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 SiO\(_2\) affords the title compounds 8 and 9 quantitatively without any epimerization at C (1). These bicyclic diketones were fully characterized by \(^1\)H- and \(^{13}\)C-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.
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 / CH$_2$Cl$_2$) system, or SiO$_2$ pretreated with 15% aq. H$_2$SO$_4$ in CH$_2$Cl$_2$. 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 $^{13}$C-chemical shifts of $8\text{a,b}$ and $9\text{a,b}$, 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 $\theta$ between the CH bond and the p-orbital of the adjacent sp$^2$– hybridized C-atom, corresponding to an – expected - value near 90° for (puckered) $8$ and 15 - 25° for (planar) $9$, respectively. In contrast, the difference in the latter - $\delta$ - 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 $6\text{a}$ or $6\text{b}$, the carbonyl C-atoms are only shielded by 2 - 3 ppm as compared to those in cis-fused $7\text{a}$ and $7\text{b}$, respectively. Increase of strain in a four-membered ring bearing a sp$^2$-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 sp$^2$-hybridized ring-C-atoms of methylenecycloalkanes,
whith values of 131, 150, 153 and 150 ppm for methylene-cyclopropane, -cyclobutane, -cyclopentane and –cyclohexane, respectively. Indeed now in these compounds there is a large decrease in the $\delta$-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.

\[ \text{H}_{\alpha}\text{H}-Coupling\ Constants \]

\[
\begin{array}{ccc}
13.4 \text{ Hz} & J(H_{\alpha}H_{\beta}) & 10.4 \text{ Hz} \\
6.5 \text{ Hz} & J(H_{\beta}H_{\gamma}) & 10.4 \text{ Hz} \\
10.3 \text{ Hz} & J(H_{\gamma}H_{\delta}) & 5.7 \text{ Hz} \\
15.1 \text{ Hz} & J(H_{\delta}H_{\gamma}) & 18.1 \text{ Hz} \\
\end{array}
\]

\[ ^{13}\text{C}-\text{Chemical\ Shifts} \]

\[
\begin{array}{ccc}
44 \text{ ppm} & C_{c,d} & 50 \text{ ppm} \\
198 \text{ ppm} & C=O & 207.5 \text{ ppm} \\
\end{array}
\]

Figure 2

**Experimental Section**

**General Procedures.** $^{1}$H-NMR spectra (500 MHz) and $^{13}$C-NMR spectra (125 MHz) – including two-dimensional plots - were recorded on a Bruker DRX 500 spectrometer. Chemical shifts ($\delta$) 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.

1α,6β-7,7-Dimethoxy-4,4-dimethylbicyclo[4.2.0]octan-2-one (6a). $^1$H-NMR (CDCl₃) δ 3.27 (3H, s), 3.19 (3H, s), 2.57 (H, dt, J = 12.8, 8.5 Hz), 2.35 (H, dt, J = 3.3, 12.8 Hz), 2.30 & 1.97 (2H, Jgem = 13.5 Hz), 2.11 & 2.09 (2H, Jgem = 11.5 Hz), 1.85 & 1.65 (2H, Jgem = 12.6 Hz), 1.17 (3H, s), 1.03 (3H, s); $^{13}$C-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⁺, 20%), 88 (100%).

1α,6α-7,7-Dimethoxy-4,4-dimethylbicyclo[4.2.0]octan-2-one (7a). $^1$H-NMR (CDCl₃) δ 3.18 (3H, s), 3.16 (3H, s), 2.85 (H, dq, J = 3.2, 9.0 Hz), 2.67 (H, q, J = 9.0 Hz), 2.47 & 2.28 (2H, Jgem = 12.1 Hz), 2.27 & 2.25 (2H, Jgem = 16.2 Hz), 1.80 & 1.63 (2H, Jgem = 13.8 Hz), 1.05 (3H, s), 0.94 (3H, s); $^{13}$C-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%).

1α,6β-7,7-Dimethoxy-5,5-dimethylbicyclo[4.2.0]octan-2-one (6b). $^1$H-NMR (CDCl₃) δ 3.21 (3H, s), 3.19 (3H, s), 2.92 (H, ddd, J = 7.0, 10.0, 13.7 Hz), 2.40 & 2.25 (2H, Jgem = 14.1 Hz), 2.20 & 2.05 (2H, Jgem = 11.4 Hz), 2.02 (H, d, J = 13.7 Hz), 1.72 & 1.68 (2H, Jgem = 12.8 Hz), 1.28 (3H, s), 1.14 (3H, s); $^{13}$C-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%).

1α,6α-7,7-Dimethoxy-5,5-dimethylbicyclo[4.2.0]octan-2-one (7b). $^1$H-NMR (CDCl₃) δ 3.21 (3H, s), 3.09 (3H, s), 2.64 (H, dt, J = 3.8, 9.8 Hz), 2.58 (H, d, J = 9.8 Hz), 2.45 & 2.39 (2H, Jgem = 16.1 Hz), 2.40 & 2.05 (2H, Jgem = 12.5 Hz), 1.62 & 1.50 (2H, Jgem = 12.8 Hz), 1.10 (3H, s), 0.99 (3H, s); $^{13}$C-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 µl 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.

1α,6β-4,4-Dimethylbicyclo[4.2.0]octane-2,7-dione (8a). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 3.31 (H(6), ddd, \(J = 3.8, 12.8, 13.8\) Hz), 3.30 & 2.60 (2H(8), \(J_{gem} = 15.1\) Hz), 3.14 (H(6), ddd, \(J = 6.6, 10.3, 13.8\) Hz), 2.45 & 2.15 (2H(3), \(J_{gem} = 13.3\) Hz), 1.95 & 1.80 (2H(5), \(J_{gem} = 12.8\) Hz), 1.06 (3H, s); \(^1\)C-NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)).

1α,6α-4,4-Dimethylbicyclo[4.2.0]octane-2,7-dione (9a). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 3.77 (H(6), dddt, \(J = 4.5, 9.3, 10.8, 13.0\) Hz), 3.42 & 3.25 (2H(8), \(J_{gem} = 18.1\) Hz), 3.06 (H(1), dt, \(J = 5.5, 10.8\) Hz), 2.32 & 2.27 (2H(3), \(J_{gem} = 15.1\) Hz), 1.90 & 1.70 (2H(5), \(J_{gem} = 14.0\) Hz), 1.05 (3H, s), 0.90 (3H, s); \(^1\)C-NMR (CDCl\(_3\)) \(\delta\) 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%).

1α,6β-5,5-Dimethylbicyclo[4.2.0]octane-2,7-dione (8b). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 3.23 & 2.60 (2H(8), \(J_{gem} = 15.0\) 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), \(J_{gem} = 14.5\) Hz), 1.80 & 1.75 (2H(4), \(J_{gem} = 12.8\) Hz), 1.25 (3H, s), 1.16 (3H, s); \(^1\)C-NMR (CDCl\(_3\)) \(\delta\) 206.5 (C(2)), 198.2 (C(7)), 76.1 (C(6)), 54.1 (C(4)), 43.3 (C(8)), 36.2 (C(5)), 35.5 (C(1)), 35.4 (C(3)), 28.72 & 28.2 (CH\(_3\)).

1α,6α-5,5-Dimethylbicyclo[4.2.0]octane-2,7-dione (9b). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 3.38 (H(6), dt, \(J = 10.0, 3.0\) Hz), 3.34 & 3.04 (2H(8), \(J_{gem} = 18.0\) Hz), 3.14 (H(1), dt, \(J = 6.0, 10.0\) Hz), 2.53 & 2.51 (2H(3), \(J_{gem} = 15.1\) Hz), 1.88 & 1.70 (2H(5), \(J_{gem} = 14.0\) Hz), 1.17 (3H, s), 1.03 (3H, s); \(^1\)C-NMR (CDCl\(_3\)) \(\delta\) 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%).

References and Notes