Efficient Total Synthesis of Racemic Bisabolane Sesquiterpenes Curcuphenol and Xanthorrhizol Starting from Substituted Acetophenones

by **Luisa E. Montiel**, **L. Gerardo Zepeda**, and **Joaquín Tamariz***

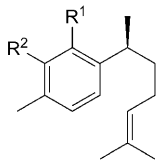
Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala, 11340 México, D. F. Mexico
(phone/fax: +52-55-57296300/46211; e-mail: jtamariz@woodward.encb.ipn.mx; jtamarizm@gmail.com)

A total synthesis of natural bisabolane sesquiterpenes curcuphenol (**1**) and xanthorrhizol (**2**) was developed by using the substituted acetophenones **4** and **5**, respectively, as starting materials. The acetyl group of the latter was activated through ethoxycarbonylation to carry out the prenylation, which was performed successfully to give their respective precursors **11a** and **11b**, and **21** that were converted into the corresponding natural sesquiterpenes **1** and **2**, respectively, over four steps and in high overall yields.

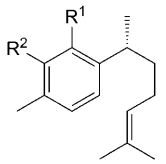
1. Introduction. – Curcuphenol (**1**) and xanthorrhizol (**2**) are naturally occurring bioactive bisabolane sesquiterpenes isolated from diverse sources. For instance, while compound (+)-(*S*)-**1** has been isolated from the marine sponges *Didiscus flavus*, *Didiscus aceratus*, *Didiscus oxeata*, *Epipolasis species*, and *Myrmekioderma styx* [1], among other genera [1d], or from the Taiwanese gorgonian coral *Echinomuricea* sp. [2], its enantiomer (−)-(*R*)-**1** has been extracted from the Caribbean gorgonian coral *Pseudopterogorgia rigida* [3], and from the plant *Lasianthaea podocephala* [4]. In the case of xanthorrhizol (**2**), only its enantiomer (−)-(*R*)-**2** has been isolated from natural sources, as constituent of rhizomes of *Curcuma xanthorrhiza* [5], and from the Mexican medicinal plant *Iostephane heterophylla* [6]. These compounds have significant biological activities. Curcuphenol (**1**) exhibits antibacterial activity against *Staphylococcus aureus*, *Candida albicans*, and *Vibrio anguillarum* [1][3], is an inhibitor of gastric H,K-ATPase, and has antitumor, antimalarial, antifungal, and antidiabetes activities [1b][1c][7]. Xanthorrhizol (**2**) inhibits cytochrome P-450 [8], has anticancer activity [9], potent antibacterial activity against a series of *Gram*-positive and *Gram*-negative bacteria [10], and potent *in vitro* anticandidal activity [11], as well as antioxidant and anti-inflammatory activities [12]. In accordance with their pharmacological potential, compounds **1** and **2** have attracted particular interest, and many racemic [13][1]) and asymmetric [14][2]) total syntheses have been reported.

In a preliminary report, we described a novel synthetic method for the introduction of the prenyl side chain of the bisabolane scaffold, which was applied in the total synthesis of (±)-α-curcumene (**3**) [15]. With the aim of improving our methodology and of establishing it as a new general synthetic approach to bisabolane compounds, we

[1]) For curcuphenol (**1**), see [13a–13c], for xanthorrhizol (**2**), see [13d–13f].
[2]) For curcuphenol (**1**), see [14a–14f], for xanthorrhizol (**2**), see [14g–14i].



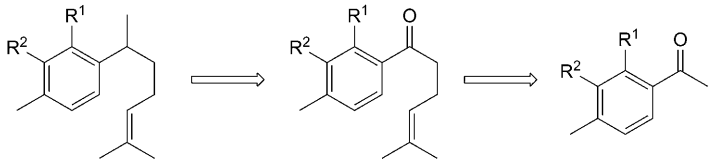
	R^1	R^2
(+)-(*S*)-**1**	OH	H
(+)-(*S*)-**2**	H	OH
(+)-(*S*)-**3**	H	H



	R^1	R^2
(–)-(*R*)-**1**	OH	H
(–)-(*R*)-**2**	H	OH
(–)-(*R*)-**3**	H	H

herein present the synthesis of racemic sesquiterpenes **1** and **2**. This approach is based on the direct prenylation of the properly activated 4-methylacetophenones **4** and **5**, the corresponding products of which, **6** and **7**, were converted to the desired racemic products **1** and **2**, respectively (*Scheme 1*).

Scheme 1



	R^1	R^2
1	OH	H
2	H	OH

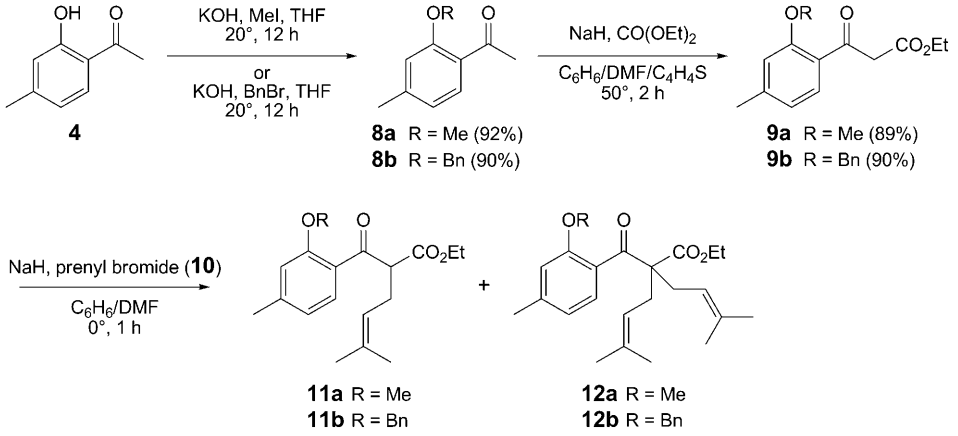
	R^1	R^2
6	OH	H
7	H	OH

	R^1	R^2
4	OH	H
5	H	OH

2. Results and Discussion. – 2.1 *Total Synthesis of* (±)-*Curcuphenol* (**1**). To achieve the appropriate functionalization of acetophenone **4**, which is commercially available, through the proposed strategy, the OH group had to be protected. We investigated two common protecting groups that are resistant to the presence of strong bases, nucleophiles, and hydrides: the Me and benzyl (Bn) groups. Thus, starting from **8a** and **8b**, we evaluated the efficacy of the route in each case. These acetophenones were readily prepared from **4** by reaction with KOH, and treatment either with MeI or BnBr to afford ethers **8a** and **8b**, respectively, in high yields (> 90%; *Scheme 2*).

Since every attempt to directly introduce the prenyl (= 3-methylbut-2-en-1-yl) side chain into these acetophenones under basic conditions failed to provide the desired products, **6a** or **6b**, the Ac group had to be activated by ethoxycarbonylation. This is not a straightforward functionalization process, because the treatment of the substrate with a base and diethyl carbonate ($CO(OEt)_2$) fails to give the desired product. That is the reason why the procedure reported by *Manjarrez et al.* [16] was a very useful method. Thus, the reaction between the acetophenone **8a** and $CO(OEt)_2$ was carried out in the presence of NaH as the base, and a mixture of benzene/DMF/thiophene 2 : 1 : 0.5 as the solvent, affording β-keto ester **9a** in a modest yield of *ca.* 50% (*Scheme 2*). Actually, the yield was drastically improved (89%), when the reaction was carried out by heating the mixture at 50° for 2 h, in contrast to our previous study in which the reaction took place

Scheme 2



at room temperature to give a moderate yield (51%) of the expected product [15]. Although the role of thiophene in the reaction has not yet been clearly understood, this reagent is crucial for accomplishing the reaction, since, in its absence, the reaction does not take place. A similar result was obtained for the derivative **8b**, which provided the β-keto ester **9b** in 90% yield.

Once we had the activated derivatives **9** to conduct the prenylation reaction with prenyl bromide (=1-bromo-3-methylbut-2-ene; **10**), every attempt to prepare compounds **11a** or **11b** was unsuccessful under analogous conditions as previously used in the synthesis of **3** [15], since the bis-prenylated products **12a** or **12b**, respectively, were isolated as a single product (*Scheme 2*, and *Table*, *Entries 1* and *2*). Even by decreasing the amount of **10**, the crude reaction mixture was also largely contaminated by **12** (*Table*, *Entries 3* and *4*). The desired compounds **11a** and **11b** were finally obtained as the main products by reducing the temperature to 0° (*Table*, *Entries 5* and *6*). Even though the bis-prenyl derivatives **12a** or **12b** could never be avoided completely in the reaction mixtures, they were easily separated by column chromatography.

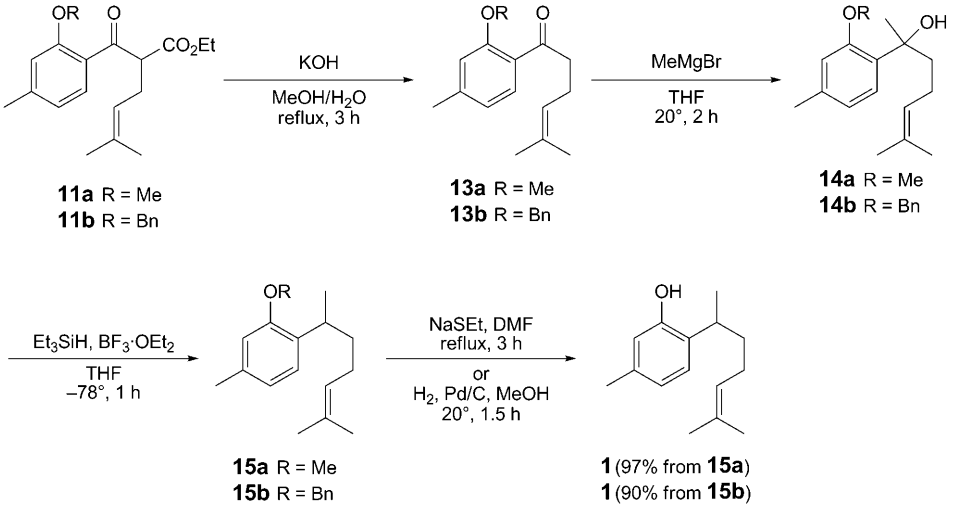
Table. *Reaction Conditions for the Prenylation of Substrates* **9a** *and* **9b**[a])

Entry	Substrate	**10** [mol-equiv.]	NaH [mol-equiv.]	*T* [°]	Time [min]	**11**/**12** [%][b])
1	**9a**	2.0	2.5	50	45	**11a** (0)/**12a** (88)
2	**9b**	2.0	2.5	50	45	**11b** (0)/**12b** (90)
3	**9a**	1.2	1.5	20	30	**11a** (20)/**12a** (30)
4	**9b**	1.2	1.5	20	30	**11b** (15)/**12b** (26)
5	**9a**	1.2	1.0	0	60	**11a** (86)/**12a** (7)
6	**9b**	1.2	1.0	0	60	**11b** (92)/**12b** (5)

[a]) Benzene/DMF 2 : 1, N_2 atmosphere. [b]) Determined as isolated products after purification by column chromatography.

Ketone **13a** was obtained in high yield by hydrolysis of compound **11a** under basic conditions (*Scheme 3*). Similarly, the preparation of derivative **13b** was achieved satisfactorily by carrying out the process according to the same procedure. The C=O group was transformed into the required Me group of the natural sesquiterpene by a simple and efficient methodology: *a*) addition of the *Grignard* reagent; and *b*) reduction of the benzylic alcohol with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ [13a][17]. Under these conditions, hydrocarbon precursors **15a** and **15b** were obtained starting from ketones **13a** and **13b**, respectively, in high overall yields (*Scheme 3*). Tertiary alcohols **14a** and **14b** were isolated as stable intermediates after the addition of the *Grignard* reagent.

Scheme 3

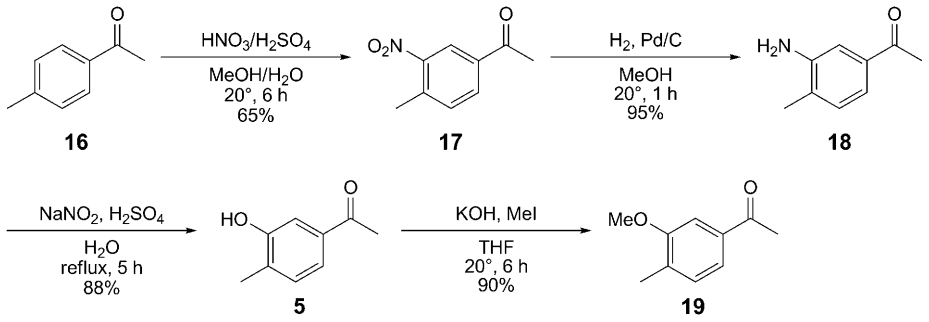


Finally, to carry out the deprotection of **15a**, two methods were applied. The use of BBr_3 [18] at 0° for 12 h led to the natural product **1** in 70% yield. However, the conversion was almost quantitative, when NaSEt was employed at high temperature (140°) [5a][13a][14f][14g][14h] (*Scheme 3*). Curcuphenol (**1**) was also obtained by deprotection of **15b** through Pd-catalyzed hydrogenolysis in a slightly lower yield than by the previous method. The structures of **1** and each intermediate were established by IR, ^{1}H- and ^{13}C-NMR spectroscopy, assisted by 2D experiments, and high-resolution mass spectrometry. Spectral data of **1** were in agreement with those reported for the natural and synthetic compound [1b][3][14d][14h].

2.2 *Total Synthesis of* (±)-*Xanthorrhizol* (**2**). 2.2.1 *Preparation of Acetophenone* **5**. Since acetophenone **5** is not commercially available, we decided to develop an alternative approach to that already reported [19] for the synthesis of **5**, which resulted in an economical and efficient starting material for the total synthesis of xanthorrhizol (**2**). Actually, compound **5** is a natural product isolated from the red seaweed *Laurencia chilensis*, which exhibits moderate antimicrobial activity [20]. The first step in its preparation consisted of the nitration of 4-methylacetophenone (**16**), under typical conditions by treatment with a mixture of HNO_3 and H_2SO_4, to furnish the nitro

derivative **17** [21] in moderate yield (*Scheme 4*). Although the reduction of the NO_2 group with NaSH provided 3-aminoacetophenone **18** [21] in good yield (80%), the reaction was improved (95%) by hydrogenation. The latter was converted into the diazonium salt, followed by substitution with H_2O, to yield the desired 3-hydroxyacetophenone **5** in 54% overall yield starting from **16**.

Scheme 4



2.2.2 *Synthesis of* (±)-*Xanthorrhizol* (**2**). The approach using the protecting Me group was slightly more efficient in the synthesis of **1** than that using the Bn group. Moreover, the purification procedures were easier, and the loss of weight in the final deprotection step was lower. Consequently, we chose this protecting group for the synthesis of **2**. Acetophenone **5** was protected with MeI to give **19** in good yield (*Scheme 4*). The latter was ethoxycarbonylated to afford the β-keto ester **20**, which was prenylated under the optimal conditions found in the synthesis of **1**, in order to avoid the formation of the bis-alkylated compound. Thus, the mono-prenylated compound **21** was isolated as the major product in high yield (*Scheme 5*). Decarboxylation of the latter under standard conditions led to ketone **22**, which underwent addition of the *Grignard* reagent to give alcohol **23**. Final reduction of the tertiary alcohol and deprotection, under the same conditions as those for **1**, afforded the naturally occurring xanthorrhizol (**2**) as a racemate over six steps and in 60% overall yield, starting from acetophenone **19**. Spectroscopic data of some precursors and the final product are in agreement with those reported for the natural and synthetic compounds [4a][14h][14i] (see *Exper. Part*).

3. Conclusions. – New total syntheses of the naturally occurring bisabolane sesquiterpenes curcuphenol (**1**) and xanthorrhizol (**2**) as racemates in high overall yields were described, starting from the properly substituted acetophenones, **8a** and **8b**, and **19**. The key step of this new approach was based on the activation of the latter compounds with the ethoxycarbonyl group, in order to introduce the prenyl side chain. The application of this strategy to the asymmetric synthesis of these and other natural sesquiterpenes is currently under investigation, and the results will be described in due course.

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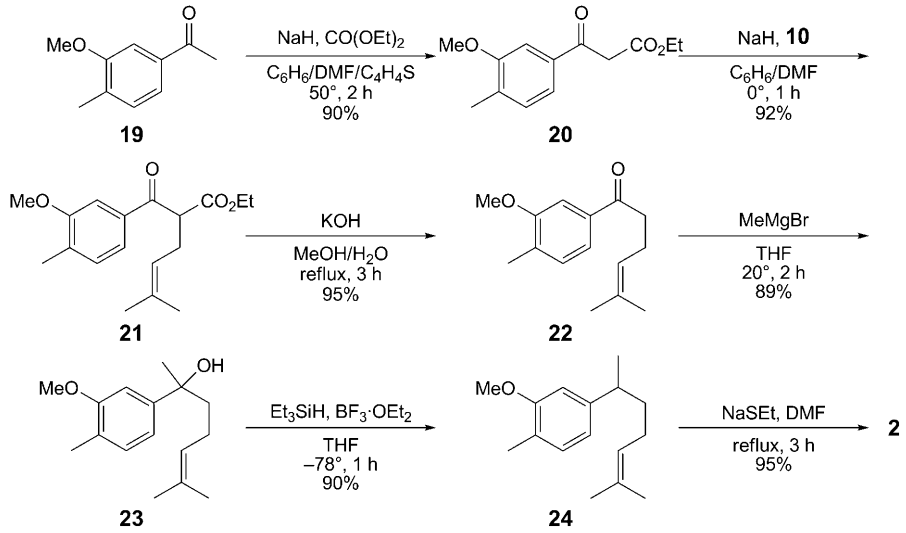
Scheme 5



20080527, 20090519, and 20100236) and *CONACYT* (Grants 43508-Q and 83446) for financial support. *L. E. M.* thanks *CONACYT* for a scholarship, and *SIP/IPN* for a scholarship complement. *L. G. Z.* and *J. T.* are fellows of the *EDI-IPN* and *COFAA-IPN* programs.

Experimental Part

General. Anal TLC: *E. Merck* silica-gel *60 F254*-coated plates were visualized by a long- and short-wavelength UV lamp. All air moisture-sensitive reactions were carried out under N_2 in oven-dried glassware. Benzene and THF were freshly distilled over Na, and CH_2Cl_2 and DMF over CaH_2. All other reagents were used without further purification. M.p.: *Electrothermal* cap. melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer 2000* spectrophotometer. ^{1}H- (300 and 500 MHz) and ^{13}C-NMR (75.4 and 125 MHz) spectra: *Varian Mercury-300* and *VNMR-500* instruments in $CDCl_3$, with Me_4Si as internal standard. MS: EI mode (70 eV); *Thermo-Finnigan Polaris Q* spectrometer. HR-MS: FAB (*m*NBA) and CI (CH_4), and EI (70 eV) modes; *Jeol JMS-AX 505 HA* and *Jeol JSM-GCMateII* spectrometers.

1-(2-Methoxy-4-methylphenyl)ethanone (**8a**) [22]. To a stirred mixture of KOH (0.28 g, 5.0 mmol) and **4** (0.50 g, 3.33 mmol) in THF (4 ml), at 20° under N_2, MeI (1.18 g, 8.31 mmol) was added dropwise, and the mixture was stirred for 12 h at the same temp. The mixture was diluted with CH_2Cl_2 (15 ml) and washed with a sat. aq. NH_4Cl soln. (2 × 8 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (20 g); hexane/AcOEt 98:2) to give **8a** (0.503 g, 92%). White solid. R_f (hexane/AcOEt 8:2) 0.47. M.p. 37–38° ([23]: 35–36°). IR (CH_2Cl_2): 1670, 1607, 1465, 1410, 1357, 1288, 1259, 1239, 1169, 1035, 815. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.38 (*s*, *Me*C$_6$H$_3$); 2.59 (*s*, *Me*CO); 3.89 (*s*, MeO); 6.76 (br. *s*, H–C(3′)); 6.80 (*dm*, *J* = 7.8, H–C(5′)); 7.68 (*d*, *J* = 7.8, H–C(6′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 21.8 (*Me*C$_6$H$_3$); 31.8 (*Me*CO); 55.3 (MeO); 112.2 (C(3′)); 121.3 (C(5′)); 125.3 (C(1′)); 130.5 (C(6′)); 144.8 (C(4′)); 159.1 (C(2′)); 199.2 (CO). EI-MS (70 eV): 165 (100, $[M+1]^+$), 164 (22, M^+), 150 (12), 149 (36), 135 (4), 106 (4), 91 (7). HR-EI-MS: 164.0838 (M^+, $C_{10}H_{12}O_2^+$; calc. 164.0837).

1-[2-(Benzyloxy)-4-methylphenyl]ethanone (**8b**). Following the procedure as for **8a**, with KOH (0.28 g, 5.0 mmol), **4** (0.50 g, 3.33 mmol), and BnBr (1.71 g, 0.01 mol): **8b** (0.72 g, 90%). White solid. R_f (hexane/AcOEt 8:2) 0.56. M.p. 56–57° ([22]: 53°). IR (CH_2Cl_2): 1663, 1607, 1567, 1493, 1453, 1416, 1381,

1289, 1252, 1242, 1171, 1137, 1020, 822. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.34 (*s*, *Me*C_6H_3); 2.55 (*s*, *Me*CO); 5.10 (*s*, PhCH_2); 6.78–6.81 (*dm*, *J* = 8.1, H–C(5′)); 6.82 (br. *s*, H–C(3′)); 7.29–7.45 (*m*, 5 arom. H); 7.69 (*d*, *J* = 8.1, H–C(6′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 21.7 (*Me*C_6H_3); 31.9 (*Me*CO); 70.4 (Ph*C*H_2); 113.3 (C(3′)); 121.5 (C(5′)); 125.6 (C(1′)); 127.4 (2 arom. C); 128.0 (arom. C); 128.5 (2 arom. C); 130.4 (C(6′)); 136.1 (arom. C); 144.6 (C(4′)), 158.1 (C(2′)); 198.9 (CO). EI-MS (70 eV): 241 (6, $[M + 1]^+$), 240 (5, M^+), 225 (12), 222 (14), 135 (18), 91 (100), 65 (18). HR-EI-MS: 240.1146 (M^+, $C_{16}H_{16}O_2^+$; calc. 240.1150).

Ethyl 3-(2-Methoxy-4-methylphenyl)-3-oxopropanoate (**9a**). To a stirred mixture of NaH (0.183 g, 7.625 mmol) and $CO(OEt)_2$ (0.719 g, 6.093 mmol) in a dry mixture of benzene/DMF/thiophene 2 : 1 : 0.5 (5 ml), at 20° under N_2, **8a** (0.500 g, 3.048 mmol) was added dropwise, and the mixture was heated to 50° and kept for 2 h at this temp. The mixture was diluted with CH_2Cl_2 (20 ml), and washed with a sat. aq. NH_4Cl soln. (2 × 10 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (20 g); hexane/AcOEt 98 : 2) to give **9a** (0.642 g, 89%). Pale yellow oil. R_f (hexane/AcOEt 8 : 2) 0.36. IR (film): 1739, 1668, 1607, 1496, 1465, 1410, 1325, 1263, 1197, 1168, 1125, 1034, 813. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, *J* = 7.2, *Me*CH_2O); 2.38 (*s*, *Me*C_6H_3); 3.87 (*s*, MeO); 3.93 (*s*, CH_2(2)); 4.17 (*q*, *J* = 7.2, MeCH_2); 6.76 (br. *s*, H–C(3′)); 6.82 (*dm*, *J* = 8.1, H–C(5′)); 7.79 (*d*, *J* = 8.1, H–C(6′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 14.0 (*Me*CH_2O); 21.8 (*Me*C_6H_3); 50.5 (C(2)); 55.0 (MeO); 60.7 (Me*C*H_2O); 112.0 (C(3′)); 121.6 (C(5′)); 123.3 (C(1′)); 130.9 (C(6′)); 145.9 (C(4′)), 159.1 (C(2′)); 168.2 (*C*O_2Et); 192.3 (Ar*C*O). EI-MS (70 eV): 166 (70, $[M - 70]^+$), 151 (94), 149 (45), 135 (18), 123 (42), 121 (100), 108 (23), 91 (52), 77 (30). HR-EI-MS: 236.1045 (M^+, $C_{13}H_{16}O_4^+$; calc. 236.1049).

Ethyl 3-[2-(Benzyloxy)-4-methylphenyl]-3-oxopropanoate (**9b**). Following the procedure as for **9a**, with NaH (0.150 g, 6.250 mmol), **8b** (0.500 g, 2.083 mmol), and $CO(OEt)_2$ (0.491 g, 4.162 mmol): **9b** (0.585 g, 90%). Pale yellow oil. R_f (hexane/AcOEt 8 : 2) 0.40. IR (CH_2Cl_2): 1738, 1668, 1606, 1496, 1415, 1325, 1259, 1195, 1169, 1024, 812, 735, 698. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (*t*, *J* = 7.0, *Me*CH_2O); 2.36 (*s*, *Me*C_6H_3); 3.95 (*s*, CH_2(2)); 4.07 (*q*, *J* = 7.0, MeCH_2); 5.15 (*s*, PhCH_2); 6.81 (br. *s*, H–C(3′)); 6.84 (*dm*, *J* = 8.1, H–C(5′)); 7.33–7.46 (*m*, 5 arom. H); 7.79 (*d*, *J* = 8.1, H–C(6′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 14.0 (*Me*CH_2O); 21.9 (*Me*C_6H_3); 50.5 (C(2)); 60.8 (Me*C*H_2); 70.6 (Ph*C*H_2); 113.4 (C(3′)); 122.0 (C(5′)); 124.3 (C(1′)); 127.6 (arom. C); 128.3 (2 arom. C); 128.7 (2 arom. C); 131.2 (C(6′)); 135.9 (arom. C); 145.8 (C(4′)); 158.4 (C(2′)); 168.3 (*C*O_2Et); 192.9 (Ar*C*O). EI-MS (70 eV): 313 (1, $[M + 1]^+$), 240 (4), 225 (12), 197 (8), 135 (18), 91 (100), 65 (22).

Ethyl 2-[(2-Methoxy-4-methylphenyl)carbonyl]-5-methylhex-4-enoate (**11a**) *and Ethyl 2-[(2-Methoxy-4-methylphenyl)carbonyl]-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-enoate* (**12a**). To a stirred suspension of NaH (0.061 g, 2.542 mmol) in a dry mixture of benzene/DMF 2 : 1 (5 ml), at 0° under N_2, a soln. of **9a** (0.600 g, 2.542 mmol) in dry benzene (2 ml) was added dropwise. After stirring at 0° for 10 min, **10** (0.455 g, 3.054 mmol) was added, and the mixture was stirred at 0° for 1 h. The mixture was diluted with CH_2Cl_2 (10 ml), and washed with a sat. aq. NH_4Cl soln. (2 × 10 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (25 g); hexane/AcOEt 98 : 2), to give 0.668 g (86%) of **11a** and 0.066 g (7%) of **12a**.

Data of **11a**. Pale yellow oil. R_f (hexane/AcOEt 8 : 2) 0.51. IR (CH_2Cl_2): 1736, 1672, 1608, 1572, 1496, 1464, 1409, 1256, 1168, 1126, 1035, 825. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.0, *Me*CH_2); 1.60 (br. *s*, *Me*C=); 1.65 (br. *s*, *Me*C=); 2.38 (*s*, *Me*C_6H_3); 2.57–2.68 (*m*, CH_2CH=); 3.86 (*s*, MeO); 4.08–4.17 (*m*, MeCH_2); 4.28 (*t*, *J* = 7.3, CH_2(2)); 5.09–5.14 (*m*, CH_2C*H*=); 6.74 (br. *s*, H–C(3′)); 6.81–6.83 (*dm*, *J* = 7.8, H–C(5′)); 7.67 (*d*, *J* = 7.8, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.1 (*Me*CH_2O); 17.7 (*Me*C=); 21.9 (*Me*C_6H_3); 25.7 (*Me*C=); 27.6 (*C*H_2CH=); 55.1 (MeO); 58.6 (C(2)); 60.7 (Me*C*H_2); 112.0 (C(3′)); 121.1 (CH_2*C*H=); 121.7 (C(5′)); 124.5 (C(1′)); 131.2 (C(6′)); 133.6 (Me_2*C*=); 145.2 (C(4′)); 158.5 (C(2′)); 170.5 (*C*O_2Et); 195.9 (Ar*C*O). EI-MS (70 eV): 305 (3, $[M + 1]^+$), 225 (22), 222 (24), 197 (12), 135 (18), 91 (100), 65 (22). HR-EI-MS: 304.1676 (M^+, $C_{18}H_{24}O_4^+$; calc. 304.1675).

Data of **12a**. Pale yellow oil. R_f (hexane/AcOEt 8 : 2) 0.60. IR (CH_2Cl_2): 1736, 1670, 1608, 1462, 1408, 1288, 1272, 1218, 1178, 1168, 1129, 1059, 1035, 938, 819. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.13 (*t*, *J* = 7.0, *Me*CH_2); 1.45 (br. *s*, 2 *Me*C=); 1.62 (br. *s*, *Me*C=); 2.36 (*s*, 2 *Me*C_6H_3); 2.56 (*dd*, *J* = 15.5, 7.5, 2 H of 2 CH_2CH=); 2.74 (*dd*, *J* = 15.5, 7.5, 2 H of 2 CH_2CH=); 3.77 (*s*, MeO); 4.07 (*q*, *J* = 7.0, MeCH_2O); 4.90–4.95 (*m*, 2 CH_2C*H*=); 6.69 (br. *s*, H–C(3′)); 6.79 (*dm*, *J* = 8.0, H–C(5′)); 7.52 (*d*, *J* = 8.0, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0 (*Me*CH_2); 17.6 (2 *Me*C=); 21.7 (*Me*C_6H_3); 26.0 (2 *Me*C=); 30.7

(2 *C*H_2CH=); 54.2 (MeO); 60.4 (Me*C*H_2); 62.5 (C(2)); 111.7 (C(3′)); 118.7 (2 CH_2*C*H=); 121.6 (C(5′)); 125.1 (C(1′)); 131.3 (C(6′)); 134.3 (2 Me_2*C*=); 143.9 (C(4′)); 157.0 (C(2′)); 171.7 (*C*O_2Et); 198.9 (Ar*C*O). EI-MS (70 eV): 373 (2, $[M+1]^+$), 303 (26), 257 (16), 181 (14), 149 (100), 135 (38), 109 (18), 91 (20), 77 (6). HR-FAB-MS: 373.2362 ($[M+1]^+$, $C_{23}H_{33}O_4^+$; calc. 373.2379).

Ethyl 2-{[2-(Benzyloxy)-4-methylphenyl]carbonyl}-5-methylhex-4-enoate (**11b**) *and Ethyl 2-{[2-(Benzyloxy)-4-methylphenyl]carbonyl}-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-enoate* (**12b**). Following the procedure as for **11a**/**12a**, with NaH (0.046 g, 1.917 mmol), **9b** (0.600 g, 1.923 mmol), and **10** (0.346 g, 2.322 mmol), 0.67 g (92%) of **11b** and 0.045 g (5%) of **12b** were obtained.

Data of **11b**. Pale yellow oil. R_f 0.52 (hexane/AcOEt 8:2). IR (CH_2Cl_2): 1734, 1671, 1606, 1496, 1454, 1414, 1240, 1169, 1123, 1019, 821, 732, 696. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.11 (*t*, *J* = 7.0, *Me*CH_2); 1.54 (br. *s*, *Me*C=); 1.58 (br. *s*, *Me*C=); 2.34 (*s*, *Me*C_6H_3); 2.57 (*tm*, *J* = 7.5, CH_2CH=); 3.99–4.09 (*m*, MeCH_2); 4.46 (*t*, *J* = 7.5, CH_2(2)); 4.90–4.95 (*m*, CH_2C*H*=); 5.15 (s, PhCH_2); 6.78 (br. *s*, H–C(3′)); 6.81 (*dm*, *J* = 8.0, H–C(5′)); 7.32–7.44 (*m*, 5 arom. H); 7.61 (*d*, *J* = 8.0, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0 (*Me*CH_2); 17.6 (*Me*C=); 21.9 (*Me*C_6H_3); 25.7 (*Me*C=); 27.6 (*C*H_2CH=); 58.2 (C(2)); 60.7 (Me*C*H_2O); 70.5 (Ph*C*H_2); 113.4 (C(3′)); 120.9 (CH_2*C*H=); 121.9 (C(5′)); 125.3 (C(1′)); 127.5 (2 arom. C); 128.2 (arom. C); 128.6 (2 arom. C); 131.1 (C(6′)); 133.6 (Me_2*C*=); 136.1 (arom. C); 144.8 (C(4′)); 157.5 (C(2′)); 170.3 (*C*O_2Et); 196.8 (Ar*C*O). EI-MS (70 eV): 308 (12, $[M-C_3H_4O_2]^+$), 223 (24), 217 (56), 135 (100), 121 (40), 105 (16). HR-FAB-MS: 381.2064 ($[M+1]^+$, $C_{24}H_{29}O_4^+$; calc. 381.2066).

Data of **12b**. Pale yellow oil. R_f 0.46 (hexane/AcOEt 8:2). IR (CH_2Cl_2): 1733, 1695, 1608, 1496, 1454, 1413, 1378, 1289, 1272, 1219, 1177, 1129, 1059, 1027, 938, 818, 735, 697. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.09 (*t*, *J* = 7.0, *Me*CH_2); 1.45 (br. *s*, 2 *Me*C=); 1.60 (br. *s*, 2 *Me*C=); 2.66 (*s*, *Me*C_6H_3); 2.60 (*dd*, *J* = 15.5, 7.5, 2 H of 2 CH_2CH=); 2.76 (*dd*, *J* = 15.5, 7.5, 2 H of 2 CH_2CH=); 4.12 (*q*, *J* = 7.0, MeCH_2); 4.93–4.97 (*m*, 2 CH_2C*H*=); 5.19 (*s*, PhCH_2); 6.65 (br. *s*, H–C(3′)); 6.75 (*dm*, *J* = 8.0, H–C(5′)); 7.26–7.30 (*m*, 1 arom. H); 7.34–7.39 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.9 (*Me*CH_2); 17.7 (2 *Me*C=); 21.7 (*Me*C_6H_3); 26.0 (2 *Me*C=); 31.0 (2 *C*H_2CH=); 60.7 (Me*C*H_2); 62.8 (C(2)); 69.8 (Ph*C*H_2); 113.5 (C(3′)); 118.7 (2 CH_2*C*H=); 121.6 (C(5′)); 126.3 (C(1′)); 126.7 (2 arom. C); 127.7 (arom. C); 128.6 (2 arom. C); 130.1 (C(6′)); 134.5 (2 Me_2*C*=); 136.8 (arom. C); 143.1 (C(4′)); 156.2 (C(2′)); 171.8 (*C*O_2Et); 200.1 (Ar*C*O). EI-MS (70 eV): 357 (2, $[M-91]^+$), 303 (20), 257 (14), 225 (8), 181 (22), 149 (100), 135 (52), 109 (26), 91 (36). HR-FAB-MS: 449.2687 ($[M+1]^+$, $C_{29}H_{37}O_4^+$; calc. 449.2692).

1-(2-Methoxy-4-methylphenyl)-5-methylhex-4-en-1-one (**13a**). A stirred mixture of KOH (0.368 g, 6.571 mmol) and **11a** (0.500 g, 1.645 mmol) in MeOH/H_2O 85:15 (8 ml), under N_2, was heated to reflux for 3 h. The mixture was diluted with CH_2Cl_2 (10 ml), and washed with a sat. aq. NH_4Cl soln. (2 × 10 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (20 g); hexane/AcOEt 98:2) to give **13a** (0.364 g, 95%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.65. IR (CH_2Cl_2): 1669, 1607, 1495, 1464, 1409, 1285, 1255, 1168, 1124, 1035, 813. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.61 (br. *s*, *Me*C=); 1.68 (br. *s*, *Me*C=); 2.33–2.38 (*m*, CH_2CH=); 2.38 (*s*, *Me*C_6H_3); 2.97 (*dd*, *J* = 8.0, 7.5, CH_2CO); 3.88 (*s*, MeO); 5.12–5.17 (*m*, CH_2C*H*=); 6.75 (br. *s*, H–C(3′)); 6.80 (*dm*, *J* = 7.5, H–C(5′)); 7.61 (*d*, *J* = 7.5, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.6 (*Me*C=); 21.8 (*Me*C_6H_3); 23.2 (*C*H_2CH=); 25.7 (*Me*C=); 43.8 (*C*H_2CO); 55.4 (MeO); 112.2 (C(3′)); 121.4 (C(5′)); 123.6 (CH_2*C*H=); 125.7 (C(1′)); 130.5 (C(6′)); 132.1 (Me_2*C*=); 144.3 (C(4′)); 158.7 (C(2′)); 201.8 (Ar*C*O). EI-MS (70 eV): 233 (13, $[M+1]^+$), 232 (6, M^+), 217 (6), 164 (32), 149 (100), 135 (7), 105 (9), 91 (28). HR-EI-MS: 232.1461 (M^+, $C_{15}H_{20}O_2^+$; calc. 232.1463).

1-[2-(Benzyloxy)-4-methylphenyl]-5-methylhex-4-en-1-one (**13b**). Following the procedure as for **13a**, with KOH (0.237 g, 4.232 mmol) and **11b** (0.400 g, 1.053 mmol) in MeOH/H_2O 85:15 (6 ml): **13b** (0.310 g, 95%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.64. IR (CH_2Cl_2): 1670, 1606, 1497, 1454, 1414, 1378, 1287, 1255, 1169, 1123, 1022, 812, 732, 696. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.54 (br. *s*, *Me*C=); 1.63 (br. *s*, *Me*C=); 2.26–2.32 (*m*, CH_2CH=); 2.36 (*s*, *Me*C_6H_3); 2.95–2.99 (*m*, CH_2CO); 4.97–5.02 (*m*, CH_2C*H*=); 5.13 (*s*, PhCH_2); 6.81–6.83 (*m*, H–C(3′), H–C(5′)); 7.32–7.44 (*m*, 5 arom. H); 7.63 (*d*, *J* = 8.5, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.5 (*Me*C=); 21.8 (*Me*C_6H_3); 23.1 (*C*H_2CH=); 27.6 (*Me*C=); 44.0 (*C*H_2CO); 70.6 (Ph*C*H_2); 113.4 (C(3′)); 121.8 (C(5′)); 123.4 (CH_2*C*H=); 126.1 (C(1′)); 127.6 (2 arom. C); 128.1 (arom. C); 128.6 (2 arom. C); 130.5 (C(6′)); 132.0 (Me_2*C*=); 136.3 (arom. C); 144.2 (C(4′)); 157.8 (C(2′)); 201.9 (Ar*C*O). EI-MS (70 eV): 232 (30, $[M-C_6H_4]^+$), 162 (54), 149 (100), 147 (48), 135 (32), 95 (30), 91 (44).

2-(2-Methoxy-4-methylphenyl)-6-methylhept-5-en-2-ol (**14a**) [13a]. To a stirred suspension of MeMgBr (0.616 g, 5.176 mmol; 3M in Et_2O) in dry THF (3 ml), at 0° under N_2, a soln. of **13a** (0.400 g, 1.724 mmol) in dry THF (3 ml) was added dropwise. After stirring at r.t. for 2 h, a sat. aq. NH_4Cl soln. (5 ml) was added at 0°; then, the mixture was diluted with CH_2Cl_2 (10 ml), and washed with sat. aq. NH_4Cl soln. (2 × 10 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (20 g); hexane/AcOEt 98:2) to give **14a** (0.385 g, 90%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.60. IR (CH_2Cl_2): 3470, 2965, 2922, 1612, 1502, 1455, 1406, 1376, 1286, 1251, 1169, 1065, 1037, 928, 814. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.52 (br. *s*, *Me*C=); 1.55 (*s*, *Me*C(OH)); 1.64 (br. *s*, *Me*C=); 1.81–2.01 (*m*, CH_2CH=); 2.33 (*s*, *Me*C_6H_3); 3.86 (*s*, MeO); 3.99 (br. *s*, OH); 5.05–5.10 (*m*, CH_2CH=); 6.72 (br. *s*, H–C(3′)); 6.75 (*dm*, *J* = 7.8, H–C(5′)); 7.61 (*d*, *J* = 7.8, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.5 (*Me*C=); 21.2 (*Me*C_6H_3); 23.3 (*C*H_2CH=); 25.6 (*Me*C=); 27.4 (*Me*C(OH)); 42.1 (*C*H_2C(OH)); 55.2 (MeO); 74.9 (MeC(OH)); 112.2 (C(3′)); 121.3 (C(5′)); 124.6 (CH_2*C*H=); 126.6 (C(6′)); 131.3 (Me_2*C*=); 131.8 (C(1′)); 137.9 (C(4′)); 156.7 (C(2′)). EI-MS (70 eV): 248 (2, M^+), 231 (22), 187 (24), 165 (100), 147, (50), 119 (56), 91, (36). HR-EI-MS: 248.1776 (M^+, $C_{16}H_{24}O_2^+$; calc. 248.1776).

2-[2-(Benzyloxy)-4-methylphenyl]-6-methylhept-5-en-2-ol (**14b**). Following the procedure as for **14a**, with MeMgBr (0.348 g, 2.924 mmol) and **13b** (0.300 g, 0.974 mmol): **14b** (0.282 g, 89%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.59. IR (CH_2Cl_2): 3523, 2965, 2919, 1611, 1501, 1453, 1378, 1288, 1248, 1171, 1063, 1023, 814, 732, 696. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.49 (br. *s*, *Me*C=); 1.56 (*s*, *Me*C(OH)); 1.63 (br. *s*, *Me*C=); 1.80–2.05 (*m*, CH_2CH_2CH=); 2.33 (*s*, *Me*C_6H_3); 3.94 (*s*, OH); 5.05–5.08 (*m*, CH_2CH=); 5.10 (*s*, PhCH_2); 6.78 (br. *d*, *J* = 8.0, H–C(5′)); 6.80 (br. *s*, H–C(3′)); 7.21 (*d*, *J* = 8.0, H–C(6′)); 7.32–7.44 (*m*, 5 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.5 (*Me*C=); 21.2 (*Me*C_6H_3); 23.3 (*C*H_2CH=); 25.7 (*Me*C=); 27.6 (*Me*C(OH)); 42.1 (*C*H_2CH$_2$CH=); 70.5 (Ph*C*H_2); 75.0 (Me*C*(OH)); 113.2 (C(3′)); 121.6 (C(5′)); 124.6 (CH_2*C*H=); 126.8 (C(6′)); 127.6 (2 arom. C); 128.2 (arom. C); 128.8 (2 arom. C); 131.4 (Me_2*C*=); 132.1 (C(1′)); 136.4 (arom. C); 137.9 (C(4′)); 155.9 (C(2′)). HR-FAB-MS: 325.2166 ([*M* + H]$^+$, $C_{22}H_{29}O_2^+$; calc. 325.2168).

2-Methoxy-4-methyl-1-(6-methylhept-5-en-2-yl)benzene (**15a**) [13a]. To a stirred soln. of **14a** (0.300 g, 1.210 mmol) in dry CH_2Cl_2 (4 ml), at −78° under N_2, Et_3SiH (0.169 g, 1.457 mmol) was added dropwise. After stirring for 10 min, $BF_3 \cdot Et_2O$ (0.257 g, 1.810 mmol) was added dropwise, and the mixture was stirred at the same temp. for 1 h. The mixture was diluted with CH_2Cl_2 (15 ml) and washed with a sat. aq. $NaHCO_3$ soln. (2 × 10 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (18 g); hexane/AcOEt 98:2): to give **15a** (0.258 g, 92%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.83. IR (CH_2Cl_2): 2959, 2923, 2855, 1611, 1578, 1505, 1463, 1411, 1285, 1259, 1157, 1043, 809. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.17 (*d*, *J* = 7.0, *Me*CHAr); 1.47–1.55 (*m*, 1 H of CH_2CHAr); 1.53 (br. *s*, *Me*C=); 1.60–1.67 (*m*, 1 H of CH_2CHAr); 1.66 (br. *s*, *Me*C=); 1.83–1.98 (*m*, CH_2CH=); 2.32 (*s*, *Me*C_6H_3); 3.12 (*sext*, *J* = 7.0, MeC*H*Ar); 3.79 (*s*, MeO); 5.09–5.14 (*m*, CH_2CH=); 6.66 (*d*, *J* = 1.0, H–C(3′)); 6.73 (*dd*, *J* = 8.0, 1.0, H–C(5′)); 7.04 (*d*, *J* = 8.0, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.6 (*Me*C=); 21.1 (*Me*CHAr); 21.4 (*Me*C_6H_3); 25.7 (*Me*C=); 26.3 (*C*H_2CH=); 31.4 (MeCHAr); 37.2 (*C*H_2CHAr); 55.3 (MeO); 111.5 (C(3′)); 121.1 (C(5′)); 124.9 (CH_2*C*H=); 126.6 (C(6′)); 131.1 (Me_2*C*=); 132.9 (C(1′)); 136.2 (C(4′)); 157.0 (C(2′)). EI-MS (70 eV): 233 (32, [*M* + 1]$^+$), 232 (100, M^+), 162 (24), 149 (98), 147 (40), 95 (28), 91 (20). HR-EI-MS: 232.1823 (M^+, $C_{16}H_{24}O^+$; calc. 232.1827).

2-(Benzyloxy)-4-methyl-1-(6-methylhept-5-en-2-yl)benzene (**15b**). Following the procedure as for **15a**, with **14b** (0.200 g, 0.617 mmol), Et_3SiH (0.086 g, 0.741 mmol), and $BF_3 \cdot Et_2O$ (0.131 g, 0.923 mmol): **15b** (0.171 g, 90%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.83. IR (CH_2Cl_2): 2960, 2919, 1610, 1504 1452, 1377, 1257, 1125, 1026, 810, 733, 695. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.19 (*d*, *J* = 7.0, *Me*CHAr); 1.49–1.56 (*m*, 1 H of CH_2CHAr); 1.51 (br. *s*, *Me*C=); 1.62 (br. *s*, *Me*C=); 1.63–1.71 (*m*, 1 H of CH_2CHAr); 1.86–1.98 (*m*, CH_2CH=); 2.31 (*s*, *Me*C_6H_3); 3.24 (*sext*, *J* = 7.0, MeC*H*Ar); 5.04 (*s*, PhCH_2); 5.08–5.11 (*m*, CH_2CH=); 6.74 (br. *s*, H–C(3′)); 6.76 (br. *d*, *J* = 7.5, H–C(5′)); 7.07 (*d*, *J* = 7.5, H–C(6′)); 7.30–7.33 (*m*, 1 arom. H); 7.36–7.40 (*m*, 2 arom. H); 7.43–7.46 (*m*, 2 arom. H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.6 (*Me*C=); 21.0 (*Me*CHAr); 21.4 (*Me*C_6H_3); 25.7 (*Me*C=); 26.3 (*C*H_2CH=); 31.4 (MeCHAr); 37.3 (*C*H_2CHAr); 70.0 (Ph*C*H_2); 112.8 (C(3′)); 121.5 (C(5′)); 124.8 (CH_2*C*H=); 126.7 (C(6′)); 127.1 (2 arom. C); 127.6 (arom. C); 128.5 (2 arom. C); 131.1 (Me_2*C*=); 133.2 (C(1′)); 136.2 (C(4′)); 137.7 (arom. C);

156.1 (C(2′)). EI-MS (70 eV): 217 (2, $[M-91]^+$), 149 (100), 135 (32), 91 (28), 77 (8). HR-FAB-MS: 308.2136 (M^+, $C_{22}H_{28}O^+$; calc. 308.2140).

Curcuphenol (=*(1,5-Dimethylhex-4-en-1-yl)-5-methylphenol*; **1**). *Method A.* To a stirred soln. of **15a** (0.100 g, 0.431 mmol) in dry CH_2Cl_2 (3 ml), at $-78°$ under N_2, BBr_3 (0.032 g, 1.280 mmol) was added dropwise. After stirring at 0° for 30 min, the mixture was stirred at r.t. for 1.5 h, and icy H_2O (3 ml) was added. The mixture was stirred for 30 min, then diluted with CH_2Cl_2 (12 ml), and washed with a sat. aq. $NaHCO_3$ soln. (2 × 5 ml) and H_2O until neutral. The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (18 g); hexane/AcOEt 98:2), to give **1** (0.066 g, 70%). Colorless oil.

Method B. To a suspension of NaH (0.083 g, 3.458 mmol) in dry DMF (2 ml), at 0° under N_2, EtSH (0.190 g, 3.065 mmol) was added dropwise. After stirring at r.t. for 2 h, **15a** (0.100 g, 0.430 mmol) in dry DMF was added, and the mixture was heated to reflux for 3 h. A 10% aq. soln. of HCl (3 ml) and CH_2Cl_2 (12 ml) were added, and the mixture washed with H_2O (2 × 3 ml). The org. layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (18 g); hexane/AcOEt 98:2): to give **1** (0.091 g, 97%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.57.

Method C. Under H_2 (25 psi), a suspension of **15b** (0.070 g, 0.227 mmol) and 0.007 g (0.006 mmol) of Pd/C (10%) in MeOH (3 ml) was stirred at r.t. for 1.5 h. The mixture was filtered over *Celite*, and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (18 g); hexane/AcOEt 98:2) to give **1** (0.045 g, 90%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.57. IR (CH_2Cl_2): 3425, 2962, 2923, 2856, 1619, 1583, 1517, 1451, 1419, 1376, 1287, 1221, 1152, 1121, 904, 809. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.22 (*d*, *J* = 7.0, *Me*CHAr); 1.54 (br. *s*, *Me*C=); 1.56–1.67 (*m*, CH_2CHAr); 1.68 (br. *s*, *Me*C=); 1.87–1.99 (*m*, CH_2CH=); 2.26 (*s*, *Me*C_6H_3); 2.96 (*sext.*, *J* = 7.0, MeC*H*Ar); 4.66 (*s*, OH); 5.10–5.15 (*m*, CH_2CH=); 6.58 (br. *s*, H–C(3′)); 6.72 (br. *d*, *J* = 7.5, H–C(5′)); 7.03 (*d*, *J* = 7.5, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.7 (*Me*C=); 20.9 (*Me*C_6H_3); 21.1 (*Me*CHAr); 25.7 (*C*H_2CH=); 26.1 (*Me*C=); 31.4 (Me*C*HAr); 37.3 (*C*H_2CHAr); 116.2 (C(3′)); 121.7 (C(5′)); 124.6 (CH_2*C*H=); 126.8 (C(6′)); 129.9 (C(1′)); 132.0 (Me_2*C*=); 136.5 (C(4′)); 152.8 (C(2′)). EI-MS (70 eV): 218 (4, M^+), 148 (100), 121 (22), 107 (16), 91 (14). HR-FAB-MS: 218.1672 (M^+, $C_{15}H_{22}O^+$; calc. 219.1671).

1-(4-Methyl-3-nitrophenyl)ethanone (**17**). At 0°, a mixture of H_2SO_4 (0.441 g, 4.50 mmol) and HNO_3 (0.236 g, 3.746 mmol) was added dropwise to **16** (0.500 g, 3.753 mmol). The mixture was stirred at r.t. for 6 h, then poured into a beaker containing icy H_2O (20 ml). The precipitate was filtered and dissolved with CH_2Cl_2 (10 ml). The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (45 g); hexane/AcOEt 95:5) to give **17** (0.436 g, 65%). Yellow solid. R_f (hexane/AcOEt 7:3) 0.48. M.p. 60–61° ([21]: MeOH) (62°). IR (CH_2Cl_2): 1692, 1617, 1531, 1348, 1282, 1251, 833, 803. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.65 (*s*, *Me*CO); 2.67 (*s*, *Me*C_6H_3); 7.47 (*d*, *J* = 8.0, H–C(5′)); 8.08 (*dd*, *J* = 8.0, 1.5, H–C(6′)); 8.52 (*d*, *J* = 1.5, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.6 (*Me*C_6H_3); 26.5 (*Me*CO); 124.6 (C(2′)); 131.9 (C(6′)); 133.3 (C(5′)); 136.1 (C(1′)); 138.6 (C(4′)); 149.2 (C(3′)); 195.5 (CO). EI-MS (70 eV): 179 (4, M^+), 164 (84), 162 (100), 147 (66), 120 (34), 118 (35), 106 (14), 90 (50), 89 (60), 77 (27). HR-FAB-MS: 180.0673 ($[M+1]^+$, $C_9H_{10}NO_3^+$; calc. 180.0661).

1-(3-Amino-4-methylphenyl)ethanone (**18**). *Method A.* A mixture of **17** (0.400 g, 2.235 mmol) in THF (5 ml) and $Na_2S_2O_4$ (2.333 g, 13.408 mmol) in H_2O (5 ml) was stirred at 50° for 12 h. The mixture was diluted with CH_2Cl_2 (15 ml) and washed with cold H_2O (2 × 8 ml). The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (25 g); hexane/AcOEt 95:5) to give **18** (0.266 g, 80%). Brown solid. R_f (hexane/AcOEt 8:2) 0.24.

Method B. Under an H_2 (30 psi), a suspension of **17** (0.400 g, 2.235 mmol) and 0.040 g (0.034 mmol) of Pd/C (10%) in MeOH (8 ml) was stirred at r.t. for 1.0 h. The mixture was filtered over *Celite*, and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (25 g); hexane/AcOEt 95:5) to give **18** (0.316 g, 95%). Brown solid. R_f (hexane/AcOEt 8:2) 0.24. M.p. 80–81° ([21]: 82°; [24]: 83–84°). IR (CH_2Cl_2): 3367, 1672, 1573, 1422, 1356, 1291, 1237, 1199. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.21 (*s*, *Me*C_6H_3); 2.54 (*s*, *Me*CO); 3.77 (br., NH_2); 7.12 (*d*, *J* = 7.5, H–C(5′)); 7.27 (*d*, *J* = 2.0, H–C(2′)); 7.28 (*dd*, *J* = 7.5, 2.0, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.5 (*Me*C_6H_3); 26.5 (*Me*CO); 113.8 (C(2′)); 119.1 (C(6′)); 128.0 (C(4′)); 130.4 (C(5′)); 136.2 (C(1′)); 144.8 (C(3′)); 198.3 (CO). EI-MS (70 eV): 149 (80, M^+), 134 (100), 106 (80), 79 (42), 77 (50). HR-FAB-MS: 150.0929 ($[M+1]^+$, $C_9H_{12}NO^+$; calc. 150.0919).

1-(3-Hydroxy-4-methylphenyl)ethanone (**5**). To **18** (0.300 g, 2.013 mmol), at r.t. and under N_2, H_2SO_4 (0.986 g, 10.061 mmol) in icy H_2O (4 ml) was added, and the mixture was vigorously stirred at 45° for 30 min. The mixture was cooled to 0°, and $NaNO_2$ (0.167 g, 2.420 mmol) dissolved in H_2O (3 ml) was added, and the mixture was stirred for 10 min and then heated to reflux for 5 h. The mixture was poured into icy H_2O (20 ml), the precipitate was filtered and dissolved with CH_2Cl_2 (10 ml). The org. layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by CC (SiO_2 (20 g); hexane/AcOEt 95:5) to give **5** (0.267 g, 88%). White solid. R_f (hexane/AcOEt 7:3) 0.39. M.p. 110–111° ([20]: 105–107°) IR (CH_2Cl_2): 3412, 1663, 1606, 1582, 1418, 1350, 1289, 1241, 898, 812. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.32 (*s*, *Me*C_6H_3); 2.58 (*s*, *Me*CO); 6.50 (br., OH); 7.20 (*d*, *J* = 8.0, H–C(5′)); 7.42 (*dd*, *J* = 8.0, 1.5, 1 H–C(6′)); 7.54 (*d*, *J* = 1.5, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.2 (*Me*C_6H_3); 26.6 (*Me*CO); 113.9 (C(2′)); 121.3 (C(6′)); 131.0 (C(5′)); 131.1 (C(4′)); 136.2 (C(1′)); 154.5 (C(3′)); 198.8 (CO). EI-MS (70 eV): 150 (28, M^+), 135 (100), 107 (30), 79 (26), 77 (52), 51 (10). HR-CI-MS: 151.0753 ($[M+1]^+$, $C_9H_{11}O_2^+$; calc. 151.0759).

1-(3-Methoxy-4-methylphenyl)ethanone (**19**) [19]. Following the procedure as for **8a**, with KOH (0.112 g, 2.00 mmol), **5** (0.250 g, 1.667 mmol), and MeI (0.473 g, 3.331 mol). After stirring at r.t. for 6 h, **19** (0.246 g, 90%) was obtained. Colorless oil. R_f (hexane/AcOEt 8:2) 0.48. IR (CH_2Cl_2): 1681, 1605, 1579, 1501, 1407, 1270, 1226, 1037, 876. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.27 (*s*, *Me*C_6H_3); 2.59 (*s*, *Me*CO); 3.89 (*s*, MeO); 7.20 (*d*, *J* = 8.0, H–C(5′)); 7.44 (*d*, *J* = 1.0, H–C(2′)); 7.45 (*dd*, *J* = 8.0, 1.0, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.5 (*Me*C_6H_3); 26.5 (*Me*CO); 55.4 (MeO); 108.4 (C(2′)); 121.4 (C(6′)); 130.4 (C(5′)); 133.0 (C(4′)); 136.3 (C(1′)); 157.9 (C(3′)); 197.9 (CO). EI-MS (70 eV): 165 (100, $[M+1]^+$), 164 (22, M^+), 150 (12), 149 (36), 135 (4), 106 (4), 91 (7). HR-EI-MS: 164.0838 (M^+, $C_{10}H_{12}O_2^+$; calc. 164.0837).

Ethyl 3-(3-Methoxy-4-methylphenyl)-3-oxopropanoate (**20**). Following the procedure as for **9a**, with NaH (0.073 g, 3.042 mmol), **19** (0.200 g, 1.220 mmol), and $CO(OEt)_2$ (0.288 g, 2.441 mmol): **20** (0.259 g, 90%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.39. IR (CH_2Cl_2): 1736, 1680, 1603, 1576, 1504, 1455, 1406, 1314, 1230, 1138, 1031, 872, 800. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.26 (*t*, *J* = 7.0, *Me*CH_2); 2.27 (*s*, *Me*C_6H_3); 3.88 (*s*, MeO); 3.97 (*s*, CH_2(2)); 4.21 (*q*, *J* = 7.0, MeC*H*$_2$); 7.21 (*d*, *J* = 7.5, H–C(5′)); 7.41 (*dd*, *J* = 7.5, 1.5, H–C(6′)); 7.40 (*d*, *J* = 1.5, H–C(2′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0 (*Me*CH_2); 16.5 (*Me*C_6H_3); 45.9 (C(2)); 55.4 (MeO); 61.4 (Me*C*H$_2$); 108.6 (C(2′)); 121.4 (C(6′)); 130.5 (C(5′)); 133.9 (C(4′)); 135.1 (C(1′)), 158.0 (C(3′)); 167.6 (*C*O$_2$Et); 192.1 (Ar*C*O). EI-MS (70 eV): 149 (40, $[M-87]^+$), 123 (100), 94 (52), 91 (32), 77 (14), 65 (12). HR-CI-MS: 237.1113 ($[M+1]^+$, $C_{13}H_{17}O_4^+$; calc. 237.1127).

Ethyl 2-[(3-Methoxy-4-methylphenyl)carbonyl]-5-methylhex-4-enoate (**21**). Following the procedure as for **11a**/**12a**, with NaH (0.020 g, 0.833 mmol), **20** (0.200 g, 0.847 mmol), and prenyl bromide (0.152 g, 1.020 mmol): **21** (0.237 g, 92%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.53. IR (CH_2Cl_2): 1736, 1682, 1603, 1578, 1504, 1463, 1408, 1258, 1210, 1150, 1038, 855. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.0, *Me*CH_2); 1.64 (br. *s*, *Me*C=); 1.66 (br. *s*, *Me*C=); 2.27 (*s*, *Me*C_6H_3); 2.62–2.76 (*m*, 2 C*H*$_2$CH=); 3.88 (*s*, MeO); 4.14 (*qd*, *J* = 7.0, 0.5, MeC*H*$_2$); 4.28 (*dd*, *J* = 7.8, 6.8, H–C(2)); 5.09–5.14 (*m*, CH_2C*H*=); 7.21 (*d*, *J* = 8.0, H–C(5′)); 7.46 (*d*, *J* = 1.5, H–C(2′)); 7.50 (*dd*, *J* = 8.0, 1.5, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0 (*Me*CH_2); 16.5 (*Me*C_6H_3); 17.8 (*Me*C=); 25.7 (*Me*C=); 27.8 (*C*H$_2$CH=); 54.5 (C(2)); 55.4 (MeO); 61.2 (Me*C*H$_2$); 109.0 (C(3′)); 120.3 (CH_2*C*H=); 121.3 (C(6′)); 130.4 (C(5′)); 133.5 (C(4′)); 134.6 (Me$_2$*C*=); 135.4 (C(1′)); 158.0 (C(3′)); 170.0 (*C*O$_2$Et); 194.5 (Ar*C*O). EI-MS (70 eV): 231 (2, $[M-73]^+$), 193 (56), 164 (46), 149 (100), 121 (30), 91 (56), 77 (22). HR-CI-MS: 305.1758 ($[M+1]^+$, $C_{18}H_{25}O_4^+$; calc. 305.1753).

1-(3-Methoxy-4-methylphenyl)-5-methylhex-4-en-1-one (**22**). Following the procedure as for **13a**, with KOH (0.110 g, 1.964 mmol) and **21** (0.150 g, 0.493 mmol) in MeOH/H_2O 85:15 (4 ml): **22** (0.109 g, 95%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.62. IR (CH_2Cl_2): 1681, 1604, 1579, 1503, 1454, 1407, 1263, 1249, 1155, 1038, 877. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.64 (br. *s*, *Me*C=); 1.69 (br. *s*, *Me*C=); 2.26 (*s*, *Me*C_6H_3); 2.41 (br. *q*, *J* = 7.5, C*H*$_2$CH=); 2.97 (*t*, *J* = 7.5, C*H*$_2$CO); 3.88 (*s*, MeO); 5.15–5.21 (*m*, CH_2C*H*=); 7.18 (*d*, *J* = 7.5, H–C(5′)); 7.44 (*d*, *J* = 1.5, H–C(2′)); 7.45 (*dd*, *J* = 7.5, 1.5, H–C(6′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.5 (*Me*C_6H_3); 17.6 (*Me*C=); 23.1 (*C*H$_2$CH=); 25.7 (*Me*C=); 38.6 (*C*H$_2$CO); 55.4 (MeO); 108.5 (C(2′)); 120.9 (C(6′)); 123.0 (CH_2*C*H=); 130.3 (C(5′)); 132.6 (C(4′)); 132.7 (Me$_2$*C*=); 136.2 (C(1′)), 157.9 (C(3′)); 199.7 (Ar*C*O). EI-MS (70 eV): 233 (20, $[M+1]^+$), 232 (40, M^+),

217 (10), 164 (100), 149 (57), 122 (44), 121 (25), 91 (34). HR-CI-MS: 233.1530 ($[M+1]^+$, $C_{15}H_{21}O_2^+$; calc. 233.1542).

2-(3-Methoxy-4-methylphenyl)-6-methylhept-5-en-2-ol (**23**) [13a]. Following the procedure as for **14a**, with MeMgBr (0.154 g, 1.294 mmol) and **22** (0.100 g, 0.431 mmol): **23** (0.095 g, 89%). Pale yellow oil. R_f (hexane/AcOEt 8:2) 0.59. IR (CH_2Cl_2): 3433, 2966, 2924, 1612, 1580, 1504, 1463, 1405, 1252, 1133, 1041, 857, 815. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.51 (br. *s*, *Me*C=); 1.53 (*s*, *Me*C(OH)); 1.65 (br. *s*, *Me*C=); 1.78–2.05 (*m*, CH_2CH_2CH=, OH); 2.20 (*s*, *Me*C_6H_3); 3.85 (*s*, MeO); 3.99 (br. *s*, OH); 5.05–5.15 (*m*, CH_2C*H*=); 6.85 (*dd*, *J* = 7.5, 1.8, H–C(6′)); 6.97 (*d*, *J* = 1.8, H–C(2′)); 7.08 (*d*, *J* = 7.5, H–C(5′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 15.8 (*Me*C=); 17.7 (*Me*C_6H_3); 23.0 (*C*H_2CH=); 25.6 (*Me*C=); 30.6 (*Me*C(OH)); 43.6 (*C*H_2C(OH)); 55.3 (MeO); 75.0 (Me*C*(OH)); 106.8 (C(2′)); 116.5 (C(6′)); 124.2 (CH_2*C*H=); 124.6 (C(4′)); 130.2 (C(5′)); 132.1 (Me_2*C*=); 147.0 (C(1′)), 157.5 (C(3′)). EI-MS (70 eV): 248 (8, M^+), 230 (31), 187 (100), 172 (34), 166 (54), 165 (28), 151 (20), 91 (17). HR-CI-MS: 249.1851 ($[M+1]^+$, $C_{16}H_{25}O_2^+$; calc. 249.1855).

4-(1,5-Dimethylhex-4-en-1-yl)-2-methoxy-1-methylbenzene (**24**) [13a]. Following the procedure as for **15a**, with **23** (0.100 g, 0.403 mmol), Et_3SiH (0.056 g, 0.483 mmol), and $BF_3 \cdot Et_2O$ (0.086 g, 0.606 mmol): **24** (0.084 g, 90%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.80. IR (CH_2Cl_2): 2953, 2923, 2853, 1612, 1586, 1456, 1376, 1256, 1134, 1045, 850, 813. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*d*, *J* = 7.2, *Me*CHAr); 1.53 (br. *s*, *Me*C=); 1.56–1.64 (*m*, CH_2CHAr); 1.68 (br. *s*, *Me*C=); 1.82–1.98 (*m*, CH_2CH=); 2.18 (*s*, *Me*C_6H_3); 2.65 (*sext.*, *J* = 7.2, MeC*H*Ar); 3.82 (*s*, MeO); 5.05–5.14 (*m*, CH_2C*H*=); 6.66 (br. *s*, H–C(2′)); 6.68 (*dd*, *J* = 7.5, 1.5, H–C(6′)); 7.04 (*d*, *J* = 7.5, H–C(5′)). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 15.8 (*Me*C=); 17.7 (*Me*CHAr); 22.5 (*Me*C_6H_3); 25.7 (*Me*C=); 26.2 (*C*H_2CH=); 38.4 (Me*C*HAr); 39.5 (*C*H_2CHAr); 55.2 (MeO); 108.9 (C(2′)); 118.7 (C(6′)); 123.8 (CH_2*C*H=); 124.5 (C(4′)); 130.3 (C(5′)); 131.4 (Me_2*C*=); 146.7 (C(1′)); 157.6 (C(3′)). EI-MS (70 eV): 232 (30, M^+), 162 (27), 150 (69), 149 (30), 135 (100), 91 (25). HR-CI-MS: 233.1916 ($[M+1]^+$, $C_{16}H_{25}O^+$; calc. 233.1905).

Xanthorrhizol (=*5-(1,5-Dimethylhex-4-en-1-yl)-2-methylphenol*; **2**). Following the procedure as for **1**, with **24** (0.100 g, 0.430 mmol), EtSH (0.190 g, 3.065 mmol), and NaH (0.083 g, 3.458 mmol): **2** (0.089 g, 95%). Colorless oil. R_f (hexane/AcOEt 8:2) 0.55. IR (CH_2Cl_2): 3392, 2960, 2923, 1589, 1505, 1454, 1421, 1375, 1258, 1121, 812. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*d*, *J* = 7.2, *Me*CHAr); 1.53 (br. *s*, *Me*C=); 1.56–1.58 (*m*, CH_2CHAr); 1.67 (br. *s*, *Me*C=); 1.84–1.93 (*m*, CH_2CH=); 2.22 (*s*, *Me*C_6H_3); 2.61 (*sext.*, *J* = 7.2, MeC*H*Ar); 4.61 (*s*, OH); 5.03–5.15 (*m*, CH_2C*H*=); 6.61 (*d*, *J* = 7.5, H–C(2′)); 6.68 (*dd*, *J* = 7.5, 1.8, H–C(6′)); 7.03 (*d*, *J* = 7.5, H–C(5′)). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.3 (*Me*C_6H_3); 17.7 (*Me*C=); 22.4 (*Me*CHAr); 25.7 (*Me*C=); 26.1 (*C*H_2CH=); 38.4 (*C*H_2CHAr); 39.0 (Me*C*HAr); 113.5 (C(2′)); 119.4 (C(6′)); 120.8 (C(4′)); 124.5 (CH_2*C*H=); 130.7 (C(5′)); 131.4 (Me_2*C*=); 147.2 (C(1′)); 153.6 (C(3′)). EI-MS (70 eV): 218 (30, M^+), 148 (58), 136 (58), 121 (100), 91 (24), 77 (13). HR-CI-MS: 219.1744 ($[M+1]^+$, $C_{15}H_{23}O^+$; calc. 219.1749).

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