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Facile generation method for conjugated allenyl esters based on retro-Dieckmann-type ring-opening reactions

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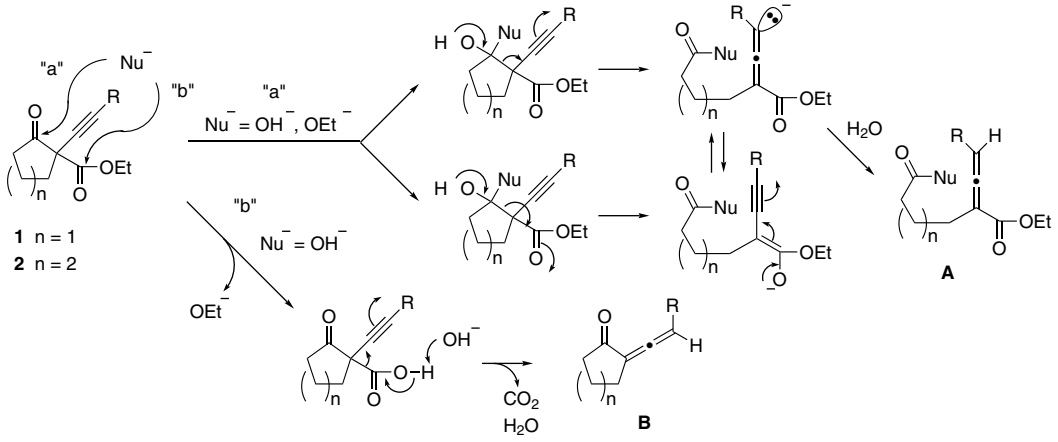
Abstract—α-Alkynyl-α-ethoxycarbonyl cyclopentanones **1a–c** and cyclohexanones **2a–c** were readily synthesized by the reaction of ethyl 2-oxocyclopentanonecarboxylate **6** and ethyl 2-oxocyclohexanonecarboxylate **7** with alkynyllead triacetates **5a–c** obtained from lithium acetylides **4a–c** and lead tetraacetate. Treatment of **1a–c** and **2a–c** with 1 N KOH in THF or with *n*-$Bu_4N^+OEt^-$ in EtOH and THF gave the corresponding conjugated allenyl esters **8a–c**, **9a–c**, **10a–c**, and **11a–c** in good to excellent yields, respectively.

Since the allenylic compounds have been particularly versatile in oxidation, reduction, addition, rearrangement, substitution, polymerization, and inter- and intramolecular cyclization reactions, various synthetic methods for the characteristic allenes have been developed.[1,2] We reported previously the mild alkaline hydrolysis of diethyl α-acetylamino(or methoxy)-α-alkynylmalonates (DAM) to generate conjugated allenyl esters that promote 5-*endo*-mode heterocyclic cyclization giving trisubstituted oxazoles, SH-enzyme inhibition, chiral pyrrolinone formation, and Myers-type biradical aromatization, each according to a specific cascade reaction.[3,4] Here, we describe a new type of facile synthesis of conjugated allenyl esters utilizing retro-Dieckmann-type ring-opening reactions of α-alkynyl-α-(ethoxycarbonyl)cyclopentanones and cyclohexanones.

Scheme 1 illustrates the generation of conjugated allenyl esters **A** via Route "a" based on the attack with anionic nucleophiles ($Nu^- = OH^-$ and EtO^-) on the ketone



Scheme 1.

Keywords: Cyclopentanone; Cyclohexanone; Retro-Dieckmann reaction; Conjugated allenyl ester; X-ray crystallographic analysis.
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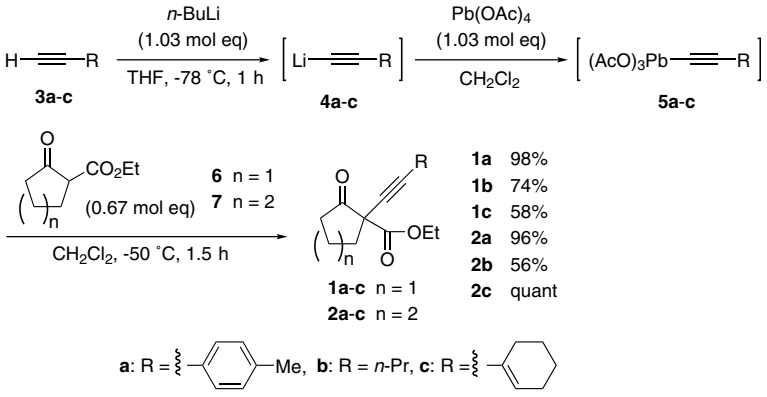
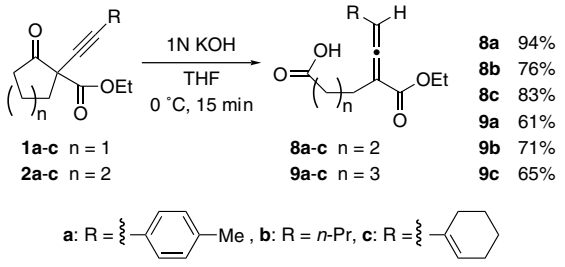


Scheme 2.

moiety of cycloalkanones followed by 'retro-Dieckmann-type ring-opening' (direct allenyl anion formation and/or enolization) or the generation of conjugated α-allenylcycloalkanones **B** via Route "b" by alkaline hydrolysis ($Nu^- = OH^-$) of the ethoxycarbonyl group followed by decarboxylation. However, we envisaged exclusive formation of the former via Route "a" due to the more favorable electrophilicity of the ketone moiety of cycloalkanones compared with that of the ester carbonyl group.

The precursor compounds, α-alkynyl-α-(ethoxycarbonyl)cyclopentanones **1a–c** and cyclohexanones **2a–c**, were readily accessible from ethyl 2-oxocyclopentane-1-carboxylate **6** and ethyl 2-oxocyclohexane-1-carboxylate **7** by utilizing the Hashimoto-modified Pinhey reaction procedure as follows (Scheme 2).[5–7] Lithium acetylide **4a**, obtained by lithiation of 4-ethynyltoluene **3a** with 1.03 mol equiv of *n*-butyllithium in THF at −78 °C, was added into a stirring suspension of 1.03 mol equiv of dried lead tetraacetate in CH_2Cl_2 at −50 °C by utilizing a cannula system. The mixture was stirred at −50 °C for 10 min and then at room temperature for 15 min to generate *p*-tolylethynyllead triacetate **5a**, to which was added a CH_2Cl_2 solution of 0.67 mol equiv of ethyl 2-oxocyclopentane-1-carboxylate **6** or ethyl 2-oxocyclohexane-1-carboxylate **7**. After stirring at room temperature for 1.5 h, the usual workup of the reaction mixture gave **1a** in 98% yield or **2a** in 96% yield based on **6** or **7**, respectively.[8] Other compounds **1b**,**c**, and **2b**,**c** were synthesized in good to excellent yields by exploiting a procedure similar to that used for **1a** and **2a**, as shown in Scheme 2.

The allene formation reactions commenced with 1 N KOH in EtOH, which we first used successfully for the cascade reaction of DAM, giving the conjugated allenyl esters.[9] Namely, treatment of **1a** with 1 N KOH in EtOH at 0 °C afforded a mixture of 5-ethoxycarbony-7-(*p*-tolyl)-5,6-heptadienoic acid **8a** in 32% yield and ethyl 5-ethoxycarbonyl-7-(*p*-tolyl)-5,6-heptadienoate **10a** in 27% yield. In order to obtain carboxylic acid **8a** with high selectivity, compound **1a** was treated with 1 N KOH in THF at 0 °C for 15 min. Thus, compound **8a** was obtained as a crystalline product (colorless plates from AcOEt–*n*-hexane, mp 86–88 °C) in 94% yield, as



Scheme 3.

shown in Scheme 3.[10] The structure of **8a** was precisely determined by the X-ray crystallographic analysis, as shown in Figure 1.[11] A similar alkaline hydrolysis of **1b**,**c**, and **2a–c** with 1 N KOH in THF at 0 °C expeditiously furnished the corresponding carboxylic acids **8b** (76% yield), **8c** (83% yield), **9a** (61% yield), **9b** (71% yield), and **9c** (65% yield), respectively. These structures were determined by the similarity of their spectroscopic data to those of **8a**.[10]

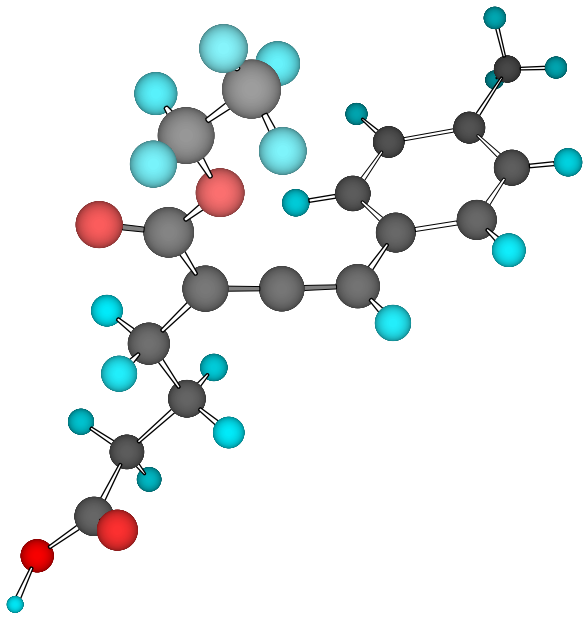
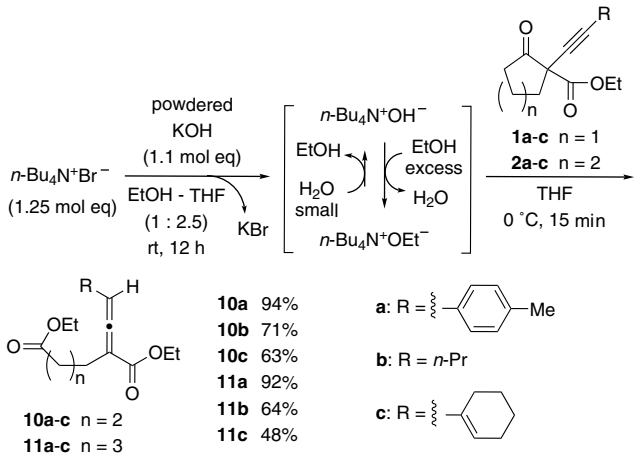


Figure 1. Computer-generated drawing from the X-ray coordinates of compound **8a**.



Scheme 4.

Finally, we have attempted a new type of mild retro-Dieckmann-type ring-opening reaction of **1a**–**c** and **2a**–**c** with *n*-$Bu_4N^+OEt^-$ generated in situ by treatment of powdered KOH with excess EtOH–THF in the presence of *n*-$Bu_4N^+Br^-$ as a phase transfer catalyst in the solid–liquid system[12,13] as follows (Scheme 4). After treatment of 1.1 mol equiv of powdered KOH and 1.25 mol equiv of *n*-$Bu_4N^+Br^-$ in a solution of EtOH and THF at room temperature for 12 h, the mixture was supplemented with a solution of **1a** at 0 °C in THF. After stirring at 0 °C for 15 min, the usual workup of the reaction mixture gave the desired compound **10a** as a pale yellow oil in 94% yield. The similar treatment of **1b**,**c**, and **2a**–**c** furnished the corresponding allenyl diesters **10b** (71% yield), **10c** (63% yield), **11a** (92% yield), **11b** (64% yield), and **11c** (48% yield), respectively. The structures of all products were assigned based on the similarity of their spectroscopic data to those of **8a**–**c** and **9a**–**c**, except for the data of the carboxyl group.[14] Thus, we have achieved formation of ethyl esters **10a**–**c** and **11a**–**c** without the use of NaOEt.

In conclusion, we have demonstrated methods for the facile and mild synthesis of the conjugated allenyl esters based on the retro-Dieckmann-type ring-opening reactions employing 1 N KOH and *n*-$Bu_4N^+OEt^-$; these methods will be available as new trigger reactions for various bioorganic and chemical cascade reactions.[3,4,15]

Acknowledgements

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8. The spectroscopic data of **1a** and **2a** are as follows: Compound **1a**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, t, J = 7.3 Hz), 2.10–2.16 (2H, m), 2.34 (3H, s), 2.39–2.44 (2H, m), 2.46–2.54 (1H, m), 2.65–2.73 (1H, m), 4.27 (2H, q, J = 7.3 Hz), 7.10 (2H, d, J = 7.8 Hz), 7.34 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 19.92, 21.49, 36.76, 36.94, 56.58, 62.45, 83.83, 85.20, 119.40, 128.93, 131.82, 138.62, 168.63, 208.12; IR (neat) 2981, 2228, 1763, 1741, 1510 cm^{-1}; EI-MS calcd for $C_{17}H_{18}O_3$ MW 270.1256, found *m/e* 270.1263 (M^+). Compound **2a**: pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.1 Hz), 1.75–2.55 (7H, m), 2.88–3.04 (1H, m), 4.30 (2H, dq, J = 2.4 and 7.1 Hz), 7.12 (2H, d, J = 8.1 Hz), 7.35 (2H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 21.49, 21.60, 27.45, 37.36, 38.72, 56.59, 62.14, 84.36, 87.78, 119.44, 129.02, 131.69, 138.73, 168.67, 203.15; IR (neat) 2943, 2227, 1743, 1725, 1511 cm^{-1}; EI-MS calcd for $C_{18}H_{20}O_3$ MW 284.1412, found *m/e* 284.1404 (M^+). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09. Found: C, 75.64; H, 7.19.
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10. The spectroscopic data of **8a** and **9a** are as follows: Compound **8a**: colorless plates (AcOEt/*n*-hexane), mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, J = 7.3 Hz), 1.79–1.87 (2H, m), 2.34 (3H, s), 2.37–2.46 (4H, m), 4.20 (2H, q, J = 7.3 Hz), 6.54 (1H, t, J = 2.9 Hz), 7.14 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.20, 21.19, 22.96, 28.19, 33.33, 61.13, 98.60, 103.44, 127.13, 129.18, 129.52, 137.70, 166.58, 179.30, 211.82; IR (KBr) 2981, 2361, 1943, 1709, 1514 cm^{-1}; EI-MS calcd for $C_{17}H_{20}O_4$ MW 288.1362, found *m/e* 288.1366 (M^+). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 75.86; H, 7.11. Compound **9a**: colorless plates (AcOEt), mp 64–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.3 Hz), 1.52–1.59 (2H, m), 1.65–1.72 (2H, m), 2.34 (3H, s), 2.29–2.42 (4H, m), 4.20 (2H, q, J = 7.3 Hz), 6.52 (1H, t, J = 2.9 Hz), 7.13 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.27, 21.23, 24.16, 27.40, 28.50, 33.71, 61.10, 98.37, 103.84, 127.14, 129.53, 131.64, 137.65, 166.77, 179.53, 211.89; IR (KBr) 2935, 1943, 1738, 1709, 1514 cm^{-1}; EI-MS calcd for $C_{18}H_{22}O_4$ MW 302.1518, found *m/e* 302.1512 (M^+).
11. The crystallographic data of **8a** is as follows: $C_{17}H_{20}O_4$, M = 288.34, monoclinic, $P2_{1/c}$ (#14), a = 10.521(5) Å, b = 5.327(7) Å, c = 28.906(4) Å, β = 100.00(2)°, V = 1595(2) Å^3, Z = 4, D_{calcd} = 1.200 g cm^{-3}, μ(Mo Kα) = 0.85 cm^{-1}.
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14. The spectroscopic data of **10a** and **11a** are as follows: Compound **10a**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.3 Hz), 1.25 (3H, t, J = 7.3 Hz), 1.80–1.87 (2H, m), 2.30–2.43 (4H, m), 2.34 (3H, s), 4.10

(2H, q, J = 7.3 Hz), 4.20 (2H, dq, J = 1.0 and 7.3 Hz), 6.53 (1H, t, J = 2.9 Hz), 7.14 (2H, d, J = 7.3 Hz), 7.17 (2H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.21, 14.27, 21.23, 23.34, 28.33, 33.72, 60.28, 61.10, 98.54, 103.64, 127.18, 129.31, 129.54, 137.67, 166.60, 173.28, 211.89; IR (neat) 2980, 1944, 1736, 1709, 1259 cm^{-1}; EI-MS calcd for $C_{19}H_{24}O_4$ MW 316.1675, found *m/e* 316.1687 (M^+). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.05; H, 7.71. Compound **11a**: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, J = 7.3 Hz), 1.24 (3H, t, J = 7.3 Hz), 1.50–1.57 (2H, m), 1.65–1.72 (2H, m), 2.26–2.41 (4H, m), 2.34 (3H, s), 4.09 (2H, q, J = 7.3 Hz), 4.20 (2H, dq, J = 1.0 and 7.3 Hz), 6.51 (1H, t, J = 2.9 Hz), 7.13 (2H, d, J = 8.3 Hz), 7.17 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.46, 14.52, 21.47, 24.78, 27.76, 28.80, 34.32, 60.42, 61.28, 98.55, 104.22, 127.37, 129.22, 129.77, 137.83, 166.97, 173.79, 212.12; IR (neat) 2981, 1943, 1737, 1514 cm^{-1}; EI-MS calcd for $C_{20}H_{26}O_4$ MW 330.1831, found *m/e* 330.1826 (M^+).

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