Synthesis of *Exo*-Methylenecyclopentane Derivatives *via* Radical Cyclization Starting from the Baylis-Hillman Adducts

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Substituted cyclopentanes have been synthesized in a variety of ways[1-3] including radical cyclizations of dienes or enynes[2] and rhodium or palladium-catalyzed cyclization of enynes.[2] These compounds also have been used as useful synthetic intermediates and act as an important backbone of some biologically important compounds.[1,2]

Recently, the synthesis of *exo*-methylenetetrahydrofurans was carried out *via* the *n*-Bu_3SnH-mediated radical cyclization as the key step starting from the Baylis-Hillman adduct by us and Shanmugam's group.[4] Meanwhile we presumed that we could synthesize the corresponding carbon analog by applying similar strategy as shown in Scheme 1.

The reaction of the Baylis-Hillman acetate and active methylene compounds in the presence of K_2CO_3 afforded the starting material **1a-f** in good yields as reported.[5] Propargylation of **1a-f** under the influence of NaH/DMF/propargyl bromide conditions gave **2a-f** in 81-95% yields. With these compounds **2a-f** in our hand, we examined the radical cyclization. Tributyltinhydride-mediated radical cyclization of **2a-f** in benzene in the presence of AIBN produced cyclopentane derivatives **3a-f** selectively *via* the *5-exo-trig* mode after hydrodestannylation.[2,4] We could not observe the corresponding cyclohexane analogs, which could be formed *via* the *6-endo-trig* mode, as in our previous paper.[4] The results are summarized in Table 1. It is interesting to note that we isolated only one stereoisomer in entries 5 and 6. But, we did not determine the stereochemistry.

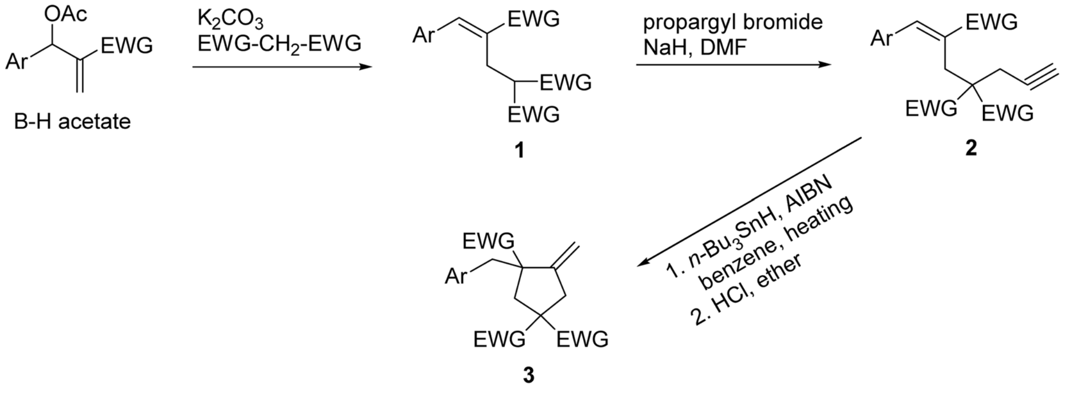
As a next trial, we examined the synthesis of *exo*-methylene cyclohexane derivatives by using **4** as starting material. The compound **4** was synthesized by using the DABCO salt concept (Scheme 2), which was already established in our group and used extensively for the regioselective introduction of nucleophile at the secondary position of the Baylis-Hillman adduct.[6] However, the radical cyclization of **4** showed the formation of many intractable mixtures of products during the radical cyclization step.

When we subjected **3a** under the Friedel-Crafts reaction conditions (Scheme 3), double bond isomerization occurred in high yield in short time to give **5** (rt, 1 h, 86%) instead of the generally expected Friedel-Crafts reaction. The use of $AlCl_3$ instead of sulfuric acid showed no reaction.

In summary, we disclosed the facile synthesis of highly substituted cyclopentane derivatives from the modified Baylis-Hillman adducts by radical cyclization protocol.

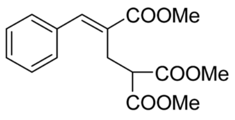
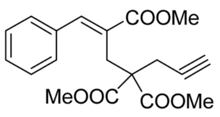
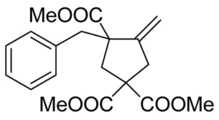
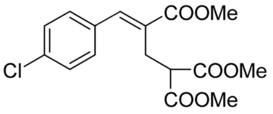
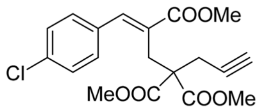
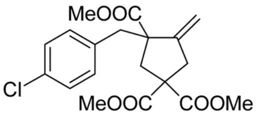
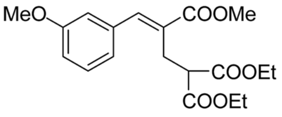
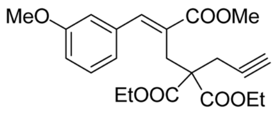
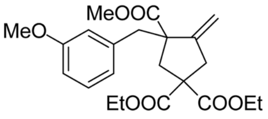
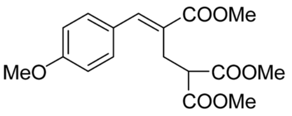
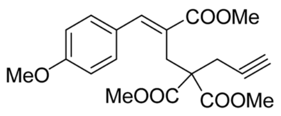
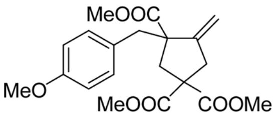
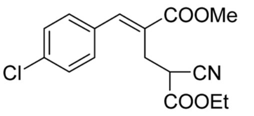
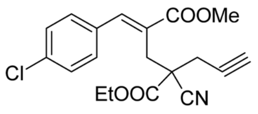
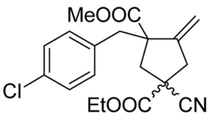
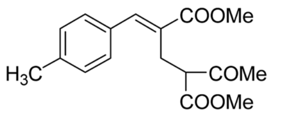
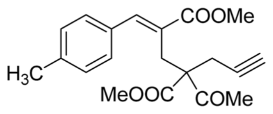
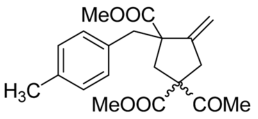
Experimental Section

Typical procedure for the synthesis of 2a: To a stirred solution of **1a**[5] (306 mg, 1.0 mmol) in DMF (2 mL) was added NaH (60% in mineral oil, 48 mg, 1.2 mmol). To the reaction mixture propargyl bromide (179 mg, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was poured into cold NH_4Cl solution and extracted with ether. After the usual aqueous extractive workup with ether and column chromatographic purification process (hexanes/EtOAc, 7 : 3) we obtained **2a** (310 mg, 90%) as colorless oil. Other compounds **2b-f** were synthesized analogously and the spectroscopic

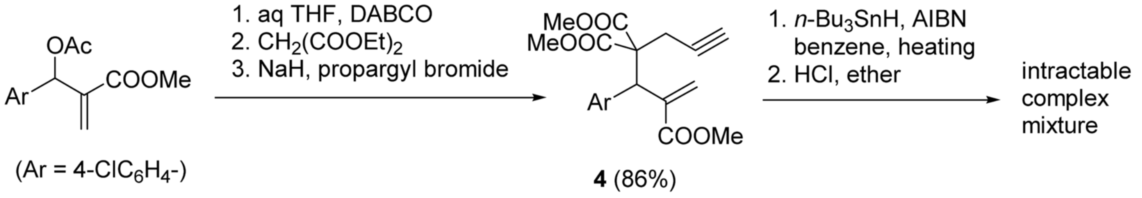


Scheme 1

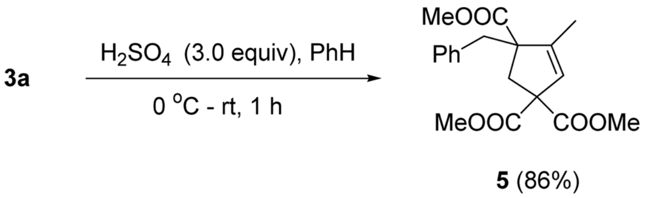
Table 1. Synthesis of methylenecyclopentane derivatives

Entry	Substrate[a]	Intermediate (%)[b]	Product (%)[c]
1	 **1a**	 **2a** (88)	 **3a** (95)
2	 **1b**	 **2b** (90)	 **3b** (90)
3	 **1c**	 **2c** (95)	 **3c** (95)
4	 **1d**	 **2d** (91)	 **3d** (97)
5	 **1e**	 **2e** (81)	 **3e** (90)[d]
6	 **1f**	 **2f** (84)	 **3f** (93)[d]

[a]Starting materials **1a-f** were prepared from the reaction of the corresponding Baylis-Hillman acetates and active methylene compounds according to the reported method.[5] [b]Conditions: Substrate **1** (1.0 mmol), NaH (1.2 equiv), DMF, propargyl bromide (1.2 equiv), rt, 12 h. [c]Conditions: (i) Intermediate **2** (1.0 equiv), n-Bu_3SnH (1.1 equiv), AIBN (cat), benzene, reflux, 1 h and (ii) conc HCl (3 drops), ether, rt, 1 h. [d]We obtained only one isomer but we did not determine the stereochemistry.



Scheme 2



Scheme 3

data of **2a-f** and **4** are as follows.

Compound 2a: colorless oil; 88%; IR (neat) 3290, 2952, 1736, 1437, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (t, J = 2.7 Hz, 1H), 2.63 (d, J = 2.7 Hz, 2H), 3.52 (s, 2H), 3.62 (s, 6H), 3.77 (s, 3H), 7.26-7.42 (m, 5H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.98, 28.16, 52.02, 52.62 (2C), 57.13, 70.70, 78.42, 128.04, 128.09, 128.28, 128.45, 129.21, 135.21, 143.18, 168.40, 170.17.

Compound 2b: colorless oil; 90%; IR (neat) 3302, 2954, 2256, 1732, 1435, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (t, J = 2.7 Hz, 1H), 2.62 (d, J = 2.7 Hz, 2H), 3.48 (s, 2H), 3.65 (s, 6H), 3.77 (s, 3H), 7.34 (s, 4H), 7.77 (s, 1H).

Compound 2c: colorless oil; 95%; IR (neat) 3284, 2983, 1732, 1435, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.22 (m, 6H), 1.63 (t, J = 2.7 Hz, 1H), 2.67 (d, J = 2.7 Hz, 2H), 3.53 (s, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 3.97-4.23 (m, 4H), 6.94-7.00 (m, 3H), 7.24-7.29 (m, 1H), 7.77 (s, 1H).

Compound 2d: colorless oil; 91%; IR (neat) 3288, 2954, 1736, 1606, 1512, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65 (t, J = 2.7 Hz, 1H), 2.67 (d, J = 2.7 Hz, 2H), 3.55 (s, 2H), 3.64 (s, 6H), 3.76 (s, 3H), 3.82 (s, 3H), 6.88 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.77 (s, 1H).

Compound 2e: colorless oil; 81%; IR (neat) 3294, 2985, 2952, 2251, 1747, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, J = 7.2 Hz, 3H), 2.10 (t, J = 2.7 Hz, 1H), 2.68 (dd, J = 16.5 and 3.0 Hz, 1H), 2.79 (dd, J = 16.5 and 3.0 Hz, 1H), 3.22 (d, J = 14.1 Hz, 1H), 3.32 (d, J = 14.1 Hz, 1H), 3.82 (s, 3H), 4.12-4.27 (m, 2H), 7.32-7.40 (m, 4H), 7.91 (s, 1H).

Compound 2f: colorless oil; 84%; IR (neat) 3284, 2954, 1736, 1437, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (t, J = 2.7 Hz, 1H), 2.14 (s, 3H), 2.34 (s, 3H), 2.55 (d, J = 2.7 Hz, 1H), 3.38 (d, J = 14.7 Hz, 1H), 3.54 (d, J = 14.7 Hz, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 7.16 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.80 (s, 1H).

Compound 4: colorless oil; 86%; IR (neat) 3294, 2952, 2258, 1730, 1279 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.07 (t, J = 2.7 Hz, 1H), 2.78 (dd, J = 16.8 and 3.0 Hz, 1H), 2.98 (d, J = 16.8 and 3.0 Hz, 1H), 3.67 (s, 3H), 3.68 (s, 6H), 5.04 (s, 1H), 6.19 (s, 1H), 6.46 (s, 1H), 7.22 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H).

Typical procedure for the radical cyclization of 2a: A mixture of **2a** (172 mg, 0.5 mmol), AIBN (2 mg, 0.01 mmol), and n-Bu_3SnH (160 mg, 0.55 mmol) in benzene (3 mL) was heated to reflux for 1 h. The reaction mixture was diluted with ether and a few drops of *c*-HCl solution was added and stirred for 1 h. After the usual aqueous extractive workup with ether and column chromatographic purification process (hexanes/EtOAc, 7 : 3) we obtained **3a** (156 mg, 95%) as colorless oil. Other compounds **3b-f** were synthesized analogously and the spectroscopic data of **3a-f** are as follows.

Compound 3a: colorless oil; 95%; IR (neat) 2952, 1732, 1496, 1435, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55 (d, J = 14.4 Hz, 1H), 2.66 (d, J = 16.5 Hz, 1H), 2.68 (d, J =13.8 Hz, 1H), 2.77 (d, J = 14.4 Hz, 1H), 3.12 (d, J = 16.5 Hz, 1H), 3.36 (d, J = 13.8 Hz, 1H), 3.56 (s, 3H), 3.60 (s, 3H), 3.63 (s, 3H), 5.13 (t, J = 2.1 Hz, 1H), 5.24 (t, J = 2.1 Hz, 1H), 7.07-7.20 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.06, 40.79, 44.17, 52.16, 52.56, 52.68, 56.90, 57.62, 110.27, 126.55, 128.10, 129.58, 137.31, 150.31, 171.30, 171.83, 173.75.

Compound 3b: colorless oil; 90%; IR (neat) 2952, 1736, 1493, 1435, 1263, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60 (d, J = 14.4 Hz, 1H), 2.75 (d, J = 13.8 Hz, 1H), 2.76 (d, J = 16.2 Hz, 1H), 2.82 (d, J = 14.4 Hz, 1H), 3.22 (d, J = 16.2 Hz, 1H), 3.40 (d, J = 13.8 Hz, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 5.22 (t, J = 2.1 Hz, 1H), 5.29 (t, J = 2.1 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.14, 40.96, 43.47, 52.44, 52.80, 52.92, 56.94, 57.81, 110.61, 128.40, 131.16, 132.65, 135.97, 150.25, 171.39, 172.01, 173.78.

Compound 3c: colorless oil; 95%; IR (neat) 2981, 2954, 1732, 1601, 1583, 1261, 1194 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20-1.26 (m, 6H), 2.64 (d, J = 14.7 Hz, 1H), 2.74 (d, J = 13.5 Hz, 1H), 2.77 (d, J = 16.5 Hz, 1H), 2.86 (d, J = 14.7 Hz, 1H), 3.18 (d, J = 16.5 Hz, 1H), 3.42 (d, J = 13.5 Hz, 1H), 4.08-4.24 (m, 4H), 5.20 (t, J = 2.1 Hz, 1H), 5.30 (t, J = 2.1 Hz, 1H), 6.74-6.79 (m, 3H), 7.14-7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 39.82, 40.26, 44.26, 52.24, 54.99, 56.97, 57.82, 61.45, 61.58, 110.15, 111.92, 115.51, 122.15, 129.10, 139.07, 150.73, 159.36, 171.01, 171.58, 173.93.

Compound 3d: colorless oil; 97%; IR (neat) 2952, 1732, 1612, 1512, 1435, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (d, J = 14.1 Hz, 1H), 2.71 (d, J = 13.8 Hz, 1H), 2.74 (d, J =16.5 Hz, 1H), 2.84 (d, J = 14.1 Hz, 1H), 3.20 (d, J = 16.5 Hz, 1H), 3.37 (d, J = 13.8 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 5.20 (t, J = 2.1 Hz, 1H), 5.30 (t, J = 2.1 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.14, 40.93, 43.47, 52.23, 52.65, 52.77, 55.03, 57.17, 57.70, 110.30, 113.57, 129.41, 130.68, 150.32, 158.32, 171.43, 171.96, 173.93.

Compound 3e: colorless oil; 90%; IR (neat) 2954, 2245, 1739, 1493, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J = 7.2 Hz, 3H), 2.42 (d, J = 14.1 Hz, 1H), 2.82 (d, J = 13.8 Hz, 1H), 2.94 (d, J =15.3 Hz, 1H), 2.97-3.00 (m, 2H), 3.42 (d, J = 13.8 Hz, 1H), 3.75 (s, 3H), 4.27 (q, J = 7.2 Hz, 2H), 5.31 (t, J = 1.8 Hz, 1H), 5.45 (t, J = 1.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.90, 42.01, 43.91, 43.99, 45.84, 52.72, 56.85, 63.29, 112.54, 119.26, 128.57, 131.08, 132.98, 135.18, 147.88, 168.42, 172.95.

Compound 3f: colorless oil; 93%; IR (neat) 2952, 1718, 1435, 1254, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 2.31 (s, 3H), 2.60 (d, J = 14.4 Hz, 1H), 2.65 (d, J = 16.5 Hz, 1H), 2.71 (d, J = 13.8 Hz, 1H), 2.75 (d, J = 14.4 Hz, 1H), 3.22 (d, J = 16.5 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.64 (s, 3H), 3.73 (s, 3H), 5.20 (t, J = 2.1 Hz, 1H), 5.30 (t, J = 2.1 Hz, 1H), 7.03-7.09 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.00, 25.99, 39.14, 39.39, 44.14, 52.23, 52.81, 57.16, 64.29, 110.26, 129.02, 129.53, 134.32, 136.28, 150.46, 172.71, 173.98, 202.63.

Synthesis of 5: To a stirred solution of **3a** (104 mg, 0.3 mmol) in benzene (3 mL) was added H_2SO_4 (88 mg, 0.9 mmol) at 0 °C and stirred the reaction mixture at room temperature for 1 h. After the usual aqueous extractive workup with ether and column chromatographic purification process (hexanes/EtOAc, 7 : 3) we obtained **5** (89 mg, 86%) as colorless oil.

Compound 5: colorless oil; 86%; IR (neat) 2954, 1734, 1435, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (d, J = 1.5 Hz, 3H), 2.60 (d, J = 3.0 Hz, 1H), 2.63 (d, J = 3.0 Hz, 1H), 2.81 (d, J = 14.0 Hz, 1H), 3.37 (d, J = 14.0 Hz, 1H), 3.58 (s, 3H), 3.61 (s, 3H), 3.62 (s, 3H), 5.54 (t, J = 1.5 Hz, 1H), 7.10-7.20 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 13.92, 38.92, 41.28, 52.03, 52.66, 52.89, 62.22, 64.31, 126.09, 126.63, 128.26, 129.85, 137.23, 146.30, 171.26, 171.27, 173.76; LCMS 346 (M$^+$).

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