# Concise Synthesis of Licochalcone A through Water-Accelerated [3,3]-Sigmatropic Rearrangement of an Aryl Prenyl Ether

Jae-Ho Jeon,[a] Mi Ran Kim,[b] Jong-Gab Jun*[a,b]

[a] Institute of Natural Medicine, Hallym University, Chuncheon 200-702, South Korea

[b] Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 200-702, South Korea
Fax +82(33)2563421; E-mail: jgjun@hallym.ac.kr

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**Abstract:** Claisen–Schmidt condensation of 4-(tetrahydropyran-2-yloxy)acetophenone with 2-methoxy-4-[(3-methylbut-2-en-1-yl)oxy]benzaldehyde gave a THP-protected chalcone ether. Removal of the THP group under mild acidic conditions gave the corresponding chalcone ether, which underwent a water-accelerated Claisen rearrangement under microwave irradiation or heating in a sealed tube in aqueous ethanol to give a good yield of licochalcone A, which has diverse biological activities; no product of deprenylation or abnormal Claisen rearrangement was formed. The abnormal Claisen rearrangement of γ-substituted allyl aryl ethers is known to be a problem in [3,3]-sigmatropic rearrangement reaction; this, however, was not detected in our water-accelerated system.

**Key words:** rearrangements, condensation, natural products, licochalcone A

Licochalcones A–E and the closely related compound echinatin (Figure 1) were isolated and identified from the root of *Glycyrrhiza inflata* (licorice).[1] The crude extract of this root finds commercial use as a food additive because it contains the sweetening principle glycyrrhizin. Licochalcones A–E and echinatin are interesting retrochalcones that are distinguished from ordinary chalcones by the absence of an oxygen functionality at the C-2′ and C-6′ positions.[1a] They have been reported to have various biological activities, such as antitumor,[2] antiparasitic,[3] antileishmanial,[4] antioxidative,[5] superoxide-scavenging,[6] and antibacterial activities,[7] as well as tyrosine-protein phosphatase non-receptor type 1-inhibitory activity.[8] Also, licochalcone A has been used as a drug to treat various abdominal spasmodic symptoms, and it was recently reported that it is a potent regulator of pathological vascular conditions such as restenosis.[9] Licochalcone A has also been shown to have antimalarial activity.[10] The discovery by our collaborators that licochalcone A has anti-inflammatory activity[7] and antimetastatic effects[2] prompted us to develop a practical method for the preparation of this compound.

Three previous routes to the total synthesis of licochalcone A have been reported. In the first route, methylation of 2-hydroxy-4-[(3-methylbut-2-en-1-yl)oxy]benzaldehyde (**1**) at the 2-position to form the protected aldehyde **2** followed by Claisen–Schmidt condensation[11] with 4-hydroxyacetophenone (**3**) gave the chalcone prenyl ether (**4**). This underwent a [3,3]-sigmatropic rearrangement with acetic anhydride in *N*,*N*-diethylaniline to give the acety-

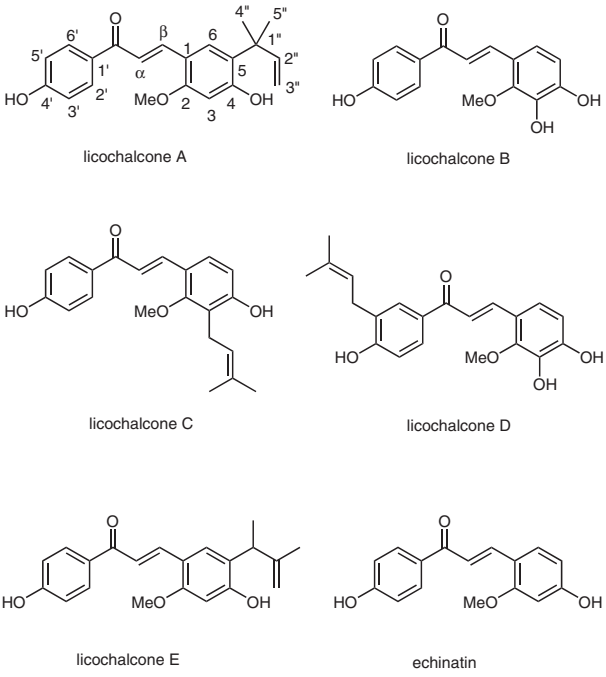
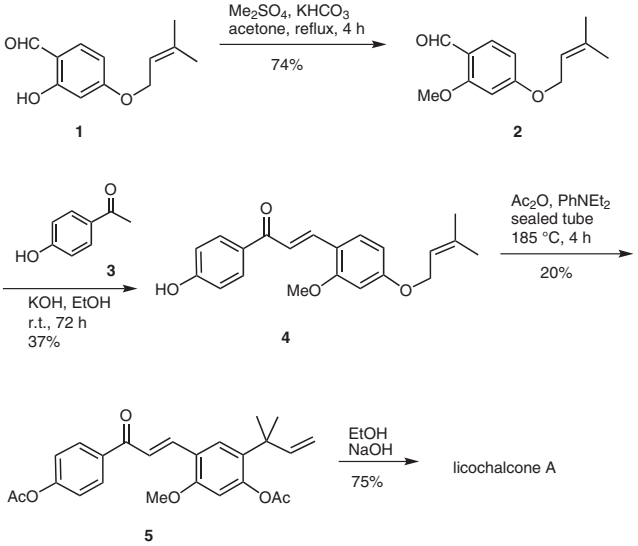



**Figure 1** Structures of the licochalcones




**Scheme 1** Licochalcone A synthesis: route 1

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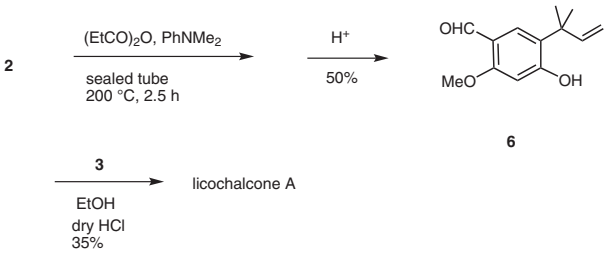
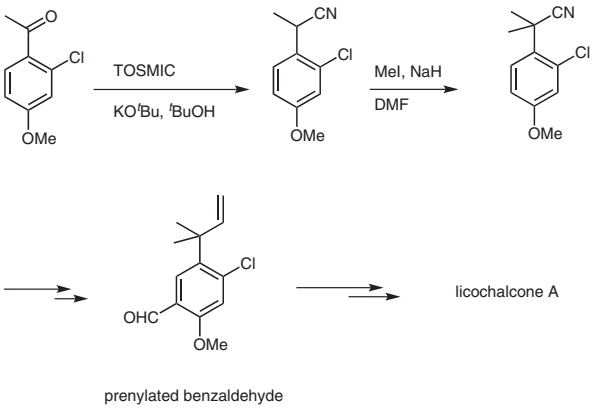
lated chalcone **5** in 20% yield. Removal of the acetyl group under basic conditions then gave licochalcone A in a 4% overall yield (four steps) (Scheme 1).[12a]

Another group used a similar procedure involving a [3,3]-sigmatropic rearrangement.[12b] They dissolved aldehyde **2** in propionic anhydride and *N,N*-dimethylaniline, and heated the mixture to 200 °C for 2.5 hours in a sealed tube. Acid hydrolysis and Claisen–Schmidt condensation[11] with 4-hydroxyacetophenone (**3**) gave licochalcone A (Scheme 2).




**Scheme 2** Licochalcone A synthesis: route 2

In the third route, treatment of 2-chloro-4-methoxyacetophenone with tosylmethyl isocyanide (TOSMIC) gave a nitrile compound that was methylated and subjected to an $S_N2$ reaction followed by a series of functional-group transformations to give the required prenylated benzaldehyde, which was converted into licochalcone A (Scheme 3).[13]




**Scheme 3** Licochalcone A synthesis: route 3

The existing Claisen rearrangements of prenyl ether **4** and **2** to give **5** and **6**, respectively (Schemes 1 and 2, respectively) were very useful for constructing the backbone of licochalcone A, but the reported yields were generally low. The route using TOSMIC (Scheme 3) is interesting, but involves seven steps. We therefore focused on methods for improving the yield of the Claisen rearrangement step.

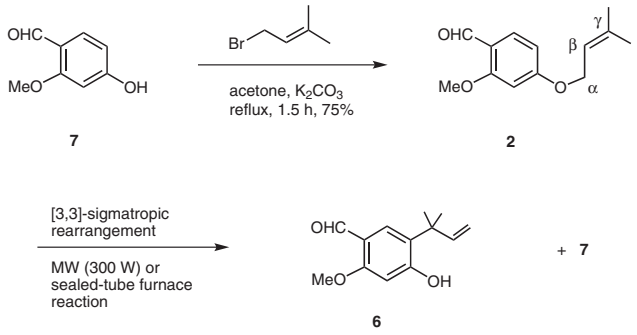
Our strategy began with determining the optimal conditions for synthesis of the prenylated benzaldehyde **6** (Scheme 4 and Table 1). Simple prenylation of 4-hydroxy-2-methoxybenzaldehyde (**7**) with 1-bromo-3-methylbut-2-ene under basic conditions gave the aryl prenyl ether **2** in 75% yield. The [3,3]-sigmatropic reaction of ether **2** was studied in various refluxing solvents at atmospheric pressure with conventional heating (entries 1–4). Because this reaction was not very successful, we attempted to accelerate the reaction by performing it at a higher pressure in a thick-walled pressure vessel (entries 8–18). Although single solvents with high boiling points were used, the reaction failed to proceed (entries 8–11).

**Table 1** [3,3]-Sigmatropic Rearrangement of Prenyl Ether **2** to Rearranged Benzaldehyde **6**

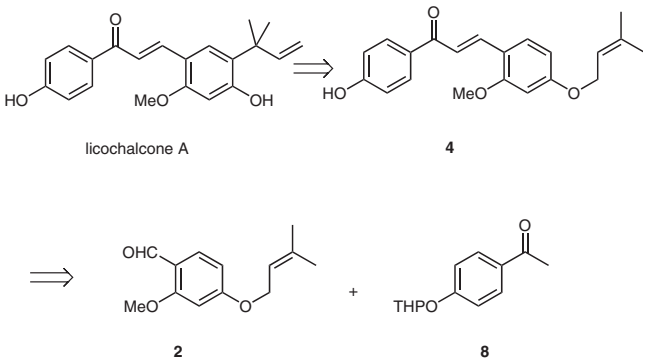
| Entry | Solvent | Temp (°C) | Time (h) | Ratio[d] (**6**:**7**) | Yield of **6**[d] (%) |
|---|---|---|---|---|---|
| 1[a] | valeric acid | reflux | 24 | – | – |
| 2[a] | xylene | reflux | 48 | – | – |
| 3[a] | toluene | reflux | 48 | – | – |
| 4[a] | DMF | reflux | 12 | – | – |
| 5[a] | DMF–$H_2O$ (4:1) | 180 | 24 | – | – |
| 6[a] | EtOH | reflux | 10 | – | – |
| 7[a] | EtOH–$H_2O$ (4:1) | 180 | 12 | – | – |
| 8[b] | valeric acid | reflux | 10 | – | – |
| 9[b] | xylene | 130 | 10 | – | – |
| 10[b] | DMF | 130 | 10 | – | – |
| 11[b] | toluene | reflux | 10 | – | – |
| 12[b] | EtOH | reflux | 10 | – | – |
| 13[b] | DMF–$H_2O$ (4:1)) | 130 | 10 | – | – |
| 14[b] | AcOH–$H_2O$ (7:2) | 130 | 10 | – | – |
| 15[b] | EtOH–$H_2O$ (4:1) | 80 | 24 | – | – |
| 16[b] | EtOH–$H_2O$ (4:1) | 130 | 24 | 80:20 | 40 |
| 17[b] | EtOH–$H_2O$ (4:1) | 180 | 15 | 70:30 | 20 |
| 18[b] | EtOH–$H_2O$ (4:1) | 210 | 15 | – | – |
| 19[c] | DMF | 210 | 0.5 | – | – |
| 20[c] | DMF–$H_2O$ (5:1) | 210 | 0.5 | – | – |
| 21[c] | acetone–$H_2O$ (4:1) | 210 | 0.5 | – | – |
| 22[c] | EtOH–$H_2O$ (4:1) | 210 | 1.5 | 85:15 | 52 |

[a] Conventional heating at atmospheric pressure.
[b] Sealed-tube furnace reactor.
[c] Microwave irradiation (300 W).
[d] Yield after purification by silica gel chromatography.

Because these results were not promising, we changed the solvent to an organic solvent–water mixture (entries 5, 7, 13–18). It is known that water can accelerate certain types of organic reactions, such as Diels–Alder reactions, 1,3-




**Scheme 4** [3,3]-Sigmatropic rearrangement reaction




**Scheme 5** Retrosynthetic analysis of licochalcone A

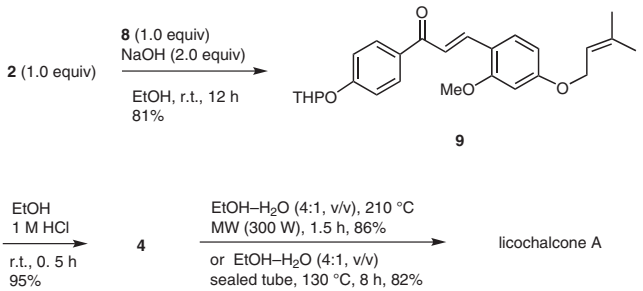
dipolar cycloadditions, cycloaddition reactions of azodicarboxylates, Claisen rearrangements, Passerini reactions, Ugi reactions, nucleophilic opening of three-membered rings, nucleophilic substitution reactions, transition-metal-induced reactions, metal-free C–C bond-forming processes, bromination reactions, oxidations, and reductions.[14a,b] It has also been reported that polar solvents can accelerate the rates of [1,3]- and [3,3]-sigmatropic reactions.[14c–e] We therefore examined the aqueous organic solvent systems for the [3,3]-sigmatropic rearrangement reaction of the aryl prenyl ether **2**.

Even though reaction in ethanol–water (4:1 v/v) at 130 °C (entry 16) gave the desired product **6** in a 40% yield within twenty-four hours, the deprenylated phenol **7** was always recovered, and this was the biggest obstacle to optimization of the reaction.[15] When we decreased the reaction temperature to 80 °C (entry 15), the reaction did not proceed at all within twenty-four hours, and when we increased the temperature to 180 °C (entry 17), the reaction proceeded within fifteen hours, but the yield of **6** decreased as a result of increased deprenylation to give **7**. When the temperature was raised to 210 °C (entry 18), decomposed materials were the main products after fifteen hours.

We therefore turned our attention to use of microwave heating (entries 19–22).[16] The best results were obtained in ethanol–water (4:1 v/v) with heating at 300 W for 1.5 hours (entry 22). In this case a 52% yield of **6** was obtained; however, the problem of deprenylation still occurred. It is well known that the [3,3]-sigmatropic rearrangement of γ-substituted allyl aryl ether systems is often complicated as a result of abnormal rearrangement leading to structural isomerization of the migrating group.[17] In the case of our substrate, no observable abnormal rearranged product was obtained. It is noteworthy that the reported method[14c] using trimethylaluminum with water or phenylboronic acid gave only the [1,3]-sigmatropic rearrangement product together with the deprenylated phenol **7**. As the reaction was not well optimized, we decided to change our entire synthesis plan, as shown in Scheme 5.

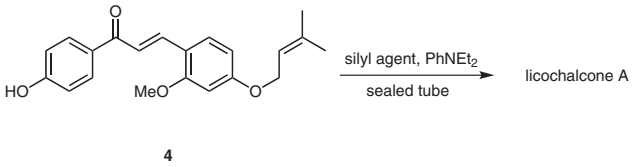
We thought that the microwave reaction would be better for converting the chalcone ether (**4**) into licochalcone A. The aryl ether **2** underwent Claisen–Schmidt condensation[11] with 4-[(tetrahydropyran-2-yl)oxy]acetophenone (**8**) to give the protected chalcone **9** in 81% yield. Removal of the tetrahydropyranyl group under mildly acidic conditions (1 M HCl, EtOH, r.t., 30 min) gave the chalcone ether **4** in 95% yield. The [3,3]-sigmatropic rearrangement reactions of chalcone ether **4** in ethanol–water (4:1 v/v) under microwave irradiation at 300 W for 1.5 hours gave the desired licochalcone A in 86% yield with no deprenylated or abnormal Claisen-rearrangement products. Similarly, when the reaction was performed with the same solvent system in a sealed-tube in a furnace for 8 hours at 130 °C, the product was obtained in 82% yield (Scheme 6).

The Claisen rearrangement of **2** to **6** resulted in significant deprenylation compared with the same rearrangement of **4** to licochalcone A, where no deprenylation occurred. The difference in the degree of deprenylation between the two reactions may arise from structural differences. We initially suspected that the phenol moiety of **4** might inhibit deprenylation during the rearrangement by acting as a radical scavenger. However, when the Claisen rearrangement of **2** to **6** was performed under identical conditions, the addition of hydroquinone as a radical scavenger showed no helpful effect in protecting against deprenylation. We now believe that the direct attachment of the carbonyl group to the phenyl ring of compound **2** may significantly reduce the electron density of the aromatic ring system. For this reason, the **2** shows less [3,3]-sigmatropic rearrangement than does the chalcone ether **4**.




**Scheme 6** Total synthesis of licochalcone A by a microwave or sealed-tube reaction

Although we did not observe any abnormal Claisen rearranged product of **4**, for the sake of comparison we examined this reaction by using Fukuyama's method with silyl trapping agents and *N*,*N*-diethylaniline as a solvent (Scheme 7, Table 2).[17b]




**Scheme 7** [3,3]-Sigmatropic rearrangement reaction with silyl agent

When we used hexamethyldisilazane (HMDS) as a trapping agent, we obtained only the decomposed products (entry 1, Table 2). When the reaction was performed at a lower temperature (185 °C) in the presence of the hexamethyldisilazane (entry 2), licochalcone A was obtained in 8% yield and the deprenylated product was obtained in 4% yield. The highest yield of licochalcone A (56%) without any deprenylation was obtained when *N*,*O*-bis(trimethylsilyl)acetamide [TMSN=C(Me)OTMS] was used as a trapping agent (entry 3).

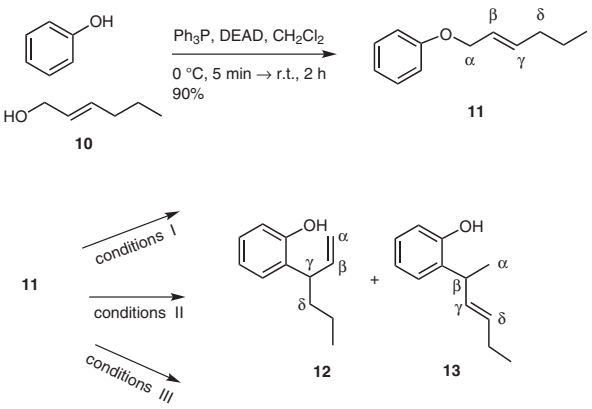
**Table 2** [3,3]-Sigmatropic Rearrangement Reaction of Chalcone **4** in the Presence of Silyl Agents

| Entry | Silyl agent[a] (equiv) | Temp (°C) | Time (h) | Yield[b] |
|---|---|---|---|---|
| 1 | HMDS (10) | 230 | 8.5 | - |
| 2 | HMDS (10) | 185 | 4.5 | 8 |
| 3 | TMSN=C(Me)OTMS (20) | 185 | 5.0 | 56 |

[a] The reaction was performed in a stainless-steel bomb with *N*,*N*-diethylaniline as the solvent.
[b] Yield after purification by silica gel chromatography.

Because we could not find any possible abnormal Claisen rearrangement products of **6** or licochalcone A, we examined another aromatic ether system **11**, which is known to be very vulnerable to the abnormal Claisen rearrangement reaction (Scheme 8 and Table 3).

The γ-alkyl substituted aryl ether (**11**), prepared by a phenolic Mitsunobu reaction,[18] underwent a water-accelerated [3,3]-sigmatropic rearrangement when subjected to microwave irradiation (300 W) for three hours to give the Claisen product **12** in 40% yield, without any of the abnormal rearranged product **13** (conditions I, entry 1). When the same solvent system was used in a stainless-steel bomb reactor (conditions II) at 130 °C for eight hours, the reaction was not successful (entry 2), but when the temperature was raised to 180 °C for five hours, the reaction proceeded well, giving 54% of **12** without any contamination by **13** (entry 3). As a control experiment, we prepared a genuine sample of **12** under Fukuyama conditions (conditions III, entry 4), which gave the same result




**Scheme 8** Test reaction for abnormal Claisen rearrangement. Conditions I: EtOH–$H_2O$ (4:1), MW (300 W); conditions II: EtOH–$H_2O$ (4:1), stainless-steel bomb reactor; conditions III: *N*,*N*-diethylaniline, TMSN=C(Me)OTMS (20 equiv) trapping agent.

as entry 3. We concluded that our water-accelerated Claisen reactions do not produce abnormal rearrangement products when the reaction is performed under microwave conditions or in a thermal bomb.

**Table 3** Study of Aromatic Claisen Rearrangement Reaction of **11**

| Entry | Conditions[a] | Temp (°C) | Time (h) | Ratio[b] (**12**/**13**) | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | I | 210 | 3 | 100:0 | 40 |
| 2 | II | 130 | 8 | – | – |
| 3 | II | 180 | 5 | 100:0 | 54 |
| 4 | III | 200 | 5 | 100:0 | 52 |

[a] For details, see the caption to Scheme 8.
[b] Determined by $^1$H NMR.
[c] Yield after purification by silica gel chromatography.

To summarize, we have developed a practical route to licochalcone A through the water-accelerated Claisen rearrangement reaction of prenyl ether **4**. This route will permit the scale-up of the synthesis of this promising lead molecule for various cancer treatments.[2] Because of the low overall yield of the previous multistep total synthesis with its low-yielding Claisen rearrangement step, this compounds was previously obtained mainly by extraction from the roots of *G. inflata*. The water-accelerated Claisen rearrangement in an ethanol–water cosolvent system should improve the crucial step of the synthesis without producing any deprenylated or abnormal Claisen-rearranged products.

All chemicals were purchased from Sigma-Aldrich Chemicals and were used without further purification unless noted otherwise. $^{13}$C NMR spectra were recorded on a Bruker Avance II 150-MHz FT-NMR spectrometer, whereas $^1$H NMR spectra were recorded on a Varian Mercury-300 MHz FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, and the coupling constants (*J*) are give in Hz. $CDCl_3$ was used as both a solvent and internal standard. IR spectra were recorded on a Shimadzu

IR-435 spectrometer. An Anthon Parr microwave synthesis system (Synthos-3000) equipped with a wireless pressure and temperature sensor was used, operating at a power of 300 W. The sample temperature was ramped to 210 °C for 1 min and kept at this temperature for the desired time while the pressure was increased to 40 bar. For GC/MS, an Agilent 7890A gas chromatograph linked to an Agilent 5975C mass spectrometer system equipped with a HP-5MS capillary column (30 m × 0.25 mm; 0.25 μm film thickness) was used. The GC oven temperature was programmed from 80 °C (3 min hold) at a rate of 10 °C/min to 300 °C (10 min hold); the inlet temperature was at 250 °C, and the sample-injection mode was splitless. The mass ion source was EI and the ionization voltage was 70 eV. The ion-source temperature was 280 °C and scan range was 50–500 *m/z*. The solvent delay time was 3 min. The CI mass spectra were recorded on a Jeol JMS-600 Mass spectrometer with methane as the reagent gas. The energy of the electron beam was 70 eV. Flash chromatography was carried out on Merck 60 silica gel (230–400 mesh). TLC was performed on DC-Plastikfolien 60, $F_{254}$ (Merck; layer thickness 0.2 mm) plastic-backed silica gel plates that were visualized with UV light (254 nm) or by staining with *p*-anisaldehyde.

**5-(1,1-Dimethylprop-2-en-1-yl)-4-hydroxy-2-methoxybenzaldehyde (6)**

***Method 1: Microwave Reaction; Typical Procedure***

Aryl prenyl ether **2** (230 mg, 1.05 mmol) was dissolved in EtOH–$H_2O$ (4:1 v/v) in the PTFE–TFM liner of an Anthon Parr MW synthesis system, the screw cap was tightened, and the vessel was subjected to irradiation at 300 W. After 1 min ramping time to 210 °C, the vessel was maintained at 210 °C and 40 bar for 1.5 h and then cooled to r.t. The screw cap was then loosened and the mixture was transferred to a 100-mL round-bottom flask. The solvent was then evaporated in vacuo. EtOAc (30 mL) was added and the organic phase was washed with deionized distilled $H_2O$ (20 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel, EtOAc–hexane (1:4)] to give a white solid; yield: 120 mg (52%); mp 194–196 °C (dec.).

***Method 2: Furnace Reaction; Typical Procedure***

Compound **2** (200 mg, 0.91 mmol) was dissolved in EtOH–$H_2O$ (4:1 v/v, 10 mL) in a 35-mL Ace pressure tube with PTFE bushes and an FETFE O-ring seal. The tube was then placed in an electric furnace at 130 °C for 24 h. When the tube had cooled to r.t., the screw-cap was loosened, and the contents were worked up in the same way as for the MW reaction; yield: 80 mg (40%).

The spectral data for the compound agreed well with those reported in the literature.[6,12b]

$R_f$ = 0.2 (EtOAc–hexane, 1:3).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 6 H), 3.87 (s, 3 H), 5.35 (dd, *J* = 10.8, 1.0 Hz, 1 H), 5.38 (dd, *J* = 17.6, 1.0 Hz, 1 H), 6.17 (dd, *J* = 17.6, 10.8 Hz, 1 H), 6.42 (s, 1 H), 6.60 (s, 1 H), 7.77 (s, 1 H), 10.27 (s, 1 H, CHO).

**(2*E*)-3-[5-(1,1-Dimethylprop-2-en-1-yl)-4-hydroxy-2-methoxyphenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one (Licochalcone A)**

***Method 1: Microwave Reaction***

Licochalcone A was prepared from compound **4** (131 mg, 0.39 mmol) by following the typical procedure given for compound **6**. The reaction time was 1.5 h. Purification by flash column chromatography [EtOAc–hexane (1:4)] gave an amorphous solid, yield: 114 mg, (86%).

***Method 2: Sealed-Tube Reaction***

Licochalcone A was prepared from compound **4** (248 mg, 0.73 mmol) by following the typical procedure given for compound **6**. The reaction time was 8 h. The product was purified by flash column chromatography [EtOAc–hexane (1:4)]; yield: 203 mg (82%).

***Method 3: [3,3]-Sigmatropic Reaction with a Silyl Reagent***

TMSN=C(Me)OTMS (0.5 mL, 2.13 mmol, 20 equiv), chalcone prenyl ether **4** (36 mg, 0.106 mmol), and $PhNEt_2$ (2 mL) were placed in a stainless-steel bomb. The bomb was tightly sealed, placed in an electric-furnace at 185 °C for 5 h, cooled to r.t., and disassembled. The crude mixture was transferred to a separatory funnel by washing with $Et_2O$ (50 mL). The organic phase was washed with 3 M HCl (2 × 20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography [silica gel, EtOAc–hexane (1:6)]; yield: 20 mg (56%).

The spectral data for this compound agreed well with the literature values.[1b]

$R_f$ = 0.2 (EtOAc–hexane, 1:2).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, 4″,5″-dimethyl), 3.90 (s, 3 H, OMe), 5.35 (d, *J* = 10.5 Hz, 1 H, $H''_3$), 5.40 (d, *J* = 17.1 Hz, 1 H, $H_3''$), 5.63 (br s, 1 H, OH), 6.20 (dd, *J* = 17.1, 10.4 Hz, 1 H, $H_2''$), 6.45 (s, 1 H, $H_3$), 6.93 (d, *J* = 8.1 Hz, 2 H, $H_3'$ and $H_5'$), 7.47 (s, 1 H, $H_6$), 7.57 (d, *J* = 15.9 Hz, 1 H, $H_\alpha$), 7.98 (d, *J* = 8.5 Hz, 2 H, $H_2'$, $H_6'$), 8.03 (d, *J* = 15.9 Hz, 1 H, $H_\beta$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 27.5, 27.5, 41.0, 56.0, 100.8, 110.7, 115.2, 115.7, 116.3, 119.3, 128.3, 130.1, 131.5, 132.0, 132.0, 142.3, 149.0, 160.5, 161.3, 163.4, 191.9.

**2-Methoxy-4-[(3-methylbut-2-en-1-yl)oxy]benzaldehyde (2)**

This compound was prepared according to the known procedure[12c,19] and obtained as a white solid, mp 47–50 °C;[20] $R_f$ = 0.30 (EtOAc–hexane, 1:3).

**(2*E*)-3-{2-Methoxy-4-[(3-methylbut-2-en-1-yl)oxy]phenyl}-1-[4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl]prop-2-en-1-one (9)**

A two-necked round-bottom flask was charged with a soln of aldehyde **2** (700 mg, 3.18 mmol) and ketone **8** (700 mg, 3.18 mmol) in EtOH (30 mL). NaOH (254 mg, 6.36 mmol) was added slowly and the mixture was stirred at r.t. for 12 h until the reaction was complete (TLC). The crude mixture was concentrated in vacuo and extracted with EtOAc. The organic phase was washed with $H_2O$ (10 mL) and brine (10 mL) then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (1:7)] to give an oily liquid; yield: 1087 mg (81%); $R_f$ = 0.36 (EtOAc–hexane, 1:4).

IR (neat): 3744, 2935, 2872, 2366, 1745, 1656, 1572, 1510 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.40–2.20 (m, 12 H), 3.62 (m, 1 H), 3.85 (m, 1 H), 3.88 (s, 3 H), 4.55 (d, *J* = 6.9 Hz, 2 H), 5.48 (m, 2 H), 5.52 (m, 1 H), 6.48 (d, *J* = 1.9 Hz, 1 H), 6.53 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 2 H, para protons), 7.54 (d, *J* = 15.6 Hz, 1 H, $H_\alpha$), 7.99 (d, *J* = 8.8 Hz, 2 H, para protons), 8.02 (d, *J* = 15.6 Hz, 1 H, $H_\beta$).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 18.1, 18.5, 25.0, 25.7, 30.0, 55.3, 61.9, 64.8, 95.8, 98.9, 105.8, 115.7, 116.9, 118.9, 119.8, 130.2, 130.4, 132.0, 138.3, 139.3, 159.9, 160.2, 161.8, 189.0.

MS (ESI, 70 eV): *m/z* 423.6 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{31}O_5$: 423.2093; found: 423.2172.

**(2*E*)-1-(4-Hydroxyphenyl)-3-{2-methoxy-4-[(3-methylbut-2-en-1-yl)oxy]phenyl}prop-2-en-1-one (4)**

1 M HCl (100 μL) was added to a soln of ketone **9** (500 mg, 1.19 mmol) in EtOH (5 mL) in a one-necked round-bottom flask, and the mixture was stirred at r.t. for 0.5 h until the reaction was complete (TLC). Sat. aq $NaHCO_3$ was then added until the pH was almost

neutral (pH paper). The solvent was evaporated under reduced pressure and the crude mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with $H_2O$ (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, EtOAc–hexane (1:5)] to give a yellowish solid; yield: 382 mg (95%); mp 95–96 °C (Lit.[12a] 94–95 °C); $R_f$ = 0.3 (EtOAc–hexane, 1:2).

The spectral data for this compound agreed well with those reported in the literature.[12a]

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 1.73 (s, 3 H), 1.75 (s, 3 H), 3.88 (s, 3 H), 4.60 (d, $J$ = 7 Hz, 2 H), 5.43 (m, 1 H), 6.60 (d, $J$ = 8 Hz, 2 H), 6.87 (d, $J$ = 8 Hz, 2 H), 7.70 (d, $J$ = 16 Hz, 1 H, $H_\alpha$), 7.85 (d, $J$ = 8 Hz, 1 H), 7.92 (d, $J$ = 16 Hz, 1 H, $H_\beta$), 7.99 (d, $J$ = 8 Hz, 2 H), 10.31 (br s, 1 H, OH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 17.9, 25.3, 55.6, 64.5, 98.7, 106.6, 115.0, 115.7, 118.8, 119.3, 129.2, 129.5, 130.5, 137.2, 159.3, 161.5, 161.6, 161.8, 186.8.

**[(2*E*)-Hex-2-en-1-yloxy]benzene(11): Test Reaction for Checking Abnormal Claisen Rearrangement Reaction**

A two-necked round-bottomed flask was charged with PhOH (516 mg, 5.48 mmol), (*E*)-hex-2-en-1-ol (692 mg, 6.91 mmol), $Ph_3P$ (1.87 g, 7.13 mmol), a 40% soln of DEAD in toluene (3.25 mL, 7.13 mmol), and anhyd $CH_2Cl_2$ (15 mL) with cooling in an ice bath (4 °C). The mixture was stirred for an additional 5 min at 4 °C and then gradually warmed to r.t. and stirred for 2 h. It was then transferred to a separatory funnel and the organic phase was washed with brine (20 mL) then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (1:20)] to give an oily liquid; yield: 869 mg (90%); $R_f$ = 0.70 (EtOAc–hexane, 1:10).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.50 (m, 2 H), 6.90–7.00 (m, 3 H), 5.75–5.90 (m, 1 H), 5.60–5.75 (m, 1 H), 4.44–4.47 (dd, $J$ = 5.7, 1.2 Hz, 2 H), 2.03–2.10 (m, 2 H), 1.36–1.49 (m, 2 H), 0.88–0.93 (t, $J$ = 7.5 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.2, 34.5, 68.7, 114.5, 120.4, 124.8, 129.3, 135.3, 158.5.

**2-(1-Propylprop-2-en-1-yl)phenol (12)**

***Method 1: MW reaction***

The compound was prepared according to the typical procedure described above for compound **6**. The reaction time was 3 h. Purification by flash column chromatography [silica gel, EtOAc–hexane (1:8)] gave an oily liquid; yield: 40 mg (40%); $R_f$ = 0.2 (EtOAc–hexane, 1:8).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.05–7.20 (m, 2 H), 6.72–6.84 (d, $J$ = 7.8 Hz, 1 H). 5.90–6.60 (m, 2 H), 4.95–5.20 (m, 1 H), 5.00 (s, 1 H, OH), 3.49–3.56 (m, 1 H), 1.70–1.77 (m, 2 H), 1.23–1.39 (m, 2 H), 0.89–0.94 (t, $J$ = 7.5 Hz, 3 H).

$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 14.0, 20.7, 35.5, 43.5, 114.8 (vinylic C=C), 116.2, 120.9, 127.4, 128.5, 129.5, 141.5 (vinylic C=C), 153.7.

***Method 2: Stainless Steel Bomb Reaction***

A soln of ether **11** (123 mg, 0.70 mmol) in EtOH–$H_2O$ (4:1 v/v, 3 mL) was placed in a stainless-steel bomb reactor that was placed inside an electric furnace at 180 °C and heated for 5 h, then cooled to r.t. The reactor was disassembled and the product was worked up as described for the MW reaction; yield: 67 mg (54%). The $R_f$ value and $^1$H NMR spectrum were identical to those of the compound obtained under MW conditions.

***Method 3: [3,3]-Sigmatropic reaction with silyl agent***

TMSN=C(Me)OTMS (2.38 mL, 9.65 mmol, 20 equiv), ether **11** (85 mg, 0.48 mmol), and $PhNEt_2$ (2 mL) were placed in a stainless-steel bomb that was tightly closed and heated in an electric furnace at 200 °C for 5 h. The bomb was then cooled to r.t. and disassembled. The crude mixture was transferred to separatory funnel by washing with $Et_2O$ (50 mL). The organic phase was washed with 3 M HCl (20 mL × 2) and brine (20 mL) then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography [silica gel, EtOAc–hexane (1:8)] to give an oily liquid; yield: 44 mg (52%). The $R_f$ value and $^1$H NMR spectrum were identical to those of compound obtained under MW conditions.

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