Synthesis of Substituted Cyclopentenes from the Baylis-Hillman Adducts *via* Ring-Closing Metathesis Reaction

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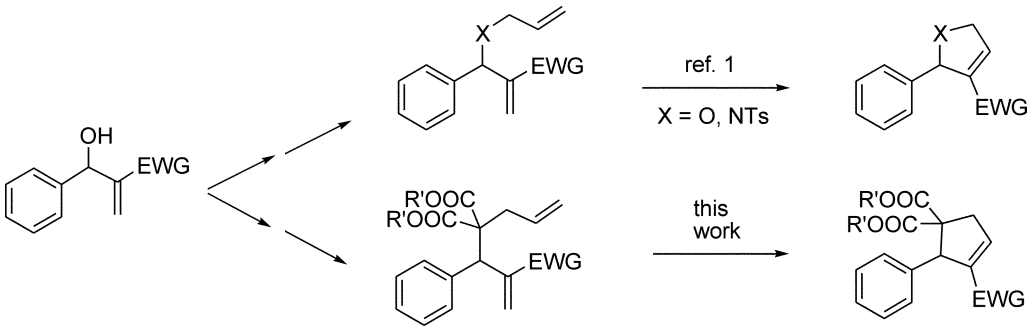
Recently, we reported the synthesis of 2,5-dihydrofuran and 2,5-dihydropyrrole systems by using the well-known ring-closing metathesis (RCM) reaction from the slightly modified Baylis-Hillman adducts.[1] As a continuing effort we intended to synthesize the cyclopentene skeleton as shown in Scheme 1. Cyclopentene ring is a carbon analog of 2,5-dihydrofuran and 2,5-dihydropyrrole systems and we thought we could construct the cyclopentene ring by using the similar strategy, namely the combination of Baylis-Hillman chemistry and RCM reaction.

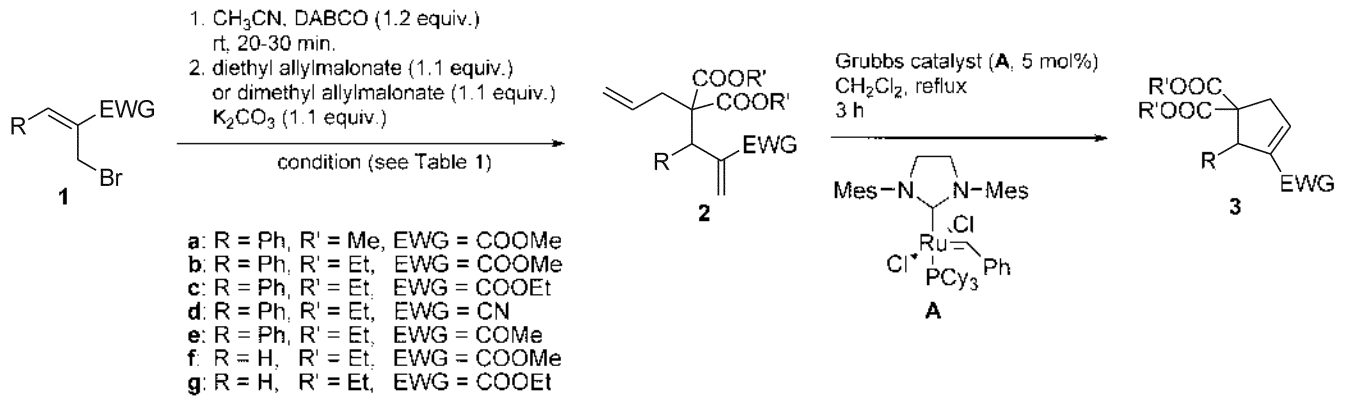
Substituted cyclopentenes have been synthesized in a variety of ways[2-4] including the ring-closing metathesis (RCM) reaction[2-4] and have been used as useful synthetic intermediates and act as an important backbone of some biologically important compounds.[4]

In order to introduce the required allyl moiety at the secondary position of the Baylis-Hillman adducts we used the well-known consecutive S_N2'-S_N2' strategy involving DABCO salt of the bromide of the Baylis-Hillman adduct **1**, which was studied extensively by us and other groups.[1,5] The reaction of dimethyl allylmalonate and the in-situ generated DABCO salt of **1a** in CH_3CN gave the corresponding addition-elimination product **2a** in good yield (84%). When we used aqueous THF instead of acetonitrile,[5] the introduction of dimethyl allylmalonate required longer reaction time and showed lower yield of product.

With the compound **2a** in our hands we examined the RCM reaction. Generally the ring-closing metathesis reaction



Scheme 1



Scheme 2

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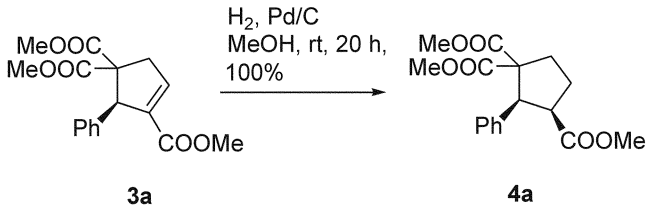
Table 1. Synthesis of diallyl malonates **2** and cyclopentenes **3**

Entry	Condition	**2** (% Yield)	**3** (% Yield)
1	rt, 48 h	**2a** (84)	**3a** (95)
2	rt, 36 h	**2b** (78)	**3b** (89)
3	30-40 °C, 48 h	**2c** (80)	**3c** (95)
4	30-40 °C, 44 h	**2d** (69)	**3d** (97)
5	30-40 °C, 36 h	**2e** (60)	**3e** (99)
6	30-40 °C, 72 h	**2f** (75)[a]	**3f** (90)
7	30-40 °C, 48 h	**2g** (59)[a]	**3g** (93)

[a]The corresponding acetate was used instead of the bromide **1**.



3a **4a**

Scheme 3

involving electron-deficient alkene moiety as in **2a-g** required the use of second-generation Grubbs catalyst.[1,6] The reaction of **2a** under the ring-closing metathesis condition using the second-generation Grubbs catalyst (**A**, 5 mol%) afforded the cyclopentene derivative **3a** in excellent yield (95%). The representative results are summarized in Table 1. As shown, excellent yields of desired RCM products were obtained irrespective of the substituents, ester, acetyl and nitrile.

As a useful transformation, we examined the catalytic hydrogenation reaction of **3a** using Pd/C (Scheme 3). The reaction at room temperature (MeOH under H_2 balloon) produced quantitative yield of desired product **4a** in a highly diastereoselective manner. Due to the steric hindrance of the phenyl moiety, the hydrogenation occurred at the opposite face.[7] Trimethyl 2-phenylcyclopentane-1,1,3-tricarboxylate (**4a**) can be used for the preparation of 2-phenyl-1,3-cyclopentanedicarboxylic acid[8] *via* sequential hydrolysis and decarboxylation.[9]

Diastereoselective decarboxylation[9] and intramolecular Friedel-Crafts acylation reactions with **3a-g** are under progress in order to prepare tricyclic compound, which could be used for further transformation.

Experimental Section

Typical procedure for the synthesis of 2a. A mixture of the bromide **1a** (255 mg, 1 mmol) and DABCO (135 mg, 1.2 mmol) in CH_3CN (3 mL) was stirred at room temperature for 30 min. To the reaction mixture K_2CO_3 (152 mg, 1.1 mmol) and dimethyl allylmalonate (189 mg, 1.1 mmol) were added and stirred at room temperature for 48 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10 : 1), **2a** was obtained as an oil, 291 mg (84%). Other compounds were synthesized similarly and their spectroscopic data are as follows.

2a: IR (neat) 1728, 1631 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (dd, J = 14.1 and 7.8 Hz, 1H), 2.88 (ddt, J = 14.1, 6.6, and 1.2 Hz, 1H), 3.59 (s, 3H), 3.62 (s, 3H), 3.66 (s, 3H), 4.79 (s, 1H), 4.99-5.02 (m, 1H), 5.06 (s, 1H), 5.60-5.75 (m, 1H), 6.31 (d, J = 0.9 Hz, 1H), 6.44 (s, 1H), 7.18-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 40.57, 49.89, 52.02, 52.04, 52.08, 62.42, 119.04, 126.80, 127.27, 127.93, 130.05, 132.95, 137.61, 140.00, 167.35, 170.16, 170.82.

2b: ^1H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 2.65 (dd, J = 14.1 and 7.8 Hz, 1H), 2.90 (ddt, J = 14.1, 6.6, and 1.2 Hz, 1H), 3.66 (s, 3H), 3.99-4.15 (m, 4H), 4.80 (s, 1H), 4.99-5.02 (m, 1H), 5.05-5.06 (m, 1H), 5.61-5.76 (m, 1H), 6.35 (d, J = 0.6 Hz, 1H), 6.45 (s, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.73, 13.84, 40.50, 49.64, 52.07, 61.12, 61.15, 62.05, 118.94, 126.95, 127.14, 127.85, 130.19, 133.06, 137.75, 140.04, 167.43, 169.73, 170.39.

2c: ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H), 2.58 (dd, J = 13.8 and 7.5 Hz, 1H), 2.84 (ddt, J = 12.6, 6.6, and 1.2 Hz, 1H), 3.92-4.09 (m, 6H), 4.72 (s, 1H), 4.94-5.00 (m, 2H), 5.55-5.69 (m, 1H), 6.26 (s, 1H), 6.38 (s, 1H), 7.09-7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.73, 13.85, 14.01, 40.56, 49.72, 60.90, 61.10, 61.14, 62.03, 118.90, 126.61, 127.10, 127.80, 130.25, 133.13, 137.84, 140.24, 166.92, 169.72, 170.40.

2d: ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 2.34 (dd, J = 14.1 and 7.8 Hz, 1H), 2.57 (ddt, J = 14.1, 6.6, and 1.5 Hz, 1H), 4.14-4.30 (m, 3H), 4.32 (s, 1H), 4.40-4.51 (m, 1H), 4.85-4.93 (m, 1H), 4.99-5.04 (m, 1H), 5.59-5.73 (m, 1H), 5.97 (s, 1H), 6.01 (s, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.70, 14.00, 39.36, 53.29, 60.84, 61.69, 61.81, 118.48, 119.36, 124.15, 128.23, 128.82, 129.59, 132.06, 134.44, 135.08, 169.68, 169.76.

2e: ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 2.28 (s, 3H), 2.64 (dd, J = 14.1 and 7.5 Hz, 1H), 2.87 (ddt, J = 14.1, 6.9, and 1.2 Hz, 1H), 3.95-4.17 (m, 4H), 4.92 (s, 1H), 4.97-5.02 (m, 1H), 5.04 (s, 1H), 5.61-5.75 (m, 1H), 6.27 (s, 1H), 6.56 (s, 1H), 7.17-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.74, 13.87, 25.91, 40.50, 47.69, 61.07, 61.12, 62.01, 118.89, 126.65, 127.02, 127.87, 130.13, 133.12, 138.19, 148.63, 169.89, 170.45, 198.75.

2f: ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 6H), 2.58 (dt, J = 7.2 and 1.2 Hz, 2H), 2.95 (d, J = 0.9 Hz, 2H), 3.70 (s, 3H), 4.04-4.22 (m, 4H), 5.04-5.11 (m, 2H), 5.63-5.65 (m, 1H), 5.66-5.76 (m, 1H), 6.24 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.95, 33.63, 37.11, 51.89, 57.54, 61.23, 119.12, 129.11, 132.47, 135.91, 167.38, 170.53.

2g: ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 1.29 (t, J = 7.2 Hz, 3H), 2.60 (dt, J = 7.2 and 1.2 Hz, 2H), 2.98 (d, J = 0.9 Hz, 2H), 4.09-4.22 (m, 6H), 5.06-5.13 (m, 2H), 5.64 (d, J = 1.5 Hz, 1H), 5.70-5.82 (m, 1H), 6.26 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.97, 14.09, 33.54, 37.12, 57.67, 60.85, 61.23, 119.05, 128.75, 132.58, 136.24, 166.95, 170.55.

Typical procedure for the ring-closing metathesis reaction of 3a. To a stirred solution of **2a** (173 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added second-generation Grubbs catalyst (**A**, 21 mg, 5 mol%) and heated to reflux for 3 h. After removal of solvent and column chromatographic purification process (hexanes/ether, 9 : 1), **3a** was obtained

as an oil. 151 mg (95%). Other compounds were synthesized similarly and their spectroscopic data are as follows.

3a: IR (neat) 1736, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (dd, J = 19.2 and 3.0 Hz, 1H), 3.15 (s, 3H), 3.59 (s, 3H), 3.67 (dt, J = 19.2 and 2.4 Hz, 1H), 3.76 (s, 3H), 5.04-5.06 (m, 1H), 6.87-6.90 (m, 1H), 7.10-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 39.67, 51.42, 51.99, 53.03, 55.56, 65.37, 127.32, 127.97, 128.39, 137.18, 137.32, 140.41, 163.70, 168.79, 171.61; Mass (70 eV) *m/z* (rel. inensity) 59 (100), 115 (44), 139 (38), 199 (47), 226 (44), 258 (46), 186 (21), 318 (M^+, 32).

3b: ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.96 (dd, J = 19.5 and 3.0 Hz, 1H), 3.46-3.52 (m, 1H), 3.59 (s, 3H), 3.65-3.75 (m, 2H), 4.15-4.31 (m, 2H), 5.03-5.05 (m, 1H), 6.86-6.89 (m, 1H), 7.12-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.43, 13.93, 39.88, 51.48, 55.43, 61.31, 61.89, 65.25, 127.34, 128.00, 128.65, 137.54, 137.63, 140.35, 163.83, 168.55, 171.25.

3c: ^1H NMR ($CDCl_3$) δ 0.77 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 2.87 (dd, J = 19.5 and 3.0 Hz, 1H), 3.37-3.44 (m, 1H), 3.58-3.67 (m, 2H), 3.87-4.05 (m, 2H), 4.10-4.75 (m, 2H), 4.96-4.98 (m, 1H), 6.78-6.80 (m, 1H), 7.05-7.15 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.28, 13.75, 13.79, 39.82, 55.44, 60.05, 61.13, 61.72, 65.07, 127.10, 127.79, 128.58, 137.78, 137.82, 139.81, 163.23, 168.46, 171.16.

3d: ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 2.93-3.01 (m, 1H), 3.39-3.45 (m, 1H), 3.65-3.74 (m, 2H), 4.17-4.34 (m, 2H), 5.05 (s, 1H), 6.73-6.76 (m, 1H), 7.14-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.35, 13.93, 40.73, 57.53, 61.69, 62.25, 64.54, 115.07, 117.00, 128.31, 128.45, 128.93, 135.23, 145.53, 168.06, 170.54.

3e: ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H), 2.14 (s, 3H), 2.94 (dd, J = 19.5 and 3.0 Hz, 1H), 3.36-3.47 (m, 1H), 3.60-3.71 (m, 2H), 4.05-4.25 (m, 2H), 5.00 (s, 1H), 6.71-6.74 (m, 1H), 7.02-7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.44, 13.94, 27.11, 40.24, 55.13, 61.34, 61.89, 65.12, 127.31, 128.05, 128.61, 137.74, 139.86, 146.23, 168.63, 171.27, 194.47.

3f: ^1H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 6H), 3.09-3.12 (m, 2H), 3.17-3.20 (m, 2H), 3.67 (s, 3H), 4.13 (q, J = 7.2 Hz, 4H), 6.55 (quintet, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.92, 39.40, 41.01, 51.52, 58.67, 61.78, 133.41, 139.72, 164.41, 171.27.

3g: ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 1.29 (t, J = 7.2 Hz, 3H), 3.16-3.19 (m, 2H), 3.24-3.27 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 4.21 (q, J = 7.2 Hz, 4H), 6.61 (quintet, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.90, 14.13, 39.38, 40.97, 58.63, 60.33, 61.73, 133.74, 139.33, 163.96, 171.29.

Catalytic hydrogenation of 3a. A mixture of **3a** (200 mg, 0.63 mmol) and 10% Pd/C (28 mg) in methanol (3 mL) was stirred at room temperature for 20 h under H_2 atmosphere (using balloon). After removal of solvent and column chromatographic purification (hexanes/ether, 2 : 1) we obtained **4a** (201 mg, oil) quantitatively. ^1H NMR ($CDCl_3$) δ 1.86-2.01 (m, 1H), 2.21-2.37 (m, 2H), 2.69-2.80 (m, 1H), 3.16 (s, 3H), 3.28-3.38 (m, 1H), 3.58 (s, 3H), 3.74 (s, 3H), 4.36 (d, J = 10.8 Hz, 1H), 7.16-7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.89, 34.44, 49.62, 52.08, 52.19, 52.97, 54.12, 65.63, 127.47, 128.26, 128.81, 138.57, 171.05, 172.41, 174.43.

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