99. Synthesis of 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentanal and its Conversion into Derivatives of Spiro[4.5]decane and of 1,6,7,7a-Tetrahydro-2*H*-indene

by **Ora Goldberg**[1]) and **André S. Dreiding**

Organisch-chemisches Institut der Universität Zürich, Rämistrasse 74–76, CH-8001 Zürich

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Synthese von 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentanal und dessen Umwandlung in Spiro[4.5]decan- und 1,6,7,7a-Tetrahydro-2H-inden-Derivate

Zusammenfassung

Es wird die Synthese von 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentanal als ein (1:1)-Gemisch von zwei Diastereoisomeren **10A** und **10B** auf folgendem Weg beschrieben: Die Umsetzung des *Grignard*-Reagens von 1,1-Äthylendioxy-3-brom-propan (**2**) mit 2-Methoxy-4-methyl-acetophenon (**1**) ergab 1,1-Äthylendioxy-4-hydroxy-4-(2'-methoxy-4'-methyl-phenyl)-pentan (**3**), welches sich mit methanolischer Salzsäure in 2-Methoxy-5-(2'-methoxy-4'-methyl-phenyl)-5-methyl-tetrahydrofuran (**7A,B**) umwandeln liess. Durch *Birch*-Reduktion von **7A,B** wurde 4-(2'-Methoxy-4'-methyl-cyclohexa-1',4'-dien-1'-yl)-pentan-1-ol (**8**), und danach durch milde Hydrolyse 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentan-1-ol (**9A,B**)[2]) erhalten. Oxydation von **9A,B** lieferte schliesslich den erwähnten Keto-aldehyd **10A,B**. Einige Produkte von Nebenreaktionen, nämlich **4**, **5**, **11**, **12** und **13A,B**, sind auch beschrieben.

Der Keto-aldehyd **10A,B** liess sich in ein Gemisch, bestehend aus drei Diastereoisomeren **A**, **B** und **C** von 1-Hydroxy-4,8-dimethyl-spiro[4.5] dec-7-en-6-on (**15**) und aus zwei Diastereoisomeren **A** und **B** von 1,5-Dimethyl-1,6,7,7a-tetrahydro-2*H*-inden-3-carbaldehyd (**14**), umwandeln. Für diese aldolartigen Cyclisierungen wurden vier verschiedene Methoden verwendet: a) Stehenlassen in Tetrachlorkohlenstofflösung, b) Behandlung mit etwas Trifluoressigsäure in Chloroformlösung, c) und d) Schütteln einer Ätherlösung mit wässeriger Salzsäure oder Natronlauge. Oxydation von **15A** und **15C** lieferte eines der Diastereoisomeren von 4,8-Dimethyl-spiro[4.5]-dec-7-en-1,6-dion (**16A**), und Oxydation von **15B** führte zum anderen (**16B**).

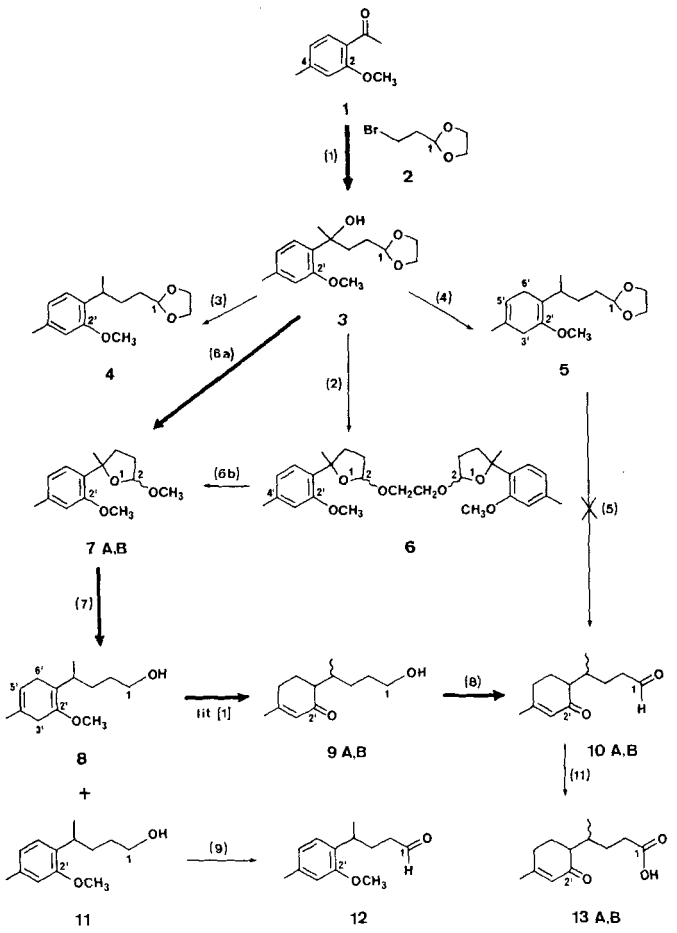
1. Introduction. – In a recent publication [1] from this laboratory the synthesis of the hydroxy-ketone **9** from the acetophenone derivative **1** *via* the diene-alcohol **8** was described. We now present an alternative synthesis of **9** and its oxidation to the keto-aldehyde **10** by reactions which are summarized in *Scheme 1*. We also report the con-

[1]) Postdoctoral Fellow, 1974–1977.

[2]) We use this nomenclature to show the similarity with **10** and **13**, which are derivatives of pentanal and pentanoic acid, respectively. The IUPAC-nomenclature of compound **9** is 6-(4'-hydroxy-1'-methyl-butyl)-3-methyl-cyclohex-2-en-1-one.

version of the keto-aldehyde **10** into a spiro and a bicyclic system, as shown in *Scheme 2*. In the two *Schemes*, each step of the synthetic procedures is numbered (in brackets) on the corresponding arrow. Further remarks on any step are given in the following paragraphs under the heading of the step number.

Scheme 1



2. Preparation of the keto-aldehyde 10 (see Scheme 1). – The thicker arrows in *Scheme 1* show the reactions along the new synthetic route to the keto-aldehyde **10**; the thinner arrows indicate the side reactions examined.

Step (1). *Grignard* reaction of 2-methoxy-4-methyl-acetophenone (**1**) and 1,1-ethylenedioxy-3-bromo-propane (**2**) [2] under the conditions described for an analogous case [2] afforded ~90% of the hydroxy-acetal **3**, which was unstable even at −20° but could be stored in the presence of triethylamine.

Step (2). Neat or in carbon tetrachloride solution, **3** was gradually trans-acetalized by combination of 2 molecules with loss of one molecule of ethylene glycol to give

one isomer of the 'dimeric' acetal **6**, m.p. 190–195° (50% from **1**). The structure of **6** was deduced from the molecular weight and from the ^{1}H-NMR. spectrum, both of which showed a loss of half a unit of ethylene glycol per molecule of **3**. The ^{1}H-NMR. spectrum also indicated a two-fold symmetry of **6**.

Step (*3*). Hydrogenolysis of the hydroxy-acetal **3** over 10% Pd/C afforded the saturated acetal **4** (83% from **1**).

Step (*4*). *Birch* reduction converted **3** to the diene-acetal **5**, which was not obtained pure. The ^{1}H-NMR. spectrum showed the absence of aromatic protons and the presence of two allylic methylene groups.

Step (*5*). Acid hydrolysis of **5** did not result in the desired keto-aldehyde **10**. Evidently the latter is not stable under acidic conditions (compare section 3). We therefore modified the synthetic scheme back *via* the hydroxy-ketone **9**, which had been obtained previously [1] in another way (see section 1).

Step (*6*). Treatment of the hydroxy-acetal **3** or of the 'dimeric' acetal **6** with hydrogen chloride in aqueous methanol afforded 93% (from **1** *via* **3**) and 80% (from **6**), respectively, of the cyclic acetal **7** as a 1:1 mixture of two diastereoisomers **A**, m.p. 73–74°, and **B**, which were separated by chromatography. The ^{1}H-NMR. spectrum indicated the presence of two methoxyl groups in both isomers.

Step (*7*). Reduction of the mixture **7A,B** with sodium in liquid ammonia and ethanol caused cleavage of the benzylic C-O bond as well as reduction of the liberated aldehyde function and of the aromatic ring, to give the diene-alcohol **8** (96%) [1], which was also characterized as its dinitrobenzoate. In one experiment the reduction of the aromatic ring did not go to completion and the product was contaminated with the aromatic alcohol **11**; in that case the mixture was carried through the acid hydrolysis procedure, and the resulting mixture was separated into **11** and the hydroxy-ketones **9A,B** as described in [1].

Step (*8*). The hydroxy-ketone **9**, obtained as a 1:1 mixture of diastereoisomers **A** and **B** by hydrolysis of the enol ether function in **8** as described in [1], was oxidized with chromium trioxide and pyridine in methylene chloride to a 1:1 mixture of the diastereoisomers **A** and **B** of the keto-aldehyde **10** (93%), separated by chromatography.

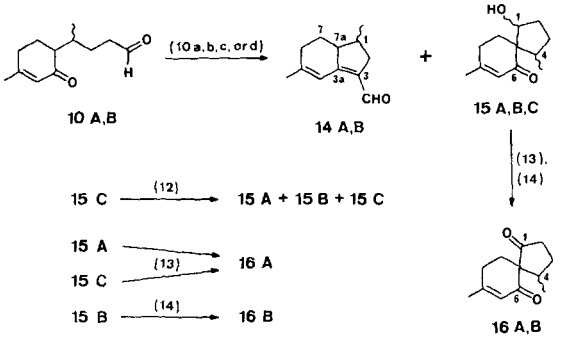
Step (9). The aromatic alcohol **11** was oxidized in a similar manner in 85% yield to the aldehyde **12**.

Step (*11*) will be described in section 3.

It was not possible to assign configurations to those compounds in *Scheme 1* which were obtained or observed as diastereoisomers, namely **7**, **10** and **13**, because of the similarities of the properties in each case.

3. Conversion of the keto-aldehyde 10 to a bicyclic and a spiro system (see Scheme 2). – *Step* (*10a*). The transformation **10** → **14** + **15** was first observed when the keto-aldehydes **10A,B** (1:1 mixture) were allowed to stand in carbon tetrachloride solution: After 5–10 days the ^{1}H-NMR. spectrum indicated that only minor amounts of **10A,B** were still present and that several new compounds had appeared. Separation by chromatography yielded: a) 19% of a 7:1 mixture of the diastereoisomeric bicyclic aldehydes **14A** and **14B**, b) 31% of a 1:1 mixture of two diastereoisomeric spiro-

Scheme 2



hydroxy-ketones **15A** and **15B**, c) 32% of a third diastereoisomer of the spiro-hydroxy-ketone, **15C**, m.p. 78–79°, and d) 5% of recovered educt **10A,B**.

Of these five products, only **14B** was not obtained pure. The structure of the bicyclic aldehyde **14A** was deduced from the intense UV. maximum at 303–304 nm and from other spectral evidence for the aldehyde function. The structure of **14B** is plausible, because of the similarity of its ^{1}H-NMR. signals with those of **14A**.

The structures of the three spiro-hydroxy-ketones **15A**, **15B** and **15C** were confirmed by the similarity of all their spectral data, such as f.i. the hydroxyl and conjugated carbonyl bands in the IR. spectra and the ^{13}C-NMR. signals for the spiro carbon atoms.

The available data did not permit an unequivocal deduction of the configurations of the compounds formed in step (10), except that **15A** and **15C** differ only in the configuration of the hydroxyl group (see steps (13) and 14)).

The formation of the bicyclic aldehydes **14** and the spiro-hydroxy-ketones **15** must be due to the two possible intramolecular aldol condensations of the keto-aldehydes **10A,B**. It is not clear why these reactions occur in carbon tetrachloride solution, but repeated experiments under given conditions (see exper. part) always led to the same result. The cyclizations of **10A,B** did not occur in deuteriochloroform solution, either alone or in the presence of triethylamine or benzoyl peroxide.

Step (10b). When a solution of **10A,B** in deuteriochloroform was allowed to stand with trifluoroacetic acid for 2 days, a mixture of **10A,B**, **14A**, **14B**, **15A**, **15B** and **15C** in the ratios of 7:8:2:9:5:9 was observed in the ^{1}H-NMR. spectrum.

Step (10c). The aldol cyclizations also took place when an ethereal solution of the keto-aldehydes **10A,B** was stirred during 48 hours with 2N aqueous HCl; in this case products **14A** and **14B** (ratio 7:3, 49%), **15A** and **15B** (ratio 1:1, 13%) and **15C** (16%) were isolated, along with recovered **10A,B** (9%).

Step (10d). Stirring an ethereal solution of **10A,B** with 2N aqueous NaOH for 2 hours also effected the intramolecular condensations, yielding **14A** and **14B** (ratio 5:2, 33%), **15A** (20%), **15B** (7%) and **15C** (11%), in addition to 4% unreacted **10A,B**.

It may be of potential synthetic interest that the changes of reaction conditions examined in this work led to ratios of the bicyclic aldehydes **14** and the spiro-hydroxy-ketones **15** varying from 1:0.6 in step (10c) to 1:3 in step (10a). Intramolecular aldolizations of keto-aldehydes in which the ketonic carbonyl group condenses on the α-

carbon atom of the aldehyde have been reported [3]. Some of these reactions led to the formation of compounds incorporating a 1,6,7,7a-tetrahydro-2*H*-indene-3-carbaldehyde unit similar to that of **14**.

Step (11). When a solution of the keto-aldehydes **10A,B** in carbon tetrachloride was kept in the presence of sodium acetate for a few days without exclusion of air, the only product isolated was a 1:1 mixture of the diastereoisomeric keto-acids **13A,B** (41%).

Step (12). In an attempt to dehydrate the spiro-hydroxy-ketones **15**, the pure isomer **15C** was treated with catalytic amounts of *p*-toluenesulfonic acid in hot *p*-xylene. The result was an isomerization of **15C**, leading to the three diastereoisomers **A**, **B** and **C** of **15** and traces of the aldehydes **14A,B**, probably due to an aldol-equilibration between the spiro-hydroxy-ketones **15** and the keto-aldehydes **10A,B**.

Step (13). Oxidation of **15A** and of **15C** with *Jones* reagent afforded the same product, namely the spiro-diketone **16A**, m.p. 60°, in about 90% yield.

Step (14). The same reagent oxidized **15B** to the second diastereoisomer of the spiro-diketone, **16B**, m.p. 55–56° (85%). The two spiro-diketones **16A** and **16B** showed separate IR. bands for the five- and six-membered ring-carbonyl groups.

4. Remarks. – The reactions and some of the compounds described here may be useful for synthetic purposes, especially in the field of sesquiterpenes. We are investigating routes for the conversion of the keto-aldehyde **10** into Arteannuin B [4] and of the spiro-hydroxy-ketone **15** into alaskanes and acoranes [5].

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Experimental Part

General. – The abbreviations used have been described [6]. Melting points are not corrected. In the mass spectra, only the peaks in the range of *m/e* 71–150 with intensities higher than 10% and above *m/e* 150 with intensities higher than 5% are recorded, except for compounds **6** and **10A** and the *dinitrobenzoate of* **8**, where some peaks of lower intensities are also mentioned. The IR., ^{1}H-NMR., ^{13}C-NMR. and mass spectra were measured in our laboratories for nuclear magnetic resonance (under Prof. *W. von Philipsborn*) for mass spectrometry (under Prof. *M. Hesse*), and for microanalysis (under Mr. *H. Frohofer*), respectively.

Step (1). 1,1-Ethylenedioxy-4-hydroxy-4-(2'-methoxy-4'-methyl-phenyl)-pentane (**3**). The procedure given by *Büchi & Wüest* [2] for the preparation of the 'desmethoxy' compound was followed. To a stirred solution of the *Grignard* reagent, made from 2.80 g (15.5 mmol) 1,1-ethylenedioxy-3-bromopropane (**2**) [2] and 360 mg (14.8 mmol) magnesium in 11 ml tetrahydrofuran at 30–35°, was added a solution of 574 mg (3.5 mmol) 2-methoxy-4-methyl-acetophenone (**1**) [7] in 3.5 ml ether. The mixture was kept at 30–35° for 2 h, left overnight at RT. and poured into cold saturated NH_4Cl solution. The aqueous phase was extracted with ether and the combined organic solutions were washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated to give 1.54 g of an oil containing, according to the ^{1}H-NMR. spectrum, more than 50% of **3**. This crude material was used in steps (3) and (4). – Bulb to bulb distillation afforded 988 mg of a colourless oil, b.p. 110–125°/0.01 Torr, consisting of ~85% (from ^{1}H-NMR.) of **3**. – ^{1}H-NMR. (60 MHz, CCl_4): 1.45/*s*, ~3H (3H–C(5)); 2.30/*s*, ~3H (H_3C–C(4')); 1.2–2.3/*m*, ~4H (2H–C(2) and 2H–C(3)); 3.53/br.*s*, 1H (OH); 3.65–4.0/*m* with a strong *s* at 3.82, ~7H (CH_3O and OCH_2CH_2O); 4.75/*t*, *J*=4, ~1H (H–C(1)); 6.65/br.*s* and 6.72/br.*d*, *J*=8, 2H (H–C(3') and H–C(5')); 7.28/*d*, *J*=8, 1H (H–C(6')). The presence of a minor amount of impurities, probably arising from the use of excess of *Grignard* reagent, is indicated by the fact that the integrations of the signals in the 1.3–3.75 ppm region are slightly too high. The yield of **3** is estimated to be near 90%.

This material was stable at RT. only in the presence of a few drops of triethylamine. It could also be kept for a few days at −20°. Neat or in CCl_4 solution at RT. some changes occurred, as was shown by the gradual decrease of the ^{1}H-NMR. signals of **3** and the appearance of new signals corresponding to a mixture of products including **6** (see step 2). After 5 days the signals of **3** had disappeared.

Step (2). Ethylene glycol di[5-(2'-methoxy-4'-methyl-phenyl)-5-methyl-tetrahydrofuran-2-yl] ether (**6**). A sample of 640 mg of distilled **3** (about 85% pure, ~2 mmol) from step (1) had solidified after standing neat for 3 weeks at −20°. The ^{1}H-NMR.spectrum showed the absence of signals corresponding to **3** and the presence of **6** as the major (estimated 70%) product. Trituration with ether gave 266 mg (50% from **1**) of ^{1}H-NMR.-pure **6** as a white powder. Recrystallization from chloroform/hexane and then from chloroform/methanol gave an analytical sample of **6** as colourless flakes, m.p. 190–195°. – IR. ($CHCl_3$): 2995*s*, 2930*s*, 2905*m* sh, 2870*m*, 2830*w*, 1615*s*, 1578*m*, 1500*s*, 1465*s*, 1405*s*, 1367*m*, 1283*s*, 1260*m*, 1248*m*, 1170*s*, 1090*s* br., 1070*vs*, 1038*vs* ,1020*s*, 998*vs*, 975*s*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 1.68/*s*, ~6H (2 × CH_3–C(5)); 2.34/*s*, ~6H (2 × CH_3–C(4')); 1.5–2.5/*m*, ~8H (2 × 2H–C(3) and 2 × 2H–C(4)); 3.6–4.1/symmetrical *m*, probably an *AA'BB'* pattern, including 3.81/*s*, 10H (OCH_2CH_2O and 2 × OCH_3); 5.30/d × *m*, *J* = ~4.5, 2H (2 × H–C(2)); 6.69/br. *s* and 6.77/br.*d*, *J* = 7.5, 4H (2 × H–C(3') and 2 × H–C(5')); 7.44/*d*, *J* = 7.5, 2H (2 × H–C(6')). – MS. (70 eV): 470 (0.4, *M*), 455 (4, *M* − CH_3), 425 (0.5, *M* − C_2H_5O), 265 (8, $C_{15}H_{21}O_4$), 251 (7), 220 (5), 205 (100, $C_{13}H_{17}O_2$), 187 (14, 205 − H_2O), 175 (8), 162 (5), 161 (15), 149 (15). Osmometric molecular weight determination: 487 ± 5%.

$C_{28}H_{38}O_6$ (470.61) Calc. C 71.46 H 8.14% Found C 71.21 H 7.96%

Step (3). 1,1-Ethylenedioxy-4-(2'-methoxy-4'-methyl-phenyl)-pentane (**4**). A solution of 330 mg of the crude material which was obtained as described in step (1) as a residue after evaporation of the ether, and which contained about 55% of 1,1-ethylenedioxy-4-hydroxy-4-(2'-methoxy-4'-methyl-phenyl)-pentane (**3**) (about 0.7 mmol), in 10 ml abs. ethanol was shaken with 100 mg of 10% Pd on charcoal under 1 atm of hydrogen. After 11 h 0.67 mmol of hydrogen were absorbed. The mixture was filtered through *Celite* and the filtrate was evaporated, leaving 253 mg of an oil which was distilled to give 163 mg of slightly impure **4**, b.p. 88–89°/0.015 Torr. Thick-plate chromatography, using 4:1 pentane/ether as eluant, gave 155 mg (83% from **1**) of **4** as a colourless oil. – IR. (CCl_4): 2955*s*, 2935*s* sh, 2870*s*, 2835*m* sh, 2760*w*, 1615*m*, 1580*m*, 1505*s*, 1465*s*, 1435*m*, 1410*s*, 1375*w*, 1355*m*, 1285*m*, 1260*s*, 1190*m*, 1160*s* sh, 1140*s* br., 1100*m*, 1045*s*. – ^{1}H-NMR. (100 MHz, CCl_4): 1.11/*d*, *J* = 7, ~3H (3H–C(5)); 1.0–1.8/*m*, 4H (2H–C(2) and 2H–C(3)); 2.24/*s*, 3H (CH_3–C(4')); 3.06/*q* × *m*, *J* = ~7, 1H (H–C(4)); 3.55–3.85/*m* including a *s* at 3.72, 7H (CH_3O and OCH_2CH_2O); 4.65/*t* × *m*, *J* = 4.5, 1H (H–C(1)); 6.50/*br.s* and 6.58/br.*d*, *J* = 8, 2H (H–C(3') and H–C(5')); 6.91/*d*, *J* = 8, 1H (H–C(6')). – MS. (70 eV): 250 (37, *M*), 163 (11), 162 (77, *M* − $C_4H_8O_2$), 150 (12), 149 (100, *M* − $C_5H_9O_2$), 148 (17), 128 (12), 119 (13), 105 (10), 103 (11), 91 (18), 86 (78), 73 (54).

$C_{15}H_{22}O_3$ (250.34) Calc. C 71.97 H 8.86% Found C 72.06 H 8,71%

Step (4). 1,1-Ethylenedioxy-4-(2'-methoxy-4'-methyl-cyclohexa-1',4'-dien-1'-yl)-pentane (**5**). To a solution of *ca.* 1.1 g of the material obtained as described in step (1) as a residue after evaporation of the ether, containing about 55% of 1,1-ethylenedioxy-4-hydroxy-4-(2'-methoxy-4'-methyl-phenyl)-pentane (**3**) and a few drops of triethylamine, in 6 ml abs. ethanol and about 30 ml liquid ammonia, under reflux, were added 3 g of sodium in small chips during 3 h. After an additional 5 h, 15 ml of ethanol were added followed by 50 ml water, and the solution was extracted with ether. The organic phase was washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated to give 676 mg of an oil. According to its ^{1}H-NMR. (60 MHz, CCl_4) spectrum, this oil is a mixture containing mostly **5**. The peaks assigned to **5** are: 0.97/*d*, *J* = 7, (3H–C(5)); 2.5–2.8/doublet-like *m*, (2H–C(3') and 2H–C(6')); 3.65–3.95/*m*, (OCH_2CH_2O); 4.75/*m*, (H–C(1)); 5.33/br.*s*, (H–C(5')); the relative intensities of these signals correspond roughly to the interpretation given.

Step (5). Acid hydrolysis of **5**. A mixture of 552 mg of crude **5** from step (4) in 4 ml methanol, 3 ml water and 1.5 ml of conc. aqueous HCl was stirred for 2 h at 0° and for 3 h at RT., saturated with NaCl and extracted with ether. The organic layer was washed with 5% $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to give 410 mg of a residue which showed 4 spots on TLC. In the ^{1}H-NMR. spectrum of this oil there is no peak corresponding to an aldehydic proton. Preparative TLC. with 2:1 pentane/ether showed a major and several minor bands. Elution of the major band gave 73 mg of an oil, which according to its ^{1}H-NMR. spectrum is a mixture containing isomer **C** of the spiro-hydroxy-ketone **15**, a compound also obtained from the aldehydes **10A,B** in step (10).

In another experiment, 124 mg of crude **5** were treated with the same solution, but only at 0° for 1 h. The mixture was neutralized at 0° with 5% $NaHCO_3$ solution and extracted with ether. The organic layer was washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated to give 98 mg of an oily mixture, the ^{1}H-NMR. spectrum of which contains signals due to an aldehydic proton and to two vinylic protons of a conjugated ketone and an isolated double bond.

Step (6). 2-Methoxy-5-(2'-methoxy-4'-methyl-phenyl)-5-methyl-tetrahydrofuran (7). a) *From the hydroxy-acetal* **3**. A solution of 160 mg of distilled 1,1-ethylenedioxy-4-hydroxy-4-(2'-methoxy-4'-methyl-phenyl)-pentane (**3**, about 85% pure, ~0.5 mmol, from step (1)) in 2 ml methanol and 0.5 ml 2N aqueous HCl was stirred during 24 h and poured into a mixture of ether and saturated NaCl solution. The ethereal layer was washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated. The residue was distilled (bulb to bulb) to give 125 mg (93% from **1**) of a 1:1 mixture (according to ^{1}H-NMR.) of the diastereoisomers **A** and **B** of **7** as a colourless oil, b.p. 70–75°/0.01 Torr.

$C_{14}H_{20}O_3$ (236.31) Calc. C 71.16 H 8.53% Found C 70.93 H 8.48%

The diastereoisomers were separated by TLC., using 5:1 hexane/ether as eluant. – The less polar *diastereoisomer* **7A** was recrystallized from pentane to give colourless needles, m.p. 73–74°. – IR. (CCl_4): 2995*w*, 2980*w* sh, 2960*m*, 2940*m*, 2915*w*, 2900*w* sh, 2835*w*, 1620*w*, 1583*w*, 1508*m*, 1470*m*, 1455*w*, 1445*w*, 1410*w*, 1370*w*, 1287*m*, 1265*m*, 1250*m*, 1215*m*, 1195*w*, 1175*m*, 1140*m* br., 1108*s*, 1075*s*, 1045*s*, 1005*m*, 962*w*, 930*w*, 900*w*, 850*w*. – ^{1}H-NMR. (100 MHz, CCl_4): 1.56/*s*, ~3H (CH_3–C(5)); 2.28/*s*, ~3H (CH_3–C(4')); 1.5–2.4/*m*, ~4H (2H–C(3) and 2H–C(4)); 3.32/*s*, 3H (CH_3O–C(2)); 3.79/*s*, 3H (CH_3O–C(2')); 4.97/*d* × *m*, *J* = 5, 1H (H–C(2)); 6.54/br.*s* and 6.59/br.*d*, *J* = 7.50, 2H (H–C(3') and H–C(5')); 7.50/*d*, *J* = 7.5, 1H (H–C(6')). – MS. (70 eV): 236 (24, *M*), 222 (16), 221 (92, *M* − CH_3), 206 (6), 205 (30, *M* − CH_3O), 190 (6), 189 (29), 187 (11), 175 (7), 165 (18), 162 (15), 161 (100), 149 (31), 147 (15), 145 (17), 135 (18), 119 (14), 115 (15), 105 (18), 91 (15), 78 (11), 77 (15), 72 (16), 71 (17).

$C_{14}H_{20}O_3$ (236.31) Calc. C 71.16 H 8.53% Found C 71.26 H 8.78%

The more polar *diastereoisomer* **7B** was obtained as an oil. – IR. (CCl_4): 3000*m*, 2980*m* sh, 2960*m*, 2935*m*, 2870*w* sh, 2840*w*, 1620*w*, 1583*w*, 1510*m*, 1470*m*, 1450*w*, 1410*w* br., 1370*w*, 1288*m*, 1260*m*, 1228*w*, 1208*m*, 1197*w*, 1188*w*, 1172*m*, 1140*m*, 1104*m*, 1070*m*, 1045*s*, 1010*m*, 962*w*, 932*w*, 920*w*, 895*w*, 846*w*. – ^{1}H-NMR. (100 MHz, CCl_4): 1.32/*s*, ~3H (CH_3–C(5)); 2.28/*s*, ~3H (CH_3–C(4')); 1.3–2.3/*m*, ~4H (2H–C(3) and 2H–C(4)); 3.30/*s*, 3H (CH_3O–C(2)); 3.76/*s*, 3H (CH_3O–C(2')); 4.94/*d* × *m*, *J* = 4, 1H (H–C(2)); 6.53/br.*s* and 6.62/br.*d*, *J* = 7.5, 2H (H–C(3') and H–C(5')); 7.43/*d*, *J* = 7.5, 1H (H–C(6')). – MS. (70 eV): 236 (37, *M*), 222 (17), 221 (89, *M* − CH_3), 206 (5), 205 (34, *M* − CH_3O), 190 (7), 189 (37), 187 (10), 175 (8), 165 (25), 162 (18), 161 (100), 149 (35), 147 (13), 145 (14), 135 (14), 119 (10), 115 (14), 105 (19), 91 (24), 77 (15), 72 (16), 71 (16).

b) *From the 'dimeric' acetal* **6**. A suspension of 47 mg (0.1 mmol) of ethylene glycol di[5-(2'-methoxy-4'-methyl-phenyl)-5-methyl-tetrahydrofuran-2-yl] ether (**6**) in 2 ml methanol and 0.5 ml 2N aqueous HCl was stirred during 40 h. After about 32 h most of the insoluble **6** had dissolved. The almost clear solution was shaken with a mixture of ether and saturated NaCl solution. The ethereal layer was washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated to give 38 mg (80%) of ^{1}H-NMR. pure **7** as a 1:1 mixture of the diastereoisomers **7A** and **7B**.

Step (7). *Birch reduction of* **7A,B**. a) To a stirred solution of 162 mg (0.686 mmol) of 2-methoxy-5-(2'-methoxy-4'-phenyl)-5-methyl-tetrahydrofuran (1:1 mixture of **7A** and **7B**), 2 ml abs. ethanol and about 10 ml liquid ammonia, at reflux, were added 700 mg (30 mmol) of sodium in small portions over a period of 6 h, the blue colour being allowed to disappear between each addition. 5 ml ethanol were added and the ammonia was allowed to evaporate. The residue was taken up in water and ether; the aqueous layer was saturated with NaCl and extracted with ether. The combined organic extracts were washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation gave 138 mg (96%) of *4-(2'-methoxy-4'-methyl-cyclohexa-1',4'-dien-1'-yl)-pentan-1-ol* (**8**) as a colourless oil with IR. and ^{1}H-NMR. spectra identical with those reported [1].

b) In one experiment the product consisted according to ^{1}H-NMR. of *ca.* 90% of **8** and *ca.* 10% of *4-(2'-methoxy-4'-methyl-phenyl)-pentan-1-ol* (**11**) [1]. Treatment of the mixture with a solution of HCl in aqueous methanol afforded a mixture of the hydroxy-ketones **9A,B** and the aromatic alcohol **11**, which was subsequently separated by TLC. (for the procedures and properties of **11** see [1], step 2b).

c) *3,5-Dinitrobenzoate of* **8**. To a solution of 105 mg (0.5 mmol) of 4-(2'-methoxy-4'-methyl-cyclohexa-1',4'-dien-1'-yl)-pentan-1-ol (**8**) and 1 g of pyridine in 5 ml of ether were added at −20°, under N_2, 138 mg (0.6 mmol) of freshly recrystallized 3,5-dinitrobenzoyl chloride. The mixture was stirred at −20° during 2 h, allowed to warm up to RT. and poured into 5% aqueous $NaHCO_3$ solution. The organic phase was washed with water, dried over $MgSO_4$ and evaporated to give 190 mg of an orange oil which solidified on cooling. According to ^{1}H-NMR. it consisted of a mixture of unreacted **8** and its dinitrobenzoate in the ratio of 1:6. Recrystallization from ether/pentane gave 140 mg (69%) of the *dinitrobenzoate of* **8** as orange prisms, m.p. 73–75°. – IR. (CCl_4): 3105*w*, 2960*m*, 2935*m*, 2910*w*, 2880*w*, 2860*w*, 2825*w*, 1740*s*, 1707*w*, 1675*w*, 1632*m*, 1600*w*, 1550*s*, 1462*m*, 1385*w*, 1375*w*, 1343*s*, 1330*m*, 1310*w*, 1278*s*, 1210*w*, 1167*s*, 1128*m*, 1075*m*, 1003*w*, 970*w*, 940*w*, 930*w*, 920*m*, 910*w*, 885*w*, 720*s*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.02/*d*, *J*=7, 3H (3H–C(5)); 1.1–2.2/*m* including a br.*s* at 1.73, 7H (2H–C(2), 2H–C(3) and CH_3–C(4')); 2.70/br.*s*, 4H (2H–C(3') and 2H–C(6')); 3.12/*q*×*m*, *J*=7, 1H (H–C(4)); 3.55/*s*, 3H (CH_3O); 4.48/*t*, *J*=6.5, 2H (2H–C(1)); 5.42/br.*s*, 1H (H–C(5')); 9.15–9.35/*m*, with an intense peak at 9.23, 3H (3H–Ar). – MS. (70 eV): 404 (12, *M*), 402 (3, *M*−2H), 195 (8, $C_7H_3N_2O_5$), 151 (31, $C_{10}H_{15}O$), 149 (33, $C_{10}H_{13}O$), 135 (10), 124 (12), 123 (100), 119 (14), 91 (12), 75 (16). The peaks at *m/e* 402 and 149 probably arise from partial aromatization occurring in the inlet system.

$C_{20}H_{24}N_2O_7$ (404.43) Calc. C 59.40 H 5.98 N 6.93% Found C 59.26 H 6.14 N 7.20%

Monitoring by ^{1}H-NMR. shows that the product aromatizes slowly with loss of two hydrogen atoms when kept in $CDCl_3$ solution at RT.

Step (8). 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentanal (**10**). Oxidation of a 1:1 mixture of the diastereoisomers of 4-(4'-methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentan-1-ol (**9A** and **9B**)[2]), obtained by hydrolysis of **8** [1], with CrO_3 and pyridine in methylene chloride according to [8] yielded 93% of an NMR.-pure 1:1 mixture of the diastereoisomers **10A** and **10B** as a colourless oil. An analytical sample was obtained by bulb to bulb distillation at 65°/0.01 Torr.

$C_{12}H_{18}O_2$ (194.28) Calc. C 74.19 H 9.34% Found C 73.93 H 9.12%

The two diastereoisomers were separated by thick-layer chromatography, using ether/pentane 2:1 as eluant. The less polar *isomer* **10A** was obtained as a colourless oil. – IR. (CCl_4): 3040*w*, 2965*m*, 2940*m*, 2880*w*, 2835*w*, 2720*w*, 1732*s*, 1678*s*, 1645*w*, 1460*w* br., 1440*w* br., 1385*m*, 1315*w*, 1255*w*, 1212*m*, 1135*w* br., 1020*w*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0.97/*d*, *J*=7, ∼3H (3H–C(5)); 1.97/*s*, ∼3H (CH_3–C(4')); 1–3/*m*, ∼10H (2H–C(2), 2H–C(3), H–C(4), H–C(1'), 2H–C(5') and 2H–C(6')); 5.90/finely split *s*, 1H (H–C(3')); 9.83/*t*, *J*=∼1.5 1H (H–C(1)). – MS. (70 eV): 194 (3.5, *M*), 151 (8, *M*−C_2H_3O), 137 (16, *M*−C_3H_5O), 111 (12), 110 (100, *M*−C_5H_8O), 109 (15), 95 (21), 91 (12), 82 (47), 81 (11).

The more polar diastereoisomer **10B** was obtained as a colourless oil. – IR. (CCl_4): practically identical with that of **10A**. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0.87/*d*, *J*=6.5, ∼3H (3H–C(5)); 1.97/*s*, ∼3H (CH_3–C(4')); 1–3/*m*, ∼10H (2H–C(2), 2H–C(3), H–C(4), H–C(1'), 2H–C(5') and 2H–C(6')); 5.93/finely split *s*, 1H (H–C(3')); 9.86/*t*, *J*=∼1.5, 1H (H–C(1)). – MS. (70 eV): 194 (6, *M*), 151 (15, *M*−C_2H_3O), 137 (18, *M*−C_3H_5O), 111 (12), 110 (100, *M*−C_5H_8O), 109 (16), 95 (22), 82 (63), 81 (11).

Step (9). 4-(2'-methoxy-4'-methyl-phenyl)-pentanal (**12**). Oxidation of 4-(2'-methoxy-4'-methyl-phenyl)-pentan-1-ol (**11**) with CrO_3 and pyridine, as described in step (8) for the oxidation of **9**, followed by bulb to bulb distillation at 60°/0.005 Torr, yielded 85% of **12** as a colourless oil. – IR. (CCl_4): 3050*w*, 3030*w*, 3000*w*, 2960*s*, 2935*s*, 2875*m*, 2835*m*, 2820*w*, 2715*m*, 1732*s*, 1618*m*, 1583*m*, 1508*m*, 1468*s*, 1458*m* sh, 1413*m*, 1390*w*, 1378*w*, 1360*w*, 1288*m*, 1260*s*, 1192*m*, 1160*m*, 1138*m*, 1100*m*, 1045*s*, 927*w*, 845*w*. – ^{1}H-NMR. (100 MHz, CCl_4): 1.18/*d*, *J*=7, ∼3H (3H–C(5)); 1.5–2.4/ structured *m*, partially covered by a singlet at 2.27, ∼7H (CH_3–C(4'), 2H–C(2) and 2H–C(3)); 3.13/*q*×*m*, *J*=7, 1H (H–C(4)); 3.72/*s*, 3H (CH_3O); 6.54/br.*s* (H–C(3')) and 6.60/br.*d*, *J*=8, (H–C(5')) (together 2H); 6.90/*d*, *J*=8, 1H (H–C(6')); 9.53/*t*, *J*=∼1.5, 1H (H–C(1)). – MS. (70 eV): 206 (14, *M*), 162 (22, *M*−C_2H_4O), 150 (12), 149 (100, *M*−C_3H_5O), 147 (10), 119 (12), 115 (10), 91 (12).

$C_{13}H_{18}O_2$ (206.29) Calc. C 75.69 H 8.80% Found C 75.47 H 9.00%

Step (10). Transformations of the keto-aldehyde **10**: *formation of 1,5-dimethyl-1,6,7,7a-tetrahydro-2*H*-indene-3-carbaldehyde* (**14**) *and 1-hydroxy-4,8-dimethyl-spiro[4.5]dec-7-en-6-one* (**15**). a) *In carbon tetrachloride.* A solution of 915 mg (4.72 mmol) of 4-(4'-methyl-2'-oxo-cyclohex-3'-en-

1'-yl)-pentanal (1:1 mixture of **10A** and **10B**) in 6 ml carbon tetrachloride (*Merck, pro analysi*) was kept at RT. Monitoring by ^{1}H-NMR. showed the slow disappearance of the signals corresponding to **10A,B** and the appearance of new signals due to several new compounds, until after 10 days only little of the keto-aldehydes **10A,B** was left. The mixture was separated by thick-layer chromatography (ether/pentane 3:2) into four bands numbered 1 to 4 with increasing polarity.

Band 1 contained 160 mg (19%) of an approximately 7:1 mixture (according to ^{1}H-NMR.) of isomer **A** of the bicyclic aldehyde **14** and probably its isomer **B**. Further purification of this material by thick-layer chromatography (pentane/ether 5:1) gave a less polar fraction, which was distilled (bulb to bulb) at 65°/0.035 Torr to yield *pure* **14A** as a colourless oil which solidified on cooling to −20°. – UV. (MeOH): 303–304 (19800); 210 (7000). – IR. (CCl_4): 3035*w*, 2960*m*, 2935*m*, 2915*m* sh, 2875*m*, 2830*m*, 2730*w*, 1667*s*, 1658*s* sh, 1628*s*, 1590*w* br., 1455*w*, 1440*w*, 1430*w*, 1383*m*, 1372*w*, 1363*w*, 1322*w*, 1300*w*, 1225*w* sh, 1215*m*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 1.18/*d*, *J*=6, ∼3H (CH_3–C(1)); 1.94/*s*, ∼3H (CH_3–C(5)); 2.84/*d*×*d*, *J*=7 and 15, ∼1H (one of 2H–C(2)); 1.2–3.0/*m*, ∼7H (H–C(1), one of 2H–C(2), 2H–C(6), 2H–C(7) and H–C(7a)); 6,71/br.*s*, 1H (H–C(4)); 10.0/*s*, 1H (HCO). – ^{13}C-NMR. (25.2 MHz, $CDCl_3$): 186.6/*d* (CHO); 160.0/*s*, (C(3a) or C(5)); 150.1/*s*, (C(5) or C(3a)); 131.8/*s*, (C(3), in the off-resonance spectrum a ^2J-coupling with the aldehydic proton was observed); 116.4/*d* (C(4)); 52.1/*d* (C(1) or C(7a)); 39.9/*d* (C(7a) or C(1)); 37.4/*t* (C(2), C(6) or C(7)); 31.9/*t* (C(6), C(7) or C(2)); 27.5/*t* (C(7), C(2) or C(6)); 24.5/*q* (CH_3–C(5)); 17.8/*q* (CH_3–C(1)). – MS. (70 eV): 176 (100, *M*), 162 (12), 161 (87), 148 (19), 147 (76), 145 (15), 143 (12), 133 (42), 131 (22), 129 (16), 128 (24), 120 (15), 119 (45), 117 (33), 116 (18), 115 (46), 106 (15), 105 (86), 104 (12), 103 (20), 93 (18), 92 (15), 91 (94), 89 (12), 81 (12), 79 (27), 78 (21), 77 (61), 75 (11), 74 (11). – The remaining amount of pure material was too small for a C,H analysis.

The second fraction of band 1 contained a ∼3:1 *mixture of* **14A** *and* **14B**. Its IR spectrum was identical with that of pure **14A** and in its ^{1}H-NMR. spectrum the following signals can be assigned to **14B**; 0.82/*d*, *J*=6.5 (CH_3–C(1)); 6.77/br.*s* (H–C(4)); 10.08/*s* (HCO).

Elution of *band 2* gave 45 mg (5%) of unreacted keto-aldehydes **10A** and **10B** (ratio ∼1:1 by ^{1}H-NMR.).

Band 3 contained 282 mg (31%) of a ∼1:1 mixture (by ^{1}H-NMR.) of diastereoisomers **A** and **B** of the spiro-hydroxy-ketone **15**. Additional TLC. (pentane/ether 1:1) gave a less polar fraction, which was distilled (bulb to bulb) at 80°/0.005 Torr to give *pure* **15A** as a colourless oil. – IR. (CCl_4): 3625*w*, 3430*m* br., 3035*w*, 2960*s*, 2940*s* sh, 2915*m* sh, 2875*m*, 2835*w* sh, 1669*s* sh, 1660*s*, 1647*s* sh, 1440*m* br., 1383*m*, 1350*w*, 1320*m*, 1280*w* br., 1222*m*, 1212*m*, 1108*m*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 0.94/*d*, *J*=7, ∼3H (CH_3–C(4)); 1.96/*s*, ∼3H (CH_3–C(8)); 1–3/*m*, ∼9H (2H–C(2), 2H–C(3), H–C(4), 2H–C(9) and 2H–C(10)); 3.08/br.*s*, 1H (OH); 4.38/*t*×*m*, *J*=7, 1H (H–C(1)); 5.86/finely split *s*, 1H (H–C(7)); after addition of D_2O, 3.08 absent. – ^{13}C-NMR. (25.2 MHz, $CDCl_3$): 202.9/*s* (C(6)); 162.2/*s* (C(8)); 126.5/*d* (C(7)); 78.8/*d* (C(1)); 56.7/*s*, (C(5)); 38.6/*d*, (C(4)); 24.2/*q* (CH_3–C(8)); 16.4/*q* (CH_3–C(4)); the signals at 31.1/*t*, at 29.5/br.*t* (overlapping signals due to two carbon atoms) and at 21.7/*t*, corresponding to C(2), C(3), C(9) and C(10), are not assigned individually. – MS. (70 eV): 194 (31, *M*), 176 (11, $M-H_2O$), 161 (9,$M-H_2O-CH_3$), 152 (12), 151 (10), 150 (33), 139 (47), 138 (15), 137 (100), 110 (21), 109 (22), 95 (13), 91 (17), 83 (12), 82 (64), 81 (10), 79 (14), 77 (18).

$C_{12}H_{18}O_2$ (194.28) Calc. C 74.19 H 9.34% Found C 73.89 H 9.19%

Bulb to bulb distillation of the more polar fraction of band 3 at 70°/0.05 Torr gave *pure* **15B** as a colourless oil. – IR. (CCl_4): 3680*w*, 3625*w*, 3450*m* br., 3040*w*, 2960*s*, 2935*s*, 2915*s*, 2875*s*, 2835*w*, 1662*s* br., 1455*m* br., 1435*m* br., 1382*s*, 1350*m*, 1310*m*, 1270*m*, 1215*s*, 1155*w*, 1135*m*, 1105*m* br., 1075*m* br., 1055*m*, 1035*m*, 1025*m*, 1010*m*, 995*m* sh, 980*m*, 950*w*, 925*m*, 910*m*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 0.84/*d*, *J*=6.5, ∼3H (CH_3–C(4)); 1.96/*s*, ∼3H (CH_3–C(8)); 2.20/*s*, 1H (OH, absent after addition of D_2O); 1–3/*m*, ∼9H (2H–C(2), 2H–C(3), H–C(4), 2H–C(9) and 2H–C(10)); 4.72/*t*×*m*, *J*=7, 1H (H–C(1)); 5.83/finely split *s*, 1H (H–C(7)). – ^{13}C-NMR. (25.2 MHz, $CDCl_3$): 201.7/*s* (C(6)); 160.9/*s* (C(8)); 127.0/*d* (C(7)); 74.4/*d* (C(1)); 56.7/*s* (C(5)); 38.5/*d* (C(4)); 24.0/*q* (CH_3–C(8)); 18.1/*q* (CH_3–C(4)); the signals at 31.2/*t*, 30.1/*t*, 28.3/*t* and at 27.2/*t*, corresponding to C(2), C(3), C(9) and C(10), were not assigned individually. – MS. (70 eV): 194 (24, *M*), 176 (12, $M-H_2O$), 161 (7, $M-H_2O-CH_3$), 152 (19), 151 (6), 139 (59), 138 (12), 137 (100), 110 (15), 109 (15), 95 (11), 91 (13), 83 (10), 82 (42), 79 (12), 77 (14).

$C_{12}H_{18}O_2$ (194.28) Calc. C 74.19 H 9.34% Found C 73.71 H 9.48%

Elution of *band 4* gave 295 mg (32%) of a third isomer of the spiro-hydroxy-ketone, **15C**, after recrystallization from ether/pentane as colourless needles, m.p. 78–79°. – UV. (MeOH): 235–236

(12800). – IR. (CCl_4): 3600–3100*m*, 3035*w*, 2960*s*, 2930*s*, 2910*m*, 2870*m*, 1655*s* br., 1560*w* br., 1465*m*, 1450*m*, 1435*m*, 1415*m*, 1380*m*, 1350*m*, 1315*m*, 1280*w*, 1250*w*, 1215*m*, 1190*m*, 1110*m*, 1095*m*, 1070*m* br., 1025*w*, 1010*m*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 0.91/*d*, *J*=7, ~3H (CH_3–C(4)); 1.94/*s*, ~3H (CH_3–C(8)); 2.59/*d*, *J*=6.5, ~1H (OH); 1–3/*m*, ~9H (2H–C(2), 2H–C(3), H–C(4), 2H–C(9) and 2H–C(10)); 4.08/*d*×*d*×*d*, *J*=7, 6.5 and 4, 1H (H–C(1)); 5.87/finely split *s*, 1H (H–C(7)); after addition of D_2O: 2.59 absent, 4.08/*d*×*d*, *J*=7 and 4. – ^{13}C-NMR. (25.2 MHz, $CDCl_3$): 202.1/*s* (C(6)); 161.1/*s* (C(8)); 127.1/*d* (C(7)); 78.1/*d* (C(1)); 57.3/*s* (C(5)); 36.9/*d* (C(4)); 24.0/*q* (CH_3–C(8)); 15.1/*q* (CH_3–C(4)); the signals at 33.6/*t*, 29.4/*t*, 28.5/*t* and at 25.9/*t*, corresponding to C(2), C(3), C(9) and C(10), were not assigned individually. – MS. (70 eV): 194 (26, *M*), 176 (20, $M-H_2O$), 161 (5, $M-H_2O-CH_3$), 151 (6), 150 (19), 139 (35), 138 (13), 137 (100), 110 (23), 109 (18), 82 (33).

$C_{12}H_{18}O_2$ (194.28) Calc. C 74.19 H 9.34% Found C 74.49 H 9.32%

This cyclization reaction of **10A,B** in carbon tetrachloride sometimes required an initiation time of 1–2 days and was finished usually after 5–10 days, the distribution of the products always being roughly the same as described above.

A solution of the keto-aldehydes **10A,B** in deuteriochloroform was stable, also in the presence of dibenzoyl peroxide or triethylamine.

b) *In deuteriochloroform and trifluoroacetic acid.* To a solution of 124 mg (0.64 mmol) of a 1:1 mixture of the isomeric keto-aldehydes **10A** and **10B** in 0.5 ml deuteriochloroform were added 2 drops of trifluoroacetic acid. After 2 days a mixture was obtained which consisted (according to ^{1}H-NMR.) of unreacted starting material, the aldehydes **14A** and **14B**, spiro-hydroxy-ketones **15A**, **15B** and **15C** in the ratios of ~7:8:2:9:5:9.

c) *In ether in the presence of 2*N *aqueous HCl.* A solution of 96 mg (0.495 mmol) of a 1:1 mixture of the isomeric keto-aldehydes **10A,B** in 5 ml of ether was stirred with 5 ml of 2N aqueous HCl during 48 h. The layers were separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with 5% $NaHCO_3$ solution followed by saturated NaCl solution and dried over $MgSO_4$. Evaporation of the solvent gave an oil which was chromatographed (thick-layer) using ether/pentane 2:1. The first (least polar) band contained 43 mg (49%) of a colourless oil which (according to ^{1}H-NMR.) was an approximately 7:3 mixture of the isomeric bicyclic aldehydes **14A** and **14B**. The second band 9 mg (9%) consisted (according to IR.) of unreacted keto-aldehyde **10**. The third band, 13 mg (13%) of a colourless oil, was shown by ^{1}H-NMR. to consist of a ~1:1 mixture of the isomers **A** and **B** of the spiro-hydroxy-ketone **15**. The last (most polar) band, 15 mg (16%), was a colourless solid with an ^{1}H-NMR. spectrum identical with that of the third isomer of the spiro-keto-alcohol **15C**.

d) *In ether in the presence of 2*N *aqueous NaOH.* A solution of 84 mg (0.43 mmol) of a 1:1 mixture of the isomeric keto-aldehydes **10A,B** in 5 ml of ether was stirred during 2.5 h with 5 ml of 2N aqueous NaOH solution. The layers were separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with 5% aqueous HCl, 5% $NaHCO_3$ and saturated NaCl solutions, dried over $MgSO_4$ and evaporated. TLC. of the residue, using ether/pentane 2:1, gave in the first (least polar) band 25 mg (33%) of an approximately 5:2 mixture (according to ^{1}H-NMR.) of the diastereoisomeric bicyclic aldehydes **14A** and **14B**. The second band contained 4 mg (5%) of unreacted keto-aldehyde **10** (according to IR.). The third band consisted of 17 mg (20%) of isomer **A** of the spiro-hydroxy-ketone **15** (according to ^{1}H-NMR.). Elution of the fourth band gave 6 mg (7%) of isomer **B** of **15** (according to TLC. and IR.). The fifth fraction consisted of 9 mg (11%) of isomer **C** of **15** (TLC. and m.p.). The sixth (most polar) band contained 10 mg of a mixture of compounds which were not identified.

Step (11). 4-(4'-Methyl-2'-oxo-cyclohex-3'-en-1'-yl)-pentanoic acid (**13A,B**). A solution of 167 mg (0.86 mmol) of a 1:1 mixture of the diastereoisomeric aldehydes **10A,B** in 10 ml carbon tetrachloride containing 14 mg of sodium acetate was kept at RT. without exclusion of air during 5 days, filtered and evaporated. The residue, which (according to ^{1}H-NMR.) contained mainly the acid **13** in addition to unchanged aldehyde, was dissolved in ether and the solution extracted with 5% aqueous NaOH solution. The aqueous phase was acidified and extracted with ether, and the ethereal solution dried over $MgSO_4$ and evaporated to give 75 mg (41%) of a 1:1 mixture of the diastereoisomeric acids **13A,B** as a colourless oil. – IR. (CCl_4): 3700–2300 br., 3040*m*, 2965*m*, 2940*m*, 2920*m* sh, 2880*m*, 2830*w* sh, 1720*s* sh, 1715*s*, 1705*s* sh, 1680*s* sh, 1675*s*, 1655*m* sh, 1640*m*, 1455*w*, 1430*m*, 1415*m*, 1380*m*, 1285*m* br., 1210*m*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 0.85/*d*, *J*=~7 (3H–C(5) of one

isomer) and 0.95/*d*, $J=\sim 6$ (3H–C(5) of the other isomer), ratio 1:1, together ~3H; 1.97/*s*, ~3H (CH_3–C(4′)); 1.1–2.9/*m*, ~10H (2H–C(2), 2H–C(3), H–C(4), H–C(1′), 2H–C(5′), 2H–C(6′)); 5.92/split *s*, 1H (H–C(3′)); 10.17/br.*s*, 1H (CO_2H), absent after addition of D_2O.

Step (12). Acid treatment of 1-hydroxy-4,8-dimethyl-spiro[4.5]dec-7-en-6-one (**15C**). A solution of 64 mg (0.33 mmol) of isomer **C** (m.p. 78–79°) of the spiro-hydroxy-ketone **15** and 4 mg of *p*-toluenesulfonic acid monohydrate in 2 ml *p*-xylene was heated at 110° for 10 min. It was diluted with ether and washed with 5% aqueous $NaHCO_3$ followed by saturated NaCl solution, dried over $MgSO_4$ and evaporated to give 54 mg of an oil. TLC. (pentane/ether 2:1) contained 3 spots with Rf-values, identical with those of isomers **A**, **B** and **C** of **15**, as well as two less polar spots. The ^{1}H-NMR. (60 MHz, CCl_4) of the mixture showed the presence of a very small amount of the bicyclic aldehydes **14A,B** (two singlets at 10.10 and 10.15) and an about 1:1:1 mixture of the three isomers **A**, **B** and **C** of **15** (three triploid signals at 4.22, 4.50 and 3.96 due to H–C(1) in the three cases). A broad multiplet at 6.7–7.4 could not be attributed to any of the above mentioned compounds.

Step (13). 4,8-Dimethyl-spiro[4.5]dec-7-ene-1,6-dione (**16A**). a) *From* **15C**. To a solution of 52 mg (0.27 mmol) of 1-hydroxy-4,8-dimethyl-spiro[4.5]dec-7-en-6-one (**15C**) in 5 ml acetone was added dropwise a solution of *Jones* reagent [9] until the orange colour persisted. The mixture was treated with ether and washed consecutively with aqueous 5% NaOH, 5% HCl, 5% $NaHCO_3$ and saturated NaCl solutions, dried over $MgSO_4$ and evaporated to give 47 mg (91% of ^{1}H-NMR.- and TLC.-pure **16A** as a colourless solid. Recrystallization from pentane yielded an analytical sample of **16A** as colourless needles, m.p. 60°. – UV. (MeOH): 236 (14900). – IR. (CCl_4): 3040*w*, 2965*m*, 2940*m*, 2915*m*, 2880*w*, 2830*w*, 1742*s*, 1668*s*, 1658*s* sh, 1645*w* sh, 1470*w*, 1450*w*, 1438*w*, 1428*w*, 1410*w*, 1383*m*, 1342*w*, 1312*w*, 1290*w*, 1275*w*, 1215*m*, 1170*w*, 1150*w*, 1090*w*, 1070*w*, 1050*w*, 1013*w*, 1000*w*, 905*w*. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 0.99/*d*, $J=7$, 3H (CH_3–C(4)); 2.01/*s*, ~3H (CH_3–C(8)); 1.2–2.8/*m*, ~8H (one of 2H–C(2), 2H–C(3), H–C(4), 2H–C(9) and 2H–C(10)); 3.03/*m* with $J=7$ visible, 1H (one of 2H–C(2)); 5.94/finely split *s*, 1H (H–C(7)). – MS. (70 eV): 192 (43, *M*), 138 (12), 137 (100), 135 (15), 82 (55).

$C_{12}H_{16}O_2$ (192.26) Calc C 74.96 H 8.39% Found C 75.24 H 8.48%

b) *From* **15A**. Oxidation of 60 mg (0.31 mmol) of 1-hydroxy-4,8-dimethyl-spiro[4.5]dec-7-ene-6-one (**15A**) and isolation in the same manner as described in a) yielded 53 mg (89%) of **16A**, m.p. 60°, with TLC., IR. and ^{1}H-NMR. identical with those of **16A** obtained by oxidation of the spiro-hydroxy-ketone **15C**.

Step (14). 4,8-Dimethyl-spiro[4.5]dec-7-ene-1,6-dione (**16B**). Oxidation of 64 mg (0.33 mmol) of 1-hydroxy-4,8-dimethyl-spiro[4.5[dec-7-en-6-one (**15B**), as described in step (13) for the oxidation of **15C**, yielded 54 mg (85%) of ^{1}H-NMR.-pure **16B**. Bulb to bulb distillation at 70°/0.005 Torr afforded **16B** as a colourless solid which was recrystallized from pentane to give colourless prisms, m.p. 55–56°. – UV. (MeOH): 236 (14200). – IR. (CCl_4): 3040*w*, 2960*s*, 2940*s*, 2920*m* sh, 2880*m*, 1750*s*, 1740*s* sh, 1658*s* br., 1460*m*, 1435*m*, 1405*m*, 1380*s*, 1355*m*, 1330*w*, 1310*m*, 1305*m*, 1290*w*, 1275*m*, 1268*m*, 1215*s*, 1205*s* sh, 1175*m*, 1165*m*, 1150*m*, 1125*w*, 1075*w*, 1060*w*, 1015*m*, 995*m*, 920*w*, 910*w*, 890*m*, – ^{1}H-NMR. (100 MHz, $CDCl_3$): 1.09/*d*, $J=6$, 3H (CH_3–C(4)); 1.99/*s*, ~3H (CH_3–C(8)); 1.2–2.8/*m*, ~9H (2H–C(2), 2H–C(3), H–C(4), 2H–C(9) and 2H–C(10)); 5.84/finely split *s*, 1H (H–C(7)). – MS. (70 eV): 192 (32, *M*), 138 (10), 137 (100), 82 (54).

$C_{12}H_{16}O_2$ (192.26) Calc. C 74.96 H 8.39% Found C 74.67 H 8.57%

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