ChemInform Abstract: Direct, Regioselective Synthesis of 2,2-Dimethyl-2H-chromenes. Total Syntheses of Octandrenolone (III) and Precocenes I (IXa) and II (IXb)

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Direct, regioselective synthesis of 2,2-dimethyl-2*H*-chromenes. Total syntheses of octandrenolone and precocenes I and II

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ABSTRACT

Herein is reported an efficient method for the synthesis of 2,2-dimethyl-2*H*-chromenes in a single step from the corresponding phenol and 3-methyl-2-butenal via microwave irradiation in $CDCl_3$. This protocol features a mild reaction environment (neutral, no added catalyst) which yields regioselective formation of the chromene and displays tolerance toward acid- and base-sensitive protecting groups.

Structural motifs which are observed in many naturally occurring organic compounds possessing varying biological activities have come to be known as 'privileged structures'.[1] One such recurring scaffold is the 2,2-dimethyl-2*H*-chromene, which appears in a range of bioactive natural products[2] including drummondin A,[3,4] rottlerin,[5,6] 4-hydroxy-3-methoxylonchocarpin,[7,8] seselin,[9] (−)-3-deoxy-MS-II,[10] and precocenes I (**18**) and II (**20**)[11] (Fig. 1).

Over the years, a variety of methods for constructing 2,2-dimethyl-2*H*-chromenes have been developed including Grignard reactions of coumarins, thermal rearrangement of phenyl propargyl ethers, dehydration of corresponding α-hydroxy- and α-methoxy-chromanes, oxidation of 2,2-dimethyl-chromanes, and oxidative cyclization of *ortho*-prenylated phenols, among others.[12] These techniques, however, require multiple steps to access 2,2-dimethyl-2*H*-chromenes from the parent phenol. Reaction protocols have also been established to generate chromenes in a single step via the thermal,[13] base-catalyzed,[13–21] or phenylboronic acid-mediated[22–25] condensation of an α,β-unsaturated aldehyde with a phenol. Single-step reactions such as these are believed to generate a transient *ortho*-quinone methide intermediate which then undergoes a 6π-electrocyclization in situ to yield the final bicyclic product as shown in Scheme 1.[26]

During a synthetic investigation of chromene-containing natural products, we attempted to utilize one of these methods to construct chromene-containing compound **7**. This iodochromane, obtained via a *para*-Claisen rearrangement of an O-prenylated precursor followed by I_2-induced cyclization, was subjected to both aqueous and anhydrous basic conditions, neither of which provided the desired chromene compound in an acceptable yield (Scheme 2).

This result sparked our interest in developing a method to prepare 2,2-dimethyl-2*H*-chromenes in a single step from the parent phenol under conditions which would be compatible with acid- and base-sensitive protecting groups. Unfortunately, none of the attempted known methods proved consistently amenable to this particular operation. Furthermore, the most commonly utilized methods to effect this general transformation suffer from long reaction times, the use of dangerous solvents, and/or complicated reaction setups. To this end, we decided to pursue a detailed investigation of an uncatalyzed, neutral, microwave-assisted[27–30] condensation of 3-methyl-2-butenal (**1**) with substituted phenols as a novel and direct route to access the family of compounds possessing this privileged structure.

In an effort to probe the relative reactivities of the selected phenols, each substrate was initially subjected to a set of standard reaction conditions; the results of these trials are presented in column 4 of Table 1.[31] Each of the explored phenols was chosen because its corresponding chromene product either is a natural product or can be taken on to a biologically relevant natural product in short order.

Several trends were noted, most markedly that increasing the number of electron-donating groups on the phenol in general increased the effectiveness of this method.

Phloroacetophenone (**2**) displayed the most striking outcome, providing the natural product octandrenolone (**3**) in 89% yield (Table 1, entry 1). This is a significant improvement on the highest previously reported yield (40%) of this molecule. While the possibility for formation of two different regioisomeric dichromene products exists, **3** was the only product observed, the structure of which was verified by comparison to previously reported spectral data.[32] We believe that the hydrogen bonding between the carbonyl and the *ortho*-phenol plays an important role in influencing the regioselective reaction of this, and all, carbonyl-containing phenols using this method.

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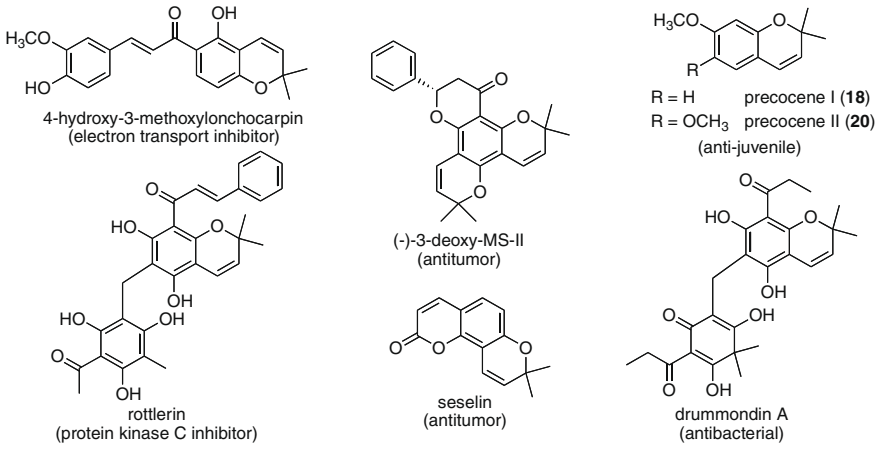
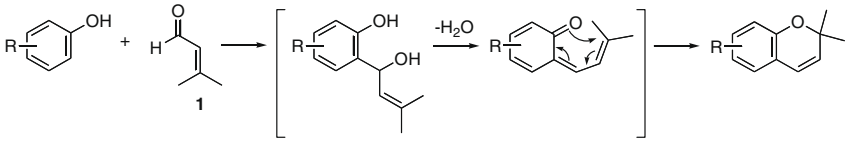
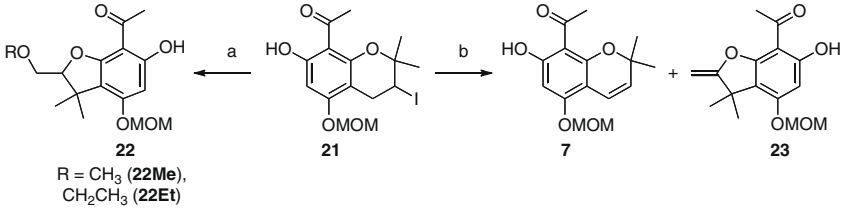


Figure 1. Examples of biologically active naturally occurring molecules containing a 2,2-dimethyl-2*H*-chromene core.



Scheme 1. Simplified mechanism for observed transformations.



Scheme 2. Unsuccessful elimination. Reagents and conditions: (a) NaOH, ROH, reflux, 5 h; (b) DBU, toluene, 80 °C.

Interestingly, under the initial reaction conditions (column 4), selective protection of the 4-hydroxy substituent of phloroacetophenone as either the *tert*-butyldimethylsilyl ether (**4**, Table 1, entry 2) or the methoxymethyl ether (**6**, Table 1, entry 3) resulted in a considerable drop in yield.

These findings, however, showed further promise for the regioselectivity of this reaction, as none of the protected dichromenylated products were observed. The structure of novel compound **5** was determined by full spectroscopic characterization, and **7** was identified by comparison to previously published spectral data.[19]

In the case of the mono-protected phenol **6** (Table 1, entry 3, column 4), the product was accompanied by significant levels of octandrenolone (**3**) and also uncharacterized polymers, both attributed to the breakdown of the mixed acetal-protecting group. Decomposition was also seen in the reaction of the acetonide-containing phenol **8** (Table 1, entry 4) under the standardized conditions (column 4), although to a lesser degree; the structure of the novel resulting chromene **9** was elucidated unambiguously by X-ray crystallography.

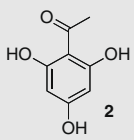
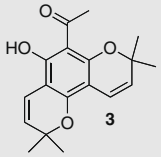
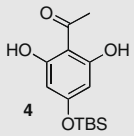
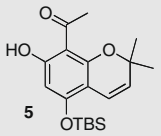
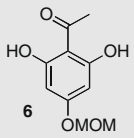
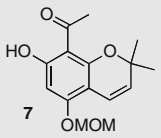
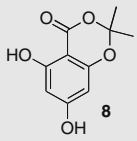
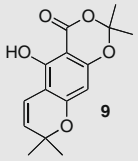
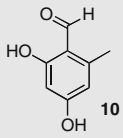
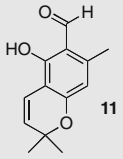
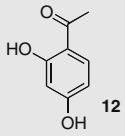
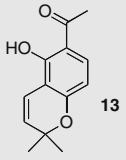
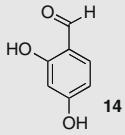
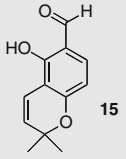
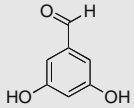
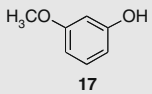
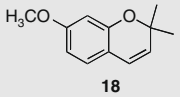
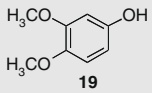
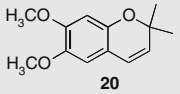
Entries 4–10 presented the possibility for regioisomeric products. In nearly all cases, the chromene product indicated was the only one observed in any significant amount.

The reactions using phenols **10**, **12**, and **14** (Table 1, entries 5–7) display remarkable regioselectivity. While there are several products which could theoretically be produced in each case including dichromenylated products and a number of regioisomeric monochromenes, the shown products and starting materials were the only compounds detected in the crude product mixtures. These isolated products were all identified based on comparison to previously reported spectral data.[17] The literature NMR data for chromene **11** were not sufficiently diagnostic to state with certainty which isomer was synthesized, and therefore an NOE experiment was performed to unambiguously establish the structure of the product. Specifically, irradiation of the benzylic methyl protons resulted in significant enhancement of the signal of the single adjacent aryl proton. No such enhancement of the α-vinyl hydrogen was observed, a result consistent only with the indicated structure.

The difference in reactivity amongst phenols **10**, **12**, and **14** (Table 1, entries 5–7) illustrates the impact a single methyl substitution can have on this method. A comparison of the relative reactivity of phenols **14** (Table 1, entry 7) and **10** (Table 1, entry 5) under the standard conditions (column 4) shows that incorporation of the C-6 methyl group resulted in a fivefold increase in yield. Similarly, going from an aldehyde (**14**, Table 1, entry 7) to a methyl ketone (**12**, Table 1, entry 6) also improved the yield. It is noteworthy that in both cases, the addition of the methyl group increases the electron density in the aromatic ring.

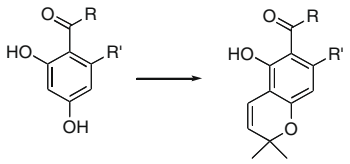
When the carbonyl was located *meta* to the hydroxyl substituents as in compound **16** (Table 1, entry 8), only uncharacterized polymer was observed after microwave irradiation. The formation of this polymer apparently involves 3-methyl-2-butenal (**1**), as irradiation of **16** without **1** provided full recovery of the starting material. Notably, 4-hydroxybenzaldehyde proved to be impervious to this annulation method under a range of reaction conditions.

Table 1
Yields for all investigated phenols under a set of standardized conditions, and highest yields (with conditions)[a]

Entry	Phenol	Chromene product	Standard:yield[b] (%)	Best:time (h); equiv **1**; yield[c] (%)
1	 **2**	 **3**	89	1; 3; 89
2	 **4**	 **5**	30	0.2; 1.5; 94[d]
3	 **6**	 **7**	<5[f,g]	0.5, 1.5; 29[e]
4	 **8**	 **9**	16[f,g]	1; 1.5; 55[d]
5	 **10**	 **11**	21	5; 3; 48
6	 **12**	 **13**	10	10; 3; 43
7	 **14**	 **15**	4	10; 3; 15
8	 **16**	None	0[g]	—
9	 **17**	 **18**	7	1; 6; 63[d]
10	 **19**	 **20**	5	1; 6; 88[d]

[a] Reaction mixtures irradiated at 150 W in a 1 M solution in $CDCl_3$ unless otherwise indicated. Crude product mixtures consisted of >95% product and starting materials only unless otherwise indicated.
[b] This column presents yields for all investigated phenols under a standard set of conditions. Reaction mixtures irradiated for 1 h with 3 equiv of 3-methyl-2-butenal (**1**).
[c] This column presents our best yields for each substrate and the conditions used to achieve each particular yield.
[d] Irradiated at 300 W.
[e] 0.25 M solution in $CDCl_3$.
[f] Crude reaction mixture contained significant amounts of undesired chromene side-products.
[g] Crude product mixture contained significant amounts of uncharacterized compounds presumed to be polymeric material.

Table 2
Selected results from the optimization trials for the series of 2,4-dihydroxycarbonylbenzenes[a]



Entry	Phenol	R	R′	Product	Power (W)	Time (h)	Yield[b] (%)
1	**10**	H	CH_3	**11**	150	1	21
2	**10**	H	CH_3	**11**	300	1	26
3	**10**	H	CH_3	**11**	150	2	25
4	**10**	H	CH_3	**11**	150	5	48
5	**12**	CH_3	H	**13**	150	1	10
6	**12**	CH_3	H	**13**	300	1	16
7	**12**	CH_3	H	**13**	150	2	21
8	**12**	CH_3	H	**13**	150	10	43
9	**14**	H	H	**15**	150	1	4
10	**14**	H	H	**15**	300	1	9
11	**14**	H	H	**15**	150	2	7
12	**14**	H	H	**15**	150	10	15

[a] Reaction mixtures contained 3 equiv of **1** in a 1 M solution in $CDCl_3$.
[b] Crude product mixtures consisted of >95% product and starting materials only unless otherwise indicated.

Several non-carbonyl-containing phenols were also attempted with varying degrees of success. Although no reaction was observed with either phenol itself or with *para*-methoxyphenol under several set of reaction conditions, both *meta*-methoxyphenol (**17**, Table 1, entry 9) and 3,4-dimethoxyphenol (**19**, Table 1, entry 10) gave low yields of chromene products when exposed to our initial reaction conditions (column 4). The low yields of precocenes I (**18**) and II (**20**) were subsequently improved dramatically by altering some of the reaction variables (column 5). These two materials were identified as the products of the reactions of their respective parent phenols based on previously published spectral data.[22]

Although it was not possible to establish a single set of microwave reaction conditions that was optimal for all substrates, by altering controllable experimental variables (time, power, equivalents of **1**, concentration) we were able to significantly improve the yields relative to our initial conditions. The end results of this pursuit (the best yields for each of the chromenes produced with the conditions used) are also presented in Table 1 (column 5). For example, this experimentation resulted in a drastic increase in the production of novel chromene **5** (30–94%), and the natural products precocenes I (**18**, 7–63%) and II (**20**, 5–88%). The reported data were compiled from several trials; a discussion of illustrative findings from these investigations accompanies the data shown in Tables 2 and 3, which track the impact of changes in the controllable experimental variables.

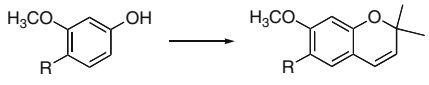
In the series of 2,4-dihydroxycarbonylbenzenes (Table 2), positive effects were noted when either the power (entries 2, 6, and 10) or the reaction time (entries 3, 7, and 11) was doubled from the original standard conditions (entries 1, 5, and 9). When exposed for yet longer reaction times (entries 4, 8, and 12), even higher yields of the desired chromene products ensued, although these effects do not appear to be linear. In all trials, no significant amount of any other products was observed.

Additional efforts were also put forth into the syntheses of the natural products precocenes I (**18**) and II (**20**) utilizing this method (Table 3). Doubling the power of the microwave irradiation (entries 2 and 7) from the standard conditions (entries 1 and 6) had a very favorable effect on the production of the desired 2,2-dimethyl-2*H*-chromenes, and when coupled with a doubling of the amount of **1** added (entries 3 and 8), yields were even further increased. Trials at this elevated wattage run at twice the concentration (entries 4 and 9) displayed a minimal boost in the production of **18**, but the yield of **20** actually suffered due to decomposition of the materials. Increasing the time of exposure (entries 5 and 10) had a positive effect on the yield of both natural products.

While $CDCl_3$ was chosen as the solvent for these reactions initially merely for facility of NMR evaluation, further studies were performed to investigate the effect of solvent choice on this reaction. While the use of $CDCl_3$ as the solvent provided the maximum yield for the conversion of this substrate to chromene product, no clear trends regarding polarity or proticity emerged from this investigation. The full results of these trials are reported in Table 4.

In an isolated trial in methanol using **6**, arguably the least amenable to this protocol of all the investigated phenols, chromene **7**

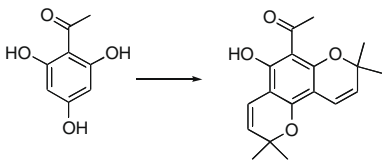
Table 3
Selected results from the optimization trials for the synthesis of the natural products precocenes I (**18**) and II (**20**)[a]



Entry	Phenol	R	Product	Time (h)	Equiv **1**	Concn (M)	Yield[b] (%)
1	**17**	H	**18**	1	3	1	7[c]
2	**17**	H	**18**	1	3	1	39
3	**17**	H	**18**	1	6	1	63
4	**17**	H	**18**	1	3	2	27[d]
5	**17**	H	**18**	2	3	1	53
6	**19**	OCH_3	**20**	1	3	1	5[c]
7	**19**	OCH_3	**20**	1	3	1	39
8	**19**	OCH_3	**20**	1	6	1	88
9	**19**	OCH_3	**20**	1	3	2	41
10	**19**	OCH_3	**20**	2	3	1	44

[a] Reaction mixtures irradiated at 300 W unless otherwise indicated.
[b] Crude product mixtures consisted of >95% product and starting materials only unless otherwise indicated.
[c] Reaction mixture irradiated at 150 W.
[d] Crude product mixture contained significant amounts of uncharacterized compounds presumed to be polymeric material.

Table 4
Synthesis of octandrenolone in various solvents[a]



Entry	Solvent	ε	Yield[b] (%)
1	Hexane	2.0	11
2	Benzene	2.3	24
3	*d*-Chloroform	4.8	60
4	Tetrahydrofuran	7.5	9
5	Acetone	21	17
6	Ethanol	24	22
7	Methanol	33	34
8	Acetonitrile	37	5
9	*N*,*N*-Dimethylformamide	38	4
10	Water	80	3
11	None	na	21

[a] Reaction mixtures contained 3 equiv of **1** in a 1 M solution in $CDCl_3$ and were irradiated at 300 W for 1 h.
[b] Yields were obtained by adding 1 equiv (based on starting phenol) of naphthalene followed by GC–MS analysis.

was synthesized in 60% yield with no evidence of any other products in the crude reaction mixture. While this phenomenon needs to be further explored, it is possible that the hydrogen-bonding ability of this solvent is helping to attenuate unwanted side reactions.

In summary, a novel, direct method to regioselectively synthesize variably substituted 2,2-dimethyl-2*H*-chromenes utilizing microwave irradiation has been developed. This is a technique which is complementary, and sometimes superior, to known methods, and provides another approach to the synthesis of chromene-containing compounds. By altering a few of the variables associated with this reaction, a variety of 2,2-dimethyl-2*H*-chromenes have been successfully generated in good yield. While optimization of the described method is ideal for its application to novel substrates, the conditions are generally applicable to a wide range of starting phenols. The results reported in this publication provide the current state of this research; work on improving the efficiency and generality of this method is ongoing.

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Supplementary data

Detailed experimental procedures, spectral data for all 2,2-dimethyl-2*H*-chromene products, ^{1}H and ^{13}C spectra of the novel structures **5** and **9**, crystallographic data for chromene **9**, and NOE experiment spectra for the structural assignment of chromene **11**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.090.

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