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An efficient synthesis of α-methylene-γ-butyrolactones from Baylis–Hillman adducts via an In-mediated Barbier reaction and stereoselective lactonization under $MeSO_2Cl/Et_3N$ conditions

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ABSTRACT

An efficient synthesis of *trans*-α-methylene-γ-butyrolactones is disclosed from *syn*-homoallylic alcohols via the intramolecular mesylate displacement reaction promoted by nearby ester group under the influence of $MsCl/Et_3N$. *syn*-Homoallylic alcohols were prepared via the In-mediated Barbier reaction of the bromides of Baylis–Hillman adducts.

α-Methylene-γ-butyrolactone derivatives have attracted much attention,[1,2] because this moiety is found in a wide range of natural substances and is a pivotal unit for their biological activities.[1] Furthermore, α-methylene-γ-butyrolactones served as versatile starting materials for many important compounds.[1,2] The easiest method for the synthesis of α-methylene-γ-butyrolactones involved the reaction of allylic metal reagents and carbonyl compounds to make homoallyl alcohols followed by acid-catalyzed lactonization.[2b,c,e,f,3b–e]

syn-Homoallylic alcohol **2a** was formed as the major product in the metal-mediated reactions of benzaldehyde and cinnamyl bromide **1a** or the acetate of Baylis–Hillman adduct, as shown in Scheme 1.[2f,3,4] An acid-catalyzed lactonization of the *syn*-homoallylic alcohols mostly produced the corresponding *cis*-3,4-disubstituted α-methylene-γ-butyrolactones.[2f,4b] In order to prepare the *trans*-lactone **4a** from *syn*-homoallyl alcohol, Kabalka et al. used CBr_4/PPh_3 to convert the alcohol moiety into a good leaving group, a phosphonium salt, and carried out the lactonization (path a).[3a] Hall[3b,c] and Ramachandran[3d,e] used strong acids, TfOH and In $(OTf)_3$, respectively, to form the benzylic carbocation intermediate for the preparation of *trans*-lactone (path b).

Very recently we reported the synthesis of indeno[2,1-*a*]indane[4a] and γ-hydroxybutenolides[4b] from *syn*-homoallylic alcohols, prepared by the In-mediated Barbier-type reaction of aldehydes and cinnamyl bromides.[2b,4] During our continuous studies on the synthetic applicability of *syn*-homoallylic alcohols, we reasoned out that *trans*-α-methylene-γ-butyrolactone **4a** could be synthesized from *syn*-homoallylic alcohol **2a** via the mesylate **3a**, as shown in Scheme 1 (path c). The mesylate **3a** could be cyclized to form **4a** in an intramolecular S_N2 manner by the nearby ester moiety.[5] The use of a strong acid[3b–e] and tedious separation of a side product such as triphenylphosphine oxide[3a] could be avoided under the conditions.

In order to examine the feasibility of our rationale, various *syn*-homoallylic alcohols **2a–h** were prepared as reported.[2b,4,6] Various conditions were examined with **2a** as a model substrate, and we found that the use of MsCl (1.5 equiv) and Et_3N (1.8 equiv) in CH_2Cl_2 (0 °C to rt) provides suitable conditions.[7] *trans*-Lactone **4a** was isolated in high yield (89%) along with a trace amount (<2%) of the corresponding *cis*-lactone **5a**, which might be formed either via a direct esterification reaction of **2a** or in situ conversion of mesylate **3a** to the chloride and a following lactonization process.[5c] The plausible reaction mechanism for the *trans*-lactone **4a** is suggested in Scheme 2. The mesylate **3a** forms the corresponding oxonium ion intermediate (**I**) via the intramolecular S_N2-type attack of the ester.[5] The oxonium ion was converted to the *trans*-lactone **4a**. The use of TsCl instead of MsCl was found to be less effective and the addition of DMAP (cat.) did not improve the yield of **4a**.

Encouraged by the results we carried out the synthesis of *trans*-lactones **4b–h**, and the results are summarized in Table 1.[6,7] The reactions of **2b**, **2d**, **2g,** and **2h** afforded desired *trans*-lactones **4b**, **4d**, **4g,** and **4h** (entries 2, 4, 7 and 8) in moderate to good yields

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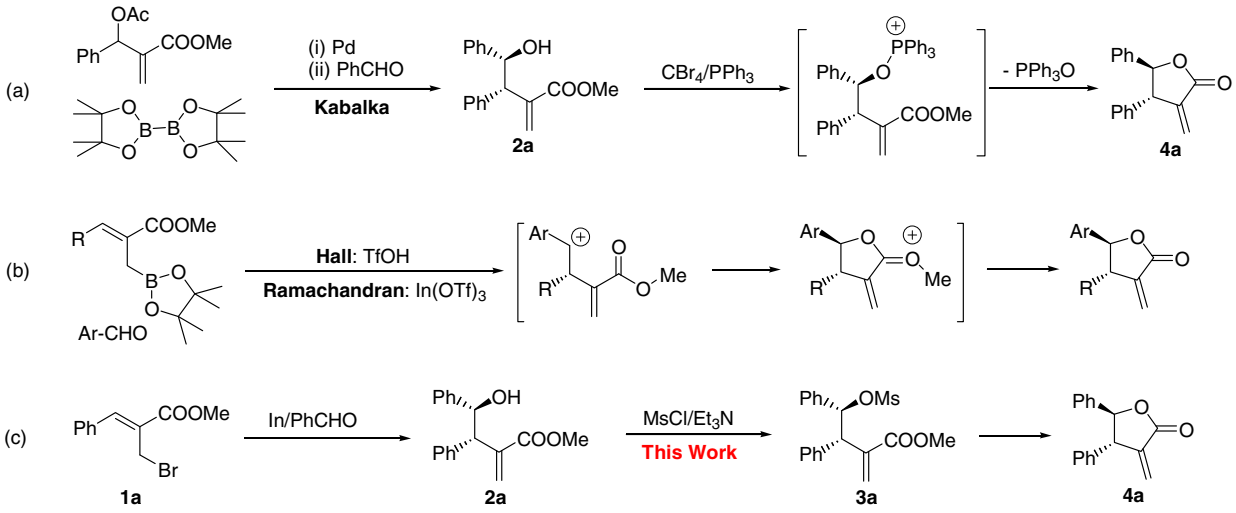
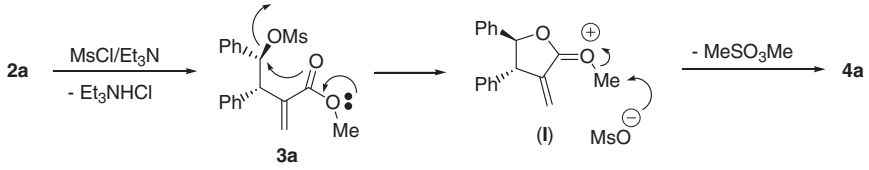
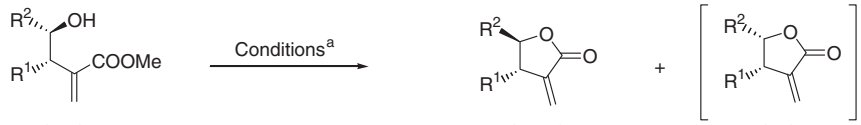


Scheme 1.



Scheme 2.

Table 1
Synthesis of *trans*-lactone from *syn* homolytic alcohol

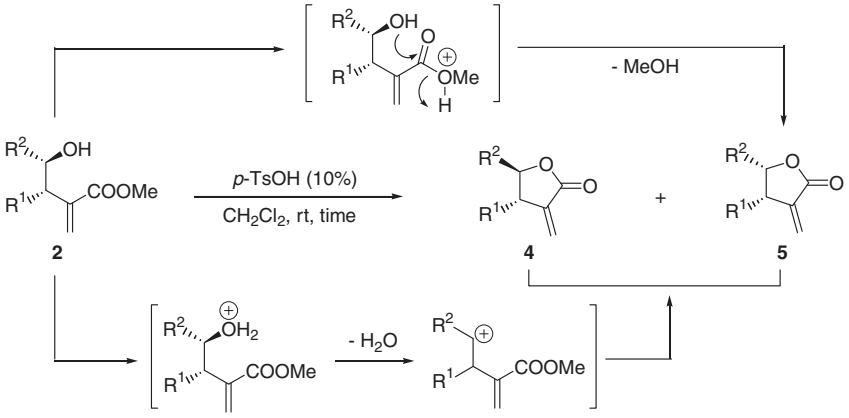


Entry	R^1	R^2	2[b] (%)	Time (h)	Products[c] (%)	Reported[d] (%)
1	Ph	Me	**2a** (93)	2	**4a** (89)	56 (**4a**),[3a] 91 (**4a**)[3d]
2	Ph	4-ClPh	**2b** (91)	4	**4b** (77)	80 (**4b**/**5b** = 69/31)[3d]
3	4-MePh	4-MeOPh	**2c** (81)	6	**4c** (50)	0 (**4c**)[3a]
4	Ph	4-MePh	**2d** (86)	2	**4d** (86)	98 (**4d**)[3d]
5	Ph	Me	**2e** (80)	30 min[e]	**4e** (85)[f]	No data
6	Ph	Cinnamyl	**2f** (81)	6	**4f** (48)	No data
7	Me	Ph	**2g** (84)	2	**4g** (87)	49 (**4g**),[3a] 85 (**4g**)[3d]
8	Me	3-ClPh	**2h** (84)	4	**4h** (72)	85 (**4h**/**5h** = 45/55)[3d]

[a] Conditions: MsCl (1.5 equiv), Et_3N (1.8 equiv), CH_2Cl_2, 0 °C to rt.
[b] Isolated yield of *syn* isomer prepared as reported.[2a,3a,4b]
[c] Trace amounts of *cis*-lactone were observed on TLC (<3%).
[d] We showed the reported data of Kabalka and Ramachandran.
[e] Corresponding mesylate **3e** was isolated in 89% instead of **4e**.
[f] *trans*-Lactone **4e** was synthesized by heating **3e** in toluene (**9h**) in the presence of DAMP (10%).

(72–87%). However, the reactions of *p*-methoxyphenyl derivative **2c** (entry 3) and cinnamyl derivative **2f** (entry 6) showed low yields of products, unexpectedly. Increased amounts of side products were observed on TLC. The reaction of **2e** did not produce **4e** at all under the same conditions (entry 5). As compared with other benzylic (**2a**–**d**, **2g** and **2h**) or allylic mesylate (**2f**), the corresponding mesylate **3e** is a secondary alkyl one and the ester-mediated lactonization of **3e** was ineffective at room temperature. Fortunately when the mesylate **3e** was heated to reflux in toluene in the presence of DMAP (10%) the lactonization occurred smoothly to afford **4e** in 85%. It is interesting to note that the reactions with the corresponding ethyl or *n*-hexyl esters of **2a** showed somewhat diminished yield of **4a** (75% and 55%, respectively). Increased amounts of side products were observed for the ethyl and hexyl esters. The results might be due to the increased steric interference during formation of the corresponding oxonium ion intermediate.

In order to overcome the low yields of *trans*-lactones in some cases (entries 3 and 6 in Table 1) we examined the lactonization of **2** under acid-catalyzed reaction conditions, as shown in Scheme 3. The reaction of **2a** under acid-catalyzed conditions (*p*-TsOH, CH_2Cl_2, rt) produced a *cis*-lactone **5a** exclusively, presumably via the Fischer esterification mechanism as reported.[3a,4b] We could



Entry	Substrate	Time (h)	Product (%)[a]
1	**2a**	1	**4a** (0),[b] **5a** (95)
2	**2c**	4	**4c** (62), **5c** (20)
3	**2c**	24	**4c** (78), **5c** (10)
4	**2c**	72	**4c** (81), **5c** (8)
5	**2f**	1	**4f** (21), **5f** (70)
6	**2f**	72	**4f** (52), **5f** (37)

[a]Isolated yield. [b]Compound **4a** was not observed after 24 h.

Scheme 3.

not observe the formation of any trace amount of a *trans*-lactone **4a** even after 24 h under the conditions.[3c] However, the reaction of **2c** produced the desired *trans*-lactone **4c** in 62% yield (entry 2), and the yield of **4c** increased to 81% when the reaction mixture was stirred for a long time (entry 4).[8] The formation of **4c** must involve the carbocation intermediate, and the ratio of **4c**/**5c** might be the result of relative thermodynamic stabilities of the lactones. The *p*-methoxy substituent of **2c** could stabilize the benzylic carbocation intermediate.[3c,3d] The slow conversion of **5c** to **4c** could be explained by ring-opening of **5c** to the carbocation intermediate and re-cyclization to the more stable **4c**, as observed by Hall in a similar case.[3c] The reaction of cinnamyl derivative **2f** produced a *cis*-lactone **5f** as the major product (70%) when we stop the reaction in short time (entry 5); however, the yield of a *trans*-lactone **4f** increased to 52% after 72 h (entry 6). The results stated that the ratio of *cis*/*trans*-lactones is highly dependent on the carbocation stability and the relative thermodynamic stabilities under the acid-catalyzed lactonization conditions.

In summary, we disclosed an efficient synthetic method of *trans*-α-methylene-γ-butyrolactone derivatives from the easily available *syn*-homoallylic alcohols under $MsCl/Et_3N$ conditions. In addition, the yields of *trans*-lactones could be increased using the equilibrium process under acid-catalyzed conditions when the yield was low under $MsCl/Et_3N$ conditions.

Acknowledgments

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6. *Preparation of starting materials* **2a**–**h**: The starting materials **2a**–**h** were prepared according to the reported procedure by the In-mediated Barbier-type reaction of corresponding aldehydes and the cinnamyl bromides of Baylis–Hillman adducts.[2b,4b] The compounds **2a**,[3a,4b] **2b**[4b] and **2g**[3a] are known, and the spectroscopic data of unknown compounds **2c**–**f** and **2h** are as follows.

Compound **2c**: 81%; colorless oil; IR (film) 3504, 2949, 1720, 1612, 1513, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (br s, 1H), 2.31 (s, 3H), 3.55 (s, 3H), 3.76 (s, 3H), 4.24 (d, J = 8.4 Hz, 1H), 5.16 (d, J = 8.4 Hz, 1H), 5.74 (s, 1H), 6.19 (s, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.97, 51.75, 53.86, 55.12, 75.32, 113.52, 126.41, 128.17, 128.91, 129.23, 134.16, 135.78, 136.70, 141.22, 159.02, 166.94; ESIMS m/z 327 (M^++H). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.87; H, 6.67.

Compound **2d**: 86%; colorless oil; IR (film) 3503, 3026, 1720, 1624, 1438, 1250, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (d, J = 3.0 Hz, 1H), 2.32 (s, 3H), 3.57 (s, 3H), 4.31 (d, J = 8.1 Hz, 1H), 5.22 (dd, J = 8.1 and 3.0 Hz, 1H), 5.79 (s, 1H), 6.23 (s, 1H), 7.10 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.25–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.11, 51.83, 54.16, 75.62, 126.70, 126.91, 127.17, 128.51, 128.93, 129.16, 137.44, 138.80, 138.98, 141.08, 166.94; ESIMS m/z 297 (M^++H). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.26; H, 6.68.

Compound **2e**: 80%; colorless oil; IR (film) 3537, 2971, 1720, 1624, 1439, 1255, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J = 6.3 Hz, 3H), 1.70 (br s, 1H), 3.68 (s, 3H), 3.84 (d, J = 7.2 Hz, 1H), 4.32–4.40 (m, 1H), 5.85 (s, 1H), 6.35 (s, 1H), 7.19–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.45, 51.96, 54.25, 69.02, 125.95, 127.12, 128.58, 129.10, 138.94, 141.66, 167.21; ESIMS m/z 221 (M^++H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.05; H, 7.25.

Compound **2f**: 81%; colorless oil; IR (film) 3480, 3026, 1717, 1438, 1253, 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.90 (br s, 1H), 3.62 (s, 3H), 4.13 (d, J = 7.5 Hz, 1H), 4.83 (dd, J = 7.5 and 7.2 Hz, 1H), 5.85 (s, 1H), 6.20 (dd, J = 15.9 and 7.2 Hz, 1H), 6.35 (s, 1H), 6.60 (d, J = 15.9 Hz, 1H), 7.19–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.96, 53.06, 74.17, 126.49, 126.78, 127.19, 127.69, 128.48, 128.59, 129.13, 130.04, 131.90, 136.53, 138.52, 141.02, 167.23; ESIMS m/z 309 (M^++H). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.69; H, 6.86.

Compound **2h**: 84%; colorless oil; IR (film) 3504, 2950, 1713, 1438, 1270, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, J = 7.2 Hz, 3H), 2.63 (d, J = 2.7 Hz, 1H), 3.05–3.14 (m, 1H), 3.78 (s, 3H), 4.86 (dd, J = 3.6 and 2.7 Hz, 1H), 5.59 (s, 1H), 6.29 (s, 1H), 7.19–7.28 (m, 3H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.29, 42.64, 52.12, 74.76, 124.33, 126.33, 126.52, 127.25, 129.26, 133.98, 142.15, 144.73, 168.06; ESIMS m/z 255 (M^++H), 257 (M^++2+H). Anal. Calcd for $C_{13}H_{15}ClO_3$: C, 61.30; H, 5.94. Found: C, 61.54; H, 6.11.

7. *Typical procedure for the synthesis of* **4a**: To a stirred solution of **2a** (141 mg, 0.5 mmol) and Et_3N (91 mg, 0.9 mmol) in dry CH_2Cl_2 (1.0 mL) was added a solution of MsCl (86 mg, 0.75 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C for 5 min by gas-tight syringe under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 15:1) compound **4a** was obtained as a white solid (mp 73–75 °C) 111 mg (89%), and the spectroscopic data were identical with the reported.[2c,3d]

When we used the procedure of **4a** for the synthesis of **4b**–**h** the yields of products decreased to some extent (5–10%) due to the increased formation of side products. Thus we used the following procedure for the synthesis of **4b**–**h**.

Typical procedure for the synthesis of **4b**: To a stirred solution of **2b** (159 mg, 0.5 mmol) and Et_3N (91 mg, 0.9 mmol) in dry CH_2Cl_2 (1.0 mL) was added a solution of MsCl (86 mg, 0.75 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C for 5 min by gas-tight syringe under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was poured into cold aqueous NH_4Cl and extracted with ether. The organic layer was separated, dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude reaction mixture was dissolved in CH_2Cl_2 (2.0 mL) and stirred for 4 h. After removal of CH_2Cl_2 and column chromatographic purification process (hexanes/EtOAc, 12:1) compound **4b** was obtained as a white solid (mp 78–79 °C) 109 mg (77%), and the spectroscopic data were identical with the reported.[3d] Other compounds **4c**–**h** were synthesized analogously and the selected spectroscopic data of unknown compounds **4c**, **4e**, **4f** and **4h** are as follows.

Compound **4c**: 50%; colorless oil; IR (film) 1768, 1613, 1514, 1250, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.80 (s, 3H), 4.01 (ddd, J = 7.8, 3.3 and 3.0 Hz, 1H), 5.29 (d, J = 7.8 Hz, 1H), 5.43 (d, J = 3.0 Hz, 1H), 6.41 (d, J = 3.3 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.07, 55.11, 55.26, 85.99, 114.05, 123.56, 127.11, 128.34, 129.80, 130.09, 134.96, 137.66, 140.20, 159.86, 169.62; ESIMS m/z 295 (M^++H). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.72; H, 6.33.

Compound **4e**: 85%; white solid; mp 37–39 °C; IR (KBr) 1767, 1387, 1224, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (d, J = 6.0 Hz, 3H), 3.72 (ddd, J = 7.8, 3.3 and 2.7 Hz, 1H), 4.48 (dq, J = 7.8 and 6.0 Hz, 1H), 5.39 (d, J = 2.7 Hz, 1H), 6.35 (d, J = 3.3 Hz, 1H), 7.19–7.23 (m, 2H), 7.29–7.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.79, 54.41, 81.71, 123.31, 127.86, 128.31, 129.10, 138.32, 140.34, 169.64; ESIMS m/z 189 (M^++H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.64; H, 6.65.

Compound **4f**: 48%; colorless oil; IR (film) 1768, 1494, 1454, 1307, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.98 (ddd, J = 7.8, 3.3 and 3.0 Hz, 1H), 4.96 (dd, J = 7.8 and 6.9 Hz, 1H), 5.46 (d, J = 3.0 Hz, 1H), 6.24 (dd, J = 15.9 and 6.9 Hz, 1H), 6.42 (d, J = 3.3 Hz, 1H), 6.59 (d, J = 15.9 Hz, 1H), 7.21–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.23, 85.35, 123.95, 124.82, 126.75, 127.97, 128.39, 128.43, 128.65, 129.18, 133.87, 135.51, 137.94, 139.44, 169.40; ESIMS m/z 277 (M^++H). Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.39; H, 5.91.

Compound **4h**: 72%; white solid; mp 78–80 °C; IR (KBr) 1768, 1308, 1252, 1209, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (d, J = 6.9 Hz, 3H), 2.88–2.97 (m, 1H), 4.88 (d, J = 7.8 Hz, 1H), 5.61 (d, J = 3.0 Hz, 1H), 6.33 (d, J = 3.3 Hz, 1H), 7.21–7.25 (m, 1H), 7.30–7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.95, 43.31, 84.88, 121.44, 123.91, 125.92, 128.91, 130.12, 134.78, 139.86, 140.49, 169.63; ESIMS m/z 223 (M^++H), 225 (M^++2+H). Anal. Calcd for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98. Found: C, 64.97; H, 5.11.

8. *Typical procedure for the synthesis of* **4c** (entry 4 in Scheme 3): To a stirred solution of **2c** (163 mg, 0.5 mmol) in dry CH_2Cl_2 (1.5 mL) was added *p*-TsOH (10 mg) and stirred at room temperature for 72 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 20:1) compound **4c** was obtained as colorless oil (119 mg, 81%) along with **5c** (12 mg, 8%). Other entries in Scheme 2 were carried out similarly, and the spectroscopic data of unknown compounds **5c** and **5f** are as follows.

Compound **5c**: 8%; colorless oil; IR (film) 1768, 1613, 1514, 1251, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 3.72 (s, 3H), 4.59 (ddd, J = 8.1, 3.3 and 2.7 Hz, 1H), 5.53 (d, J = 2.7 Hz, 1H), 5.76 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 3.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.95, 51.78, 55.15, 82.57, 113.29, 124.38, 127.17, 128.31, 128.87, 129.17, 133.13, 136.98, 138.28, 159.20, 170.86; ESIMS m/z 295 (M^++H). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.85; H, 6.27.

Compound **5f**: 37% (entry 6 in Scheme 3); colorless oil; IR (film) 1764, 1496, 1453, 1313, 1262, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.52 (ddd, J = 8.1, 3.0 and 2.7 Hz, 1H), 5.39 (dd, J = 8.1 and 6.6 Hz, 1H), 5.61 (dd, J = 15.9 and 6.6 Hz, 1H), 5.62 (d, J = 2.7 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 15.9 Hz, 1H), 7.09–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.54, 81.24, 124.78 (2C), 126.61, 127.88, 128.11, 128.52, 128.73, 129.29, 133.00, 135.81, 136.74, 138.09, 170.20; ESIMS m/z 277 (M^++H). Anal. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.72; H, 6.03.