106. Acid-Catalysed Cyclisation of *p*-Mentha-1,8(9)-diene- and *p*-Mentha-1,8(10)-diene-9-carboxylic Acid. Novel Access to the Bicyclo[3.2.1]octane Skeleton

by **Wolfgang Giersch, Robert Brauchli, Walter Thommen,** and **Karl H. Schulte-Elte***

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

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Treatment of the title compounds with either H_3PO_4 or $BF_3 \cdot Et_2O$ affords the bridged tricyclic lactones **3** and **7** as main products (57 and 70% yield, resp.). This is an efficient and novel access to specifically functionalised molecules possesing the bicyclo[3.2.1]octane skeleton. Lactones **4** and **5** and the bicyclic ketone **6** were formed as by-products (2, 7, and 10% yield, resp.).

Introduction. – Synthetically useful cyclisations of *p*-mentha-1,8-dienes resulting in the formation of bridged bicyclic compounds have been seldom reported [1][1]). Because of the readiness of the C(8) double bond to undergo migration, acidic or basic treatment usually leads to a variety of isomeric dienes and aromatic products without change of the *p*-menthane skeleton [2].

In the context of synthetic studies involving organoleptically interesting lactones possessing a monoterpenoid substructure [3], we have now found that the presence of a COOH group at C(9) or C(10) of *p*-mentha-1,8-diene causes a fundamental change in isomerisation behaviour under acidic conditions. In these cases, the major reaction pathway becomes an intramolecular cyclisation involving both C,C-double bonds and leads to the formation of tricyclic lactones possessing the bicyclo[3.2.1]octane skeleton. In particular, we report herein our results concerning the acid-catalysed transformations of *p*-mentha-1,8(9)-diene-9-carboxylic acid (**1**) and *p*-mentha-1,8(10)-diene-9-carboxylic acid (**2**) under various reaction conditions and include detailed NMR spectral evidence to confirm the structures of the principal cyclisation products.

Results and Discussion. – The preparations of **1** ((*E*/*Z*)-isomers, 83:17) and **2** as well as the acylchloride **8** (required for structure confirmation, see the *Table* and *Exper. Part*) were effected following literature procedures [6] [7]. Of the various acid catalysts applied for the cyclisation of **1** and **2**, 85% H_3PO_4 and $BF_3 \cdot Et_2O$ in toluene were found to be the most efficient. Both reagents converted **1** and **2** efficiently into mixtures of cyclised products which consist almost entirely of bi- and tricyclic lactones and ketones, *i.e.* **3**–**6** from **1** and **5** and **7** from **2** *(Scheme 1)*. Only small amounts of the distilled product mixtures (*ca.* 10–15%) represent acidic (*i.e.* $NaHCO_3$-soluble) material. The reaction

[1]) The formation of cyclic compounds from limonene [4], identified as 1,3- and 1,4-dimethylbicyclo[3.2.1]oct-2(3)-enes [5], has been observed only under special conditions, *i.e.* heating (> 179°) with P_2O_5-supported SiO_2 for 36 h (*ca.* 10% yield).

Scheme 1

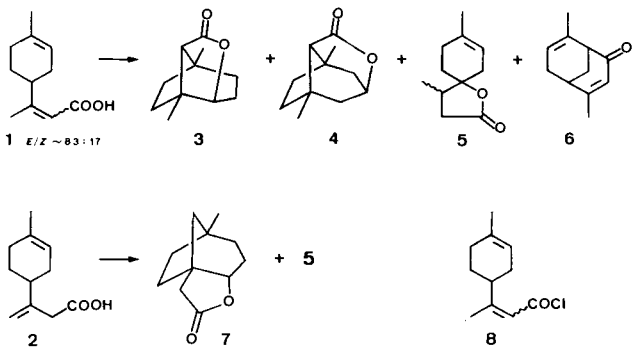


Table. *Acid-Catalysed Cyclisation of Compounds* **1**, **2**, *and* **8**

Exper.	Starting compound	Reaction conditions	Combined yield [%]	Product distribution [%]					
				3	**4**	**5**	**6**	**7**	Unidentified
1	**1**	H_3PO_4(85%); 90°, 1 h	70	81	2	2	5	0	10
2	**1**	$BF_3 \cdot Et_2O$; toluene; 100°, 1 h	77	61	2	9	13	0	15
3	**2**	H_3PO_4(85%); 20°, 24 h	55	6	0	2	0	82	10
4	**2**	$BF_3 \cdot Et_2O$; CH_2Cl_2; 20°, 3 h	90	1	0	12	0	78	9
5	**8**	$SnCl_4$; CH_2Cl_2; −70→20°, 1 h	75	–	–	–	95	–	5

conditions, yields, and distributions of the products (determined by GC analysis of the distilled cyclisation mixtures) are reported in the *Table*.

From these results, it can be seen that **1** and **2** both afford tricyclic lactones (**3** and **7**) as the main products (57 and 70% yield, resp.). Apparently, $BF_3 \cdot Et_2O$ shows higher efficiency in the case of **2**, while H_3PO_4 is the reagent of choice for **1**. One of the principal by-products, the bicyclic lactone **5** (*cis*/*trans*-mixture) was formed from both **1** and **2**, but its proportion varies from 9 to 12% in the $BF_3 \cdot Et_2O$ experiments *(cf. Exper. 2* and *4)* to *ca.* 2% or less in the experiments using H_3PO_4 *(cf. Exper. 1* and *3)*. However, careful GC monitoring of the reaction showed that this result is probably a consequence of the higher instability of **5** towards H_3PO_4. In contrast, lactone **4** and ketone **6**, the two other by-products from **1**, are relatively acid-stable and their concentrations did not change significantly after prolonged reaction times; the higher yield of **6** in the $BF_3 \cdot Et_2O$ experiment *(Exper. 2)* thus appears to be catalyst-dependent.

Structure Assignments of Compounds **3**–**7**. While the spirolactone **5** could be directly identified by comparison with a known reference [8], complete structural assignments of the new compounds **3**, **4**, **6**, and **7** were unambiguously achieved by inspection of their spectral data combined with mechanistic considerations.

Compounds **3**, **4**, and **7** were all characterised as lactones by their significant IR absorptions at *ca.* 1770 cm^{-1} (γ-lactone in **3** and **7**) and at 1740 cm^{-1} (δ-lactone in **4**). Their molecular ions in the MS are 180 indicating the molecular formula $C_{11}H_{16}O_2$ in each case, and their ^{1}H-NMR and ^{13}C-NMR spectra exhibit signals consistent with the indicated structures.

The ^{13}C-NMR spectrum of **3** has 2 *q*, 4 *t*, 2 *d*, and 3 *s* and the ^{1}H-NMR spectrum 2 *s* at 1.13 and 1.22 (2 CH_3) and 1 *d* ($J \approx 2$ Hz) at 4.27 ppm (1 H). The ^{13}C-NMR spectrum of **4** exhibits 1 *q* (2 CH_3), 2 *t* (4 CH_2), 2 *d*, and 2 *s* (3 C) and the ^{1}H-NMR spectrum 2 *s* at 1.17 (6 H) and 2.12 (1 H) and a br. *s* at 4.6 ppm (1 H). The ^{13}C-NMR spectrum of **7** shows 1 *q*, 6 *t*, 1 *d*, and 3 *s* and the ^{1}H-NMR spectrum 1 *s* at 1.03 (CH_3), a *t* at 4.12 (1 H), and an *AB* system at 2.57 and 2.26 ppm (see also *Exper. Part*).

However, to obtain conclusive structural proof, additional ^{1}H-NMR experiments were carried out for **3** and **7**. A solution of the shift reagent Eu(fod)$_3$ added to the original NMR solution of **3** expanded the ^{1}H-NMR spectrum from which 7 isolated protons could be identified besides a *m* of 3 protons and 2 CH_3 groups. The ^{1}H,^{1}H-COSY experiment of this solution *(Fig. 1)* shows couplings between H–C(4), H–C(3), H–C(4), H′–C(3),

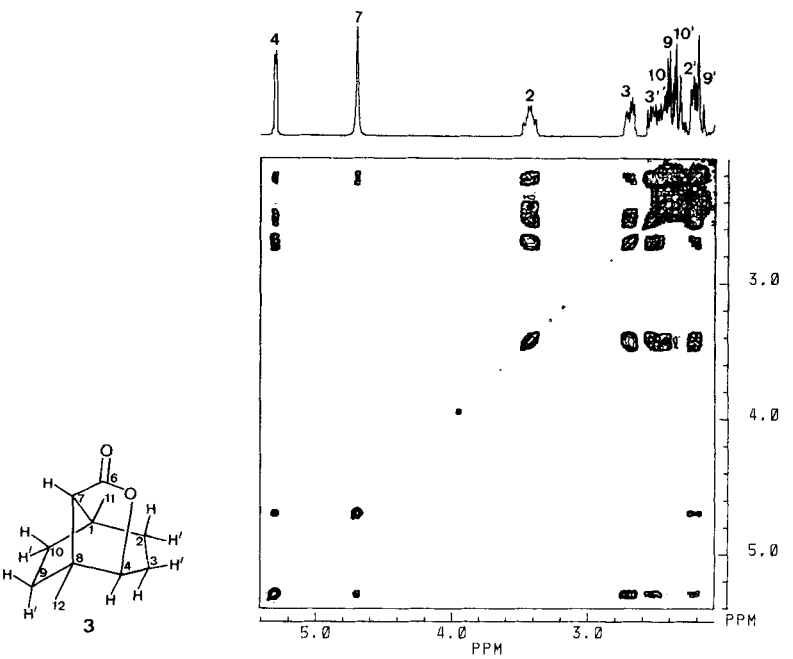


Fig. 1. *Homonuclear shift-correlated 2D-NMR experiment* (COSY) *of* **3** (1D-^{1}H-NMR on top) *showing vicinal couplings* (H–C(4), H–C(3), H–C(4), H′–C(3), H–C(2), H–C(3), H–C(2), H′–C(3), H– and H′–C(9), H– and H′–C(10)) *and long-range couplings* (H–C(4), H′–C(2), H–C(4), H–C(7), H–C(7), H′–C(2), H–C(2), H–C(10))

H–C(2), H–C(3), H–C(2), H′–C(3), and in the more crowded part of the *m* are less distinct couplings between H– and H′–C(9), H– and H′–C(10). Furthermore, important long-range couplings between H–C(4), H′–C(2), H–C(4), H–C(7), H–C(7), H′–C(2), and H–C(2), H–C(10) are visible.

In the second 2D-NMR *(Fig. 2)*, the heteronuclear shift-correlated experiment shows the ^{13}C,H correlations. The 1D-^{13}C-NMR broad-band and DEPT experiments show 2 *q*, 4 *t*, 2 *d*, and 3 *s* which were correlated with the ^{1}H-signals. In particular, the 4 CH_2 groups at C(2), C(3), C(9), and C(10) with the accompanying proton signals were confirmed.

In addition to C, H shift correlation using *J*(C,H), in the RELAY experiment *(Fig. 3)* correlations from more distant protons using *J*(H, H) appear. This also gives information

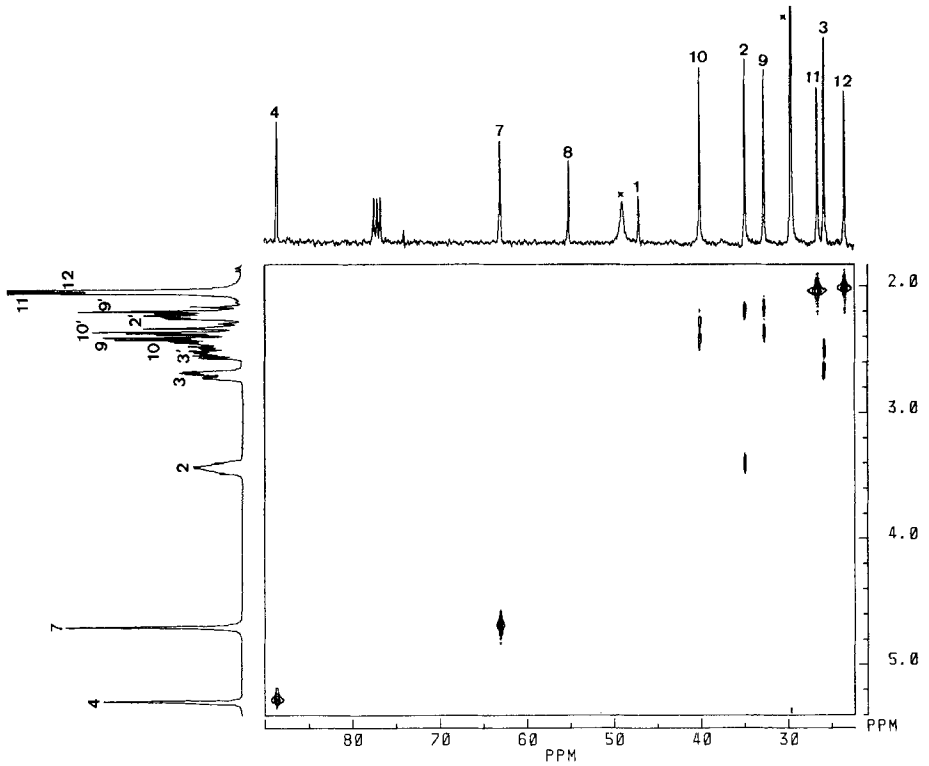
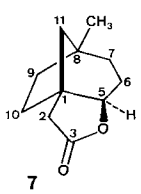


Fig. 2. *Heteronuclear shift-correlated 2D-NMR* (CH-CORR) *experiment of* **3** *shows* ^{1}H, ^{13}C *correlation.* 1D-^{1}H-NMR (360 MHz) on left side, 1D-^{13}C-NMR (90 MHz) on top; x = Eu(fod)$_3$.

about the C-nuclei connectivities but only between C-atoms bonded to H-atoms. The relations shown are C(4)–C(3), C(2)–C(3), and C(9)–C(10).

The 2D-^{13}C-INADEQUATE experiment shows C–C connectivities using J(C,C). This spectrum *(Fig. 4)* confirmed all previous experiments. The connectivities shown are C(4)–C(8), C(4)–C(3), C(7)–C(8), C(7)–C(1), C(8)–C(12), C(8)–C(9), C(9)–C(10), C(10)–C(1), C(1)–C(11), C(1)–C(2), and C(2)–C(3).

With the two 2D experiments ^{13}C,^{1}H-correlation and ^{1}H,^{1}H-correlation, the chemical shifts for compound **7** could also be attributed. Important were the long-range couplings H–C(5), H–C(11), H–C(5), H–C(7), and H–C(11), H–C(7), which confirm the position of H–C(5) as indicated in formula **7**.



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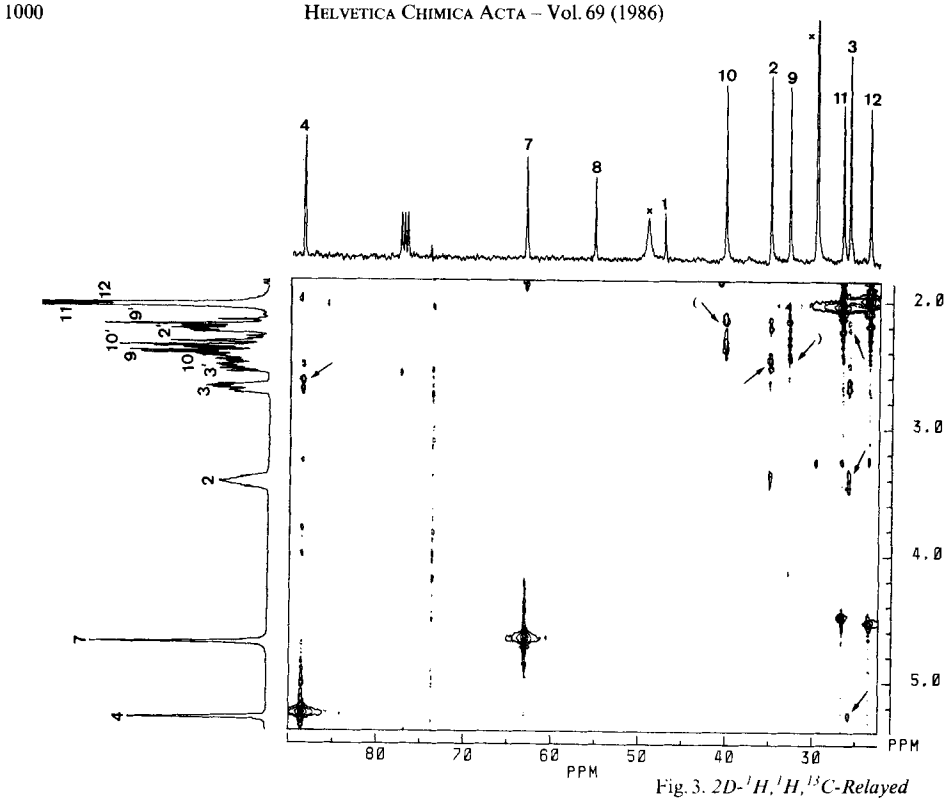


Fig. 3. *2D-$^1H,^1H,^{13}C$-Relayed heteronuclear chemical shift correlation experiment* (RELAY) *for* **3**. ^{13}C-nucleus shows not only directly bonded ^1H, but also protons vicinal to this proton. Compared to *Fig. 2*: relations C(4)–C(3), C(2)–C(3), C(9)–C(10) (relations shown by arrows). x = $Eu(fod)_3$.

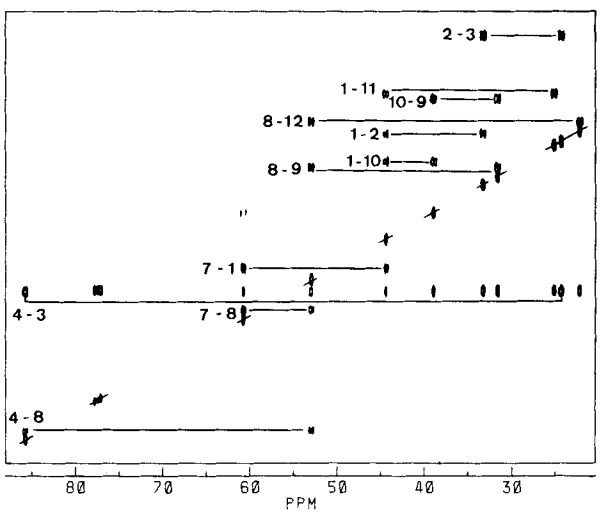
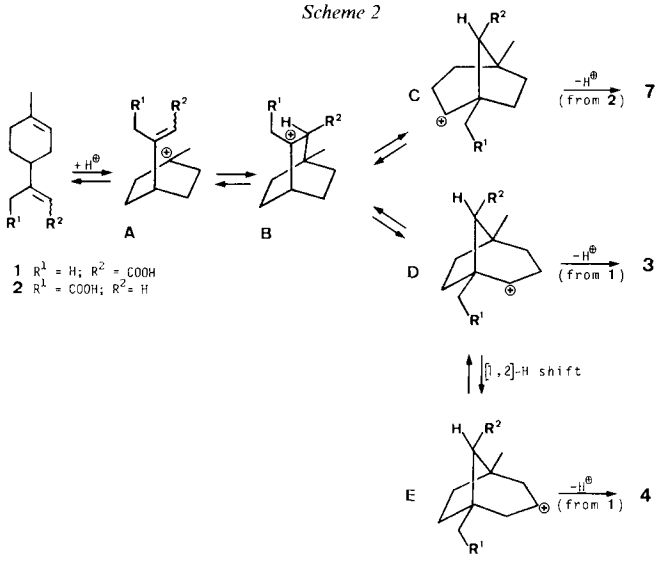


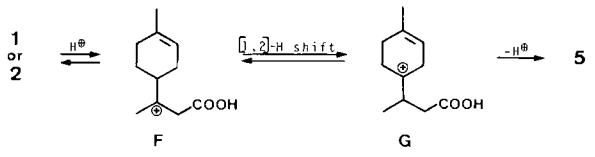
Fig. 4. *2D-^{13}C-INADEQUATE experiment* (90 MHz) *for* **3** *showing C–C connectivities using* $^1J(C,C)$. On top, broad-band decoupled 1D-^{13}C-NMR spectrum.

Mechanism. – The formation of lactones **3** and **7** from **1** and **2**, respectively, may be explained as follows. Firstly, protonation of the C(1)-double bond affords carbenium ion **A** which undergoes cyclisation to carbenium ion **B**; *Wagner-Meerwein* rearrangement of the bicyclo[2.2.2]octane skeleton to the bicyclo[3.2.1]octane skeleton then leads to carbenium ions **C** and **D** which are trapped intramolecularly by the COOH group to give **3** and **7**, respectively (see *Scheme 2*). Similarly, the formation of lactone **4** probably proceeds *via*

Scheme 2

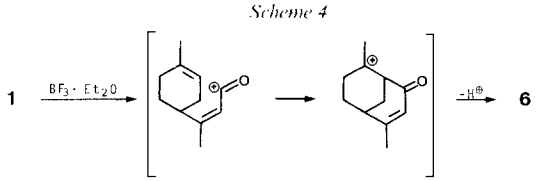


Scheme 3



carbenium ion **E**, derived from **D** by a [1,2]-H shift prior to internal lactonisation. The presence of spirolactone **5**, a minor product from either **1** or **2**, requires the intermediacy of carbenium ions **F** and **G** *(Scheme 3)* which may be formed by protonation of the C(8) (or C(9)) double bond followed by a [1,2]-H shift. Finally, the bicyclic ketone **6** which is only formed from acid **1** is presumably the consequence of an intramolecular *Friedel-Crafts* acylation *(Scheme 4)*. In support of this explanation, the acylchloride **8**, prepared from **1** by treatment with $SOCl_2$, readily affords **6** (70% yield) in the presence of $SnCl_4$ (see *Table*).

Scheme 4



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Experimental Part

1. *General.* GC: *Carlo Erba* instrument, Model *Fractovap 2900*, capillary column *Chrompack CP Wax 57 CP* (10 m); *Varian 1700* instrument, packed glass column with 10% *SE-30* on *Chromosorb W* (3 m). Prep. GC: *Varian* Autoprep. *Model 700*, glass column packed with *Carbowax 20 M*, 10% on *Chromosorb W* (3 m). IR: *Perkin-Elmer 297* spectrometer. NMR: *Bruker WH-360* modified in a *AM*-model and interfaced to an *Aspect 2000* computer; solvent, $CDCl_3$; chemical shifts in ppm relative to TMS; for the COSY, CH-CORR, and RELAY experiments [9], a soln. with the shift reagent $Eu(fod)_3$ was added to expand the whole spectrum; for the INADEQUATE experiment [9], 0,02M $Cr(acac)_3$ was added to 0.13M of **3** in 0.6 ml of $CDCl_3$. Adding $Cr(acac)_3$ to the NMR soln. reduces the T_1 relaxation times for all C-atoms from 18–2.7 s to below 0.6 s, enabling the use of a short recycle delay (1 s), which is important because of the low sensitivity of the INADEQUATE experiment. MS: *Varian MAT 112* mass spectrometer with *ca.* 70 eV.

2. *NMR-Experiments. Homonuclear Shift-Correlated 2D-NMR* (COSY) [9] (see *Fig. 1*). The mixing pulse was chosen at 45° (90° pulse 17 μs), relaxation time D_1 3 s, spectral width 1700 Hz in F_2 data matrix 1024 × 512, zero filling in F_1, 32 scans during 256 time increments, 2 dummy scans, squared *sine*-bell multiplications in both dimensions. The illustrated spectrum was symmetrised.

Heteronuclear Shift-Correlated 2D-NMR (CH-CORR) [9] (see *Fig. 2*). Relaxation time D_1 3 s, 90° ^1H pulse 17 μs, polarization time D_3 3.8 ms, 180° ^{13}C pulse 19 μs, refocussing time D_4 2 ms, spectral width in F_2 6500 Hz in F_1 850 Hz (0.5 × (1 H-shift range)), data matrix 1024 × 256, zero filling in F_1, 480 scans during 128 time increments, 2 dummy scans, *Gaussian* multiplication in both dimensions.

^2D-1H,^{13}C-Relayed Heteronuclear Chemical Shift Correlated Experiment (RELAY) [9] (see *Fig. 3*). Relaxation time 3 s, 90° ^1H pulse 17 μs, 180° ^{13}C pulse 19 μs, mixing time D_2 25 ms, polarization time D_3 3.8 ms, refocussing time D_4 2 ms, spectral width 6500 Hz in F_2 850 Hz in F_1, data matrix 1024 × 256, zero filling in F_1, 608 scans during 128 time increments, 2 dummy scans, *sine*-bell multiplication in both dimensions.

^{13}C-1NADEQUATE 2D-NMR (1NAD2D) [9] (see *Fig. 4*). Relaxation time D_1 1 s, 90° ^{13}C pulse 9.5 μs, 120° conversion pulse 12.7 μs, D_2 $(2N + 1)/4\,J$ 7 ms, spectral width 6500 Hz in $F_1 + F_2$ which gave 25.4 and 12.7 Hz/pt, resp. The data matrix was 1024 × 512, two times zero filling in F_1, 4 × 384 scans during 128 time increments, 2 dummy scans, *sine*-bell multiplication in both dimensions.

3. *Starting Materials. (E/Z)-p-Mentha-1,8(9)-diene-9-carboxylic Acid* (**1**; 82% *E*, 18% *Z*) was obtained by hydrolysis of the corresponding ester [6] [10] with NaOH in EtOH at reflux for 1 h. After evaporation, mixture was diluted with Et_2O, washed with H_2O, and then dried over Na_2SO_4. After filtration and concentration, **1** was obtained as white crystals, m.p. 72–84°. IR: 2600, 1680, 1630. ^1H-NMR: 1.68 (br. *s*, 3 H); 2.18 (br. *s*, 3 H); 5.4 (br. *s*, 1 H); 5.7 (br. *s*, 1 H); 11.6 (br. *s*, 1 H).

p-*Mentha-1,8(10)-diene-9-carboxylic Acid* **2** was prepared following [7]. ^1H-NMR: 1.67 (br. *s*, 3 H); 3.14 (*s*, 2 H); 4.98 (*s*, 2 H); 5.35 (br. *s*, 1 H); 11.17 (br. *s*, 1 H).

p-*Mentha-1,8(9)-diene-9-carbonyl Chloride* **8** was prepared by adding dropwise **1** (10 g) to $SOCl_2$ (30 ml) with caution following [11]. After stirring at r.t. for 3 h and concentration at 30°/0.02 Torr for 1 h, the crude **8** (11.2 g) was used as such. IR: 1760, 1600. ^1H-NMR: 1.68 (br. *s*, 3 H); 2.18 (br. *s*, 3 H); 5.4 (br. *s*, 1 H); 6.02 (br. *s*, 1 H).

4. *Acid-Catalysed Rearrangement of* **1**. 4.1. *H_3PO_4*. A soln. of **1** (1.0 g) and H_3PO_4 (85%, 7 ml) was kept at 90° with stirring. After the indicated time (see the *Table*), the mixture was poured onto ice and extracted with Et_2O. The org. phase was washed with dil. $NaHCO_3$ soln. and brine. After evaporation of the solvent, the residue was distilled *i.v.* to give a mixture (0.6 g) of **3**–**6**; product distribution, see the *Table*. From the alkaline aq. phase, after acidification with dil. H_2SO_4 and extraction with Et_2O, a complex non-identified mixture of acids (0.15 g) was recovered.

4.2. *$BF_3 \cdot Et_2O$*. A soln. of **1** (1.0 g), $BF_3 \cdot Et_2O$ (0.5 ml), and toluene (10 ml) was kept at 100° with stirring. The treatment was as described above.

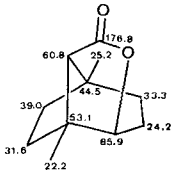
5. *Acid-Catalysed Rearrangement of* **2**. 5.1. *H_3PO_4*. A soln. of **2** (2 g) and H_3PO_4 (85%, 10 ml) was left at 20° with stirring for 24 h and treated as above to yield a mixture (0.9 g); product distribution, see the *Table*. A pure sample of **7** was obtained by prep. GC.

5.2. *$BF_3 \cdot Et_2O$*. To a stirred soln. of **2** (1 g) in CH_2Cl_2 (20 ml) was added $BF_3 \cdot Et_2O$ (3 ml). After 24 h, the usual workup afforded a mixture (0.8 g); product distribution, see the *Table*.

6. *$SnCl_4$-Catalysed Cyclisation of* **8**. A soln. of **8** (0.45 g) in CH_2Cl_2 (5 ml) was added to $SnCl_4$ (1 ml) in CH_2Cl_2 (10 ml) at −70° under stirring[2]). After 3 h, the mixture was allowed to reach r.t. during 2 h. Then, the mixture was poured onto ice and washed with dil. $NaHCO_3$ soln. and H_2O. After evaporation and distillation (bulb-to-bulb, bath temp. 80°/0.08 Torr), **5** (0.3 g) was obtained pure (95% by GC).

7. *Other Data. 1,8-Dimethyl-5-oxatricyclo[3.3.0.0^{4,8}]decan-6-one* (**3**). IR: 1770. MS: 180 (3, $M^{+\cdot}$), 152 (6), 134 (12), 108 (18), 95 (100), 82 (10), 77 (10), 67 (11), 53 (8), 39 (17).

^{13}C-NMR Spectra:



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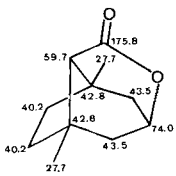

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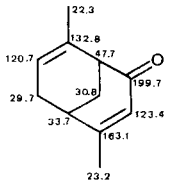

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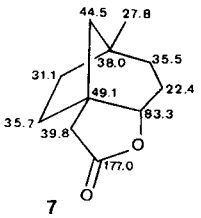

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3,6-Dimethyl-9-oxatricyclo[4.3.1.0^{3,7}]decan-8-one (**4**). IR: 1740. ^{1}H-NMR: 1.17 (*s*, 6 H); 2,12 (*s*, 1 H); 4.6 (br. *s*, 1 H). MS: 180 (2, $M^{+\cdot}$), 152 (3), 134 (7), 124 (6), 108 (13), 95 (100), 82 (12), 77 (8), 55 (6), 41 (8).

4,8-Dimethyl-1-oxaspiro[4.5]dec-7-en-2-one (**5**) [8]. GC: *ca.* 1:1 isomeric mixture . IR: 1778. ^{1}H-NMR: 1.05 (*d*, *J* = 6, 3 H); 1.70 (br. *s*, 3 H); 5.31 (br. *s*, 1 H). MS: 180 (17, $M^{+\cdot}$), 120 (14), 112 (33), 99 (32), 84 (27), 68 (100), 42 (63).

4,8-Dimethylbicyclo[3.3.1]nona-3,7-dien-2-one (**6**). IR: 1660. ^{1}H-NMR: 1.69 (*s*, 3 H); 1.965 (*s*, 3 H); 5.38 (br. *s*, 1 H); 5.71 (*s*, 1 H). MS: 162 (92, $M^{+\cdot}$), 147 (95), 129 (37), 119 (100), 105 (43), 91 (98), 77 (57), 65 (32), 55 (39), 39 (44).

8-Methyl-4-oxatricyclo[6.2.1.0^{1,5}]undecan-3-one (**7**). IR: 1775. ^{1}H-NMR: 1.03 (*s*, 3 H); 2.25 (*d*, *J* = 16, 1 H); 2.57 (*d*, *J* = 16, 1 H); 4.12 (*t*, *J* = 5, 1 H). MS: 180 (1, $M^{+\cdot}$), 179 (1), 151 (14), 136 (30), 121 (36), 107 (37), 94 (100), 79 (76), 68 (34), 55 (31), 41 (33).

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[2]) For a cyclisation using $(CF_3CO)_2O$, see [12].