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Synthesis of β,β-disubstituted-α-methylene-γ-butyrolactones via the regioselective oxidation of *exo*-methylenetetrahydrofurans

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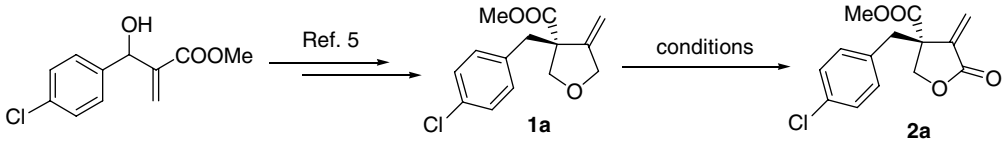
Abstract—The synthesis of various β,β-disubstituted-α-methylene-γ-butyrolactones was carried out from the corresponding methylenetetrahydrofuran derivatives by using PCC/Ac_2O or Jones oxidation conditions.

A number of α-methylene-γ-butyrolactones display a significant biological activity, and many syntheses of this class of molecules have been described.[1–4] Especially, β-carboxy-α-methylene-γ-butyrolactones is the basic skeleton of a number of biologically active compounds, which showed antitumor, antibacterial, antifungal, and growth regulating effects.[2] Roy and co-workers have published the synthesis of methylenolactocin, a kind of natural β-carboxy-α-methylene-γ-butyrolactone, via the sequential radical cyclization of epoxide to form methylenetetrahydrofuran and the following allylic oxidation.[2a] Srikrishna also reported an interesting approach toward α-methylene-γ-butyrolactones via the combination of Ueno–Stork radical cyclization and allylic oxidation protocol.[3b] In addition, some elegant synthesis of α-methylene-γ-butyrolactones starting from the Baylis–Hillman adducts have been published recently.[4]

In these contexts, we reasoned that we could convert the *exo*-methylenetetrahydrofuran derivatives into the corresponding α-methylene-γ-butyrolactones under suitable oxidation conditions. Thus, we examined the oxidation conditions for the efficient synthesis of **2a** from **1a**, which could be synthesized starting from the Baylis–Hillman adduct according to the reported method (Scheme 1).[5]

Scrutinizing the reported methods for the oxidation of similar structures revealed that the oxidations involving chromium could be the choice.[2a,3,6] Thus, we examined the oxidations of **1a** under the chromium-based oxidation conditions including PDC/Ac_2O/DMF,[6] PCC/CH_2Cl_2, PCC/Ac_2O/CH_2Cl_2, PCC/Ac_2O, and Jones oxidation conditions[2a] (Table 1). From the experiments we found that the use of PCC/Ac_2O (Table 1, entry 3) and Jones oxidation conditions (Table 1, entry 5) could be used efficiently. Actually, we could obtain **2a** in a good isolated yield (72%) under the conditions of PCC (3.0 equiv)/Ac_2O (0.2 equiv) in CH_2Cl_2 at refluxing temperature.[7] Under the Jones oxidation conditions we obtained a somewhat lower yield (64%) of **2a**.

With the successful results, we decided to examine the synthesis of various α-methylene-γ-butyrolactone and lactam derivatives. The requisite starting materials,



Scheme 1.

Keywords: α-Methylene-γ-butyrolactones; Regioselective oxidation; PCC/Ac_2O; Jones oxidation; Baylis–Hillman adducts.
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Table 1. Optimization of the oxidation conditions of compound **1a**

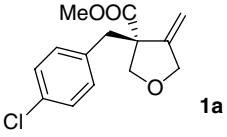
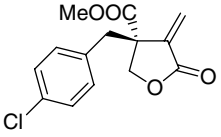
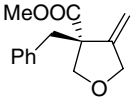
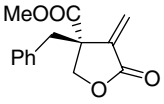
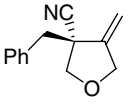
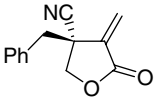
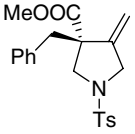
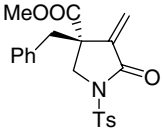
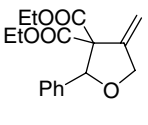
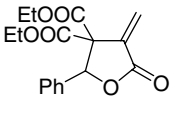
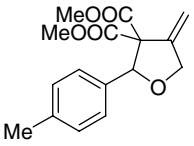
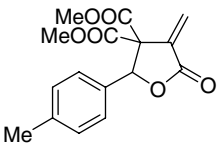
Entry	Conditions	Results (**1a**:**2a**)[a]
1	PDC (10 equiv), AC_2O (0.2 equiv), DMF, rt, 120 h	90:10
2	PCC (3 equiv), CH_2Cl_2, reflux, 72 h	50:50
3	PCC (3 equiv), AC_2O (0.2 equiv), CH_2Cl_2, reflux, 60 h	5:95 (72)[b]
4	PCC (3 equiv), AC_2O (as solvent), 40 °C, 1 h	Complex
5	CrO_3 (5 equiv), H_2SO_4 (0.5 equiv), aq acetone, 0 °C–rt, 18 h	0:100 (64)[b]

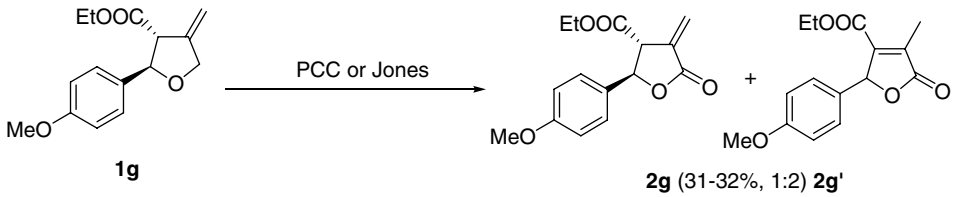
[a] Estimated ratio of **1a** versus **2a** on TLC.
[b] Isolated yield.

4,4-disubstituted-3-methylenetetrahydrofurans and tetrahydropyrrole **1a**–**d**, were easily prepared by the radical cyclization of propargyloxy-substituted cinnamyl alcohols or their nitrogen analogs, which were readily prepared from Baylis–Hillman adducts.[5] 3-Methylene-4,4,5-trisubstituted tetrahydrofurans, **1e** and **1f**, were synthesized according to our previous paper.[8] With these substrates **1a**–**f**, we examined the oxidations and the results are summarized in Table 2. For substrates **1b**–**d**, PCC/Ac_2O conditions gave reasonable yields of products (entries 3–5). However, for substrates **1e** and **1f** we could obtain lactones **2e** and **2f** under the Jones conditions only (entries 6–8). It is interesting to note that 4-mono-substituted analog **1g**[9] afforded **2g** and **2g′** as a 1:2 inseparable mixture in a low yield (Scheme 2).

In summary we disclosed a facile synthetic method of β,β-disubstituted- or β,β,γ-trisubstituted-α-methylene-γ-butyrolactone derivatives by the oxidation of the corresponding *exo*-methylenetetrahydrofuran derivatives with PCC/Ac_2O and/or CrO_3/aq H_2SO_4 in acetone.

Table 2. Synthesis of β,β-disubstituted-α-methylene-γ-butyrolactones

Entry	Substrate	Conditions	Product (%)
1	 **1a**	PCC (3.0 equiv) AC_2O (0.2 equiv) CH_2Cl_2, reflux, 60 h	 **2a** (72)
2	**1a**	CrO_3 (5.0 equiv) H_2SO_4 (0.5 equiv) aq acqtone, 0 °C–rt, 18 h	**2a** (64)
3	 **1b**	PCC (3.0 equiv) AC_2O (0.2 equiv) CH_2Cl_2, reflux, 30 h	 **2b** (77)
4	 **1c**	PCC (3.0 equiv) AC_2O (0.2 equiv) CH_2Cl_2, reflux, 90 h	 **2c** (76)
5	 **1d**	PCC (3.0 equiv) AC_2O (0.2 equiv) CH_2Cl_2, reflux, 44 h	 **2d** (55)
6	 **1e**	CrO_3 (5.0 equiv) H_2SO_4 (0.5 equiv) aq acqtone, 0 °C–rt, 20 h	 **2e** (71)
7	**1e**	PCC (3.0 equiv) AC_2O (0.2 equiv) CH_2Cl_2, reflux, 60 h	Complex mixtures (5–10% of **2e**)
8	 **1f**	CrO_3 (5.0 equiv) H_2SO_4 (0.5 equiv) aq acqtone, 0 °C–rt, 20 h	 **2f** (69)



Scheme 2.

Acknowledgements

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5. For the synthesis of starting materials **1a–d** and the synthetic applications, see: Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859, and references cited therein.
6. For the use of PDC/Ac_2O system in oxidations, see: (a) Kim, J. N.; Ryu, E. K. *Tetrahedron Lett.* **1992**, *33*, 3141; (b) Classon, B.; Samuelsson, B. *Acta Chem. Scand. B* **1985**, *39*, 501.
7. *Typical procedure for the oxidation of* **1a–2a**: To a stirred solution of **1a** (266 mg, 1.0 mmol) and Ac_2O (20 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was added PCC (324 mg, 1.5 mmol) and heated to reflux for 30 h. PCC (324 mg, 1.5 mmol) was added again and the reaction mixture was continued to reflux for 30 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite pad. After the removal of solvent and column chromatographic purification process (hexanes/EtOAc, 97:3) we obtained **2a**, 202 mg (72%). Spectroscopic data of **2a–d** are as follows.
Compound **2a**: colorless oil; 72%; IR (film) 2954, 1768, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.04 (d, $J = 13.8$ Hz, 1H), 3.32 (d, $J = 13.8$ Hz, 1H), 3.77 (s, 3H), 4.28 (d, $J = 9.9$ Hz, 1H), 4.64 (d, $J = 9.9$ Hz, 1H), 5.95 (s, 1H), 6.47 (s, 1H), 7.03 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.86, 53.02, 53.44, 70.53, 125.88, 128.78, 130.94, 133.10, 133.61, 136.26, 168.54, 170.88; ESIMS *m*/*z* 281 (M^++1). Anal. Calcd for $C_{14}H_{13}ClO_4$: C, 59.90; H, 4.67. Found: C, 59.68; H, 4.75.
Compound **2b**: colorless oil; 77%; IR (film) 3032, 2954, 1768, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (d, $J = 13.8$ Hz, 1H), 3.36 (d, $J = 13.8$ Hz, 1H), 3.77 (s, 3H), 4.32 (d, $J = 9.9$ Hz, 1H), 4.64 (d, $J = 9.9$ Hz, 1H), 5.97 (s, 1H), 6.48 (s, 1H), 7.07–7.10 (m, 2H), 7.26–7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.68, 52.95, 53.60, 70.63, 125.74, 127.60, 128.63, 129.57, 134.64, 136.53, 168.78, 171.10; ESIMS *m*/*z* 247 (M^++H).
Compound **2c**: colorless oil; 76%; IR (film) 2235, 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.02 (d, $J = 13.7$ Hz, 1H), 3.16 (d, $J = 13.7$ Hz, 1H), 4.46 (s, 2H), 5.66 (d, $J = 0.8$ Hz, 1H), 6.49 (d, $J = 0.8$ Hz, 1H), 7.25–7.28 (m, 2H), 7.36–7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.04, 43.52, 71.12, 118.63, 127.15, 128.44, 128.79, 130.28, 132.31, 134.35, 166.68; ESIMS *m*/*z* 214 (M^++H).
Compound **2d**: colorless oil; 55%; IR (film) 2925, 1734, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 3H), 2.92 (d, $J = 14.0$ Hz, 1H), 3.28 (d, $J = 14.0$ Hz, 1H), 3.64 (s, 3H), 3.84 (d, $J = 10.5$ Hz, 1H), 4.12 (d, $J = 10.5$ Hz, 1H), 5.77 (s, 1H), 6.27 (s, 1H), 6.99–7.01 (m, 2H), 7.19–7.20 (m, 3H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.80 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.69, 43.89, 50.06, 50.96, 53.00, 124.11, 127.63, 128.23, 128.71, 129.66, 129.67, 134.64, 134.75, 140.64, 145.35, 163.80, 171.26.

Typical procedure for the oxidation of **1e**–**2e**: Chromium(IV) oxide (100 mg, 1.0 mmol) was dissolved in aqueous acetone (1 mL) and H_2SO_4 (10 mg, 0.1 mmol) was added slowly at 0 °C and the resulting solution was stirred for 30 min. To the reaction flask was added a solution of **1e** (61 mg, 0.2 mmol in 1 mL of acetone) and the reaction mixture was stirred at room temperature for 20 h. After the removal of acetone, the reaction mixture was poured into cold water and extracted with CH_2Cl_2 (2×25 mL). After the removal of solvent and column chromatographic purification process (hexanes/EtOAc, 97:3), we obtained **2e** as a colorless oil, 46 mg (71%). Spectroscopic data of **2e**–**g′** are as follows.

Compound **2e**: colorless oil; 71%; IR (film) 2983, 1770, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, $J =$ 7.2 Hz, 3H), 1.32 (t, $J = 7.0$ Hz, 3H), 3.52–3.76 (m, 2H), 4.30–4.39 (m, 2H), 6.25 (s, 1H), 6.29 (s, 1H), 6.71 (s, 1H), 7.33 (s, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.30, 13.88, 62.25, 63.06, 65.06, 81.04, 126.79, 128.28, 129.21, 129.23, 132.33, 134.86, 165.86, 166.62, 167.59; ESIMS *m*/*z* 319 (M^++H).

Compound **2f**: colorless oil; 69%; IR (film) 2924, 1770, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.24 (s, 3H), 3.87 (s, 3H), 6.21 (s, 1H) 6.26 (s, 1H), 6.68 (s, 1H), 7.12–7.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.09, 52.64, 53.80, 65.15, 80.95, 126.38, 128.90, 129.11, 131.56, 132.13, 139.08, 166.18, 167.02, 167.45.

Compound **2g**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, $J = 7.2$ Hz, 3H), 3.81 (s, 3H), 3.83–3.87 (m, 1H), 4.11–4.30 (m, 2H), 5.79 (d, $J = 6.0$ Hz, 1H), 5.97–6.00 (m, 1H), 6.47 (d, $J = 3.0$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.7$ Hz, 2H).

Compound **2g′**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, $J = 7.2$ Hz, 3H), 2.28 (d, $J = 2.1$ Hz, 3H), 3.80 (s, 3H), 4.11–4.30 (m, 2H), 5.97–6.00 (m, 1H), 6.87 (d, $J = 9.0$ Hz, 2H), 7.17 (d, $J = 9.0$ Hz, 2H).

8. For the synthesis of **1e** and **1f** and the synthetic applications, see: Gowrisankar, S.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1826, and references cited therein.
9. For the synthesis of **1g** and the synthetic applications, see: Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052, and references cited therein.