was purified by column chromatography to give **4** (43 mg, 0.17 mmol, 93%). Colourless solid, m.p. 116–118 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.08 (s, 1 H), 7.06 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 2.9 Hz, 1 H), 5.27 (t, J = 7.4 Hz, 1 H), 3.27 (d, J = 7.4 Hz, 2 H), 2.68 (s, 2 H), 1.72 (s, 6 H), 1.42 (s, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 192.6, 152.1, 151.5, 133.2, 133.1, 124.8, 123.0, 121.3, 108.4, 79.3, 49.2, 28.9, 26.7, 25.9, 17.9 ppm. IR (ATR): $\tilde{\nu}$ = 3362 (br w), 2925 (s), 1670 (m), 1465 (s), 1166 (m) cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{20}O_3$ [M]$^+$ 260.1412; found 260.1406. The spectroscopic data match those reported by Liu et al.[58] for the natural product pestaloficiol J.

Acknowledgments

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