

## Synthesis of $\beta,\gamma,\gamma$ -Tri- or $\gamma,\gamma$ -Disubstituted $\alpha$ -Methylene- $\gamma$ -butyrolactones Starting from the Baylis-Hillman Adducts

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A number of  $\alpha$ -methylene- $\gamma$ -butyrolactones display significant biological activity, and many syntheses of this class of molecules have been described.<sup>1-5</sup> Especially  $\alpha$ -methylene- $\gamma$ -butyrolactones having carboxylic acid or ester group are the basic skeletons of a number of biologically active compounds, which showed antitumor antibiotic, antibacterial, antifungal and growth regulating effects.<sup>5</sup> Roy and co-workers have published the synthesis of methylenolactocin, a kind of natural  $\beta$ -carboxy- $\alpha$ -methylene- $\gamma$ -butyrolactone, via the sequential radical cyclization of epoxide to form  $\alpha$ -methylene- $\gamma$ -butyrolactone and the following allylic oxidation.<sup>3c</sup> Srikrishna also reported an interesting approach toward  $\alpha$ -methylene- $\gamma$ -butyrolactones via the combination of Ueno-Stork radical cyclization and allylic oxidation protocol.<sup>5k</sup> Paquette and co-workers reported indium-mediated reactions of cinnamyl bromides and  $\alpha$ -oxy aldehydes<sup>6a</sup> or azetidinediones.<sup>6d</sup>

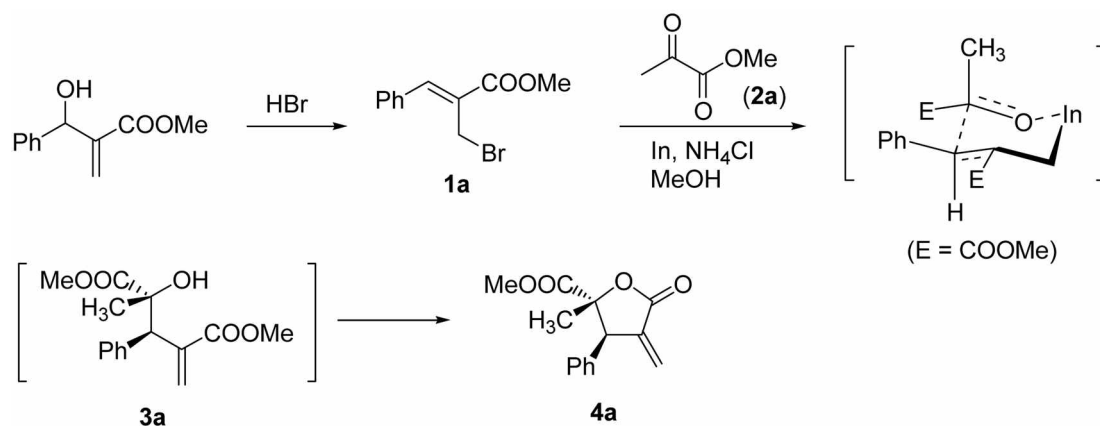
Although indium-mediated synthesis of lactones<sup>1</sup> would provide an effective method for  $\alpha$ -methylene- $\gamma$ -butyrolactones having carboxylic acid or carbonyl group at the  $\gamma$ -position, such trials were not reported to our surprise. In these respects, we examined the synthesis of this class of lactones from the reaction of indium-mediated reaction of cinnamyl bromide **1a** and  $\alpha$ -dicarbonyl compound **2a** as shown in Scheme 1.<sup>6,7</sup>

As shown in Scheme 1 and in Table 1, we examined the reaction of the cinnamyl bromide **1a** (made from the Baylis-Hillman adduct and HBr)<sup>8</sup> and methyl pyruvate (**2a**) in

MeOH in the presence of indium metal (1.1 equiv) and ammonium chloride (1.1 equiv) at around 50 °C for 4 h.<sup>7a</sup> We obtained the desired  $\alpha$ -methylene- $\gamma$ -butyrolactone derivative **4a** in 54% yield. As shown in Scheme 1, one (shown as **4a**) of the two possible diastereomers was formed selectively and the stereochemistry was confirmed by NOE experiment (Figure 1). The reaction was presumed to proceed via the most stable six-membered transition state (Scheme 1) to produce **3a** and eventually **4a** exclusively. We could not observe nor detect the corresponding intermediate **3a** in the reaction mixtures in this case (*vide infra*).

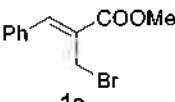
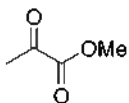
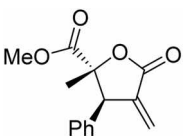
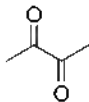
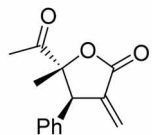
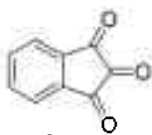
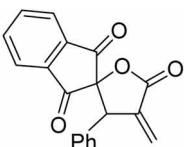
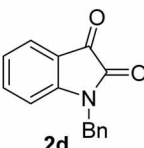
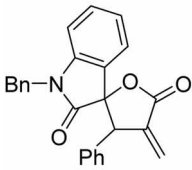
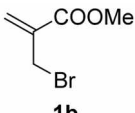
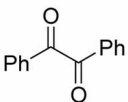
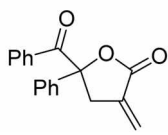
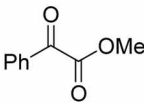
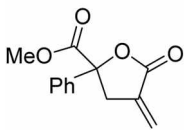
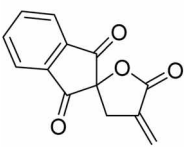
Encouraged by the successful results, we examined a variety of reactive carbonyl compounds **2b-f** and the results are summarized in Table 1. As shown in entry 2, the reaction of **1a** and 2,3-butanedione (**2b**) gave **4b** in 48% yield, similarly. The reaction of **1a** and ninhydrin (**2c**) or *N*-benzylisatin (**2d**), as the other reactive ketone derivatives, afforded spiro compounds **4c** and **4d** in 66% and 42% yields, respectively (entries 3 and 4). However, the reaction of **1a** and benzil (**2e**) or methyl benzoylformate (**2f**) did not give the corresponding lactone derivatives to our surprise. This failure might be due to severe steric hindrance in their corresponding transition states during the cyclization (cf. Scheme 1).

Thus, we examined the reactions of **2e** and **2f** by using the sterically less hindered allylic bromide **1b**.<sup>8</sup> As expected, the reactions of **1b** and **2e** or **2f** showed the formation of the corresponding lactone derivatives **4e** and **4f** on TLC.



Scheme 1

**Table 1.** Synthesis of  $\alpha$ -methylene- $\gamma$ -butyrolactones

Entry	Substrate	Ketone	Conditions	Product (%)
1	 <b>1a</b>	 <b>2a</b>	In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, 50 °C, 4 h	 <b>4a</b> (54)
2	<b>1a</b>	 <b>2b</b>	In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, 50 °C, 4 h	 <b>4b</b> (48)
3	<b>1a</b>	 <b>2c</b>	In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, 50 °C, 10 h	 <b>4c</b> (66) <sup>a</sup>
4	<b>1a</b>	 <b>2d</b>	In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, 50 °C, 4 h	 <b>4d</b> (42)
5	 <b>1b</b>	 <b>2e</b>	1. In (1.2 equiv), NH <sub>4</sub> Cl (1.2 equiv) MeOH, 50 °C, 5 h 2. column chromatography 3. benzene, PPTS (1.0 equiv) reflux, 60 h	 <b>4e</b> (44)
6	<b>1b</b>	 <b>2f</b>	1. In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, 50 °C, 6 h 2. column chromatography 3. benzene, PPTS (1.0 equiv) reflux, 60 h	 <b>4f</b> (42) <sup>b</sup>
7	<b>1b</b>	<b>2c</b>	1. In (1.1 equiv), NH <sub>4</sub> Cl (1.1 equiv) MeOH, rt, 3 h 2. column chromatography 3. benzene, PPTS (1.0 equiv) reflux, 15 h	 <b>4g</b> (64) <sup>c</sup>

<sup>a</sup>When the reaction was carried out in aq THF at rt the corresponding intermediate  $\gamma$ -hydroxy ester was observed in appreciable amounts on TLC.

<sup>b</sup>Methyl mandelate was also isolated in 8% yield. <sup>c</sup>We could isolate the corresponding  $\gamma$ -hydroxy ester **3g** in 49% yield before treatment with PPTS.

However, in these cases the corresponding  $\gamma$ -hydroxyester derivatives **3** were observed together with the lactones **4** in variable ratios. Thus we separated them together and treated with pyridinium *p*-toluenesulfonate (PPTS)<sup>13</sup> and could obtain the desired lactones **4e** and **4f** in moderate yields (entries 5 and 6). The reaction of **1b** and **2c** in the presence of In/NH<sub>4</sub>Cl at around 50 °C led to the formation of complex

mixtures of products. However, fortunately, when the reaction was carried out at room temperature we observed the formation of two major spots on TLC, corresponding  $\gamma$ -hydroxy ester derivative **3g** and the lactone **4g**. By following the similar protocol (treatment with PPTS after column separation) spiro compound **4g** was isolated in 64% yield (entry 7). In this case we could isolate  $\gamma$ -hydroxyester **3g**

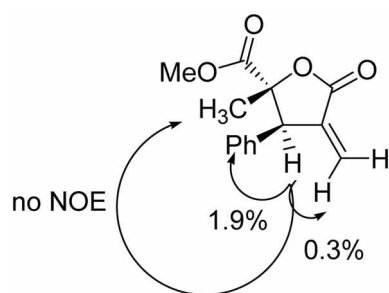
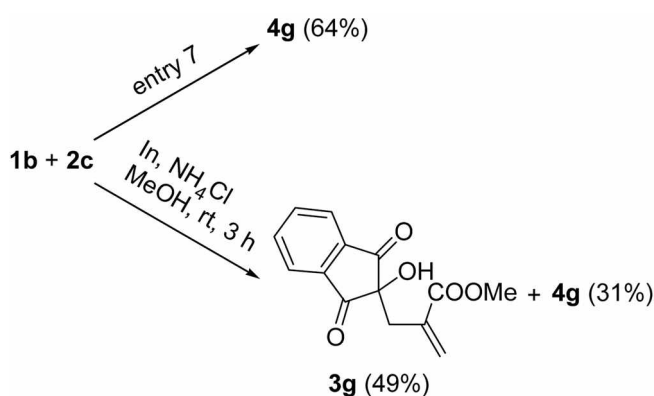


Figure 1. NOE results of **4a**.



Scheme 2

(49%) and lactone **4g** (31%) when we stopped the reaction before treatment with PPTS (Scheme 2).

In summary we disclosed the facile synthetic procedures of  $\alpha$ -methylene- $\gamma$ -butyrolactones having carbonyl substituent at the  $\gamma$ -position by using the indium-mediated lactone synthesis protocol.

## Experimental Section

**Typical procedure for the synthesis of 4a:** To a stirred mixture of **1a** (255 mg, 1.0 mmol), **2a** (tech., 90%, 115 mg, ca. 1.0 mmol), and indium (127 mg, 1.1 mmol) in MeOH (5 mL) was added  $\text{NH}_4\text{Cl}$  (59 mg, 1.1 mmol) and the reaction mixture was stirred at 50 °C for 4 h. After cooling to room temperature the reaction mixture was poured into cold water and extracted with  $\text{CH}_2\text{Cl}_2$ . After removal of solvent and column chromatographic purification process (hexanes/ether, 7 : 1) we obtained **4a** (133 mg, 54%) as a white solid. Other compounds were synthesized analogously and the spectroscopic data of **4a-g** and **3g** are as follows.

**Compound 4a:** 54%; white solid, mp 84–85 °C; IR (KBr) 1776, 1747, 1454, 1236, 1074  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.20 (s, 3H), 3.84 (s, 3H), 4.49 (t,  $J$  = 2.4 Hz, 1H), 5.66 (d,  $J$  = 2.4 Hz, 1H), 6.52 (d,  $J$  = 2.4 Hz, 1H), 7.15–7.19 (m, 2H), 7.32–7.40 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  20.88, 52.54, 53.15, 84.57, 125.70, 128.15, 128.76, 129.21, 136.73, 137.57, 168.78, 172.17; LCMS  $m/z$  246 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_4$ : C, 68.28; H, 5.73. Found: C, 68.12; H, 5.81.

**Compound 4b:** 48%; white solid, mp 110–111 °C; IR

(KBr) 1773, 1722, 1358, 1221, 1101, 1065  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.09 (s, 3H), 2.36 (s, 3H), 4.51 (t,  $J$  = 2.7 Hz, 1H), 5.66 (d,  $J$  = 2.7 Hz, 1H), 6.54 (d,  $J$  = 2.7 Hz, 1H), 7.17–7.22 (m, 2H), 7.31–7.40 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  21.05, 25.42, 50.64, 89.56, 126.33, 128.04, 128.72, 129.50, 136.69, 137.61, 168.75, 207.88; LCMS  $m/z$  230 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_5$ : C, 73.03; H, 6.13. Found: C, 73.35; H, 6.03.

**Compound 4c:** 66%; white solid, mp 144–145 °C; IR (KBr) 1790, 1751, 1724, 1599, 1275, 1228, 1022  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  4.63 (t,  $J$  = 3.3 Hz, 1H), 5.66 (d,  $J$  = 3.3 Hz, 1H), 6.62 (d,  $J$  = 3.3 Hz, 1H), 6.99–7.02 (m, 2H), 7.12–7.14 (m, 3H), 7.62 (d,  $J$  = 7.5 Hz, 1H), 7.75 (td,  $J$  = 7.5 and 1.2 Hz, 1H), 7.83 (td,  $J$  = 7.5 and 1.2 Hz, 1H), 8.00 (d,  $J$  = 7.5 Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  53.22, 84.13, 123.62, 123.74, 124.78, 128.66, 128.82, 129.39, 131.87, 135.20, 136.67, 137.12, 140.70, 141.06, 168.39, 194.00, 194.24; LCMS  $m/z$  304 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{12}\text{O}_4$ : C, 74.99; H, 3.97. Found: C, 74.87; H, 4.17.

**Compound 4d:** 42%; white solid, mp 149–150 °C; IR (KBr) 1780, 1732, 1614, 1468, 1365  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  4.72 (d,  $J$  = 15.6 Hz, 1H), 4.77 (t,  $J$  = 3.0 Hz, 1H), 5.02 (d,  $J$  = 15.6 Hz, 1H), 5.79 (d,  $J$  = 3.0 Hz, 1H), 6.54 (d,  $J$  = 8.1 Hz, 1H), 6.68 (t,  $J$  = 3.0 Hz, 1H), 6.79–6.82 (m, 2H), 6.99–7.30 (m, 11H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  44.05, 53.60, 84.29, 109.68, 122.74, 123.94, 124.84, 125.65, 127.02, 127.79, 128.24, 128.55, 128.80, 129.22, 130.72, 134.28, 134.69, 136.39, 142.67, 169.13, 173.40; LCMS  $m/z$  381 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{19}\text{NO}_3$ : C, 78.72; H, 5.02; N, 3.67. Found: C, 78.79; H, 5.30; N, 3.55.

**Compound 4e:** 44%; white solid, mp 77–78 °C; IR (KBr) 1778, 1680, 1448, 1261, 1175  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.01 (dt,  $J$  = 17.4 and 2.7 Hz, 1H), 4.24 (dt,  $J$  = 17.4 and 2.7 Hz, 1H), 5.70 (t,  $J$  = 2.7 Hz, 1H), 6.29 (t,  $J$  = 2.7 Hz, 1H), 7.28–7.50 (m, 8H), 7.94–7.98 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{DMSO-d}_6$ , 75 MHz)  $\delta$  38.94, 88.08, 122.71, 122.76, 122.77, 127.27, 127.59, 128.31, 129.77, 131.79, 132.46, 138.98, 167.77, 193.88; LCMS  $m/z$  278 ( $\text{M}^+$ ).

**Compound 4f:** 42%; white solid, mp 68–69 °C; IR (KBr) 1778, 1740, 1452, 1435, 1269, 1167  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.25 (dt,  $J$  = 17.1 and 3.0 Hz, 1H), 3.75 (s, 3H), 3.85 (dt,  $J$  = 17.1 and 3.0 Hz, 1H), 5.72 (t,  $J$  = 3.0 Hz, 1H), 6.30 (t,  $J$  = 3.0 Hz, 1H), 7.32–7.53 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  39.44, 53.44, 83.91, 123.56, 124.94, 128.70, 128.84, 132.59, 138.35, 168.25, 170.78; LCMS  $m/z$  232 ( $\text{M}^+$ ).

**Compound 4g:** 64%; white solid, mp 133–134 °C; IR (KBr) 1780, 1720, 1250, 1045  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.10 (t,  $J$  = 2.7 Hz, 2H), 5.82 (t,  $J$  = 2.7 Hz, 1H), 6.42 (t,  $J$  = 2.7 Hz, 1H), 7.98–8.03 (m, 2H), 8.06–8.11 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  32.61, 77.81, 124.14, 124.56, 131.09, 137.37, 140.45, 168.26, 194.53; LCMS  $m/z$  228 ( $\text{M}^+$ ).

**Compound 3g:** 49%; white solid, mp 114–115 °C; IR (KBr) 3444, 1751, 1714, 1599, 1441, 1173  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.84 (s, 2H), 3.73 (s, 3H), 4.31 (s, 1H), 5.76 (s, 1H), 6.35 (s, 1H), 7.89–7.94 (m, 2H), 7.95–8.00 (m,

2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  38.41, 52.25, 77.30, 123.89, 131.09, 133.28, 136.48, 139.72, 167.57, 198.55.

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