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One-Pot Synthesis of Adamantane Derivatives by Domino Michael Reactions from Ethyl 2,4-Dioxocyclohexanecarboxylate

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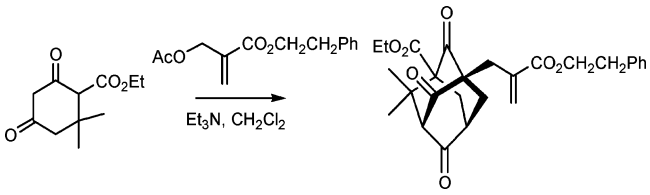

Adamantane derivatives were constructed by the one-pot reaction of ethyl 2,4-dioxocyclohexanecarboxylate with 2-phenylethyl 2-(acetoxymethyl)acrylate or 2-(acetoxymethyl)-1-phenyl-2-propen-1-one via domino Michael reactions and a Dieckmann condensation or an aldol-type reaction (four-bond formation). This is the first one-pot construction of adamantane derivatives from cyclohexanone derivatives not involving enamines.

The unique structural features of the adamantane framework have fascinated chemists over the years.[1] Since adamantane derivatives are rather chemically and thermally stable, they have long been utilized as experimental probes[2] of stereoselectivity in nucleophilic, electrophilic, and cycloaddition reactions. There are also derivatives that are either already applied in the treatment of some human diseases or promising candidates for such use.[3] Furthermore, adamantane derivatives have recently found numerous applications in material science.[4]

Adamantane derivatives have been synthesized by the ring-closing procedure,[5,6] the skeletal rearrangement of other polycyclic hydrocarbons,[1,7] and derivatization of readily available adamantane compounds.[8] The ordinary ring-closing method for constructing the adamantane skeleton would be the ring closure of bicyclo[3.3.1]-nonanones,[5] which requires several steps from readily available material. However, it has also been shown that enamines[6] of monocyclic cyclohexanone derivatives can furnish adamantanes in an elegant cascade manner.

We have been interested in the synthesis of biologically active polycyclic polyprenylated acylphloroglucinols and have recently developed a method for the one-pot construction of the bicyclo[3.3.1]nonanone core by successive Michael reactions of 2-cyclohexenone derivatives and acrylates.[9] In the course of the examination, we found that when ethyl 2,4-dioxocyclohexanecarboxylate **1** was used as the substrate, adamantane derivatives were formed by four-bond formation in one-pot via domino Michael reactions and a Dieckmann condensation or an aldol-type addition. The details are reported in this paper.

Initially, the stepwise Michael reactions of readily available ethyl 2,4-dioxocyclohexanecarboxylate **1**[10] with acrylates **2a**,**b**[11] were examined (Scheme 1). Treatment of the cyclohexadionecarboxylate **1** with acrylate **2a** (1.0 equiv) in the presence of Et_3N as a base gave mono-Michael adduct **3a** in 67% yield. In an attempt to obtain a bicyclo[3.3.1]nonanedione derivative, a solution of the monoadduct **3a** in CH_2Cl_2 was refluxed using Et_3N as a base. However, the monoadduct **3a** was unreacted, probably due to enolization at C3. The reaction of monoadduct **3a** with another equivalent of acrylate **2a** furnished a mixture of bis-alkylated **4a** and **5a** in 57% combined yield (in a ratio of 1:1.8). Intramolecular Michael reactions of the mixture of **4a** and **5a** in the presence of Et_3N did not

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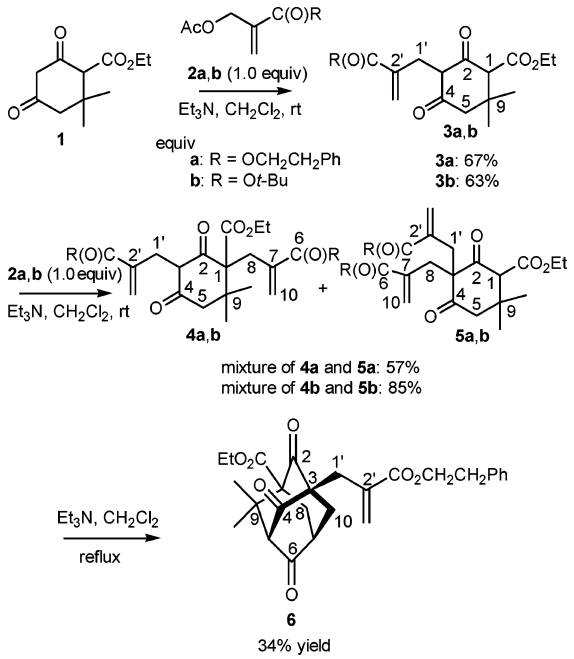
SCHEME 1



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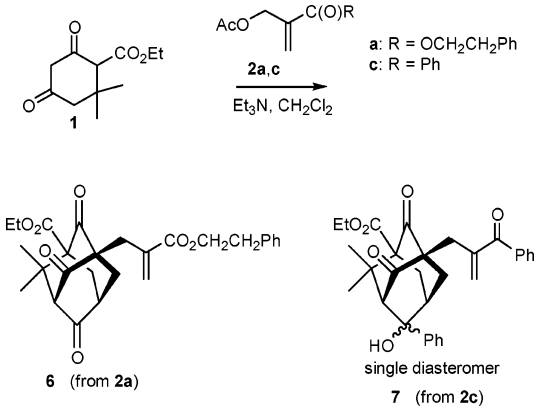


proceed at room temperature. However, when the reaction mixture was refluxed, the adamantane derivative **6** was obtained in 34% yield, via an intramolecular Michael addition (**4a**: C3 to C10; **5a**: C1 to C10) followed by spontaneous Dieckmann cyclization (C5 to C6). Other conditions (K_2CO_3, TBAB, toluene; NaH, THF) examined for the intramolecular Michael reaction did not give the expected adamantane derivative.

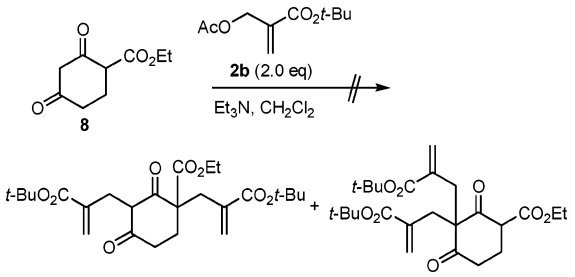
The domino Michael reactions of **1** with acrylate **2b** (2.0 equiv overall) also gave a mixture of the bis-alkylated **4b** and **5b** in 54% yield over two steps (in a ratio of 1:1.3). However, the subsequent intramolecular Michael reaction did not proceed, and the mixture of the bis-alkylated **4b** and **5b** was recovered. Thus, the Michael reaction for forming the bicyclic ring system seems to be sensitive to structural factors.

Having succeeded in obtaining adamantane derivatives in sequential reactions, we decided to attempt the whole process in a one-pot reaction using cyclohexadionecarboxylate **1** with acrylates **2a**,**c** (Scheme 2, Table 1). First of all, bis-alkylation was examined with **2a**. Treatment of **1** with acrylate **2a** (2.0 equiv) at room temperature

TABLE 1. One-Pot reaction of 1 with Acrylates 2a,c

entry	substrate	conditions	product	yield (%)
1	**1**	**2a** (2.0 equiv), Et_3N, rt, 1 day	a mixture of **4a** and **5a**	95
2	**1**	**2a** (2.0 equiv), Et_3N, rt, 1 day, then refluxed, 1 day	**6**	63
3	**1**	**2c** (2.0 equiv), Et_3N, rt, 1 day	**7**	78

SCHEME 3



for 1 day gave a mixture of **4a** and **5a** in 95% yield in a ratio of 1:1.7 (entry 1). Next, the full process was investigated. Subsequent refluxing for 1 day of a mixture of **4a** and **5a** prepared similarly provided the adamantane derivative **6** in 63% yield (entry 2). The one-pot procedure afforded a better yield of the adamantane product than the three-step method.

The domino Michael reaction using α,β-unsaturated ketone **2c**[12] as the Michael acceptor (entry 3) proceeded smoothly at room temperature to give adamantyl derivative **7** in 78% yield as a single diastereomer.

One-pot bis-alkylation of cyclohexadionecarboxylate **8**[13] with acrylate **2b** was also examined (Scheme 3). However, the reaction failed, probably due to self-condensation of the cyclohexadionecarboxylate **8** and/or alkylated cyclohexadionecarboxylate.

In conclusion, adamantane derivatives **6** and **7** could be constructed by the one-pot four-bonds formation reaction of the cyclohexadionecarboxylate **1** via domino inter- and intramolecular Michael reactions and ensuing Dieckmann condensation or aldol-type reaction. This procedure, which does not use enamines, serves as a very efficient variant of Stetter's cascade method[6a] to produce highly functionalized adamantanes.

Experimental Section

Typical Procedure for One-Pot Construction of the Adamantane Derivatives: Preparation of 6. To a mixture of cyclohexadionecarboxylate **1** (119.3 mg, 0.56 mmol) and acrylate **2a** (278.5 mg, 1.12 mmol) in CH_2Cl_2 (1.2 mL), was added Et_3N (0.62 mL, 4.45 mmol). The reaction mixture was stirred at room temperature for 1 day and then refluxed. After 32 h, the reaction mixture was cooled to room temperature and quenched with satd NH_4Cl solution. The resulting mixture was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated. The resulting residue was purified by column chromatography (SiO_2, hexane/EtOAc 1:1) followed by recycling HPLC to give adamantane derivative **6** (164.2 mg, 0.35 mmol, 63%): yellow

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oil; R_f = 0.83 (SiO_2, CH_2Cl_2/MeOH 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.13 (s, 3 H), 1.31 (t, J = 7.0 Hz, 1 H), 1.69 (dt, J = 3.4, 13.4 Hz, 1 H), 1.95 (dd, J = 2.7, 13.4 Hz, 1 H), 2.54 (dd, J = 3.1, 14.6 Hz, 1 H), 2.67 (dt, J = 3.4, 14.6 Hz, 1 H) 2.75−2.78 (m, 1 H), 2.94 (dd, J = 0.6, 14.3 Hz, 1 H), 2.98 (t, J = 6.7 Hz, 2 H), 3.01 (dd, J = 0.6, 14.3 Hz, 1 H), 3.16 (d, J = 1.5 Hz, 1 H), 4.25 (dq, J = 7.0, 15.8 Hz, 2 H), 4.26 (dq, J = 7.0, 15.8 Hz, 2 H), 4.37 (t, J = 6.7 Hz, 2 H), 5.93 (dt, J = 0.6, 1.5 Hz, 1 H), 6.33 (d, J = 1.5 Hz, 1 H), 7.19−7.30 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.3, 25.9, 27.3, 35.0, 36.3, 37.5, 43.5, 43.6, 61.7, 63.4, 65.4, 68.1, 78.1, 126.6, 128.5 (×2), 128.9 (×2), 131.3, 135.6, 137.9, 167.6, 167.9, 197.7, 201.5, 203.5; EI-HRMS *m*/*z* calcd for $C_{27}H_{30}O_7$ [M^+] 466.1992, found 466.2008. Anal. Calcd for $C_{27}H_{30}O_7$: C, 69.51; H, 6.48. Found: C, 69.28; H, 6.63.

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Supporting Information Available: Spectroscopic data for new compounds **3a**, **3b**, a mixture of **4a** and **5a**, a mixture of **4b** and **5b**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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