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Facile synthesis of γ-alkenylbutenolides from Baylis–Hillman adducts: consecutive in-mediated Barbier allylation, PCC oxidation, isomerization, and Zn-mediated Barbier allylation

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ABSTRACT

Alkenylbutenolides were synthesized regioselectively in good to moderate yields from Baylis–Hillman adducts via a consecutive indium-mediated Barbier type reaction between Baylis–Hillman bromide and aldehyde, PCC oxidation of the homoallylic alcohol, double bond isomerization, and zinc-mediated Barbier type alkenylation protocol.

Butenolides are valuable synthetic intermediates and key structural sub-units of a variety of natural products.[1,2] Due to their wide range of biological activity there is a continuing need for the development of simple and versatile methods for their synthesis. γ-Alkyl- and γ-alkenylbutenolides have received a special attention among the numerous butenolides.[2] Although numerous synthetic approaches of butenolides have been reported, synthesis of γ-alkenylbutenolides is somewhat limited.[2] Recently Baylis–Hillman adducts have been used for the synthesis of numerous cyclic and acyclic compounds including α-methylene-γ-butyrolactones and butenolides.[3–5]

Recently, we reported the synthesis of butenolide **A** from homoallylic alcohol **3a**, prepared from Baylis–Hillman bromide **1a** by an indium-mediated Barbier reaction, via an acid-catalyzed lactonization and a following Pd/C-catalyzed isomerization of double bond, as shown in Scheme 1.[4b] DBU-mediated allylation of the butenolide **A** produced a mixture of γ- and α-allyl products, **7a** (14%) and **8a** (67%).[4b] The introduction of an allyl group at the γ-position was difficult by simply modifying the reaction conditions such as base, temperature, and solvent. Thus we turned our attention to another route for the selective synthesis of γ-allylbutenolide (γ-adduct) **7a**, as shown in Scheme 1. Oxidation of homoallylic alcohol **3a** with PCC (pyridinium chlorochromate) afforded the corresponding γ-ketoester **4a** (vide infra, Table 1). Double bond isomerization of **4a** with Et_3N afforded **5a**. With this compound **5a**, we examined an allylation in the presence of indium powder (1.2 equiv) and allyl bromide (2.5 equiv) in refluxing THF (20 h); however, the desired product **7a** was formed in low yield (<10%). When we increased the amounts of indium (3.0 equiv), the yield of **7a** increased slightly (31%). Moreover, indium metal is highly expensive, thus we examined a zinc-mediated allylation. To our delight, zinc-mediated allylation of **5a** in the presence of zinc dust (5.0 equiv) and allyl bromide (2.5 equiv) in refluxing THF (5 h) produced **7a** in a reasonable yield (70%).[2f]

Encouraged by the results, we prepared the starting materials **5a–e** from Baylis–Hillman bromides **1a–c** via a three-step process, namely, an indium-mediated Barbier type reaction, PCC oxidation, and double bond isomerization.[4a,b,6,7] The results are summarized in Table 1. An indium-mediated Barbier reaction of **1** and **2** afforded homoallylic alcohols **3a–e** in good yields (81–95%) as *syn*-form, as reported previously.[4a,b,6] Oxidation of the alcohols **3** with PCC (1.5 equiv, CH_2Cl_2, rt, 15 h) gave **4a–e** in good to moderate yields (62–90%).[7] Treatment of **4a–e** with Et_3N (1.0 equiv, DMF, 90 °C, 2 h) afforded starting materials **5a–e** in moderate yields (67–74%).[7] Although the corresponding *E*-isomer was formed in low yield (8–13%) during the isomerization process, we separated the major *Z*-isomer and used in the next step.

With these compounds **5a–e** we synthesized γ-alkenylbutenolides **7a–g**, under zinc-mediated Barbier type allylation conditions, as summarized in Table 2.[7] The reactions of **5a** with allyl bromide (**6a**), methallyl bromide (**6b**), and crotyl bromide (**6c**) afforded

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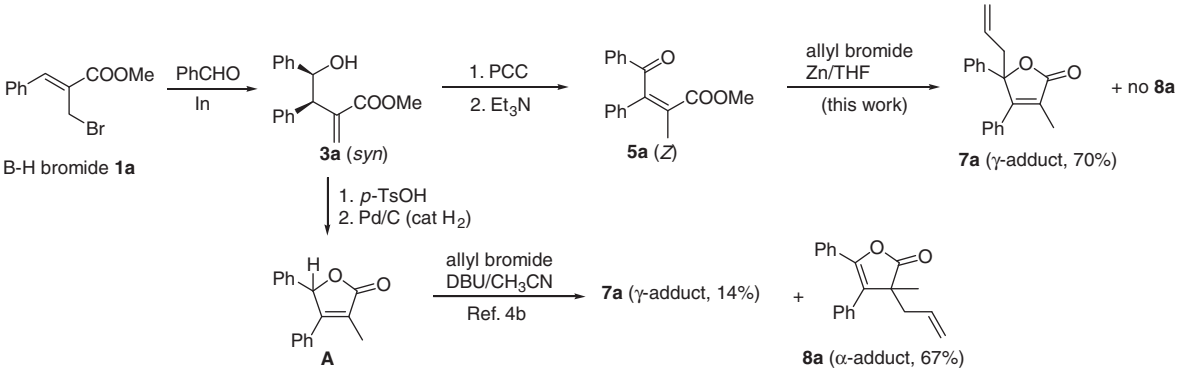
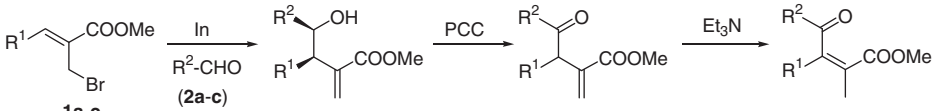


Scheme 1.

Table 1
Synthesis of starting materials **5a–e**

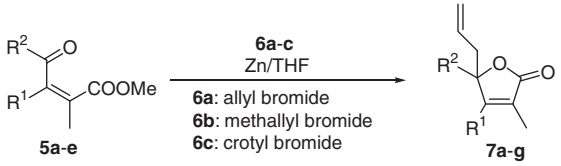


1a: R^1 = Ph **2a**: R^2 = Ph
1b: R^1 = 2-BrPh **2b**: R^2 = 4-ClPh
1c: R^1 = -CH=CHPh **2c**: R^2 = Me

Entry	Substrates	**3**[a] (%)	**4**[b] (%)	**5**[c] (%)
1	**1a** + **2a**	**3a** (95)	**4a** (90)	**5a** (71)
2	**1a** + **2b**	**3b** (94)	**4b** (89)	**5b** (72)
3	**1a** + **2c**	**3c** (81)	**4c** (62)	**5c** (67)
4	**1b** + **2a**	**3d** (92)	**4d** (89)	**5d** (68)
5	**1c** + **2a**	**3e** (88)	**4e** (84)	**5e** (74)

[a] Conditions: **1** (2.0 mmol), **2** (1.1 equiv), aq THF, in (1.1 equiv), rt, 1 h; isolated yield *syn* isomer.
[b] Conditions: **3** (1.5 mmol), CH_2Cl_2, PCC (1.5 equiv), rt, 15 h; isolated yield.
[c] Conditions: **4** (1.0 mmol), DMF, Et_3N (1.0 equiv), 90 °C, 2 h; isolated yield of *Z*-isomer.

Table 2
Synthesis of γ-alkenylbutenolides **7a–g**



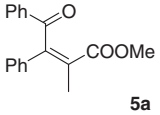
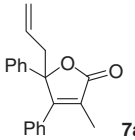
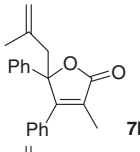
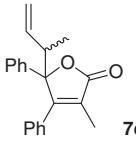
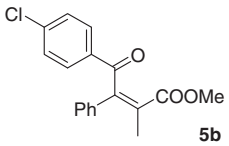
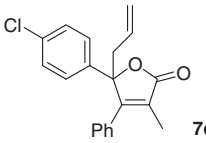
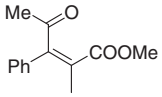
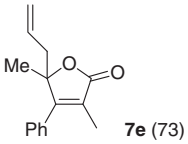
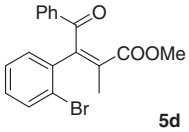
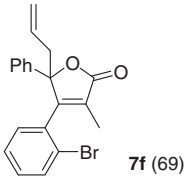
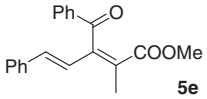
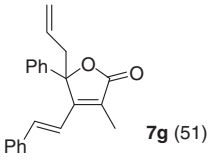
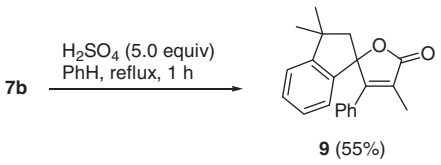
Entry	Substrate **5**	**6a–c**	Product **7**[a] (%)
1	 **5a**	**6a**	 **7a** (70)
2	**5a**	**6b**	 **7b** (81)
3[b]	**5a**	**6c**	 **7c** (66)[c]

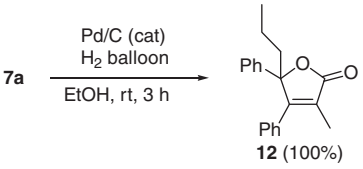
Table 2 (*continued*)

Entry	Substrate **5**	**6a–c**	Product **7**[a] (%)
4	 **5b**	**6a**	 **7d** (69)
5	 **5c**	**6a**	 **7e** (73)
6	 **5d**	**6a**	 **7f** (69)
7	 **5e**	**6a**	 **7g** (51)

[a] Conditions: **5** (0.7 mmol), Zn (5.0 equiv), **6** (2.5 equiv) THF, reflux, 5 h, isolated yield.
[b] Conditions: Reaction time 20 h.
[c] Conditions: Mixture of *syn*/*anti* (ca. 20:1 based on ^{1}H NMR).



Scheme 2.



Scheme 4.

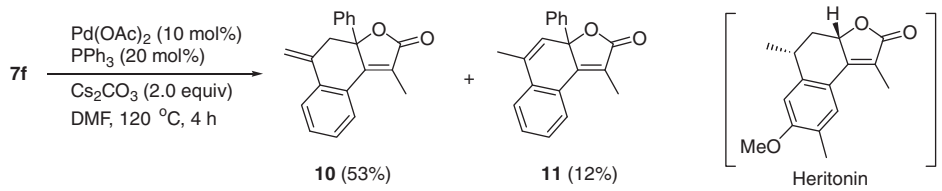
7a–c in moderate to good yields (66–81%), respectively (entries 1–3). Similarly, γ-allylbutenolides **7d–g** were synthesized in moderate yields (51–73%) from **5b–e** and allyl bromide.

Synthesis of various spirobutenolides has received much attention due to their interesting biological activities.[8] Thus we examined the synthesis of spirobutenolide **9** via an acid-catalyzed Friedel–Crafts reaction of **7b**, as shown in Scheme 2. The phenyl group at the β-position is conjugated to an electron-withdrawing lactone moiety and cannot participate in the Friedel–Crafts reaction, while the phenyl group at the γ-position can react with a tertiary carbocation intermediate, generated under acidic conditions, to produce the desired spirobutenolide **9** in moderate yield (55%).[7]

Various fused-butenolides have also received much attention due to their interesting biological activities.[9] As another synthetic application of γ-allylbutenolide, a palladium-catalyzed cyclization of compound **7f** was examined. Two types of fused-butenolides **10** and **11** were obtained in a reasonable combined yield, as shown in Scheme 3.[7] The basic skeleton of **10** or **11** is closely related to that of heritonin, a naturally occurring sesquiterpene lactone.[9b,c]

As a last synthetic application, a catalytic hydrogenation of **7a** (EtOH, Pd/C, under H_2 balloon atmosphere) gave γ-propyl derivative **12** in a quantitative yield.[7] The result stated that γ-alkylbutenolide[2d,e,h] could also be synthesized by introduction of an alkenyl moiety and a following catalytic hydrogenation process Scheme 4.

In summary, we disclosed an efficient synthesis of γ-alkenylbutenolides from the bromide of Baylis–Hillman adduct via a consecutive indium-mediated Barbier type reaction with aldehyde, PCC oxidation, double bond isomerization, and zinc-mediated Barbier type alkenylation protocol. In addition, we demonstrated the synthetic applicability of three γ-alkenylbutenolides. Further synthetic applications are currently underway.[10]



Scheme 3.

Acknowledgments

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7. *Typical procedure for the synthesis of* ***4a***, ***5a***, *and* ***7a***: To a stirred solution of homoallylic alcohol **3a** (423 mg, 1.5 mmol) in CH_2Cl_2 (4.0 mL) was added PCC (485 mg, 2.25 mmol) at room temperature and stirred for 15 h. After dilution with CH_2Cl_2, the reaction mixture was filtered through a Celite pad. After the aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 9:1), compound **4a** was obtained as a white solid, 378 mg (90%). A stirred mixture of **4a** (280 mg, 1.0 mmol) and Et_3N (101 mg, 1.0 mmol) in DMF (2.0 mL) was heated to 90 °C for 2 h. After the aqueous extractive workup and column chromatographic purification process (hexanes/ether, 12:1), compound **5a** was obtained as a white solid, 199 mg (71%). To a stirred mixture of **5a** (196 mg, 0.7 mmol) and allyl bromide (**6a**, 212 mg, 1.75 mmol) in THF (2.0 mL) was added zinc dust (230 mg, 3.5 mmol), and the reaction mixture was heated to reflux for 5 h. After dilution with THF, the reaction mixture was filtered through a Celite pad. After removing the solvent and column chromatographic purification process (hexanes/ether, 7:1), compound **7a** was obtained as a white solid, 142 mg (70%). Other compounds were synthesized similarly, and the known compounds **3a**,[4a,b,5m,11] **3b**,[4b] **3c**,[4a] **3d**,[6c] **4a**,[11] **5a**,[4b] and **7a**[4b] were identified by comparison their spectroscopic data with the reported. Selected spectroscopic data of unknown compounds **3e**, **4c**, **4e**, **5e**, **7b**, **7e**, **7f**, **7g**, **9**, **10**, **11**, and **12** are as follows.
Compound ***3e***: 88%; colorless oil; IR (film) 3482, 3027, 2950, 1716, 1439, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67 (br s, 1H), 3.71 (s, 3H), 3.64–3.77 (m, 1H), 5.00 (d, *J* = 6.3 Hz, 1H), 5.61 (s, 1H), 6.19 (s, 1H), 6.39–6.51 (m, 2H), 7.19–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.01, 54.00, 75.72, 126.33, 126.63, 126.97, 127.44, 127.53, 127.55, 128.08, 128.48, 133.71, 136.86, 140.32, 141.87, 167.28; ESIMS *m*/*z* 309 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.74; H, 6.62.
Compound ***4c***: 62%; colorless oil; IR (film) 1719, 1138 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 3.78 (s, 3H), 4.99 (s, 1H), 5.24 (s, 1H), 6.38 (s, 1H), 7.17–7.21 (m, 2H), 7.29–7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.61, 52.16, 60.44, 127.89, 128.13, 129.07, 129.61, 134.80, 139.55, 167.16, 205.77; ESIMS *m*/*z* 219 $[M+H]^+$. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.77; H, 6.29.
Compound ***4e***: 84%; pale yellow solid, mp 128–130 °C; IR (KBr) 1717, 1684, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 5.45 (d, *J* = 8.7 Hz, 1H), 5.84 (s, 1H), 6.34 (dd, *J* = 15.9 and 8.7 Hz, 1H), 6.47 (s, 1H), 6.56 (d, *J* = 15.9 Hz, 1H), 7.20–7.58 (m, 8H), 8.02–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.88, 52.23, 124.98, 126.43, 127.94 (2C), 128.55, 128.62, 128.72, 133.13, 134.80, 136.19, 136.40, 138.83, 166.68, 197.99; ESIMS *m*/*z* 307 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.19; H, 5.87.
Compound ***5e***: 74%; white solid, mp 126–128 °C; IR (KBr) 1720, 1675, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 3.55 (s, 3H), 6.56 (d, *J* = 16.5 Hz, 1H), 7.21–7.57 (m, 9H), 7.92–7.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.82, 51.96, 122.77, 125.69, 127.14, 128.53, 128.63, 128.68, 129.12, 133.04, 136.03, 136.63, 138.39, 148.01, 167.27, 197.45; ESIMS *m*/*z* 307 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.68; H, 6.04.
Compound ***7b***: 81%; colorless oil; IR (film) 1756, 1445, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 3H), 1.90 (s, 3H), 2.82 (d, *J* = 14.4 Hz, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 4.60 (s, 1H), 4.84 (s, 1H), 6.82–6.85 (m, 2H), 7.21–7.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.68, 24.19, 43.29, 89.99, 116.56, 124.66, 125.96, 128.25 (2C), 128.32, 129.05, 131.62, 137.54, 139.21, 163.79, 173.86. (one carbon is overlapped); ESIMS *m*/*z* 305 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.53; H, 6.76.
Compound ***7e***: 73%; colorless oil; IR (film) 1757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 1.82 (s, 3H), 2.43 (ddt, *J* = 14.4, 6.9 and 1.2 Hz 1H), 2.59 (ddt, *J* = 14.4, 7.2 and 1.2 Hz, 1H), 5.04–5.15 (m, 2H), 5.61–5.76 (m, 1H), 7.21–7.26 (m, 2H), 7.40–7.50 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.47, 23.85, 41.85, 87.82, 119.75, 125.66, 127.65, 128.83, 129.10, 131.10, 132.15, 163.98, 173.25; ESIMS *m*/*z* 229 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.59; H, 7.31.
Compound ***7f***: 69%; colorless oil; IR (film) 1762, 1433, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 1.5H), 1.76 (s, 1.5H), 2.88–3.14 (m, 2H), 5.04–5.30 (m, 2H), 5.69–5.84 (m, 1H), 6.98–7.50 (m, 8H), 7.53 (d, *J* = 7.8 Hz, 0.5H), 7.68 (d, *J* = 7.8 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.73, 9.89, 40.76, 41.57, 90.28, 90.87, 119.48, 120.21, 122.50, 124.23, 124.72, 126.52, 126.61, 127.13, 127.23, 127.79, 128.33, 128.41, 130.36, 130.41, 130.90, 131.68, 131.90, 132.43, 133.06, 133.29, 135.67, 137.64, 161.63, 163.27, 173.04, 173.47. (four carbons are overlapped); ESIMS *m*/*z* 369 $[M+H]^+$, 371 $[M+H+2]^+$. Anal. Calcd for $C_{20}H_{17}BrO_2$: C, 65.05; H, 4.64. Found: C, 65.34; H, 4.76. It is interesting to note that compound **7f** exists as an atropisomeric mixture (ca. 1:1) around the C–C single bond between 2-bromophenyl and butenolide moieties. The methyl peaks (δ = 1.72 and 1.76 ppm) of **7f** in ^1H NMR spectrum coalesced a little when we took the spectrum in DMSO-d_6 at 50–60 °C; however, the rotation was not free even at the temperature.
Compound ***7g***: 51%; pale yellow oil; IR (film) 1737, 1684, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H), 3.03 (dd, *J* = 14.4 and 7.2 Hz, 1H), 3.31 (dd, *J* = 14.4 and 6.9 Hz, 1H), 5.08–5.19 (m, 2H), 5.52–5.67 (m, 1H), 6.68 (d, *J* = 16.5 Hz, 1H), 6.82 (d, *J* = 16.5 Hz, 1H), 7.28–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.52, 39.89, 88.48, 117.55, 120.14, 124.98, 126.03, 127.03, 128.72 (2C), 128.80, 129.39, 130.24, 135.64, 138.19, 138.40, 157.47, 173.63; ESIMS *m*/*z* 317 $[M+H]^+$. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.26; H, 6.35.
Compound ***9***: 55%; pale yellow oil; IR (film) 1752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.41 (s, 3H), 2.12 (s, 3H), 2.20 (d, *J* = 14.1 Hz, 1H), 2.29 (d, *J* = 14.1 Hz, 1H), 6.98–7.01 (m, 2H), 7.14–7.16 (m, 1H), 7.26–7.36 (m, 5H), 7.41–7.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.50, 28.69, 31.41, 43.22, 50.24, 95.78, 123.11, 123.72, 125.19, 127.74, 128.41, 128.62, 129.33, 130.45, 131.77, 138.28, 154.02, 159.87, 173.62; ESIMS *m*/*z* 305 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.73; H, 6.39.
Compound ***10***: 53%; pale yellow solid, mp 158–160 °C; IR (KBr) 1751, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 3.01 (dt, *J* = 13.8 and 2.4 Hz, 1H), 3.65 (d, *J* = 13.8 Hz, 1H), 5.15 (d, *J* = 2.4 Hz, 1H), 5.66 (d, *J* = 2.4 Hz, 1H), 7.18–7.29 (m, 5H), 7.37–7.47 (m, 2H), 7.69–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.35, 45.50, 85.54, 114.61, 121.86, 125.03, 126.01, 127.85, 128.63, 128.80, 129.07, 129.13, 130.68, 135.26, 137.91, 137.99, 158.21, 173.96; ESIMS *m*/*z* 289 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.19; H, 5.82.
Compound ***11***: 12%; pale yellow oil; IR (film) 1753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 2.17 (s, 3H), 6.35 (s, 1H), 7.20–7.46 (m, 9H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 9.34, 19.48, 88.07, 121.34, 124.99, 125.17, 126.86, 128.13, 128.28, 128.33, 128.43, 128.53, 130.60, 134.45, 134.93, 138.67, 160.58, 174.21; ESIMS *m*/*z* 289 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.05; H, 5.64.

Compound **12**: 100%; white solid, mp 112–114 °C; IR (KBr) 1757, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, *J* = 7.5 Hz, 3H), 1.32–1.44 (m, 2H), 1.88 (s, 3H), 1.99–2.10 (m, 1H), 2.24–2.35 (m, 1H), 6.79–6.84 (m, 2H), 7.17–7.23 (m, 2H), 7.28–7.39 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.57, 13.97, 16.50, 37.80, 90.74, 124.40, 125.79, 127.89, 128.17, 128.38, 128.46, 129.05, 131.75, 137.88, 164.10, 174.20; ESIMS *m*/*z* 293 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 82.01; H, 7.08.

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10. Ring-closing metathesis (RCM) reaction of **7g** was examined with second-generation Grubbs catalyst. However, a dimerization product was formed as a 1:1 mixture of cis and trans. Unfortunately we did not obtain any trace amount of RCM product even though the reaction was carried out under highly diluted conditions. The reason is not clear at this stage.
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