Stereoselective Synthesis of (Z)-α-Alkylidene-γ-Butyrolactones via Pd-Catalyzed CO Insertion and Cyclization

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Abstract: Four new (Z)-2-phenoxymethylene-4-pentanolide derivatives and four (Z)-2-phenoxymethyl-2-penten-γ-lactone derivatives were prepared via Pd-catalyzed carbon monoxide insertion and intramolecular cyclization. All compounds were characterized by IR, ¹H NMR, ¹³C NMR, MS spectra and elemental analysis. The plausible mechanism of the reaction was discussed.

Key words: carbon monoxide insertion, stereoselective synthesis, γ-lactone

The stereoselective synthesis of (Z)-α-alkylidene-γ-butyrolactones has recently become attractive because these compounds can be used as a plant growth regulator[1] or as an important intermediate in the synthesis of obtusilactone isolated from Lindela obtusiloba, a cytotoxic natural product[2,3]. Although several methods have been reported for the introduction of an alkylidene group at the α-position of a γ-butyrolactone[4,5], the literature has not discussed the stereoselective synthesis of the exocyclic double bond, with the (Z)-configuration. In this paper, we inspect the stereoselective synthesis of α-alkylidene-γ-lactones via Pd-catalyzed carbon monoxide insertion and intramolecular cyclization.

All materials were used without further purification. A flask was charged under nitrogen with 1 mmol of M₁–M₄, 1 mmol of triethyl amine, 0.1 mmol of tetrakis palladium(0), and 3 ml of toluene. A balloon was flushed with CO three times and then connected to a condenser attached to the reaction flask. The system was flushed with a gentle stream of CO for 1 min and placed in an oil bath at 50 °C for 3–10 h. The reaction mixture was quenched with a 10% ammonium hydroxide solution. After extraction (ethyl acetate), washing, drying, concentration, and purification of the solution, the product of (Z)- α-alkylidene-γ-butyrolactone was achieved.

Purification of the products by column chromatography was carried out with EM silica gel 60 (70–230 mesh ASTM). Pre-coated silica gel 60F-254 on aluminum plates, manufactured by the EM chemical company, was used for thin-layer chromatography. IR spectra were recorded on a Perkin-Elmer 882 infrared spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker AC200, AC300 or AMX400 spectrometer, and chemical shifts (ppm) were reported relative to Me₄Si. MS spectra were obtained on an HP 5971, Fisons MD800 GC/MS, or VG 70-250S spectrometer. VG 70-250S spectrometers acquired the HRMS, and elemental analyses were performed on a Perkin-Elmer EA-2400.

The reactions of α-alkylidene-γ-lactones via Pd-catalyzed carbon monoxide insertion and intramolecular cyclization are:

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into the palladium-carbon complex, followed by the carbon monoxide insertion and CO in toluene, intramolecular cyclization of M→P and regeneration of palladium (0) catalyst. 

Analytical results of the products are shown below.

The stereochemistry of the exocyclic double bond was determined by 2D NOESY (phase sensitive) and 1H NMR spectral analyses. Under similar reaction conditions, the intramolecular cyclization of M→P give enol lactones with substituted group at the γ-position in good yield.

The following products could be synthesized by via Pd-catalyzed carbon monoxide insertion and intramolecular cyclization. The reaction results and analytical results of the products are shown below.

(1) (Z)-2-phenoxymethyl-2-penten-γ-lactone

Colorless oil, 0.177 g, 87% yield; 1H NMR (CDCl₃): δ=1.43 (d, J=6.9 Hz, 3H), 4.77 (t, J=1.9 Hz, 2H), 5.05–5.15 (m, 1H), 6.84 (d, J=8.1 Hz, 2H), 6.97 (t, J=7.2 Hz, 1H), 7.30 (t, J=8.1 Hz, 2H), 7.39 (s, 1H); 13C NMR (CDCl₃): δ=18.83, 61.86, 78.46, 114.50, 121.48, 129.59, 129.94, 151.49, 171.69; IR (film): νmax=1,755, 1,683, 15,99, 1,496, 1,234, 1,083, 1,022, 755; MS: m/z=204 (M⁺), 159, 111, 94; HRMS calculated for C₁₂H₁₂O₃: 204.0786; found 204.0798.

(2) (Z)-2-phenoxymethylene-4-pentanolide

Colorless oil, 0.17 g, yield 84%; 1H NMR (CDCl₃): δ=1.43 (d, J=6.2 Hz, 3H), 2.56 (ddd, J=15.1, 8.6, 2.1 Hz, 1H), 3.06 (ddd, J=15.1, 7.5, 1.7 Hz, 1H), 4.6–4.7 (m, 1H), 6.9 (s, 1H), 7.11 (d, J=8.9 Hz, 2H), 7.16 (t, J=7.5 Hz, 1H), 7.37 (t, J=7.9 Hz, 2H); 13C NMR (CDCl₃): δ=21.72, 33.02, 74.02, 106.29, 117.53, 124.63, 129.76, 148.69, 157.08, 167.87; MS: m/z=204 (M⁺), 160, 132, 131, 104, 103; Anal. calculated for C₁₂H₁₁O₂: C, 70.57; H, 5.92; found C, 70.77; H, 5.99.

(3) (Z)-2-[4-Fluorophenoxy)methyl-2-penten-γ-lactone

Colorless oil, 0.21 g, yield 95%, 1H NMR (CDCl₃): δ=1.47 (d, J=6.9 Hz, 3H), 4.76 (t, J=1.8 Hz, 2H), 5.1–5.15 (m, 1H), 6.85–6.9 (m, 2H), 6.95–7.0 (m, 2H), 7.4 (s, 1H); 13C NMR (CDCl₃): δ=18.84, 62.57, 78.47, 115.67 (d, J=8 Hz), 116.01 (d, J=23 Hz), 130.23, 151.64, 154.01, 157.65 (d, J=238 Hz), 171.63; IR (film): νmax=1,748, 1,504, 1,290, 1,087, 1,017, 825; MS: m/z=222 (M⁺), 176, 154, 136; HRFABMS calculated for C₁₂H₁₁O₃F: 223.0770, found 223.0769.

(4) (Z)-2-[4-Fluorophenoxy)methylene]-4-pentanolide

Colorless oil, 0.19 g, yield 86%, 1H NMR (CDCl₃): δ=1.44 (d, J=6.2 Hz, 3H), 2.55 (ddd, J=15.2, 6.5, 2.1 Hz, 1H), 3.06 (ddd, J=15.2, 7.5, 1.7 Hz, 1H), 4.66–4.75 (m, 1H), 6.82 (t, J=1.7 Hz, 1H), 7.0–7.15 (m, 4H); 13C NMR (CDCl₃): δ=21.79, 33.05, 74.08, 106.59, 116.40 (d, J=24 Hz), 119.15 (d, J=8 Hz), 148.83, 153.29, 159.57 (d, J=242 Hz), 167.79; IR (film): νmax=1,751, 1,673, 1,501, 1,202, 1,080, 835; MS: m/z=222 (M⁺), 131, 112, 83; Anal. calculated for C₁₂H₁₁O₃F: C, 64.86; H, 4.99; found: C, 64.98; H, 5.10.

where X=H, R=CH₃ (M₁, M₅); X=H, R=3,4,5-trimethoxyphenyl (M₄, M₆); X=F, R=CH₃ (M₂, M₆); X=F, R=3,4,5-trimethoxyphenyl (M₃, M₇).

In the presence of the Pd[PPh₂]₃ catalyst, Et₃N and CO in toluene, intramolecular cyclization of M₁→M₆ stereoselectively afforded (Z)-α-alkylidene-γ-butyralactone with substituted group at the γ-position in good yield.

Figure 1. The mechanism of the reaction.
(5) (Z)-2-[(4-Fluorophenoxy)methylene]-4-(3,4,5-trimethoxyphenyl)-4-pentanolide

Colorless oil, 0.25 g, yield 68%, $^1$H NMR (CDCl$_3$): $\delta=2.92$ (dd, $J=15.3$, 7.2, 2.2 Hz, 1H), 3.35 (dd, $J=15.3$, 7.0, 1.8 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 6H), 5.49 (t, $J=7.5$ Hz, 1H), 6.57 (s, 2H), 6.88 (t, $J=1.9$ Hz, 1H), 7.0–7.15 (m, 4H); $^{13}$C NMR (CDCl$_3$): $\delta=34.36$, 56.29, 60.85, 78.14, 102.36, 104.24, 105.13, 116.48 (d, $J=35$ Hz), 119.16 (d, $J=13$ Hz), 135.63, 149.29, 153.23, 153.64, 159.69 (d, $J=363$ Hz), 168.08; IR (film): $\nu_{max}=1,755$, 1,673, 1,593, 1,502, 1,463, 1,202, 1,127, 835; FAB Ms: $m/z=374$ (M$^+$), 280, 279, 263. HRMS calculated for C$_{20}$H$_{19}$O$_6$F: 374.1166; found: 374.1175.

(6) 2-[(4-Fluorophenoxy)methyl]-4-(3,4,5-trimethoxyphenyl)-2-penten-1-lactone

Colorless oil, 0.27 g, yield 72%, $^1$H NMR (CDCl$_3$): $\delta=3.81$ (s, 6H), 3.83 (s, 3H), 4.68 (s, 2H), 5.65–5.75 (m, 1H), 6.60 (s, 2H), 6.8–7.2 (m, 4H), 7.75 (d, $J=6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$): $\delta=56.80$, 61.34, 63.50, 80.34, 102.43, 117.68 (d, $J=39$ Hz), 119.03 (d, $J=8$ Hz), 129.67, 137.87, 143.43, 150.34, 153.78, 156.65, 157.89 (d, $J=270$ Hz), 169.69; IR (film) $\nu_{max}=1,755$, 1,673, 1,593, 1,502, 1,463, 1,202, 1,127, 835; FAB Ms: $m/z=374$ (M$^+$), 280, 279, 263. HRMS calculated for C$_{20}$H$_{19}$O$_6$F: 374.1166; found: 374.1178.

(7) (Z)-2-Phenoxymethylene-4-(3,4,5-trimethoxyphenyl)-4-pentanolide

Colorless oil, 0.23 g, yield 63%, $^1$H NMR (CDCl$_3$):

$\delta=2.92$ (dd, $J=15.3$, 7.4, 2.1 Hz, 1H), 3.35 (dd, $J=15.3$, 7.8, 1.4 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 6H), 5.48 (t, $J=7.5$ Hz, 1H), 6.57 (s, 2H), 6.96 (t, $J=1.8$ Hz, 1H), 7.1–7.4 (m, 5H); $^{13}$C NMR (CDCl$_3$): $\delta=34.38$, 56.23, 60.82, 78.11, 102.28, 105.44, 117.60, 124.87, 129.87, 135.73, 137.96, 149.23, 153.57, 157.08, 167.58; IR (film): $\nu_{max}=1,755$, 1,673, 1,593, 1,502, 1,463, 1,202, 1,127, 835; FAB Ms: $m/z=374$ (M$^+$), 280, 279, 263. HRMS calculated for C$_{20}$H$_{19}$O$_6$F: 374.1166; found: 374.1178.

(8) (Z)-2-Phenoxymethyl-4-(3,4,5-trimethoxyphenyl)-2-penten-$\gamma$-lactone

Colorless oil, 0.28 g, yield 78%, $^1$H NMR (CDCl$_3$): $\delta=3.81$ (s, 6H), 3.83 (s, 3H), 4.62 (s, 2H), 5.6–5.7 (m, 1H), 6.60 (s, 2H), 6.8–7.1 (m, 5H), 7.68 (d, $J=6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$): $\delta=56.25$, 61.63, 63.67, 79.96, 103.04, 115.36, 121.40, 130.04, 137.90, 143.43, 150.89, 155.78, 158.96, 168.90; IR (film): $\nu_{max}=1,755$, 1,673, 1,593, 1,502, 1,463, 1,202, 1,127, 835; FAB Ms: $m/z=374$ (M$^+$), 280, 279, 263. HRMS calculated for C$_{20}$H$_{19}$O$_6$F: 374.1166; found: 374.1178.

References