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Synthesis of indenoindene-fused α-methylene-γ-butyrolactones via a tandem intra- and intermolecular Friedel–Crafts reaction

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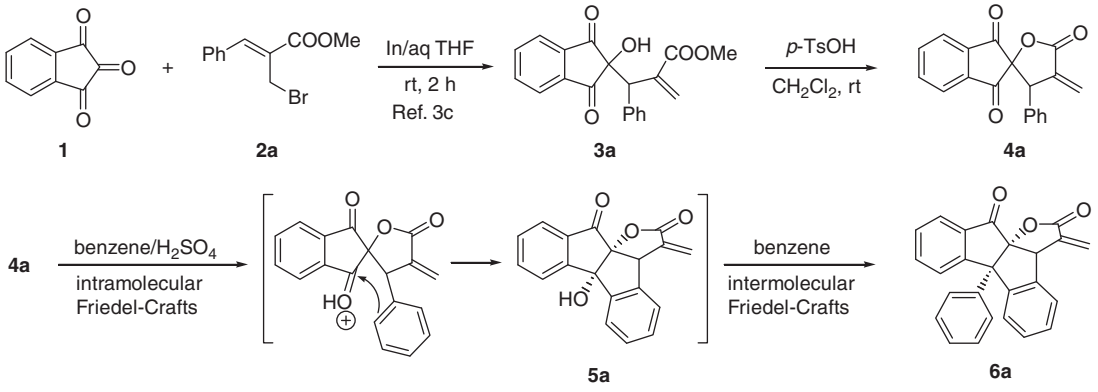
ABSTRACT

An efficient synthesis of indenoindene-fused α-methylene-γ-butyrolactones was carried out via a tandem intra- and intermolecular Friedel–Crafts reaction from the spiro-lactone, which can be easily prepared from ninhydrin by indium-mediated Barbier reaction of cinnamyl bromide.

α-Methylene-γ-butyrolactone derivatives have attracted much attention,[1,2] because they are found in a wide range of natural substances and are pivotal units for the observed biological activities.[1,2] Furthermore, α-methylene-γ-butyrolactones serve as versatile starting materials for many important compounds.[1–4] In addition, various fused α-methylene-γ-butyrolactones[4a–d] and their double-bond isomerized butenolide derivatives[4e–j] have also attracted much attention. The most straightforward method for the synthesis of α-methylene-γ-butyrolactones involves the reaction of allylic metal reagents and carbonyl compounds to generate homoallyl alcohols followed by acid-catalyzed lactonization.[2b–e,3]

Recently, we have been interested in the development of efficient synthetic methods for various α-methylene-γ-butyrolactones from Baylis–Hillman adducts.[3] In continuation of our studies, we decided to synthesize indenoindene-fused α-methylene-γ-butyrolactones[5,6] using the spiro-lactone derivative derived from ninhydrin and Baylis–Hillman bromide,[3c] as shown in Scheme 1. The indenoindene moiety should fix the target compound **6a** as a



Scheme 1.

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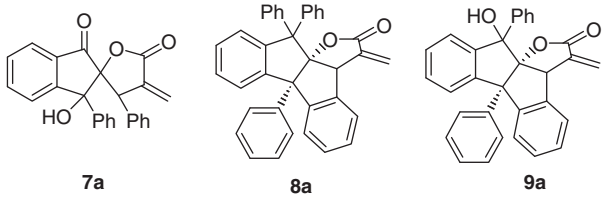
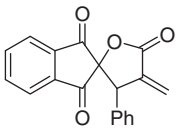
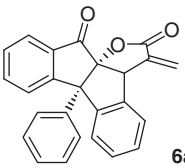
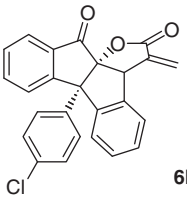
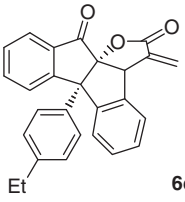
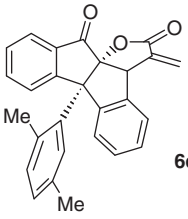
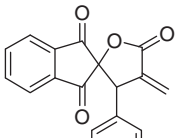
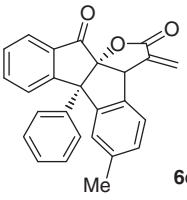
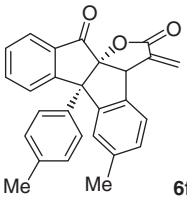
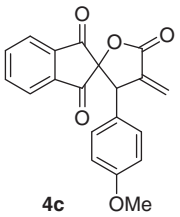
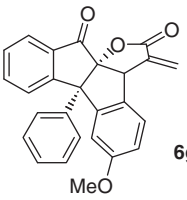


Figure 1.

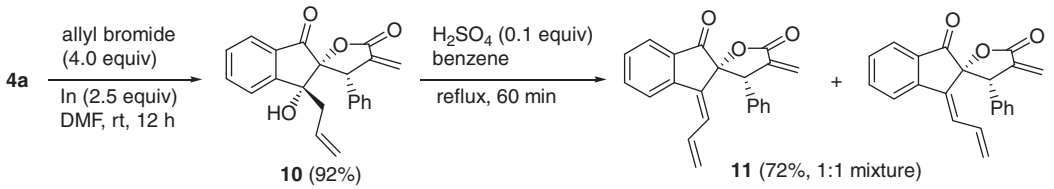
butterfly-like conformation, which was known to be essential in some NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) including nevirapine.[7]

Required starting material **4a** was prepared according to our previous paper.[3c] The reaction of ninhydrin (**1**) and cinnamyl bromide **2a** in the presence of indium metal afforded γ-hydroxy ester **3a**, and subsequent acid-catalyzed lactonization of **3a** with *p*-TsOH provided the spiro-lactone **4a** in good yield (77%).[3c,8] With compound **4a** in hand, we examined Friedel–Crafts type reactions in

Table 1
Synthesis of pentacyclic lactones

Entry	Substrate	Conditions	Product (%)
1	 **4a**	H_2SO_4 (5 equiv) benzene reflux, 9 h	 **6a** (95%)
2	**4a**	H_2SO_4 (20 equiv) chlorobenzene reflux, 2 h	 **6b** (87%)[a]
3	**4a**	H_2SO_4 (20 equiv) ethylbenzene reflux, 6 h	 **6c** (53%)[a]
4	**4a**	H_2SO_4 (20 equiv) *p*-xylene reflux, 20 h	 **6d** (58%)
5	 **4b**	H_2SO_4 (5 equiv) benzene reflux, 2 h	 **6e** (94%)
6	**4b**	H_2SO_4 (30 equiv) toluene reflux, 48 h	 **6f** (81%)[a]
7	 **4c**	PPA benzene reflux, 80 h	 **6g** (28%)

[a] Single isomer.



Scheme 2.

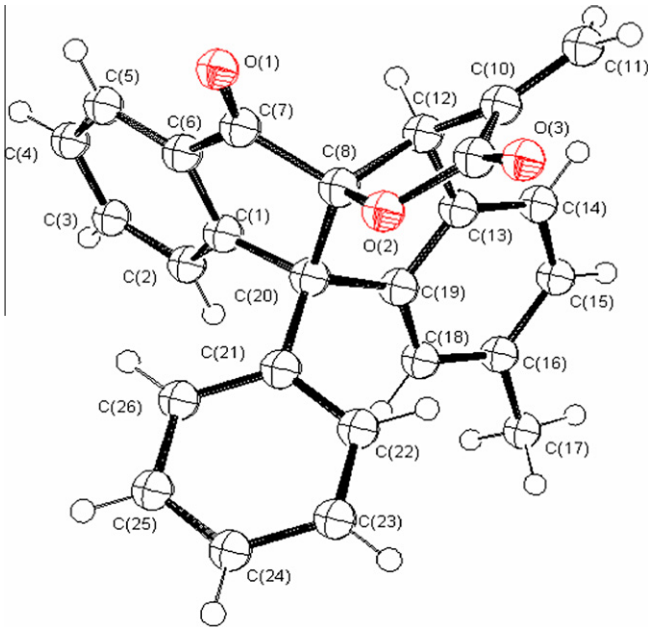
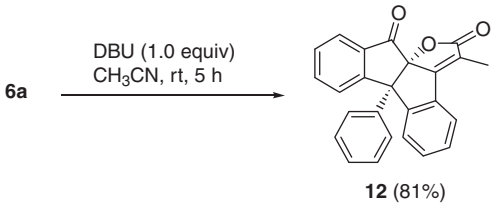


Figure 2. ORTEP drawing of compound **6e**.



Scheme 3.

benzene in the presence of H_2SO_4.[9] The reactions proceeded via an initial intramolecular Friedel–Crafts type reaction to form intermediate **5a** via the corresponding oxonium intermediate, and the subsequent intermolecular Friedel–Crafts reaction with benzene generates the final pentacyclic lactone **6a** in good yield (95%).[8] We did not observe the formation of **5a** or **7a**-**9a** (Fig. 1), which could be formed if the intermolecular Friedel–Crafts reaction was more facile than the intramolecular reaction.[5g,h] Based on these results, the reaction sequence presumably involves sequential intramolecular cyclization followed by an intermolecular Friedel–Crafts reaction. When we used AcOH as the acid catalyst, compound **6a** was not formed even after refluxing for a long time. When TfOH was used, the amounts of intractable side products were increased. Thus H_2SO_4 was chosen as the acid catalyst.

Encouraged by the results, we carried out the synthesis of similar pentacyclic lactones, as shown in Table 1. The reaction of **4a** in chlorobenzene required larger excess amounts of H_2SO_4 (20 equiv), and compound **6b** was obtained in 87% (entry 2). It is interesting to note that only the *p*-isomer was formed. The corresponding *ortho*-isomer was not formed presumably due to steric hindrance. The reaction of **4a** and ethylbenzene also produced the *p*-isomer **6c** in 53% (entry 3). The reaction of **4a** in *p*-xylene required a longer reaction time (20 h) to obtain moderate yield (58%) of **6d** (entry 4). The reason might be due to steric crowding around the carbocation in the second intermolecular Friedel–Crafts reaction with *p*-xylene. Product **6d** showed atropisomeric restricted rotation around the C–C bond between the xylyl moiety and indenoindene ring based on its ^1H and ^{13}C NMR spectra.[5h,8,11] The reaction of **4b** in benzene or toluene afforded **6e** and **6f** in good yields, respectively (entries 5 and 6). However, the reaction of methoxy derivative **4c** in benzene did not produce the expected product **6g,** which might be attributed to the loss of nucleophilicity of the *p*-anisole moiety by protonation with H_2SO_4. When we used PPA (polyphosphoric acid), compound **6g** was obtained (entry 7), albeit in low yield (28%). The structure of indenoindene-fused α-methylene-γ-butyrolactone **6** was confirmed unequivocally by its crystal structure (**6e** as an example, Fig. 2)[10] and the spectroscopic data.[8]

As a last entry, spiro-lactone **10** was prepared by the reaction of **4a** and allylindium reagents (Scheme 2). When we ran the reaction of **10** in benzene in the presence of H_2SO_4, we did not obtain the corresponding pentacyclic lactone via the intramolecular Friedel–Crafts reaction. Instead, 1,3-diene derivative **11** was isolated as a *cis/trans* mixture in 72%.[8]

The α-methylene-γ-butyrolactone moiety of **6a** could be converted easily to a butenolide moiety of **12** by treatment with DBU in CH_3CN at room temperature, as shown in Scheme 3. Such a fused butenolide moiety is found in many natural substances,[4e–j] and our method could provide an alternative route for numerous fused butenolides.

In summary, we disclose an efficient synthesis of indenoindene-fused α-methylene-γ-butyrolactones via a tandem intra- and intermolecular Friedel–Crafts reaction from the spiro-lactone, which can be easily obtained from ninhydrin and Baylis–Hillman adduct. Further studies on the structure modification and screening of their antiviral activities are currently underway.

Acknowledgments

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8. *Typical procedure for the synthesis of* **4a**:[3c] To a stirred solution of ninhydrin (231 mg, 1.3 mmol) and cinnamyl bromide **2a** (255 mg, 1.0 mmol) in aqueous THF (1:1, 3.0 mL) was added indium powder (148 mg, 1.3 mmol), and the reaction mixture was stirred at room temperature for 2 h under N_2 atmosphere. After the usual aqueous extractive workup and removal of solvent afforded crude γ-hydroxy ester **3a**. To the crude **3a** in CH_2Cl_2 (2.0 mL) was added *p*-TsOH (19 mg, 0.1 mmol), and the reaction mixture was stirred at room temperature for 12 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 5:1:1) compound **4a** was obtained as a white solid, 234 mg (77%).[3c] Other compounds were synthesized similarly, and the spectroscopic data of unknown compounds **4b** and **4c** are as follows.
Compound **4b**: 75%; white solid, mp 146–148 °C; IR (KBr) 1789, 1755, 1724, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 3H), 4.60 (dd, J = 3.6 and 3.3 Hz, 1H), 5.63 (d, J = 3.3 Hz, 1H), 6.59 (d, J = 3.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.95, 52.86, 84.11, 123.63, 123.71, 124.64, 128.68, 129.22, 129.48, 135.41, 136.67, 137.09, 138.51, 140.74, 141.04, 168.49, 194.13, 194.30; ESIMS (positive ion) *m*/*z* 319 (M^++H). Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.75; H, 4.54.
Compound **4c**: 71%; white solid, mp 123–125 °C; IR (KBr) 1788, 1755, 1725, 1514, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 4.59 (dd, J = 3.6 and 3.0 Hz, 1H), 5.63 (d, J = 3.0 Hz, 1H), 6.58 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 7.5 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.58, 55.11, 84.17, 114.14, 123.44, 123.60, 123.69, 124.55, 130.54, 135.59, 136.67, 137.15, 140.68, 141.04, 159.51, 168.46, 194.14, 194.44; ESIMS (positive ion) *m*/*z* 335 (M^++H). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.79; H, 4.52.
Typical procedure for the synthesis of **6a:** A mixture of compound **4a** (152 mg, 0.5 mmol) and H_2SO_4 (245 mg, 2.5 mmol) in benzene (2.0 mL) was heated to reflux for 9 h under nitrogen atmosphere. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 17:1:4) compound **6a** was obtained as a white solid, 173 mg (95%). Other compounds were synthesized similarly, and the spectroscopic data of **6a-g** are as follows. Compounds **10**–**12** were prepared as shown in Scheme 2 and Scheme 3, and the spectroscopic data of **10**–**12** are also noted herewith.
Compound **6a**: 95%; white solid, mp 227–229 °C; IR (KBr) 1778, 1727, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.51 (dd, J = 2.7 and 2.1 Hz, 1H), 6.01 (d, J = 2.1 Hz, 1H), 6.38 (d, J = 2.7 Hz, 1H), 6.70–6.77 (m, 2H), 7.19–7.28 (m, 3H), 7.34–7.46 (m, 4H), 7.53 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.19, 67.29, 95.18, 124.08, 124.37, 124.74, 125.88, 126.61, 127.76, 128.21, 129.14, 129.19, 129.48, 129.49, 133.20, 135.84, 137.16, 140.05, 140.25, 145.03, 155.96, 168.53, 199.18; ESIMS (positive ion) *m*/*z* 365 (M^++H). Anal. Calcd for $C_{25}H_{16}O_3$: C, 82.40; H, 4.43. Found: C, 82.65; H, 4.71.
Compound **6b**: 87%; white solid, mp 260–262 °C; IR (KBr) 1779, 1728, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.51 (dd, J = 2.4 and 2.1 Hz, 1H), 6.03 (d, J = 2.1 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.34–7.42 (m, 4H), 7.54 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.18, 66.78, 95.06, 124.37, 124.50, 124.90, 125.70, 126.46, 128.43, 129.43, 129.68, 129.71, 130.49, 133.09, 133.90, 135.58, 137.35, 138.69, 140.23, 144.56, 155.38, 168.40, 198.79; ESIMS (positive ion) *m*/*z* 399 (M^++H), 401 (M^++H+2). Anal. Calcd for $C_{25}H_{15}ClO_3$: C, 75.29; H, 3.79. Found: C, 75.03; H, 4.05.
Compound **6c**: 53%; white solid, mp 188–191 °C; IR (KBr) 1778, 1728, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7.5 Hz, 3H), 2.59 (q, J = 7.5 Hz, 2H), 4.50 (s, 1H), 6.01 (s, 1H), 6.37 (s, 1H), 6.64 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 7.8 Hz, 2H), 7.36–7.48 (m, 4H), 7.51 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.10, 28.26, 51.18, 67.04, 95.25, 123.99, 124.30, 124.67, 125.88, 126.64, 127.69, 129.07, 129.10, 129.39, 129.42, 133.12, 135.90, 137.09, 137.25, 140.19, 143.63, 145.21, 156.08, 168.62, 199.26; ESIMS (positive ion) *m*/*z* 393 (M^++H). Anal. Calcd for $C_{27}H_{20}O_3$: C, 82.63; H, 5.14. Found: C, 82.71; H, 5.02.
Compound **6d**: 58% (major/minor, 3:2); white solid, mp 226–229 °C; IR (KBr) 1778, 1727, 1219 cm^{-1}; ^1H NMR (major, $CDCl_3$, 300 MHz) δ 1.52 (s, 3H), 2.08 (s, 3H), 4.47 (dd, J = 2.7 and 2.4 Hz, 1H), 6.09 (d, J = 2.7 Hz, 1H), 6.14 (br s, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.99 (br s, 2H), 7.33–7.91 (m, 8H); ^1H NMR (minor, $CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 2.10 (s, 3H), 4.59 (dd, J = 3.3 and 3.0 Hz, 1H), 5.85 (d, J = 3.3 Hz, 1H), 6.24 (d, J = 3.0 Hz, 1H), 6.52 (br s, 1H), 6.96 (br s, 2H), 7.33–7.91 (m, 8H); ^{13}C NMR (major + minor, $CDCl_3$, 75 MHz) δ 20.97 (2C), 22.03, 22.66, 51.32, 51.53, 67.47, 67.50, 93.36, 96.22, 123.59, 124.38, 124.43, 124.72, 124.76, 125.11, 125.34, 127.29, 127.57, 128.55, 128.81, 128.86, 129.04, 129.09 (2C), 129.46, 131.09, 132.06, 132.68, 133.50, 134.83, 135.17, 135.40, 135.57, 136.00, 136.58 (2C), 136.61, 136.82, 137.30, 138.75, 139.17, 145.84, 146.30, 156.06, 159.86, 168.53, 169.01, 199.03, 200.56 (four carbons are overlapped); ESIMS (positive ion) *m*/*z* 393 (M^++H). Anal. Calcd for $C_{27}H_{20}O_3$: C, 82.63; H, 5.14. Found: C, 82.86; H, 5.43.
Compound **6e**: 94%; white solid, mp 260–262 °C; IR (KBr) 1778, 1727, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 4.47 (dd, J = 2.4 and 2.1 Hz, 1H), 5.98 (d, J = 2.1 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 6.73–6.77 (m, 2H), 7.18–7.24 (m, 6H), 7.52 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.47, 50.89, 67.20, 95.43, 123.85, 124.03, 124.72, 126.12, 126.65, 127.71, 128.20, 129.12, 129.20, 130.49, 133.24, 136.12, 137.11, 137.39, 139.59, 140.16, 145.14, 156.05, 168.62, 199.31; ESIMS (positive ion) *m*/*z* 379 (M^++H). Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79. Found: C, 82.33; H, 4.58.
Compound **6f**: 81%; white solid, mp 266–268 °C; IR (KBr) 1768, 1730, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.36 (s, 3H), 4.45 (s, 1H), 5.97 (s, 1H), 6.35 (s, 1H), 6.62 (d, J = 6.0 Hz, 2H), 7.03 (d, J = 6.0 Hz, 2H), 7.16–7.26 (m, 3H), 7.51 (t, J = 6.3 Hz, 1H), 7.60 (d, J = 6.3 Hz, 1H), 7.74 (t, J = 6.3 Hz, 1H), 7.88 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.97, 21.46, 50.84, 66.94, 95.43, 123.80, 123.98, 124.68, 126.11, 126.62, 128.95, 129.07 (2C), 130.42, 133.19, 136.19, 137.07, 137.20, 137.35, 137.44, 139.53, 145.26, 156.19, 168.70, 199.41; ESIMS (positive ion) *m*/*z* 393 (M^++H). Anal. Calcd for $C_{27}H_{20}O_3$: C, 82.63; H, 5.14. Found: C, 82.60; H, 5.45.
Compound **6g**: 28%; white solid, mp 232–234 °C; IR (KBr) 1777, 1727, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H), 4.44 (dd, J = 2.4 and 2.1 Hz, 1H), 5.97 (d, J = 2.1 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.72–6.78 (m, 2H), 6.91–6.96 (m, 2H), 7.20–7.29 (m, 4H), 7.54 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.56, 55.62, 67.32, 95.73, 110.74, 115.77, 123.77, 124.79, 125.13, 126.60, 127.81, 128.26, 129.21 (2C), 132.27, 133.31, 136.27, 137.10, 139.89, 146.46, 155.77, 160.90, 168.64, 199.20; ESIMS (positive ion) *m*/*z* 395 (M^++H). Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.44; H, 4.56.
Compound **10**: 92%; white solid, mp 140–142 °C; IR (KBr) 3464, 1780, 1764, 1729, 1287 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (dd, J = 13.8 and 7.2 Hz, 1H), 2.83 (dd, J = 13.8 and 7.8 Hz, 1H), 3.39 (s, OH), 5.07 (dd, J = 3.6 and 3.3 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 5.53 (d, J = 3.3 Hz, 1H), 5.76–5.90 (m, 1H), 6.53 (d, J = 3.6 Hz, 1H), 6.72–7.00 (m, 5H), 7.11–7.21 (m, 2H), 7.51–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 46.29, 50.17, 77.18, 96.09, 122.08, 122.71, 123.96, 127.46, 127.95 (2C), 129.15, 129.72, 131.40, 133.01, 134.34, 135.38, 137.37, 153.05, 169.48, 197.51; ESIMS (positive ion) *m*/*z* 347 (M^++H). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.47; H, 5.42.
Compound **11**: 72% (*cis*/*trans*, 1:1); white solid, mp 248–250 °C (decomp.); IR (KBr) 1779, 1726, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.47 (t, J = 0.6 Hz, 0.5H), 4.69 (t, J = 0.6 Hz, 0.5H), 5.52–5.70 (m, 2H), 5.59 (d, J = 3.3 Hz, 0.5H), 5.64 (d, J = 3.3 Hz, 0.5H), 6.57 (d, J = 3.9 Hz, 0.5H), 6.62 (d, J = 3.9 Hz, 0.5H), 6.70 (d, J = 11.7 Hz, 0.5H), 6.88–7.57 (m, 9.5H), 7.62 (d, J = 7.8 Hz, 0.5H), 7.78 (d, J = 7.8 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.23, 57.18, 88.36, 89.42, 120.11, 123.23, 123.58, 123.73, 123.89, 123.96, 124.24, 124.79, 125.94, 127.49, 128.15, 128.21, 128.31 (2C), 129.05, 129.18, 129.23, 129.37, 130.80, 131.45, 132.16, 132.27, 132.37, 132.75, 133.72, 133.88, 136.01, 136.03, 136.58, 146.63, 148.52, 169.43 (2C), 198.04, 198.42 (one carbon is overlapped); ESIMS (positive ion) *m*/*z* 329 (M^++H). Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.61; H, 5.03.
Compound **12**: 81%; white solid, mp 207–209 °C; IR (KBr) 1767, 1726, 1286 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 6.85–6.88 (m, 2H), 7.25–7.26 (m, 3H), 7.33–7.36 (m, 1H), 7.43–7.52 (m, 3H), 7.58–7.66 (m, 2H), 7.75 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.79, 63.78, 96.73, 121.84, 124.59, 125.34, 125.43, 127.31, 127.93, 128.44, 128.88, 129.13, 129.27, 130.97, 131.77, 133.45, 136.71, 137.06, 150.87, 158.06, 158.24, 174.96, 197.17; ESIMS (positive ion) *m*/*z* 365 (M^++H). Anal. Calcd for $C_{25}H_{16}O_3$: C, 82.40; H, 4.43. Found: C, 82.59; H, 4.56.
9. For the similar Friedel–Crafts type reaction of ketone and arenes under strong acid conditions, see: (a) Sai, K. K. S.; Esteves, P. M.; da Penha, E. T.; Klumpp, D. A.

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10. Crystal data of compound **6e**: solvent of crystal growth ($EtOH/CH_2Cl_2$); empirical formula $C_{26}H_{18}O_3$, $F_w = 378.40$, crystal dimensions $0.38 \times 0.35 \times 0.23\ mm^3$, monoclinic, space group $P2(1)/n$, $a = 9.1254(2)$ Å, $b = 21.5910(5)$ Å, $c = 10.0847(3)$ Å, $\alpha = 90°$, $\beta = 105.9510(10)°$, $\gamma = 90°$, $V = 1910.45(8)$ $Å^3$, $Z = 4$, $D_{calcd} = 1.316\ mg/m^3$, $F_{000} = 792$, MoKα ($\lambda = 0.71073$ Å), $R_1 = 0.0453$, $wR_2 = 0.1118$ ($I > 2\sigma(I)$). The X-ray data has been deposited in CCDC with number 802634.

11. For the examples of atropisomerism, see: (a) Boiadjiev, S. E.; Lightner, D. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1721–1732; (b) Casarini, D.; Foresti, E.; Gasparrini, F.; Lunazzi, L.; Macciantelli, D.; Misiti, D.; Villani, C. *J. Org. Chem.* **1993**, *58*, 5674–5682.