

A Homodienolate-Enone Addition

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Dedicated to Professor Alex Nickon on his 71st birthday and Professor Andre Dreiding on his 80th birthday

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On treatment with sodium hydride, a mixture of ketone **1** and enone **4** gives a 48% yield of adduct **2**, which contains two new carbon–carbon bonds. The reaction very likely involves homodienolate **3**, which may either undergo a Michael addi-

tion or a cycloaddition to enone **4** to give intermediate adduct **6** or **7**, respectively. Adduct **6** may then undergo homo-Michael addition to give adduct **7**. Cyclopropane ring-opening of adduct **7** and protonation give the observed adduct **2**.

Introduction

During our polycyclopentanoid synthesis studies,^[1] an attempted alkylation of ketone **1** with propargyl bromide/NaH gave a crystalline product whose characterization led to the unexpected results described below.

Results and Discussion

The mass spectrum of the substance indicated it to be two protons short of being a dimer of ketone **1**, suggesting its formation from two molecules of ketone **1** and none of propargyl bromide. The heptacyclic structure **2** was deduced from an HMQC/HMBC/NOESY NMR study (which permitted complete proton and carbon chemical-shift assignments) and verified by an X-ray diffraction study (Figure 1).^[2] The most likely mechanisms (Scheme 1) for obtaining **2** involve reaction of homodienolate **3** with enone **4**. When the crude ketone **1** used for the alkylation was examined, it was found to contain enone **4**, resulting from incomplete zinc reduction of ketone **5** in the preparation of ketone **1**.

The previously unknown enone **4** was then synthesized and purified. When an equimolar mixture of ketones **1** and **4** was treated with NaH, diketone **2** was formed in 48% yield, increasing the likelihood that Scheme 1 is correct. Di-

ketone **2** was not obtained unless both ketones **1** and **4** were present.

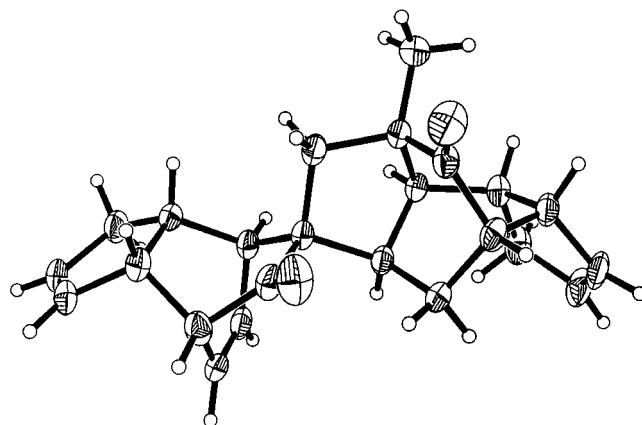
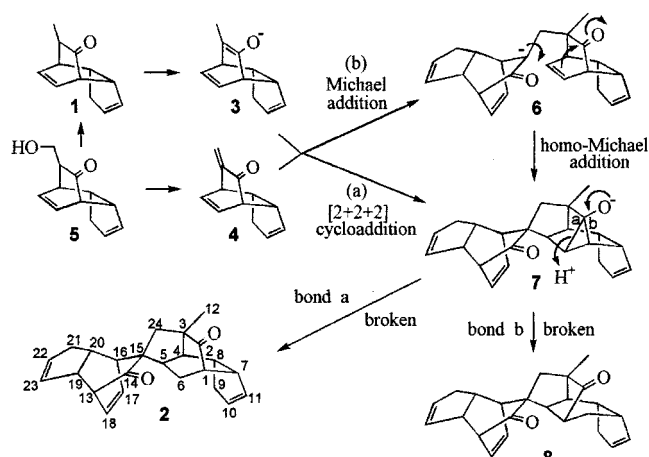


Figure 1. The X-ray structure of **2**, with 50% probability ellipsoids for non-hydrogen atoms



Scheme 1. Possible mechanisms for the formation of **2**

Two possible mechanisms for the reaction of homodienolate **3** with enone **4** are shown in Scheme 1: (a) a

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$[\pi 2_s + \pi 2_s + \pi 2_s]$ cycloaddition to give cyclopropanolate anion **7** directly. $[2+2+2]$ Cycloadditions of alkenes to bicyclo[2.2.1]hepta-2,5-dienes are well-known,^[3] but this would apparently be the first such reaction involving a homodienolate; (b) Michael addition of enolate **3** to α,β -unsaturated ketone **4** to give **6**, followed by intramolecular homo-Michael addition to give **7**. To the best of our knowledge, no homo-Michael addition has been reported. Electrophilic additions to bicyclo[2.2.1]hept-5-en-2-ones and bicyclo[2.2.2]oct-5-en-2-ones have been studied,^[4] but this would be a nucleophilic addition. Homoenolates of bicyclo[2.2.1]heptan-2-ones and bicyclo[2.2.2]octan-2-ones^[5] are well known, and apparently form more readily than most homoenolates,^[6] so it would not be surprising if the first homo-Michael addition found should be to a bicyclo[2.2.2]oct-5-en-2-one. We presently have no way of distinguishing whether mechanism (a) or (b) is followed, but either pathway to **2** has novelty.

We have supported the reasonableness of the last step in Scheme 1 by calculating diketone **2** (heat of formation using PM-3, -28.5 kcal/mol) to be much more stable than isomer **8** (heat of formation using PM-3, -16.4 kcal/mol), which would arise by an alternative cyclopropane ring-opening of **7**.

This synthesis of adduct **2** was done with racemic starting materials. In forming this adduct, one enantiomer of dienolate **3** selects the opposite enantiomer of enone **4**. No other stereoisomers of adduct **2** were detected, though lesser amounts of its stereoisomers may have been formed.

Though its mechanism is not clear, the ease with which this homodienolate-enone cyclization occurs makes this carbon-carbon bond-forming reaction attractive for additional applications.

Experimental Section

General Remarks: NMR spectra were measured in CDCl_3/TMS at 300 and 500 MHz (^1H) and 125.7 MHz (^{13}C) with Bruker spectrometers. X-ray data were collected with a Bruker diffractometer with a SMART 1000 CCD detector.

Enone 4: To ketol **5**^[1] (230 mg, 1.21 mmol) in THF/ H_2O (4:1, 10 mL) were added KOH pellets (600 mg) and the mixture was stirred at 30 °C for 1 h. THF was removed in vacuo. The residue was diluted with water (15 mL) and extracted with EtOAc (3×25 mL). Drying (Na_2SO_4), solvent evaporation, and chromatography on silica gel gave enone **4** as a liquid (200 mg, 96%), EIMS: $m/z = 172$ [M^+]. – UV: $\lambda = 340$ nm. – IR (neat): $\tilde{\nu} = 1710, 1360$

cm^{-1} . – ^1H NMR (CDCl_3 , 300 MHz): $\delta = 2.04$ (br d, $J = 15$ Hz, 1 H), 2.56 (br dd, $J = 15, 9$ Hz, 1 H), 2.74 (m, 1 H), 3.21 (br d, $J = 8$ Hz, 1 H), 3.28 (br d, $J = 6$ Hz, 1 H), 3.55 (m, 1 H), 5.19 (s, 1 H), 5.48 (m, 1 H), 5.66 (m, 1 H), 5.80 (d, $J = 2$ Hz, 1 H), 6.11 (br t, $J = 8$ Hz, 1 H), 6.32 (br t, $J = 8$ Hz, 1 H).

Diketone 2: Ketone **1** (200 mg, 1.15 mmol) in THF (10 mL) was added to a suspension of NaH (140 mg, 5.83 mmol) in THF (5 mL). After refluxing for 30 min, enone **4** (200 mg, 1.16 mmol) in THF (5 mL) was added. After refluxing for 4 h, the reaction was quenched with cold water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel chromatography (EtOAc/petroleum ether 8:92) gave 190 mg (48%) of diketone **2**, m.p. 206 °C; EIMS: $m/z = 346$ [M^+], 281 [$\text{M} - \text{C}_5\text{H}_5$], 280 [$\text{M} - \text{C}_5\text{H}_6$], 228, 162, 118, 117. – ^1H NMR (CDCl_3 , 500 MHz): $\delta = 1.21$ (s, 3 H, H-12), 1.33 (dd, $J = 14.4, 4.8$ Hz, 1 H, H-6_{exo}), 1.56 (dd, $J = 14.4, 9.5$ Hz, 1 H, H-6_{endo}), 1.58 (d, $J = 13.6$ Hz, 1 H, H-24_{exo}), 1.92 (br d, $J = 17.0$ Hz, 1 H, H-21_{endo}), 1.98 (d, $J = 13.6$ Hz, 1 H, H-24_{endo}), 2.15 (m, 1 H, H-1), 2.19 (m, 1 H, H-4), 2.23 (dd, $J = 9.5, 4.8$ Hz, 1 H, H-5), 2.30 (br d, $J = 14.1$ Hz, 1 H, H-9_{exo}), 2.54 (m, 1 H, H-21_{exo}), 2.61 (m, 1 H, H-9_{endo}), 2.66 (m, 1 H, H-8), 2.73 (m, 1 H, H-20), 2.77 (m, 1 H, H-16), 2.98 (m, 1 H, H-7), 3.07 (m, 1 H, H-19), 3.14 (m, 1 H, H-13), 5.37 (m, 1 H, H-11), 5.39 (m, 1 H, H-23), 5.64 (m, 1 H, H-22), 5.87 (m, 1 H, H-10), 5.99 (t, $J = 7.2$ Hz, 1 H, H-18), 6.43 (t, $J = 7.2$ Hz, 1 H, H-17). – ^{13}C NMR (CDCl_3 , 125.7 MHz): $\delta = 17.9$ (C-6), 19.5 (C-12), 30.9 (C-8), 34.6 (C-20), 37.5 (C-9), 39.1 (C-21), 44.4 (C-1), 46.5 (C-5), 46.6 (C-24), 47.3 (C-7), 49.4 (C-16), 49.4 (C-4), 52.3 (C-19), 54.2 (C-13), 55.2 (C-3), 57.0 (C-15), 126.7 (C-18), 130.0 (C-11), 130.2 (C-23), 132.8 (C-22), 133.1 (C-10), 134.6 (C-17), 214.9 (C-14), 219.9 (C-2).

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^[2] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118968. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk].

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