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FULL PAPER

Microwave-assisted synthesis of phenylpropanoids and coumarins: total synthesis of Osthol

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Dedicated to professor Milan Potáček on the occasion of his upcoming 75th birthday anniversary.

Abstract: Herein we describe a one-pot microwave-assisted synthesis of cinnamic acid derivatives and coumarins. The synthesis starts from an aldehyde synthon and the choice of the product, coumarin or cinnamic acid derivative, is determined by the reaction conditions. A regioselective Claisen rearrangement can be also efficiently incorporated into the synthetic sequence to further increase the rapid product complexity. Of note, (1) no phenol protecting group is required. (2) high yields and selectivity are achieved.

Introduction

Phenylpropanoids are plant secondary metabolites biosynthesized within the Shikimate biosynthetic pathway.[1] The phenylpropanoid skeletal core is then further modified within the plant cells to furnish many structurally diverse secondary plant metabolites – natural products – with interesting biological properties. As a consequence, phenylpropanoid subunits are presented within the plants in the form of polyhydroxy monomers (e.g. cinnamic acid derivatives, monolignols, coumarins), dimers[2] (e.g. lignans, neolignans, flavonoids), and polymers[1d] (lignin) (Figure 1). Such secondary metabolites serve the plant in many ways as e.g. protection from UV light, defense against herbivores and pathogens, or mediators of plant-pollinator interactions (floral pigments and scent compounds).

Our interest is to understand the oxidation processes[3] related to phenolic plant secondary metabolites on a molecular level, and to describe the effect of these oxidized compounds on human health, leading us to immerge into the world of plant produced phenolic compounds.[4] However, the plant metabolome contains thousands of structurally diverse secondary metabolites, thus the identification of phenols of interest is far from being simple. The identification of phenolic derivatives possibly active in the oxidation processes in plants on molecular level has become our primary goal. To address the challenge, we have decided to develop a short and versatile protecting group-free synthetic approach that would allow us to prepare phenylpropanoids (mainly cinnamic acid derivatives) and polyfunctionalized coumarins in a short and efficient manner. [13-16]

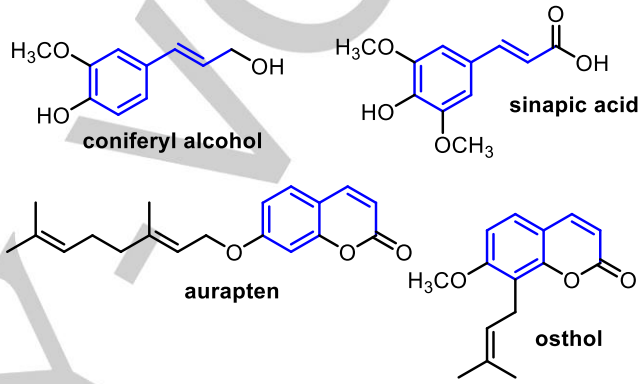

Figure 1. Examples of phenylpropanoids and coumarins.

The synthesis of cinnamic acid derivatives and coumarins was previously intensively studied.[1c,3e,6] Unfortunately, to the best of our knowledge, there is no general approach that would allow us to efficiently prepare either cinnamic acid derivatives or coumarins starting from the same building block (Scheme 1). In this article we report our synthetic approach to both classes of the targeted structures, cinnamic acid derivatives and coumarins, starting from commercially available aromatic aldehydes with use of the microwave promoted Wittig reaction of stabilized ylides. This efficient and protecting group-free method is then applied to the synthesis of several natural products and their derivatives.

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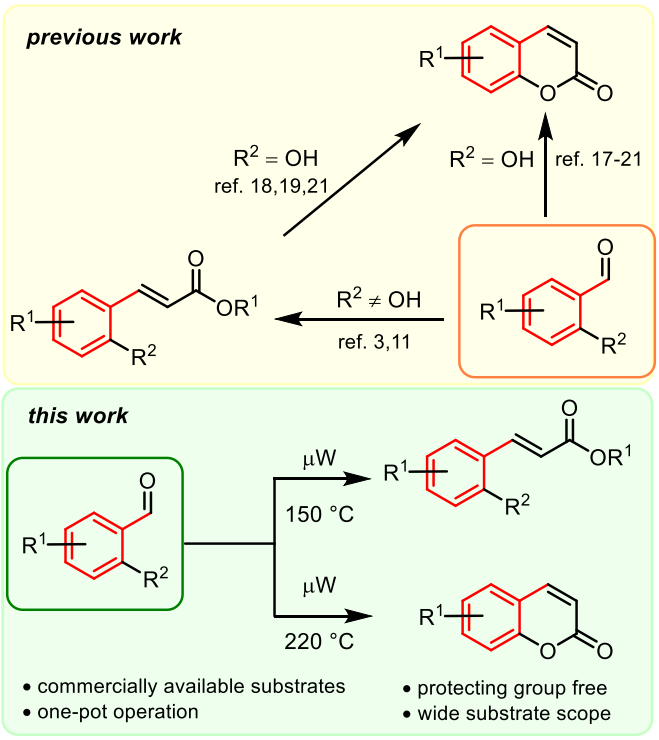


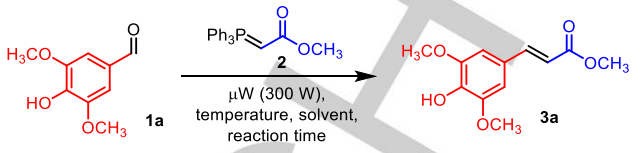
Scheme 1. Synthetic routes to phenylpropanoids and coumarins.

Results and Discussion

Our first goal was to find out if our approach was feasible. Thus the reaction of the aldehyde **1a**[7] with stabilized Wittig ylide **2**[8] was attempted (Table 1). Based on our previous experience with the cycloaddition reactions initiated by microwave irradiation[9] and by literature[10], the reaction between aldehyde **1a** and ylide **2** were performed under solvent-free conditions (Table 1, entries 1 and 2) or in THF and EtOAc, respectively (entries 3 and 4). Unfortunately, the desired product **3a** was obtained in low yields. At this stage it was expected that the employed reaction conditions could cause the degradation of starting materials or formed product, and that the degradation might have been caused by the presence of the phenolic hydroxy group.[11] To avoid additional protecting/deprotecting steps, we decided to perform the reaction of unprotected aldehyde **1a** and ylide **2** in toluene (entries 5-13). The argument behind this was that a small solubility of starting materials **1a** and **2** in toluene might avoid most of the undesired side reactions, and still allow us to perform the olefination reaction in good yield and *E/Z* selectivity. And indeed, after some reaction condition optimization (entries 5 to 13), the desired product **3a** was obtained in 95 % yield and >95:5 *E/Z* selectivity (entry 9).

Optimized reaction conditions were then extended to other aromatic aldehydes **1a-o** (Table 2, entries 1-15) and ketones **1p-s** (entries 16-19). In all cases, and regardless of the steric or electronic properties of the aldehyde or ketone, the desired cinnamoyl ester derivatives **3** were formed in good to excellent yields and *E/Z* selectivity.

Table 1. Optimization of the reaction conditions[a].



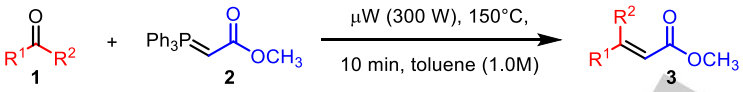
Entry	Conditions	Yield[b] (%)	E/Z[c]
1[d]	Solvent-free, 150 °C, 30 min	degradation	-
2[d]	Solvent-free, 100 °C, 30 min	degradation	-
3[e]	THF (0.1 M), 100 °C, 60 min	20	91:9
4[e]	EtOAc (0.1 M), 100 °C, 60 min	6	85:15
5	toluene (0.1 M), 100 °C, 60 min	35	>95:1
6	toluene (0.1 M), 150 °C, 60 min	42	>95:1
7[f]	toluene (0.1 M), 150 °C, 60 min	85	>95:1
8[f]	toluene (0.1 M), 150 °C, 10 min	40	>95:1
9	toluene (1.0 M), 150 °C, 10 min	95	>95:1
10	toluene (1.0 M), 110 °C, 10 min	85	>95:1
11	toluene (1.0 M), 150 °C, 6 min	94	>95:1
12	toluene (1.0 M), 170 °C, 10 min	78	>95:1
13	toluene (2.0 M), 150 °C, 10 min	73	>95:1

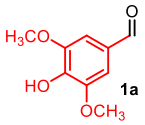
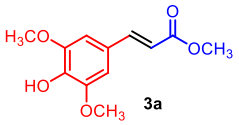
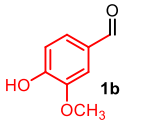
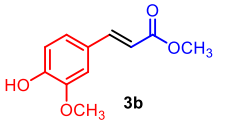
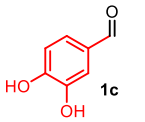
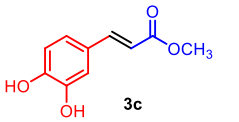
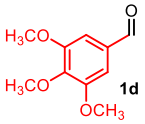
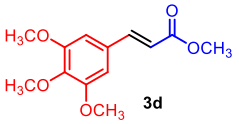
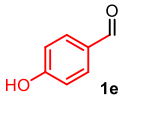
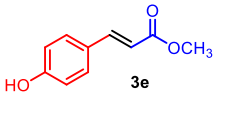
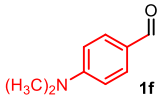
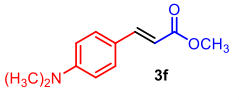
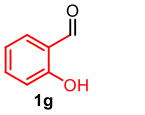
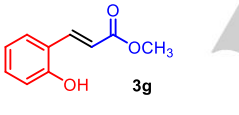
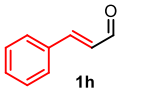
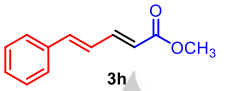
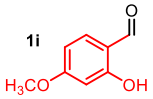
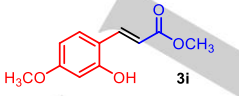
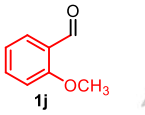
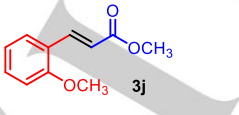
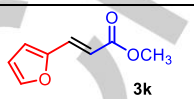
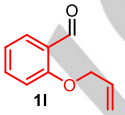
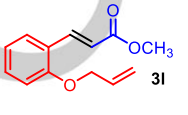
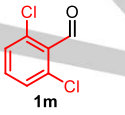
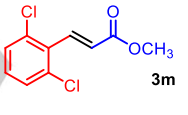
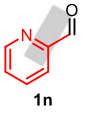
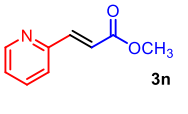
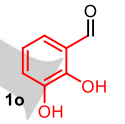
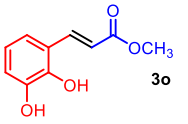
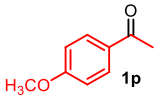
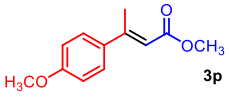
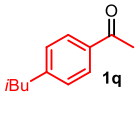
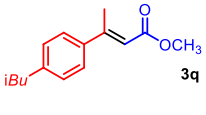
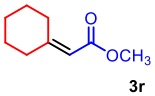
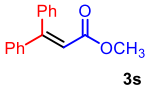
[a] Reaction conditions: **1a** (2.75 mmol) and **2** (3.0 mmol) were dissolved/suspended in appropriate solvent and placed in a microwave vessel for the indicated reaction time. [b] Isolated reaction yields. [c] Based on ^{1}H NMR spectra of the crude reaction mixture. [d] Inspired by ref. 26. [e] Inspired by ref. 25. [f] **2** (6.0 mmol) was used.

Interestingly, when 2-hydroxy aldehydes **1g,i,o** were used, no product of the thermally driven intramolecular lactonization, coumarins (see later), were detected (entries 7, 9 and 15).[12] Similarly, no product of Claisen rearrangement[13] was observed under the studied reaction conditions when aldehyde **1l** was used as a starting material (entry 12).

Having an easy access to cinnamic acid derivatives **3** we have turned our attention to the synthesis of monolignols **5a-c** and monolignol aldehydes **6a-c** (Scheme 2). The desired allylic alcohols **5a-c** were prepared via DIBAL-H mediated reduction of the corresponding esters **3**. DDQ mediated[14] oxidation of allylic alcohols **5a-c** then yielded the desired aldehydes **6a-c** in very good yields. Again, no phenol protecting group was used within the reaction sequence.

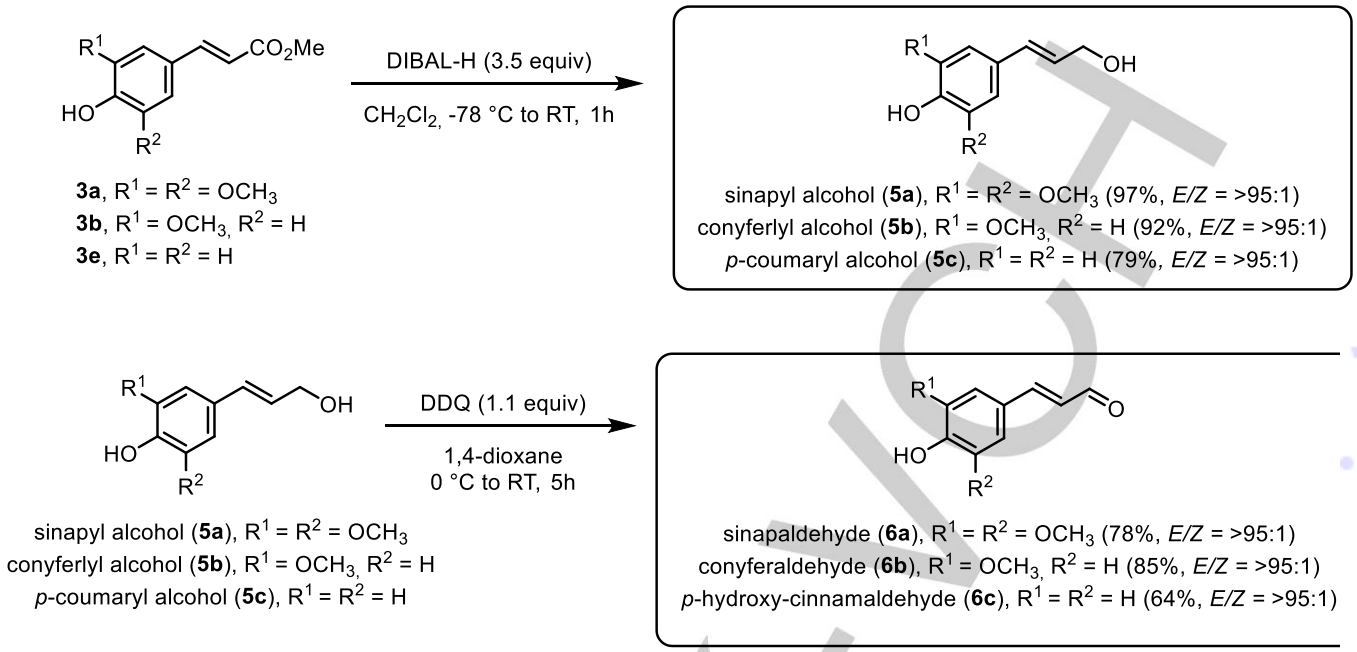
Table 2. Scope of microwave irradiation promoted cinnamic acid derivatives synthesis[a]



Entry	Aldehyde or ketone (**1**)	Product (**3**)	Yield[b] (%)	E/Z[c]
1			95	>95:1
2			98	>95:1
3			92	>95:1
4			98	>95:1
5			97	>95:1
6			94	92:8
7			82	92:8
8			95	90:10
9			89	>95:1
10			91	81:19
11			84	92:8
12			95	92:8
13			98	>95
14			92	>95
15			94	>95
16			76	80:2
17			78	82:1
18			75	-
19			62	-

[a] Reaction conditions: **1** (5.0 mmol) and **2** (5.5 mmol) were placed in a microwave reaction vessel and toluene (1.0M, 5.0 mL) was added. The reactic vessel was sealed with an aluminum/Teflon®crimp top and placed into the microwave reactor. The reaction was carried out at 150 °C (fixed reactic temperature) for 10 min. [b] Isolated reaction yields. [c] Based on ^{1}H NMR spectra of crude reaction mixture.

Having secured the synthesis of phenylpropanoid derivatives **3**, **5** and **6**, our attention turned to coumarins **4**. It is known from the literature[6a] that the thermally initiated *E/Z*-isomerization of ester **3g** can lead to the formation of the corresponding coumarin **4a**. Based on these observations, a one-pot synthesis of coumarin **4a** starting from aldehyde **1g** was attempted (Table 3).



Scheme 1. Monolignol and monolignal synthesis.

As a starting point of the transformation, prolonged reaction conditions used in the case of cinnamic acid ester **3g** synthesis were employed (Table 3, entry 1). Only traces of the desired product **4a** were obtained. However, gradual increase of the reaction temperatures (entries 2 to 6) and variation in the reaction time (entries 7 to 11) helped to identify suitable reaction conditions (entry 9). These conditions were then applied to some other 2-hydroxy benzaldehyde derivatives (**1i**,**o**,**s** and **t**) and even in these cases the desired coumarins **4b-e** were formed in good yields (Table 4).

Additionally, we have explored the incorporation of Claisen rearrangement into the coumarin synthetic sequence (Scheme 3). The idea behind this was, with help of 2-hydroxy group, to incorporate regioselectively an allylic sidechain into the newly created coumarin skeleton. It was expected that under the reaction conditions suitable for the coumarin formation, *O*-allyl salicyl aldehyde **1l** would undergo a Claisen rearrangement. The rearrangement step would selectively incorporate the allylic chain α to the hydroxy group (Scheme **3**). Rearranged intermediate **7** would yield *in situ* 2-hydroxy cinnamic acid derivative **8** that could further undergo isomerization/cyclization transformations and yield the desired coumarin ring subunit **9**. (A study with similar idea behind was recently independently published by Schmidt and Riemer[15]) In this sequence, three new C-C bonds along with one C-O bond should be formed stereoselectively in a *one-pot* protocol. Gratifyingly, the reaction proceeded as planned and the desired product **9** was formed in 85 % yield.[16]

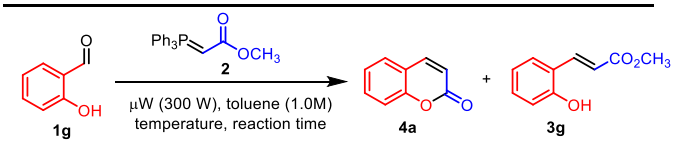
To demonstrate the synthetic utility and versatility of the above developed synthetic methods, *O*-prenylated coumarin **10**, a potent 15-lipoxygenase inhibitor,[17] was prepared in two steps and 51 % overall yield from aldehyde **1t** (Scheme 4a). Similarly, osthol **13**, calcium channel blocker,[18] was prepared starting from 2-hydroxy aldehyde **1i** in a two-pot protocol (3 steps, one purification step) and in 78 % overall yield.

Conclusions

In conclusion we have described short and efficient protecting group free microwave-assisted synthesis of cinnamic acid derivatives and coumarins. The targeted compounds are prepared in good yields and, in the case of cinnamic acid derivatives, excellent *E/Z* selectivity. These prepared compounds are, or can be transformed in 1 to 2 steps into the key members of cinnamate/monolignol biosynthetic pathway[19] and various coumarin core-containing natural products. In the case of coumarin derivatives, the method was further extended by incorporation of Claisen rearrangement step. This extension allowed us additional selective incorporation of allylic side chains to the coumarin core structure during the coumarin synthesis. Efficacy of the protocol was demonstrated by two-pot synthesis of osthol natural product.

The application of these developed methods on an understanding of the oxidation processes of plant phenolics on a molecular level, and on the development of new drug candidates with antileishmanial activity, is now in progress and will be reported in the near future.

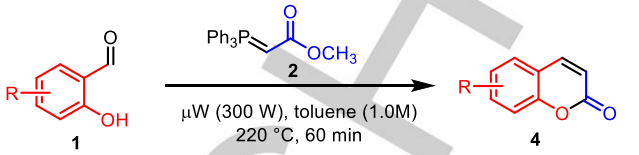
Table 3 Optimization of coumarin **4a** reaction conditions[a]

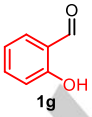
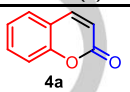
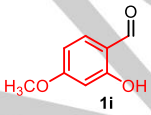
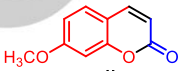
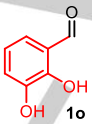
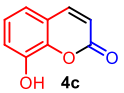
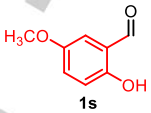
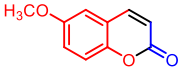
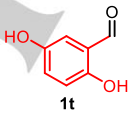
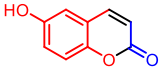
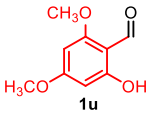
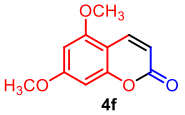


Entry	Conditions	**4a**[b] (%)	**3g**[b] (%)
1	150 °C, 30 min	-[c]	94
2	175 °C, 30 min	21	67
3	185 °C, 30 min	36	52
4	210 °C, 30 min	68	12
5	220 °C, 30 min	72	5
6	230 °C, 30 min	54	-[c]
7	210 °C, 60 min	78	-[c]
8	220 °C, 45 min	83	-[c]
9	220 °C, 60 min	88	-[c]
10	220 °C, 75 min	83	-[c]
11[d]	220 °C, 60 min	89	-[c]

[a] Reaction conditions: **1a** (2.75 mmol) and **2** (3.0 mmol) were suspended in toluene (1.0M, 2.75 mL) and placed into a microwave vessel for the indicated reaction time. [b] Isolated reaction yields. [c] Traces (<5%) in ^{1}H NMR spectra of the crude reaction mixture. [d] Reaction carried out with 2 g of aldehyde **1g**.

Table 4 Coumarin **4** synthesis[a]



Entry	Aldehyde (**1**)	Product (**4**)	Yield[b] (%)
1	 **1g**	 **4a**	89
2	 **1i**	 **4b**	86
3	 **1o**	 **4c**	72
4	 **1s**	 **4d**	78
5	 **1t**	 **4e**	68
6	 **1u**	 **4f**	74

[a] Reaction conditions: **1** (5.0 mmol) and **2** (5.5 mmol) were placed into a microwave reaction vessel and toluene (1.0M, 5.0 mL) was added. The reaction vessel was sealed with an Silicone/PTFE Vial caps top and placed into a microwave reactor. The reaction was carried out at 150 °C (fixed reaction temperature) for 10 min. [b] Isolated reaction yields.

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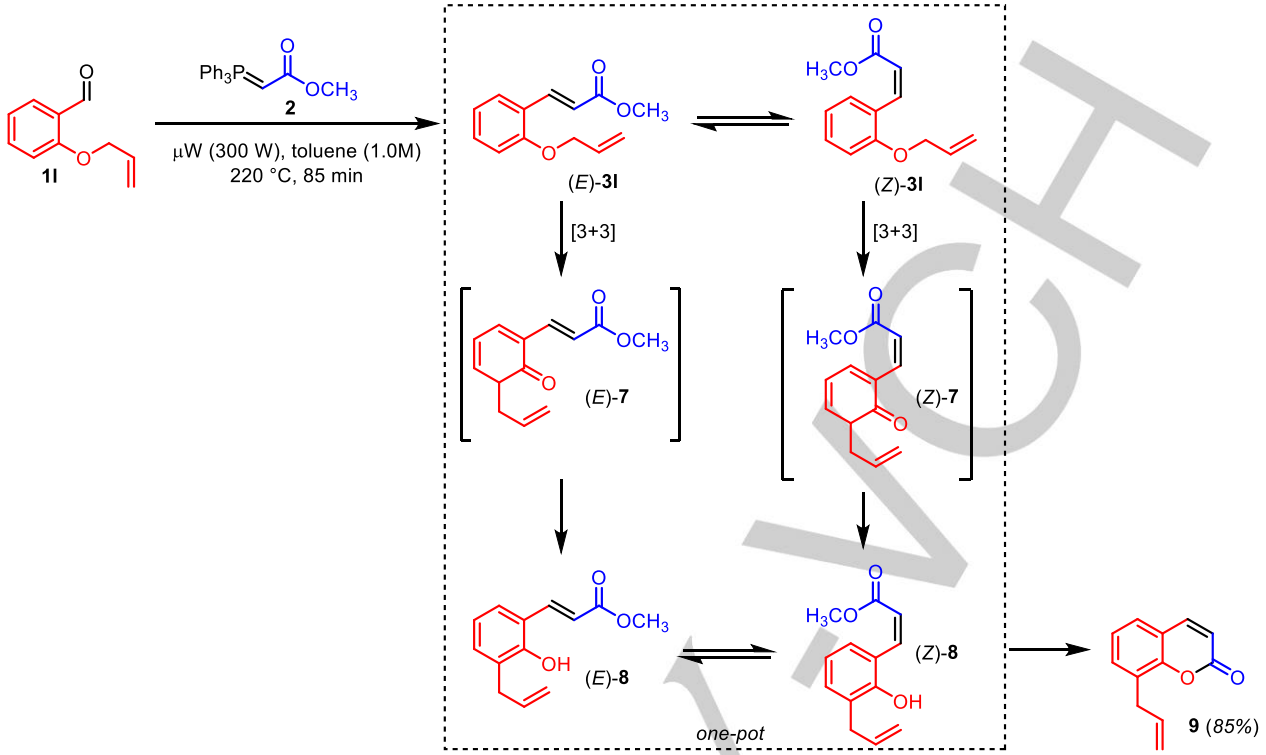
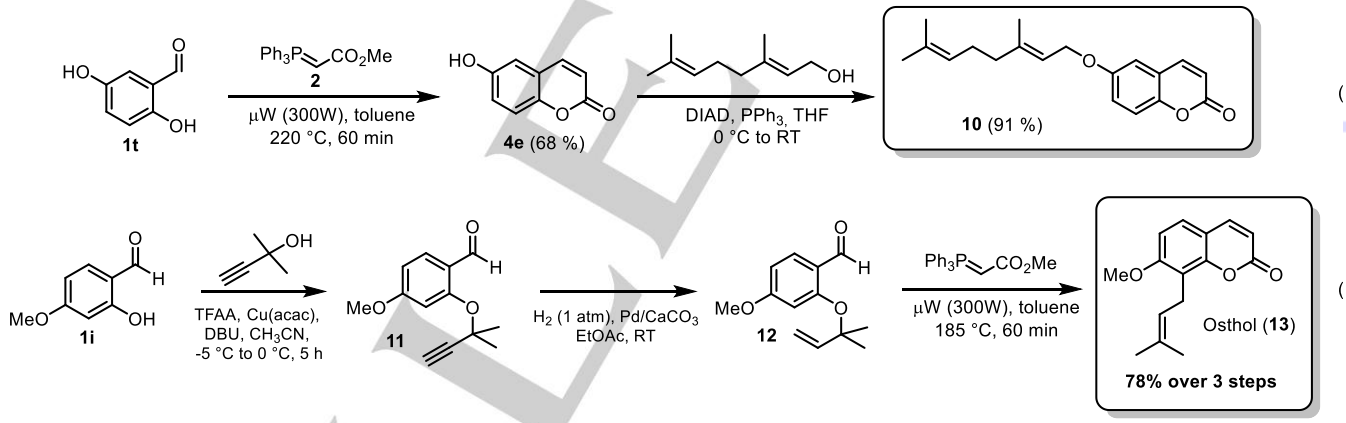


Scheme 2. Reaction sequence of Wittig olefination/Claisen rearrangement/olefin isomerization/cyclization steps yielding coumarin **9**.



Scheme 3. Application of developed methodology to selected natural product synthesis.

Experimental Section

All starting materials were used as received from commercial sources without further purification. The Wittig reagent **2** was prepared from the corresponding methyl 2-bromoacetate according to the published procedure. All reactions were carried out using the standard laboratory techniques. Column chromatography was performed on silica gel 60 (40-63 μm). Melting points were determined on a Büchi melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 and 125 MHz, respectively in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) of ^{1}H NMR are reported in a standard fashion with relative to the remaining $CHCl_3$ present in $CDCl_3$ (δH = 7.27 ppm). ^{13}C NMR chemical shifts (δ ppm) are reported relative to $CHCl_3$ (δC = 77.23 ppm, central line of triplet). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), and multiplet (m). HRMS data were obtained using quadrupole/ion trap mass analyser. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments.

All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 mL glass vials sealed with an Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

General protocol for cinnamic acid derivatives (3) synthesis

A suspension of aldehyde **1** (5.00 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (5.5 mmol, 1.1 equiv) in toluene (5.0 mL, 1.0 M to **1**) was placed in a microwave vial (35 mL) equipped with a magnetic stirring bar. The vial was sealed an Silicone/PTFE Vial cap and placed in a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 10 minutes (fixed time) at 150°C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum.

Methyl (E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylate (3a). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1) yielded resulting ester **3a** (1.13 g, 95%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 15.9 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.10 (broad s, 1H), 3.91 (s, *J* = 4.6 Hz, 3H), 3.79 (s, 3H);); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.69, 145.28, 145.25, 137.19, 125.93, 115.60, 105.09, 56.40, 51.74; MS (ESI, *m/z*): 239 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{15}O_5^+$) 239.0919, found 239.0920.

Methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (3b). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1) yielded resulting ester **3b** (1.02 g, 98%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 16.0 Hz, 1H), 7.03 (ddd, *J* = 16.2, 7.9, 1.9 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.27 (d, *J* = 15.9 Hz, 1H), 6.15 – 5.98 (m, 1H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.92, 148.10, 146.89, 145.11, 126.98, 123.13, 115.15, 114.87, 109.48, 56.00, 51.74; MS (ESI, *m/z*): 209 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{13}O_4^+$) 209.0814, found 209.0815.

Methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (3c). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 2:1->1:1->0:100) yielded resulting ester **3c** (893 mg, 92%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J* = 15.9 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.05, 147.61, 145.40, 145.09, 121.86, 115.58, 114.37, 51.52; MS (ESI, *m/z*): 195 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_4^+$) 195.0657, found 195.0658.

Methyl (E)-3-(3,4,5-trimethoxyphenyl)acrylate (3d). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3d** (893 mg, 92%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 15.9 Hz, 1H), 6.74 (s, 2H), 6.34 (d, *J* = 15.9 Hz, 1H), 3.87 (d, *J* = 4.5 Hz, 9H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.50, 153.51 , 144.99, 140.15, 129.95, 117.03, 105.29, 60.99, 56.14, 51.75; MS (ESI, *m/z*): 253 $[M+H]^+$; HRMS (ESI): calculated (for $C_{13}H_{17}O_5^+$) 253.1076, found 253.1076.

Methyl (E)-3-(4-hydroxyphenyl)acrylate (3e). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3e** (864 mg, 97%) in >95:1 *E/Z* ratio. M.p. = 133-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.65 (broad s, 1H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.32, 158.01, 144.96, 130.12, 127.14, 116.00, 115.10, 51.85; MS (ESI, *m/z*): 179 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_3^+$) 179.0708, found 179.0702.

Methyl (E)-3-(4-(dimethylamino)phenyl)acrylate (3f). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3f** (1.06 g, 94%) in >95:1 *E/Z* ratio. M.p. = 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 15.9 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.9 Hz, 1H), 3.77 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.44, 156.23, 145.47, 129.87, 125.42, 121.13, 111.93, 51.45, 40.24; MS (ESI, *m/z*): 206 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{16}NO_2^+$) 206.1181, found 206.1185.

Methyl (E)-3-(2-hydroxyphenyl)acrylate (3g). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3g** (804 mg, 82%) in 92:8 *E/Z* ratio. M.p. = 136-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.26 (s, 1H), 7.83 (d, *J* = 16.2 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.72, 157.31, 140.67, 132.38, 129.43, 121.16, 120.00, 117.35, 116.74, 51.80; MS (ESI, *m/z*): 179 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_3^+$) 179.0708, found 179.0706.

Methyl (2E,4E)-5-phenylpenta-2,4-dienoate (3h). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1->1:1) yielded ester **3h** (883 mg, 95%) in 90:10 *E/Z* ratio. M.p. = 68-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.51 – 7.43 (m, 3H), 7.40 – 7.35 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.95 – 6.84 (m, 2H), 6.01 (d, *J* = 15.4 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.60, 144.97, 140.67, 136.06, 129.20, 128.92, 127.31, 126.28, 120.95, 51.74; MS (ESI, *m/z*): 189 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{13}O_2^+$) 189.0916, found 189.0917.

Methyl (E)-3-(2-hydroxy-4-methoxyphenyl)acrylate (3i). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3i** (1.01 g, 89%) in >95:1 *E/Z* ratio. M.p. = 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.63 (broad s, 1H), 7.92 (d, *J* = 15.9 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.55-6.47 (m, 3H), 6.45 (d, *J* = 16.2 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.96, 161.81, 159.62, 137.50, 129.85, 115.93, 114.91, 106.85, 102.35, 55.83, 51.96; MS (ESI, *m/z*): 209 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{12}O_4Na^+$) 231.0633, found 231.0630.

Methyl (E)-3-(2-methoxyphenyl)acrylate (3j). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3j** (962 mg, 91%) in 89:19 *E/Z* ratio. M.p. = 290-294 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 16.2 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.91 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.06, 158.43, 140.38, 131.62, 129.04, 123.42, 120.80, 118.40, 111.18, 55.50, 51.66; MS (ESI, *m/z*): 193 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{13}O_3^+$) 193.0865, found 193.0862. ^{1}H NMR characteristic peaks of minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17 (dd, *J* = 12.4, 0.5 Hz, 1H), 5.97 (d, *J* = 12.5 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H).

Methyl (E)-3-(furan-2-yl)acrylate (3k). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3k** (703 mg, 84%) in 92:8 *E/Z* ratio. M.p. = 27-30 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48 (d, *J* = 1.3 Hz, 1H), 7.44 (d, *J* = 15.7 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.47 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.32 (d, *J* = 15.7

Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.69, 151.03, 144.90, 131.42, 115.62, 115.03, 112.48, 51.90; MS (ESI, *m/z*): 153 $[M+H]^+$; HRMS (ESI): calculated (for $C_8H_9O_3^+$) 153.0552, found 153.0551.

Methyl (E)-3-(2-(allyloxy)phenyl)acrylate (3l). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3l** (1.04 g, 95%) in 92:8 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, *J* = 16.2 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 6.98 (td, *J* = 7.4, 0.6 Hz, 1H), 6.92 (dd, *J* = 8.3, 0.6 Hz, 1H), 6.56 (d, *J* = 16.2 Hz, 1H), 6.10 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.45 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.64 (dt, *J* = 5.2, 1.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.06, 157.39, 156.30, 140.39, 131.55, 131.55, 129.03, 128.98, 118.44, 112. 60, 112.49, 69.26, 51.64; MS (ESI, *m/z*): 219 $[M+H]^+$; HRMS (ESI): calculated (for $C_{13}H_{15}O_3^+$) 219.1021, found 219.1019. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (d, *J* = 12.4 Hz, 1H), 6.00 (d, *J* = 12.5 Hz, 1H), 5.30 (dq, *J* = 10.6, 1.5 Hz, 1H *one of the* =C*H*$_2$), 4.58 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.69 (s, 3H).

Methyl (E)-3-(2,6-dichlorophenyl)acrylate (3m). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1) yielded ester **3m** (1.13 g, 98%) in >95:1 *E/Z* ratio. M.p. = 50-53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 16.4 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (126 MHz,) δ 166.87, 138.52, 135.17, 132.14, 130.00, 128.93, 126.67, 52.23; MS (ESI, *m/z*): 231 and 233 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_9Cl_2O_2^+$) 230.9980, found 230.9981.

Methyl (E)-3-(pyridin-2-yl)acrylate (3n). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3n** (750 mg, 92%) in >95:1 *E/Z* ratio. M.p. = 30-32 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.66–8.58 (m, 1H), 7.73 – 7.64 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.30-7.23 (m, 1H), 6.94 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.32, 152.89, 150.12, 143.52, 136.96, 124.44, 124.29, 121.97, 51.89; MS (ESI, *m/z*): 164 $[M+H]^+$; HRMS (ESI): calculated (for $C_9H_{10}NO_2^+$) 164.0712, found 164.0715.

Methyl (E)-3-(2,3-dihydroxyphenyl)acrylate (3o). Residue was purified by column chromatography (SiO_2; CH_2Cl_2:MeOH = 100:1->50:1) yielded ester **3o** (913 mg, 94%) in >95:1 *E/Z* ratio.

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.98 (d, *J* = 16.1 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.89 (s, 1H), 6.74 (t, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 16.1 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 167.73, 146.43, 146.19, 146.05, 140.90, 121.75, 119.70, 117.43, 117.21, 51.76; MS (ESI, *m/z*): 195 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_4^+$) 195.0657, found 195.0660.

Methyl (E)-3-(4-methoxyphenyl)but-2-enoate (3p). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1) yielded ester **3p** (783 mg, 76%) in 80:20 *E/Z* ratio. M.p. = 50-53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.45 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.11 (d, *J* = 1.0 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 2.56 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.59, 160.55, 155.37, 134.32, 127.71, 114.81, 113.86, 55.51, 51.21, 17.84; MS (ESI, *m/z*): 207 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{15}O_3^+$) 207.1021, found 207.1025. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.87 (d, *J* = 1.1 Hz, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 2.16 (d, *J* = 1.2 Hz, 3H).

Methyl (E)-3-(4-isobutylphenyl)but-2-enoate (3q). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3q** (905 mg, 78%) in 82:12 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.14 (s, 1H), 3.74 (s, 3H), 2.57 (d, *J* = 1.1 Hz, 3H), 2.55 – 2.46 (m, 2H), 1.88 (dq, *J* = 13.3, 6.7 Hz, 1H), 0.90 (dd, *J* = 6.6, 2.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.54, 155.94, 143.16, 139.43, 129.37, 128.41, 115.81, 51.14, 45.17, 30.27, 27.29, 22.46; MS (ESI, *m/z*): 233 $[M+H]^+$; HRMS (ESI): calculated (for $C_{15}H_{21}O_2^+$) 233.1542, found 233.1545. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.88 (d, *J* = 1.3 Hz, 1H), 3.55 (s, 3H), 2.17 (d, *J* = 1.3 Hz, 3H).

Methyl 2-cyclohexylideneacetate (3r). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3r** (578 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm:) 5.63 (d, *J* = 0.8 Hz, 1H), 3.70 (s, 3H), 2.92 – 2.82 (m, 2H), 2.27 – 2.16 (m, 2H), 1.72 – 1.56 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.46, 164.14, 112.77, 51.03 50.93, 30.04, 28.82, 28.02, 26.44, 21.67, 21.62; MS (ESI, *m/z*): 155 $[M+H]^+$; HRMS (ESI): calculated (for $C_9H_{15}O_2^+$) 155.1072, found 155.1074.

Methyl 3,3-diphenylacrylate (3s). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3s** (740 mg, 62%). M.p. = 197-200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 (qd, *J* = 3.5, 2.0 Hz, 3H), 7.38 – 7.32 (m, 2H), 7.31 – 7.28 (m, 3H), 7.23 – 7.20 (m, 2H), 6.37 (s, 1H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.45, 157.11, 140.79, 138.80, 129.48, 129.11, 128.39, 128.33, 128.22, 127.91, 116.79, 51.29; MS (ESI, *m/z*): 239 $[M+H]^+$; HRMS (ESI): calculated (for $C_{16}H_{15}O_2^+$) 239.1072, found 239.1071.

General protocol for coumarin derivative (4) synthesis

A suspension of aldehyde **1** (3.6 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (4.0 mmol, 1.1 equiv) in toluene (3.6 mL, 1.0 M to **1**) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 60 minutes (fixed time) at 220 °C (see representative reaction protocol KAH-02-045 (for compound **4c**)). The reaction mixture was allowed to cool down transferred to a round-bottom flask and the toluene was removed under vacuum.

Coumarin (4a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4a** as a slightly yellow solid (468 mg, 89 %). M.p. = 69-70°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J* = 9.5 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.48 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 6.41 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm:) 160.92, 154.14, 143.64, 131.97, 128.03, 124.58, 118.95, 116.98, 116.78; HRMS (ESI): calculated (for $C_9H_7O_2^+$) 147.0446 $[M+H]^+$, found 147.0445.

7-methoxy-2H-chromen-2-one (4b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4b** as a slightly yellow solid (545 mg, 86 %). M.p. = 114-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.24 (d, *J* = 9.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 162.93, 161.34), 156.01, 143.50, 128.93, 113.27, 113.11, 112.65, 100.98, 55.80; HRMS (ESI): calculated (for $C_{10}H_9O_3^+$) 177.0552 $[M+H]^+$, found 177.0551.

8-hydroxy-2H-chromen-2-one (4c). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding

the desired product **4c** as slightly yellow solid (420 mg, 72 %). M.p. = 159-161 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 10.17 (s, 1H), 7.97 (d, *J* = 9.5 Hz, 1H), 7.16 – 7.03 (m, 3H), 6.43 (d, *J* = 9.5 Hz, 1H).; ^{13}C NMR (126 MHz, CMSO-*d*$_6$) δ (ppm): 160.44, 145.23, 145.14, 142.71, 125.04, 120.23, 118.89, 116.66, 116.58; HRMS (ESI): calculated (for $C_9H_8O_3^+$) 163.0395 $[M+H]^+$, found 163.0394.

6-methoxy-2H-chromen-2-one (4d). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4d** as a slightly yellow solid (495 mg, 78 %). M.p. = 102-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.65 (d, *J* = 9.5 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 2H), 7.11 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.24, 156.27, 148.67, 143.40, 119.62, 119.37, 118.08, 117.29, 110.13, 56.00; HRMS (ESI): calculated (for $C_{10}H_9O_3^+$) 177.0552 $[M+H]^+$, found 177.0551.

6-hydroxy-2H-chromen-2-one (4e). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4e** as slightly yellow solid (397 mg, 68 %). M.p. = 221-222 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 8.98 (s, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.30 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 161.26, 156.17, 143.43, 140.00, 124.08, 118.52, 114.91, 112.63, 110.00; HRMS (ESI): calculated (for $C_9H_7O_3^+$) 163.0395 $[M+H]^+$, found 163.0395.

5,7-dimethoxy-2H-chromen-2-one (4f). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4f** as a slightly yellow solid (549 mg, 74 %). M.p. = 145-146 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 7.99 (d, *J* = 9.6 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.17 (d, *J* = 9.7 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 168.88, 165.60, 162.01, 161.52, 115.94, 108.37, 100.29, 98.39, 61.61, 61.31; HRMS (ESI): calculated (for $C_{11}H_{11}O_4^+$) 207.0657 $[M+H]^+$, found 207.0656.

General protocol for monolignol (5) synthesis

Methyl ester of cinnamic acid (**3**, 8.5 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (55 mL, 0.15M to **3**) and the whole mixture was cooled to -78 °C (dry ice/acetone). DIBAL-H (29.5 mL, 29.5 mmol, 3.5 equiv; 1.0 M solution in CH_2Cl_2) was subsequently added dropwise and the whole mixture slowly turned yellowish. After additional 10 min, the cooling bath was removed and the whole mixture was allowed to stir at RT for 1 h. The whole mixture was then cooled to -78 °C and stirred for additional 10 min. Saturated aqueous solution of Rochel's salt (30 mL) was added and the whole mixture was allowed to worm to RT and stir for additional 12h. The resulting layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with sat. aq. NaCl (35 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was then purified by column chromatography (silica gel).

Sinapyl alcohol (5a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **5a** as a slightly yellow solid (1.73 g, 97 %, *E/Z* = >95:1). M.p. = 62-63°C (from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.64 (s, 2H), 6.53 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.59 (broad s, 1H), 4.32 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.90 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 147.29, 134.90, 131.69, 128.39, 126.75, 103.45, 63.97, 56.47, 56.43; HRMS (ESI): calculated (for $C_{11}H_{14}O_4Na^+$) 233.0790, found 233.0789.

Conyferlyl alcohol (5b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a slightly yellow solid (1.40g, 92%, *E/Z* = >95:1). M.p. = 74-75°C (from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.02 – 6.76 (m, 3H), 6.54 (d, *J* = 15.3 Hz, 1H), 6.23 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.72 (broad s, 1H), 4.31 (dd, *J* = 6.1, 1.5 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 146.81, 145.76, 131.58, 129.40, 126.30, 120.50, 114.64, 108.49, 64.07, 56.09; HRMS (ESI): calculated (for $C_{10}H_{12}O_3Na^+$) 203.0684, found 203.0686.

***p*-coumaryl alcohol (5c)**. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (1.01 g 79 %, *E/Z* = >95:1). M.p. = 117-120°C (from P.E.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 9.09 (broad s, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.5 Hz, 2H), 6.66 (dd, *J* = 8.5, 1.7 Hz, 2H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.05 (dtd, *J* = 15.9, 5.5, 1.8 Hz, 1H), 4.07 (dd, *J* = 5.5, 1.6 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 157.64, 133.82, 129.20, 128.81, 128.13, 116.33, 62.39; HRMS (ESI): calculated (for $C_9H_{10}O_2Na^+$) 173.0579, found 173.0578.

General protocol for propnionaldehyde (6) synthesis

Monolignol **5** (5.5 mmol, 1.0 equiv) in dry 1,4-dioxane (55 mL, 0.1M) was cooled to 0 °C and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.89 g, 0.83 mmol, 1.5 equiv) was added in 5 portions over a period of 5 minutes. The resulting mixture (yellow-red) was stirred at 0 °C for 30 min and then at RT for 5 h. The whole mixture was then filtered and the filtrate was evaporated under reduced pressure to yield the crude product.

Sinapaldehyde (6a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (4.58 g, 85 %, *E/Z* = >95:1). M.p. = 107-109 °C; ^{1}H NMR (500 MHz, acetone-*d*$_6$) δ (ppm): 9.65 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.09 (s, 2H), 6.70 (dd, *J* = 16.0, 7.5 Hz, 1H), 3.92 (s, 6H); ^{13}C NMR (126 MHz, acetone-*d*$_6$) δ (ppm): 192.92, 153.51, 148.18, 139.32, 126.41, 125.32, 106.49, 55.92; HRMS (ESI): calculated (for $C_{11}H_{12}O_4Na^+$) 231.0633, found 231.0632.

Conyferaldehyde (6b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (4.58 g, 85 %, *E/Z* = >95:1). M.p. = 78-80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.62 (d, *J* = 6.8 Hz, 1H), 7.76 (broad s, 1H), 7.38 (dd, *J* = 15.1, 0.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 5.6 Hz, 1H), 7.06 (dd, *J* = 5.6, 1.3 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.59 (dd, *J* = 15.2, 6.2 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 193.61, 153.10, 148.96, 146.96, 126.62, 126.37, 124.03, 114.94, 109.50, 55.97; HRMS (ESI): calculated (for $C_{10}H_{10}O_3Na^+$) 178.0477, found 178.0479.

***p*-hydroxy cinnamaledehyde (6c)**. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (3.52 g, 64 %, *E/Z* = >95:1). M.p. = 136-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.52 (d, *J* = 7.2 Hz, 1H), 8.98 (broad s, 1H), 7.41 (dd, *J* = 15.1, 0.8 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.52 (dd, *J* = 15.1, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 194.50, 160.25, 154.15, 130.71, 125.69, 125.43, 116.08; HRMS (ESI): calculated (for $C_9H_8O_2Na^+$) 171.0422, found 171.0420.

Coumarin 10 synthesis via Claisen rearrangement/cyclization sequence and subsequent Mitsunobu substitution

A suspension of aldehyde **1l** (500 mg, 3.1 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (1.14 g, 3.4 mmol, 1.1 equiv) in toluene (3.1 mL, 1.0 M) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 85 minutes (fixed time) at 220 °C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->20:1->10:1->4:1) and yielded coumarin **9** (491 mg, 85%) as colorless low-melting point crystals. M.p. = 40-42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.72 (d, *J* = 9.5 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 6.03 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.15 (ddd, *J* = 12.0, 3.1, 1.6 Hz, 1H), 5.12 (dt, *J* = 4.5, 1.5 Hz, 1H), 3.63 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.06, 151.86, 144.07, 135.58, 132.52, 128.58, 126.36, 124.33, 118.94, 117.05, 116.59, 33.41; HRMS (ESI): calculated (for $C_{12}H_{11}O_2^+$) 187.0759 $[M+H]^+$, found 187.0758. **Coumarin derivative 10**. A solution of coumarin **4e** (80 mg, 0.49 mmol, 1.0 equiv) in THF (5 mL, 0.1 M) was cooled to 0 °C (water/ice) and PPh_3 (155 mg, 0.59 mmol, 1.2 equiv) followed by geraniol (128 □L, 0.74 mmol, 1.5 equiv) were added. The resulting mixture was stirred at 0 °C for 5 min before diisopropyl (*E*)-diazene-1,2-dicarboxylate (DIAD) (153 □L, 0.78 mmol, 1.6 equiv) was added dropwise. The resulting mixture was allowed to warm to RT and stirred at RT for 11 h. The whole reaction mixture was evaporated to dryness and purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 20:1->10:1->4:1) to yield the desired product **10** (133 mg, 91%) as colorless crystals. M.p. = 96-97 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): ^{1}H NMR (500 MHz,) δ 7.66 (d, *J* = 9.5 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.13 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 5.49 (ddd, *J* = 7.8, 5.4, 1.2 Hz, 1H), 5.09 (ddd, *J* = 6.8, 4.1, 1.3 Hz, 1H), 4.57 (d, *J* = 6.5 Hz, 2H), 2.20 – 2.01 (m, 4H), 1.76 (s, 3H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.61 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.29, 155.53, 148.54, 143.50, 142.20, 132.17, 123.85, 120.35, 119.34, 119.07, 118.05, 117.22, 111.25, 65.76, 39.74, 26.45, 25.91, 17.94, 16.95; MS (ESI^+, *m/z*): 299 $[M+H^+]$ (100%), 300 (60%), 301 (28%); HRMS (ESI): calculated (for $C_{19}H_{23}O_3^+$) 299.1647 $[M+H]^+$, found 299.1646.

Osthol (13) synthesis

Preparation of the aldehyde 11. A solution of 2-methylbut-3-yn-2-ol (1.12 mL, 10.95 mmol, 1.0 equiv) in CH_3CN (11.0 mL, 1.0M) was cooled to -5 °C (water/ice/NaCl) and DBU (2.13 mL, 14.2 mmol, 1.3 equiv) was added. The resulting mixture was stirred at -5 °C for 5 min and trifluoracetic acid anhydride – TFAA (1.52 mL, 10.95 mmol, 1.0 equiv) was added dropwise over a 20 min period. The mixture was warmed up to 0 °C (exchange of cooling baths) and stirred at 0 °C for an additional 30 min. In a separate flask, aldehyde **1i** (1.5 g, 9.9 mmol, 0.9 equiv) in CH_3CN (11 mL, 1.0M) was cooled to 0 °C and DBU (2.13 mL, 14.2 mmol, 1.3 equiv) was slowly added. The reaction mixture was stirred at 0 °C for an additional 5 min. $Cu(acac)_2$ (573 mg, 2.2 mmol, 0.2 equiv) was added and the mixture was stirred for the next 10 min at 0 °C. The resulting cold mixture was then slowly, over a period of 40 min, added into a mixture of activated propargylic alcohol and the mixture was allowed to stir at 0 °C for 5 h. The mixture was then poured into a separating funnel containing EtOAc:H_2O = 5:1 (V/V) (120 mL) and the resulting layers were separated. The organic layer was washed with water (3x25 mL), 1.0M aq. HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->25:1) yielding the desired substituted aldehyde **11** (1.84 g, 85% - calculated to aldehyde **1i**) in the form of a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.27 (d, *J* = 0.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 6.67 (ddd, *J* = 8.8, 2.4, 0.6 Hz, 1H), 3.87 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 189.08, 165.30, 160.43, 130.00, 122.53, 108.88, 105.74, 85.33, 75.47, 73.84, 55.81, 29.72; MS (ESI^+, *m/z*): 219 $[M+H^+]$; HRMS (ESI): calculated (for $C_{13}H_{15}O_3^+$) 219.1021 $[M+H]^+$, found 219.1020.

From aldehyde 11 to osthol 13. A solution of aldehyde **11** (900 mg, 4.13 mmol, 1.0 equiv) in EtOAc (21 mL, 0.2M) was stirred at RT and Rosenmund catalyst (5% Pd on $BaSO_4$) (41 mg, 10 mg/mmol loading) was added. The mixture was placed under hydrogen atmosphere (1 atm) and vigorously stirred for 12h. The mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (2x25 mL) and the collected organic layers were evaporated to dryness to yield crude olefin **12** in sufficient purity to be used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.32 (d, *J* = 0.7 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.3 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.19 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.28 (d, *J* = 17.7 Hz, 1H), 5.24 (dd, *J* = 10.9, 0.6 Hz, 1H), 3.80 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (126 MHz,) δ 189.45, 165.24, 161.34, 144.08, 130.00, 121.29, 114.41, 107.74, 105.27, 81.42, 55.70, 27.25; MS (ESI^+, *m/z*) = 221 $[M+H]^+$. A suspension of aldehyde **12** (crude from the previous reaction, 4.13 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (1.52 g, 4.54 mmol, 1.1 equiv) in toluene (4.1 mL, 1.0 M) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 60 minutes (fixed time) at 220 °C (see PLJ-06-073 microwave reaction monitoring record). The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->20:1->10:1->4:1) and yielded osthol **13** (928 mg, 92%) as colorless crystals. M.p. = 77-79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 9.5 Hz, 1H), 7.28 (dd, *J* = 10.0, 4.7 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.23 (d, *J* = 9.4 Hz, 1H), 5.26 – 5.17 (m, 1H), 3.92 (s, 3H), 3.53 (d, *J* = 7.3 Hz, 2H), 1.84 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.66 160.39, 152.97, 144.00, 132.85, 126.40, 121.28, 118.12, 113.14, 107.53, 56.23, 25.98, 22.10, 18.12; MS (ESI^+, *m/z*): 245 $[M+H^+]$; HRMS (ESI): calculated (for $C_{15}H_{17}O_3^+$) 245.1178 $[M+H]^+$, found 245.1178; elemental analysis (for $C_{15}H_{16}O_3$): calc. C 73.75%, H 6.60%; found C 73.72%, H 6.59%.

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[1] a) T. J. Mabry and A. Ulubelen, *J. Agric. Food Chem.* **1980**, *28*, 188-196; b) E. Fuss, *Phytochem. Rev.* **2003**, *2*, 307-320; c) M. Bunzel, *Phytochem. Rev.* **2009**, *9*, 47-64; d) J.-K. Weng and C. Chapple, *New Phytol.* **2010**, *187*, 273-285.

[2] a) J. S. Piotrowski, H. Okada, F. Lu, S. C. Li, L. Hinchman, A. Ranjan, D. L. Smith, A. J. Higbee, A. Ulbrich, J. J. Coon, R. Deshpande, Y. V. Bukhman, S. McIlwain, I. M. Ong, C. L. Myers, C. Boone, R. Landick, J. Ralph, M. Kabbage and Y. Ohya, *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, E1490-E1497; b) B. Sathish Kumar, A. Singh, A. Kumar, J. Singh, M. Hasanain, A. Singh, N. Masood, D. K. Yadav, R. Konwar, K. Mitra, J.

Sarkar, S. Luqman, A. Pal, F. Khan, D. Chanda and A. S. Negi, *Bioorg. Med. Chem.* **2014**, *22*, 1342-1354.

[3] a) G. Noctor, *Plant. Cell. Environ.* **2006**, *29*, 409-425; b) F. Shahidi and A. Chandrasekara, *Phytochem. Rev.* **2010**, *9*, 147-170; c) D. G. Deavall, E. A. Martin, J. M. Horner and R. Roberts, *J. Toxicol.* **2012**, *2012*, 13; d) N. Razzaghi Asl, J. Garrido, H. Khazraei, M. Borges and O. Firuzi, *Curr. Med. Chem.* **2013**, 20; e) G. Magoulas and D. Papaioannou, *Molecules* **2014**, *19*, 19769-19835.

[4] J. Grúz, J. Pospíšil, H. Kozubíková, T. Pospíšil, K. Doležal, M. Bunzel and M. Strnad, *Food Chem.* **2015**, *171*, 280-286.

[5] a) O. Chew, J. Whelan and A. H. Millar, *J. Biol. Chem.* **2003**, *278*, 46869-46877; b) C. Sgherri, E. Cosi and F. Navari-Izzo, *Phys. Plant.* **2003**, *118*, 21-28; c) J. Huang, L. Wu, S.-i. Tashiro, S. Onodera and T. Ikejima, *J. Pharm. Sci.* **2008**, *107*, 370-379; d) F. M. F. Roleira, C. Siquet, E. Orrù, E. M. Garrido, J. Garrido, N. Milhazes, G. Podda, F. Paiva-Martins, S. Reis, R. A. Carvalho, E. J. T. d. Silva and F. Borges, *Bioorg. Med. Chem.* **2010**, *18*, 5816-5825.

[6] a) N. S. Narasimhan, F. S. Mali and M. V. Barve, *Synthesis* **1979**, *1979*, 906-909; b) S. M. Sethna and N. M. Shah, *Chem. Rev.* **1945**, *36*, 1-62; c) S. R. Trenor, A. R. Shultz, B. J. Love and T. E. Long, *Chem. Rev.* **2004**, *104*, 3059-3078; d) B. Wagner, *Molecules* **2009**, *14*, 210; e) F. Boeck, M. Blazejak, M. R. Anneser and L. Hintermann, *Beilstein J. Org. Chem.* **2012**, *8*, 1630-1636.

[7] The electronic properties of the substitution on aldehyde **1a** (strong electron donor) led us to identify the aldehyde **1a** as the model substrate. Most of targeted phenylpropanoids and coumarins have at least one hydroxy or methoxy group within its skeleton.

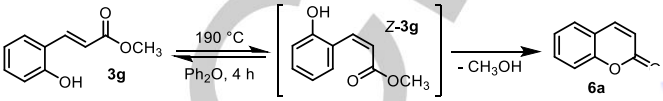
[8] Stabilized Wittig reagent **2** was chosen due to its non-basicity. It is known that cinnamic acid derivatives and monolignols are relatively unstable under basic conditions,[1c,3e,11] thus non-basic olefination reagent **2** was chosen to avoid possible side reactions.

[9] a) J. Pospíšil and M. Potáček, *Eur. J. Org. Chem.* **2004**, *2004*, 710-716; b) J. Pospíšil and M. Potáček, *Tetrahedron* **2007**, *63*, 337-346; c) J. Pospíšil, T. Béres and M. Strnad, *Tetrahedron Lett.* **2017**, *58*, 1421-1424.

[10] a) S. Frattini, M. Quai and E. Cereda, *Tetrahedron Lett.* **2001**, *42*, 6827-6829; b) C. Xu, G. Chen, C. Fu and X. Huang, *Synth. Commun.* **1995**, *25*, 2229-2233.

[11] Y. Zhu, M. Regner, F. Lu, H. Kim, A. Mohammadi, T. J. Pearson and J. Ralph, *RSC Adv.* **2013**, *3*, 21964-21971.

[12] It is known from the literature[6a] that product **3g** can undergo intramolecular thermal double bond isomerization/cyclization.



[13] a) C. J. Davis, T. E. Hurst, A. M. Jacob and C. J. Moody, *J. Org. Chem.* **2005**, *70*, 4414-4422; b) A. M. Jacob and C. J. Moody, *Tetrahedron Lett.* **2005**, *46*, 8823-8825.

[14] A. Sharma, N. Sharma, A. Shard, R. Kumar, D. Mohanakrishnan, Saima, A. K. Sinha and D. Sahal, *Org. Biomol. Chem.* **2011**, *9*, 5211-5219.

[15] B. Schmidt and M. Riemer, *Synthesis* **2016**, *48*, 141-149.

[16] For more details about the optimization of the reaction cascade see supplementary information.

[17] a) M. Iranshahi, A. Jabbari, A. Orafaie, R. Mehri, S. Zeraatkar, T. Ahmadi, M. Alimardani and H. Sadeghian, *Eur. J. Med. Chem.* **2012**, *57*, 134-142; b) C. M. Farley, D. F. Dibwe, J.-y. Ueda, E. A. Hall, S. Awale and J. Magolan, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1471-1474; c) M. Jun, A. F. Bacay, J. Moyer, A. Webb and D. Carrico-Moniz, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4654-4658.

[18] Z.-R. Zhang, W. N. Leung, H. Y. Cheung and C. W. Chan, *Evid. Based Complement. Alternat. Med.* **2015**, *2015*, 10.

[19] T. Umezawa, *Phytochem. Rev.* **2010**, *9*, 1-17.

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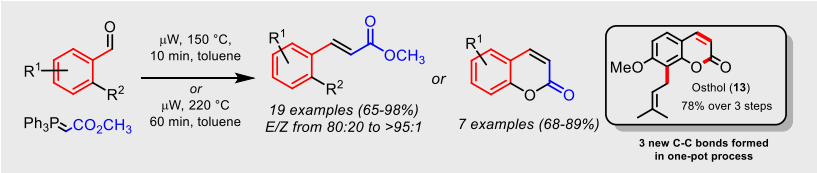

Synthetic method*

Daniela Konrádová, Hana Kozubíková, Karel Doležal, and Jiří Pospíši*

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Microwave-assisted synthesis of phenylpropanoids and coumarins: total synthesis of Osthol

Microwave-assisted one-pot synthesis of phenylpropanoids, monolignols and coumarins. The choice of the reaction conditions and substrate determines the product of the reaction. Developed reaction conditions were applied to the synthesis of osthol (**13**) and several other natural products.

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