

Synthesis and NMR-spectroscopic characterization of diastereomeric bicyclo[4.2.0]octane-2,7-diones

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Dedicated to Dr. Arlette Solladié-Cavallo on the occasion of her birthday

Abstract

Irradiation ($\lambda = 350$ nm) of cyclohexenones **4** in the presence of 1,1-dimethoxyethylene (**5**) affords mixtures of diastereomeric 7,7-dimethoxybicyclo[4.2.0]octan-2-ones **6** and **7**. Careful hydrolysis of these acetals with acidic SiO₂ affords the title compounds **8** and **9** quantitatively without any epimerization at C (1). These bicyclic diketones were fully characterized by ¹H- and ¹³C-NMR spectroscopy.

Keywords: Enone photocycloaddition, acetal hydrolysis, *trans*-fused cyclobutanones

Introduction

Bicyclo[4.2.0]octanes are easily accessible by [2+2]-cycloaddition of a cyclohexene moiety to an alkene.^{1,2} Regarding the two diastereomeric parent bicycloalkanes **1a** and **2a**, the *trans*-fused stereoisomer **1a** is expected to be more strained by about 25 kJ/mol than its *cis*-fused counterpart **2a**.³ Insertion of a trigonal planar C-atom into the six-membered ring leads to a slight increase in strain energy for both diastereomers and it is therefore not surprising, that *trans*-fused bicyclo[4.2.0]octan-2-ones, e.g. **1b**, epimerize readily to the thermodynamically more stable *cis*-fused diastereomer **2b** on treatment with base or acid.⁴ Incorporation of an additional carbonyl group, now into the four-membered ring, should not influence the relative stability of the resulting bicyclo[4.2.0]octane-2,7-diones **1c** and **2c**, as the strain energy of cyclobutanone is very similar to that of cyclobutane itself.⁵ Interestingly, up to now only one such *trans*-fused (polycyclic) cyclobutanone **3**, resulting from [2+2]-photocycloaddition of a steroidal cyclohexenone to a ketene acetal, followed by hydrolysis of the acetal function and then characterized mainly by IR-spectroscopy, has been reported in the literature (Figure 1).⁶ Here we report on the synthesis and full NMR-spectroscopic characterization of such pairs of bicyclic title compounds.

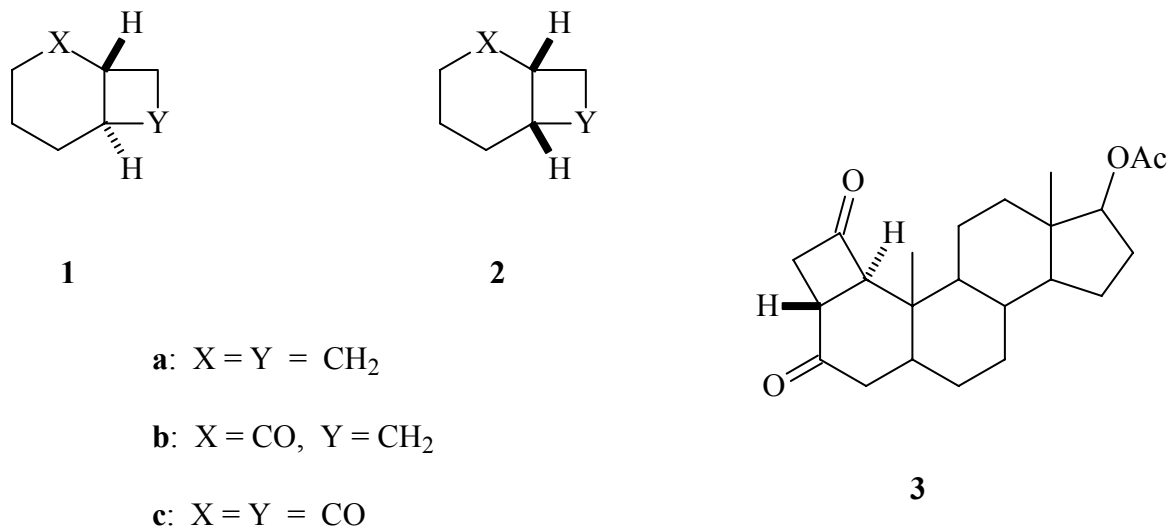
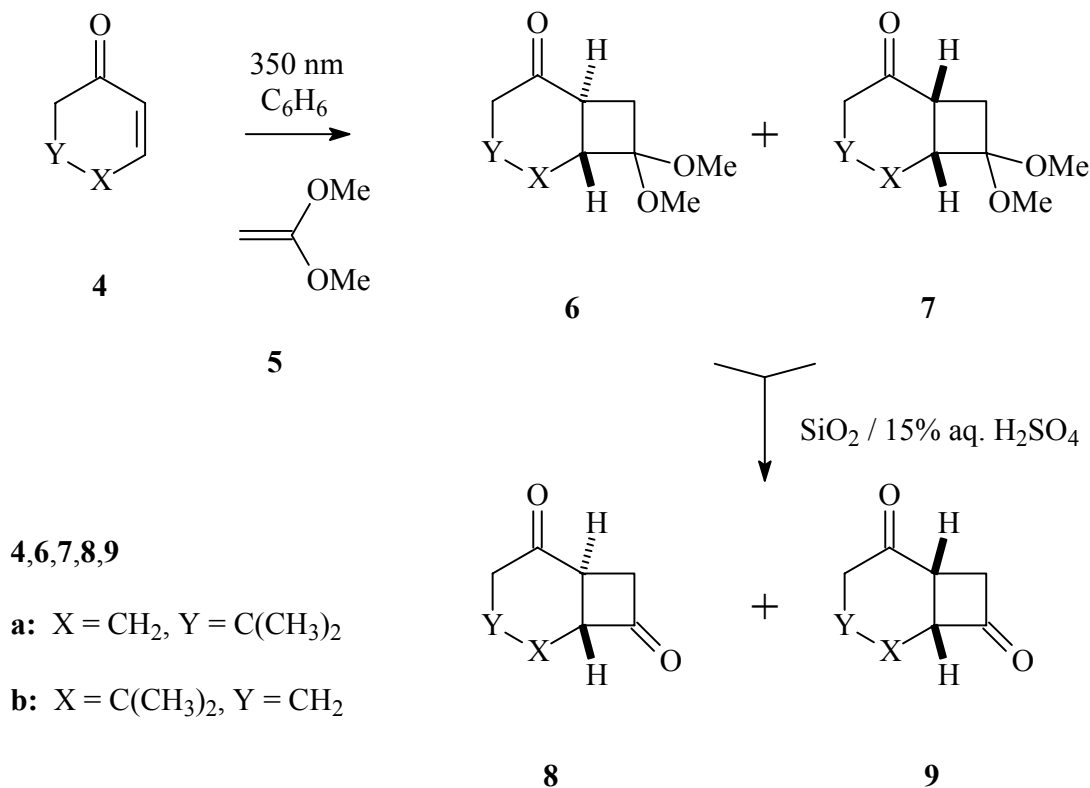


Figure 1

Results and Discussion

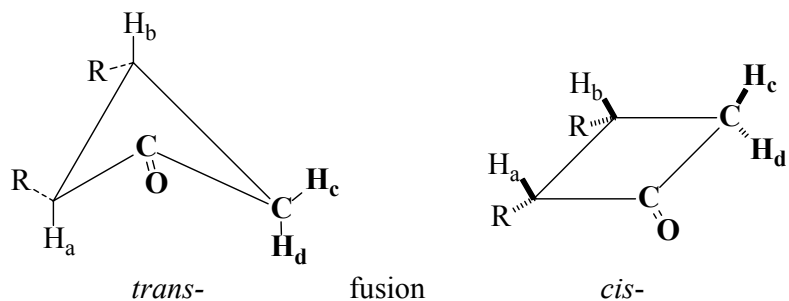
Irradiation (350 nm) of cyclohexenones **4** in benzene in the presence of a tenfold molar excess of 1,1-dimethoxyethylene (**5**) affords regioselectively diastereomeric mixtures of 7,7-dimethoxybicyclo[4.2.0]octan-2-ones **6** and **7**. The excess of added alkene prevents photodimerization of **4**. For 5,5-dimethylcyclohex-2-enone (**4a**) the product ratio **6a/7a** is 3:2, and for 4,4-dimethylcyclohex-2-enone (**4b**) the ratio **6b/7b** is 5:2, respectively. Differentiation between the (major) *trans*- and (minor) *cis*-fused bicyclooctanones **6** and **7** is straightforward by means of the magnitude of the vicinal coupling constant for the bridgehead H-atoms ($^3J \approx 13 - 14$ Hz for **6a/7a**, and $\approx 10 - 11$ Hz for **6b/7b**), and also by the ease of epimerization of the former to the latter diastereomers in the presence of either base or acid. Hydrolysis of the acetal function can be achieved quantitatively under mild aqueous acidic conditions, either using a two phase (10% aq. HCl / CH₂Cl₂) system,⁷ or SiO₂ pretreated with 15% aq. H₂SO₄ in CH₂Cl₂.⁸ Whereas the first method is accompanied by rapid epimerization of the *trans*-fused diketones to the *cis*-fused diastereomers, hydrolysis of the product mixtures **6a/7a** or **6b/7b** according to the second method for 4h at room temp. affords mixtures of **8a/9a** or **8b/9b** without any epimerization, i.e. again 3:2 and 5:2, respectively (Scheme 1). Attempted separation of the product mixtures **8/9** either by chromatography or by preparative GC failed as both conditions lead to quantitative epimerization **8** \rightarrow **9**. Therefore the spectroscopic data of *trans*-fused cyclobutanones **8** discussed below stem from the original product mixtures and only those of the *cis*-fused diastereomers **9** from isolated/purified compounds.



Scheme 1

The NMR-data (Fig. 2) summarizes averaged values for the (almost identical) H,H-coupling constants and ¹³C-chemical shifts of **8a,b** and **9a,b**, respectively. As both the vicinal coupling constants ³J and the long range coupling constants ⁴J are typical for all diastereomeric pairs of bicyclo[4.2.0]octanes, it becomes evident that the best criteria to differentiate between *trans*- and *cis*-fused cyclobutanones are *a*) the geminal coupling constant of the methylene H-atoms adjacent to the carbonyl group (15 Hz vs 18 Hz), and *b*) the chemical shift of the carbonyl C-atom (198 vs 207 ppm), respectively. The former value reflects the dihedral angle θ between the CH bond and the p-orbital of the adjacent sp²-hybridized C-atom, corresponding to an – expected - value near 90° for (puckered) **8** and 15 - 25° for (planar) **9**, respectively.⁹ In contrast, the difference in the latter - δ - values, i.e. almost 10 ppm, is remarkable, as for cyclohexanones where the ring is only slightly distorted from an ideal chair by the *trans*- ring fusion to a four membered ring, e.g. in **6a** or **6b**, the carbonyl C-atoms are only shielded by 2 - 3 ppm as compared to those in *cis*-fused **7a** and **7b**, respectively. Increase of strain in a four-membered ring bearing a sp²-hybridized C-atom should thus reflect on the chemical shift of this latter nucleus by becoming more similar to that of a corresponding one in a three membered ring. Unfortunately, no reliable carbonyl chemical shifts of cyclopropanones have been reported in the literature, as these compounds are not stable at room temperature. On the other side there is experimental data for the corresponding sp²-hybridized ring-C-atoms of methylenecycloalkanes,

with values of 131, 150, 153 and 150 ppm for methylene-cyclopropane, -cyclobutane, -cyclopentane and -cyclohexane, respectively.¹⁰ Indeed now in these compounds there is a large decrease in the δ -value in going from the four- to the three membered ring, which fits with the observation mentioned above. In conclusion, we have, for the first time, identified and fully characterized spectroscopically two *trans*-fused bicyclo[4.2.0]octane-2,7-diones.



H,H-Coupling Constants

13.4 Hz	³ J (H _a H _b)	10.4 Hz
6.5 Hz	³ J (H _b H _c)	10.4 Hz
10.3 Hz	³ J (H _b H _d)	5.7 Hz
15.1 Hz	²J (H_cH_d)	18.1 Hz

¹³C-Chemical Shifts

44 ppm	C _{c,d}	50 ppm
198 ppm	C=O	207.5 ppm

Figure 2

Experimental Section

General Procedures. ¹H-NMR spectra (500 MHz) and ¹³C-NMR spectra (125 MHz) – including two-dimensional plots - were recorded on a Bruker DRX 500 spectrometer. Chemical shifts (δ) are given in ppm rel. to TMS (0 ppm) as internal standard. Mass spectra were measured on a Varian MAT 311 A instrument at 70 eV. Photolyses were run in a Rayonet RPR-100 photochemical reactor equipped with (16) 350 nm lamps. Analytical GC was performed on a 30 m 5% SE-30 capillary column.

Starting materials. Cyclohexenones **4a** and **4b** were synthesized according to the literature.^{11,12} 1,1-Dimethoxyethylene (**5**) was generously provided by Wacker Chemie AG (Munich).

Photolyses. Ar-Degassed solns. of either **4a** or **4b** (248 mg, 2 mmol) and **5** (1.76 g, 20 mmol) in benzene (5 ml) were irradiated for 16 h up to total enone conversion (GC). Irradiation of **4a** affords (100%) a 3:2 mixture of **6a** and **7a**, whereas irradiation of **4b** gives (100%) a 5:2 mixture of **6b** and **7b**, respectively. On attempted separation/purification by chromatography on SiO₂, quantitative epimerization of **6** to **7** occurs, and therefore only the *cis*-fused 7,7-dimethoxybicyclo[4.2.0]octan-2-ones were isolated as pure compounds, both colourless liquids.

1 α ,6 β -7,7-Dimethoxy-4,4-dimethylbicyclo[4.2.0]octan-2-one (6a). ¹H-NMR (CDCl₃) δ 3.27 (3H, s), 3.19 (3H, s), 2.57 (H(1), dt, $J = 12.8, 8.5$ Hz), 2.35 (H(6), dt, $J = 3.3, 12.8$ Hz), 2.30 & 1.97 (2H(3), $J_{gem} = 13.5$ Hz), 2.11 & 2.09 (2H(8), $J_{gem} = 11.5$ Hz), 1.85 & 1.65 (2H(5), $J_{gem} = 12.6$ Hz), 1.17 (3H, s), 1.03 (3H, s); ¹³C-NMR (CDCl₃) δ 205.9 (C(2)), 103.2 (C(7)), 55.5 (C(3)), 53.8 (C(6)), 49.2 & 48.8 (CH₃O), 44.1 (C(1)), 40.2 (C(4)), 40.1 (C(5)), 33.5 (C(8)), 32.1 & 29.5 (CH₃); MS m/z 181 (M⁺ - OCH₃, 20%), 88 (100%).

1 α ,6 α -7,7-Dimethoxy-4,4-dimethylbicyclo[4.2.0]octan-2-one (7a). ¹H-NMR (CDCl₃) δ 3.18 (3H, s), 3.16 (3H, s), 2.85 (H(6), dq, $J = 3.2, 9.0$ Hz), 2.67 (H(1), q, $J = 9.0$ Hz), 2.47 & 2.28 (2H(8), $J_{gem} = 12.1$ Hz), 2.27 & 2.25 (2H(3), $J_{gem} = 16.2$ Hz), 1.80 & 1.63 (2H(5), $J_{gem} = 13.8$ Hz), 1.05 (3H, s), 0.94 (3H, s); ¹³C-NMR (CDCl₃) δ 207.8 (C(2)), 101.5 (C(7)), 52.5 (C(3)), 49.5 & 48.9 (CH₃O), 43.8 (C(6)), 34.7 (C(1)), 34.6 (C(4)), 34.2 (C(5)), 34.1 (C(8)), 31.1 & 26.8 (CH₃); MS m/z 212 (M⁺, 0.2%), 88 (100%).

1 α ,6 β -7,7-Dimethoxy-5,5-dimethylbicyclo[4.2.0]octan-2-one (6b). ¹H-NMR (CDCl₃) δ 3.21 (3H, s), 3.19 (3H, s), 2.92 (H(1), ddd, $J = 7.0, 10.0, 13.7$ Hz), 2.40 & 2.25 (2H(3), $J_{gem} = 14.1$ Hz), 2.20 & 2.05 (2H(8), $J_{gem} = 11.4$ Hz), 2.02 (H(6), d, $J = 13.7$ Hz), 1.72 & 1.68 (2H(4), $J_{gem} = 12.8$ Hz), 1.28 (3H, s), 1.14 (3H, s); ¹³C-NMR (CDCl₃) δ 208.2 (C(2)), 106.9 (C(7)), 65.1 (C(6)), 50.0 & 49.8 (CH₃O), 44.9 (C(5)), 44.1 (C(4)), 39.5 (C(1)), 36.9 (C(3)), 32.0 (C(8)), 29.8 & 22.1 (CH₃); MS m/z 212 (M⁺, 0.5%), 88 (100%).

1 α , 6 α -7,7-Dimethoxy-5,5-dimethylbicyclo[4.2.0]octan-2-one (7b). ¹H-NMR (CDCl₃) δ 3.21 (3H, s), 3.09 (3H, s), 2.64 (H(1), dt, $J = 3.8, 9.8$ Hz), 2.58 (H(6), d, $J = 9.8$ Hz), 2.45 & 2.39 (2H(3), $J_{gem} = 16.1$ Hz), 2.40 & 2.05 (2H(8), $J_{gem} = 12.5$ Hz), 1.62 & 1.50 (2H(4), $J_{gem} = 12.8$ Hz), 1.10 (3H, s), 0.99 (3H, s); ¹³C-NMR (CDCl₃) δ 211.5 (C(2)), 101.2 (C(7)), 56.5 (C(6)), 49.8 & 49.2 (CH₃O), 44.3 (C(4)), 37.2 (C(1)), 36.1 (C(5)), 35.1 (C(3)), 33.1 (C(8)), 31.2 & 30.1 (CH₃); MS m/z 212 (M⁺, 1.5%), 88 (100%).

Hydrolyses. To a suspension of 150 mg SiO₂ in CH₂Cl₂ (1 ml) is added 15 μ l of 15% H₂SO₄. After stirring for 5 min. a soln. of the mixture **6/7** (21.2 mg, 0.1 mmol) in CH₂Cl₂ (1 ml) is added, and the mixture stirred for 4h at rt. Then solid NaHCO₃ (10 mg) is added, and stirring continued for 5 min. The SiO₂ is removed by filtration and the solvent evaporated to afford quantitatively mixtures **8/9** of the same diastereomeric composition as that of the photocycloadducts, i.e. 3:2 for **8a** and **9a**, and 5:2 for **8b** and **9b**, respectively. On attempted separation/purification by chromatography on SiO₂, again quantitative epimerization of **8** to **9**

occurs, and therefore only the *cis*-fused 7,7-bicyclo[4.2.0]octane-2,7-diones were isolated as pure compounds, both colourless liquids.

1 α ,6 β -4,4-Dimethylbicyclo[4.2.0]octane-2,7-dione (8a). $^1\text{H-NMR}$ (CDCl_3) δ 3.31 (H(6), ddd, $J = 3.8, 12.8, 13.8$ Hz), 3.30 & 2.60 (2H(8), $J_{\text{gem}} = 15.1$ Hz), 3.14 (H(6), ddd, $J = 6.6, 10.3, 13.8$ Hz), 2.45 & 2.15 (2H(3), $J_{\text{gem}} = 13.3$ Hz), 1.95 & 1.80 (2H(5), $J_{\text{gem}} = 12.8$ Hz), 1.17 (3H, s), 1.06 (3H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ 204.8 (C(2)), 198.2 (C(7)), 66.5 (C(6)), 56.2 (C(3)), 44.2 (C(8)), 41.6 (C(1)), 41.5 (C(4)), 39.5 (C(5)), 31.92 & 27.7 (CH_3).

1 α ,6 α -4,4-Dimethylbicyclo[4.2.0]octane-2,7-dione (9a). $^1\text{H-NMR}$ (CDCl_3) δ 3.77 (H(6), dddd, $J = 4.5, 9.3, 10.8, 3.0$ Hz), 3.42 & 3.25 (2H(8), $J_{\text{gem}} = 18.1$ Hz), 3.06 (H(1), dt, $J = 5.5, 10.8$ Hz), 2.32 & 2.27 (2H(3), $J_{\text{gem}} = 15.1$ Hz), 1.90 & 1.70 (2H(5), $J_{\text{gem}} = 14.0$ Hz), 1.05 (3H, s), 0.90 (3H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ 211.5 (C(2)), 208.5 (C(7)), 58.1 (C(6)), 54.1 (C(4)), 52.2 (C(3)), 52.1 (C(8)), 36.2 (C(5)), 34.1 (C(1)), 30.3 & 30.1 (CH_3); MS m/z 166 (M^+ , 30%), 68 (100%).

1 α ,6 β -5,5-Dimethylbicyclo[4.2.0]octane-2,7-dione (8b). $^1\text{H-NMR}$ (CDCl_3) δ 3.23 & 2.60 (2H(8), $J_{\text{gem}} = 15.0$ Hz), 3.01 (H(6), d, $J = 13.0$ Hz), 3.00 (H(1), ddd, $J = 6.6, 10.3, 13.0$ Hz), 2.50 & 2.32 (2H(3), $J_{\text{gem}} = 14.5$ Hz), 1.80 & 1.75 (2H(4), $J_{\text{gem}} = 12.8$ Hz), 1.25 (3H, s), 1.16 (3H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ 206.5 (C(2)), 198.2 (C(7)), 76.1 (C(6)), 43.3 (C(8)), 43.2 (C(4)), 38.3 (C(3)), 35.5 (C(1)), 34.5 (C(5)), 28.72 & 28.2 (CH_3).

1 α ,6 α -5,5-Dimethylbicyclo[4.2.0]octane-2,7-dione (9b). $^1\text{H-NMR}$ (CDCl_3) δ 3.38 (H(6), dt, $J = 10.0, 3.0$ Hz), 3.34 & 3.04 (2H(8), $J_{\text{gem}} = 18.0$ Hz), 3.14 (H(1), dt, $J = 6.0, 10.0$ Hz), 2.53 & 2.51 (2H(3), $J_{\text{gem}} = 15.1$ Hz), 1.88 & 1.70 (2H(5), $J_{\text{gem}} = 14.0$ Hz), 1.17 (3H, s), 1.03 (3H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ 211.5 (C(2)), 207.5 (C(7)), 72.5 (C(6)), 50.2 (C(8)), 36.1 (C(1)), 35.5 (C(3)), 34.5 (C(5)), 33.8 (C(4)), 26.6 & 26.5 (CH_3); MS m/z 166 (M^+ , 2%), 82 (100%).

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