270. Macrocyclic Ring Closure of OH-assisted *Prins* Reaction. A New and Efficient Synthesis of (*R, S*)-Muscone

by **Karl H. Schulte-Elte, Arnold Hauser** and **Günther Ohloff**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

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Summary

A new strategy for the synthesis of muscone (**1**) using the OH-assisted *Prins* reaction for macrocyclic ring closure has been developed. The monoacetal **4** of (*Z, E*)-4,8-dodecadienedial (**3**), easily obtainable from (*Z, E, E*)-1,5,9-cyclododecatriene (**2**), is treated with methallylmagnesium chloride, and the resulting C_{16}-precursor **5** is subjected to acid-catalyzed cyclization in dilute ($\leq 1\%$) solutions. This results in formation of the bicyclic dihydropyran derivatives **6** which directly yield muscone (**1**) on heating with a noble metal catalyst saturated with hydrogen. The five-step pathway proceeds with readily available starting materials in conventional steps and excellent overall yield ($\sim 40\%$). This new principle of macrocyclic ring formation has also been used successfully for the preparation of 3-methylcyclotridecanone (**34**) and should be generally applicable for other suitable ring systems.

In the preceding communication *Büchi & Wüest* describe a new method for the preparation of macrocyclic ketones by the direct coupling of α,ω-C_{12}-dialdehydes with 1,3-bis(dimethylphosphono)-2-propanone [1]. In this way cyclopentadecanone (Exaltone®) is obtained in an elegant and novel manner.

We now describe a new and direct pathway to muscone (**1**) from the same readily accessible C_{12}-dialdehydes [2], which is particularly efficient when (*Z, E*)-4,8-dodecadienedial (**3**) *(Scheme)* is used. The key step is the acid-catalyzed cyclization of the (*E, Z*)-isomeric hydroxyacetals **5** to the bicyclic dihydropyran derivatives **6**, in which the 16 C- and the O-atoms are already positioned as in muscone (**1**).

When carrying out the cyclization with *p*-toluenesulfonic acid in boiling toluene, the formation of **6** proceeds smoothly, attaining 75% yield, provided that the concentration of **5** is kept below $\sim 1\%$. Substantial reductions in the yield due to an increase of higher molecular weight by-products is observed only if the concentration of **5** exceeds $\sim 1.5\%$.

The final step is effected by heating the bicyclic ether **6** to $\geq 135°$ with H_2-activated noble metal catalysts (Pd/C, Pt, *etc.*) in xylene in a N_2/H_2 mixture to give muscone (**1**) in *ca.* 75% yield. There is also formed *ca.* 15% of the saturated ether **18** which is stable under these conditions. A virtually complete conversion of the bicyclic ethers, including the saturated compound **18**, into muscone (**1**) then

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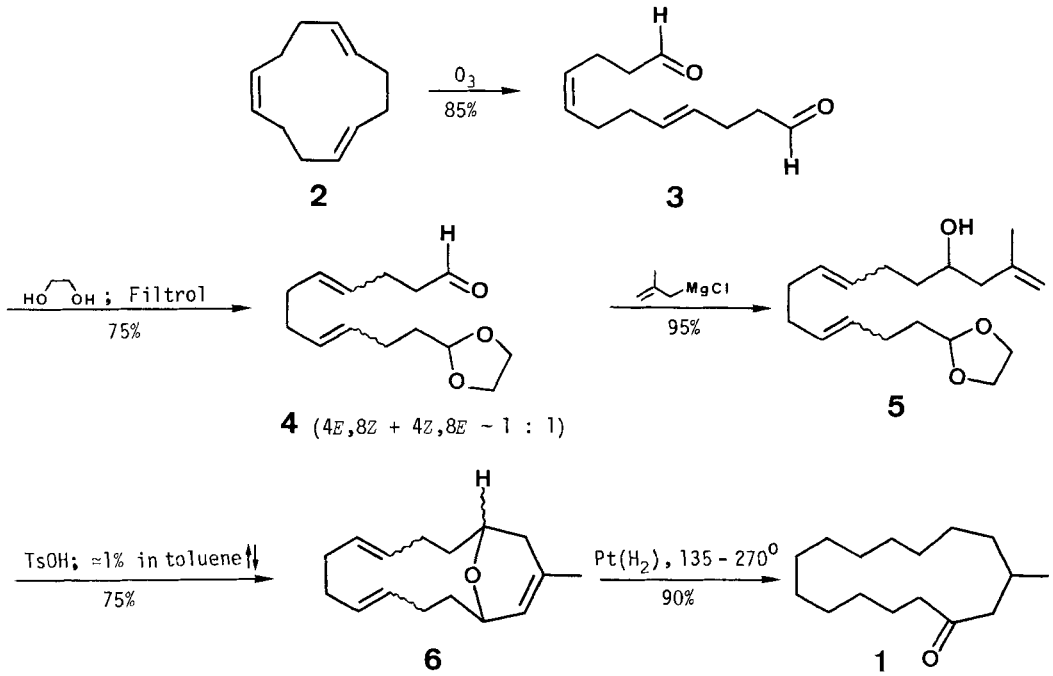
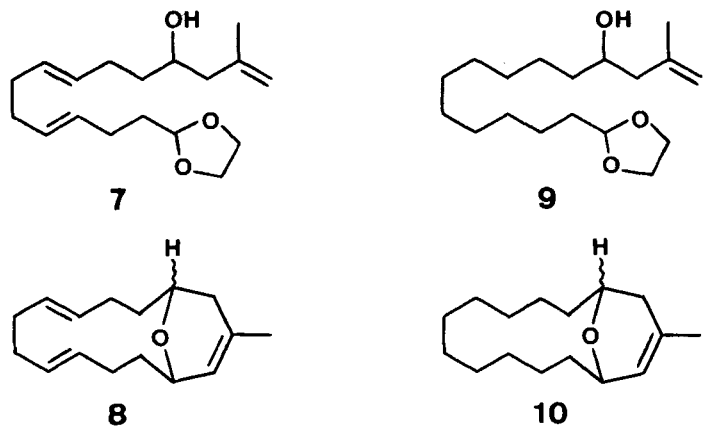
Scheme

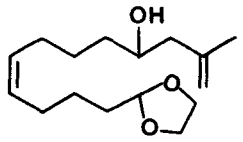


takes place in a temperature range from 135 to 270° under pressure. Under milder conditions ($\leqslant 135°$) only the transposition of the dihydropyran double bond is observed; thus with noble metal catalysts at 100° **10** leads only to the enol ether **17**.

The intermediate **5** was prepared almost quantitatively by the *Grignard* reaction of methallylmagnesium chloride with monoacetal **4** in ether. The C_{12}-monoacetal **4** was prepared as a mixture of (*E*/*Z*)-isomers from (*Z*, *E*, *E*)-1,5,9-cyclododecatriene (**2**) by mono-ozonolysis [2] and subsequent partial acetalization of the resulting dialdehyde **3**.



The acid-catalyzed cyclization (**5**→**6**) represents an OH-assisted *Prins*-type reaction [3–7]. The presence of the 1,5-diene in the precursor seems to be of particular importance for the smooth course of the cyclization. Indeed, hydroxyacetal **9**, which is saturated in the chain, only yields about 20% of the analogous cyclization product **10**. The configuration of the double bonds also exerts a marked influence. Thus in going from (*E*, *Z*)-diene **5** to (*E*, *E*)-diene **7** the yield of cyclization product decreases from 75% to 55%. Furthermore, the presence of the isopropenyl group is a prerequisite for a successful reaction; under the same cyclization conditions, the non-branched homoallyl alcohols analogous to **5** gave merely traces of the expected bicyclic dihydropyrans, thus excluding an analogous preparation of Exaltone® by this method.



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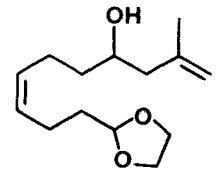

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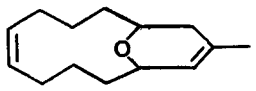

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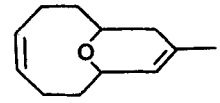

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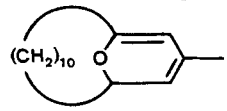
Applied to the synthesis of smaller rings, the reaction was also found to be suitable for the preparation of 3-methylcyclotridecanone (**34**). The intermediate dihydropyran derivative **12** is formed from **11** in a yield of 40%. On the other hand, the bicyclic ether **14** was only obtained in traces from its precursor **13**, probably due to the sterically unfavourable combination of a nine- and a six-membered ring. Nevertheless, this new ring forming process should be generally useful for the synthesis of other analogous ring systems.



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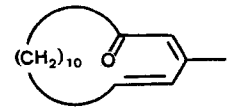

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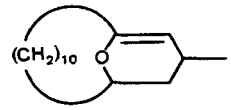

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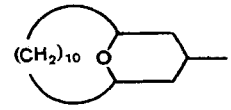

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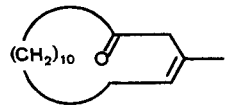

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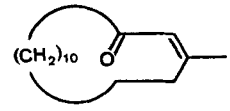

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Concerning the mechanism of the noble metal-catalyzed conversion of the pyran-type ethers **6**, **12**, **17** and **18** into the corresponding macrocyclic ketones we assume, in agreement with others [6], that the first step is a dehydrogenation process thus forming the pyran rings. These are in equilibrium with their dienone through an electrocyclic ring opening reaction [8]. The two conjugated double bonds of the dienone system are subsequently hydrogenated. Thus muscone (**1**) may be formed from **6** after hydrogenation of the two 1,5-double bonds *via* the non-isolated intermediates **15** and **16**. This hypothesis is supported by the isolation of the enones **19** [9] and **20** [10] which can be considered as intermediates from a partially transformed reaction mixture.

Experimental Part

General. – The IR. spectra were recorded on a *Perkin-Elmer* 125 spectrophotometer, typical bands are in cm^{-1}. The 60-MHz-^{1}H-NMR. spectra were recorded on *Varian* A 60 and *Hitachi Perkin-Elmer* R-20B instruments, using $CDCl_3$ as solvent and TMS ($\delta = 0.00$ ppm) as internal standard; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet. Chemical shifts are given in ppm, spin-spin coupling constants *J* in Hz. Mass spectra (MS.) were measured on an *Atlas* CH_4 mass spectrometer, inlet temperature *ca.* 150°, electron energy *ca.* 70 eV; the molecular ions (*M*) and fragment ions are given as *m/e* with relative intensities in % of the most abundant fragment. For gas chromatography (GC.) on packed glass columns a *Varian* Aerograph (Series 1800) instrument was used; carrier gas: 40 ml He/min; column carrier: Chromosorb W/60–80 mesh. The silica gel (0.05–0.2 mm) used for column chromatography was obtained from *E. Merck AG*, Darmstadt. – Other abbreviations: RT. = room temperature, i.V. = *in vacuo*, i.HV. = in high vacuum.

Starting materials. – The dialdehydes **3**, **21**, **22** [2], **23** and **24** [11] were obtained by ozonization of the corresponding cycloolefins using classical procedures; a solution of the cycloolefin (1 mol) in petroleum ether (2 l; b.p. 40–60°) and acetic acid (160 ml) was treated at −10° with a stream of O_3/O_2 to complete transformation (GC.). The reaction mixture was diluted with ethyl acetate (800 ml) and acetic acid (200 ml) was added. Zn-powder (200 g) was added in small portions to the stirred solution at 0–10° (external cooling) till the peroxide test (KI/acetic acid) was negative (*ca.* 10–12 h). After filtration and evaporation the dialdehydes **3**, **21**, **22**, **23** and **24** were obtained pure by distillation (0.1 Torr) using a *Vigreux*-column.

(Z,E)-4,8-Dodecadienedial (**3**) [2]. Yield: 85% from *(Z,E,E)*-1,5,9-cyclododecatriene (**2**, *Fluka*), b.p.: 100–102°/0.1 Torr. – IR.: 2700, 1723 (CHO), 965 (CH=CH, *E*). – ^{1}H-NMR.: 1.95–2.6 (*m*, 12 H); 5.19–5.91 (*m*, 4 H); 9.7 (*t*, *J* = 1.5, 2 H). – MS.: 194 (M^+, < 1), 178 (1), 150 (6), 97 (40), 79 (57), 67 (58), 55 (30), 41 (100), 29 (20).

(E,E)-4,8-Dodecadienedial (**21**) [2]. Yield: 76% from *(E,E,E)*-1,5,9-cyclododecatriene *(Fluka)*, b.p. 104–106°/0.1 Torr. – IR.: 2700, 1723 (CHO), 965 (CH=CH, *E*). – ^{1}H-NMR.: 1.95–2.5 (*m*, 12 H); 5.21–5.47 (*m*, 4 H); 9.27 (*t*, *J* = 1.5, 2 H). – MS.: 194 (M^+, < 1), 97 (48), 79 (62), 67 (64), 55 (33), 41 (100), 29 (19).

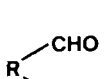
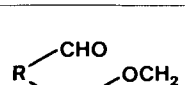
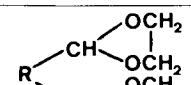
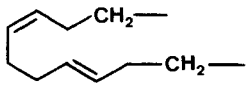
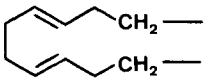
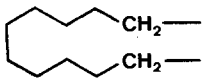
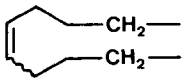
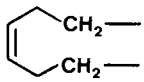
Dodecanedial (**22**) [2]. Yield: 70% from cyclododecene *(Fluka)*, b.p. 100–101°/0.1 Torr. – IR.: 2700, 1720 (CHO). – ^{1}H-NMR.: 1.2–1.85 (*m*, 16 H); 2.2–2.5 (*m*, 4 H); 9.6 (*t*, *J* = 1.5, 2 H). – MS.: 198 (M^+, < 1), 170 (1), 137 (10), 95 (59), 81 (68), 67 (57), 55 (89), 41 (100), 29 (65).

(Z)-5-Decenedial (**23**) [11]. Yield: 76% from *(Z,E)*-1,5-cyclodecadiene *(Fluka)*, b.p. 80–82°/0.1 Torr. – IR.: 2720, 1725 (CHO). – ^{1}H-NMR.: 1.2–1.8 (*m*, 4 H); 2.2–2.6 (*m*, 8 H); 5.2–5.4 (*m*, 2 H). – MS.: 168 (M^+, < 1), 150 (2), 124 (25), 95 (30), 80 (100), 67 (45), 55 (53), 41 (85).

(Z)-4-Octenedial (**24**) [11]. Yield: 68% from *(Z,Z)*-1,4-cyclooctadiene *(Fluka)*, b.p. 67–68°/0.1 Torr. – IR.: 2720, 1730 (CHO). – ^{1}H-NMR.: 2.35–2.55 (*m*, 8 H); 5.35 (*m*, 2 H); 9.72 (*d*, *J* ≃ 1.5, 2 H). – MS.: 140 (M^+, < 1), 122 (4), 115 (4), 96 (33), 84 (36), 67 (98), 55 (65), 41 (100), 27 (45).

2. Preparation of the monoacetals 4, and 25–28 and the diacetals 29–33. – *General procedure.* The dialdehydes **3** and **22–24** (1 mol) were refluxed together with ethylene glycol (1.1 mol) and

Table. *Dialdehydes, monoacetals and diacetals*

R			
	3	4	29
	21	25	30
	22	26	31
 (E/Z 1 : 9)	23	27	32
	24	28	33

Filtrol[1]) (1 g) in diisopropylether (1 l). The water formed was removed using a *Dean-Stark* apparatus. In all cases GC. revealed maximum formation of monoacetals (*ca.* 55–60%) after 6–8 h, together with diacetals (~30–35%) and starting dialdehydes (~10%). The solution was cooled, filtered and dried (Na_2SO_4). After evaporation the residue was fractionally distilled (0.1 Torr) using a *Vigreux*-column to give the monoacetals in 40–50% yield together with recovered dialdehydes (8–10%) and the diacetals (25–30%). The yields of the monoacetals rose to 75% if the dialdehyde, recovered and regenerated from the diacetals by hydrolysis (see below), was recycled.

Data of the monoacetals **4** *and* **25–28**. – *11-(1,3-Dioxolan-2-yl)-4,8-undecadienal* (**4**; ~1:1 mixture of (*E,Z*) and (*Z,E*) isomer). Yield: 75%, b.p. 110–112°/0.1 Torr. – IR.: 2700, 1720 (CHO). – ^{1}H-NMR.: 1.5–2.6 (*m*, 12 H); 3.88 (*d*, *J*=2, 4 H); 4.84 (*t*, *J*=4, 1 H); 5.2–2.6 (*m*, 4 H); 9.77 (*s*, 1 H). – MS.: 238 (M^+, <1), 220 (2), 195 (15), 175 (8), 103 (2), 141 (13), 119 (14), 99 (30), 73 (100), 55 (16), 41 (42), 29 (13).

*(*E,E*)-11-(1,3-Dioxolan-2-yl)-4,8-undecadienal* (**25**). Yield: ~60%, b.p. 108–110°/0.1 Torr. – IR.: 2720, 1720 (CHO), 975 (CH=CH, *E*). – ^{1}H-NMR.: 1.5–2.6 (*m*, 12 H); 3.88 (*d*, *J*=2, 4 H); 4.83 (*t*, *J*=4, 1 H); 5.51 (*m*, 4 H); 9.72 (*s*, 1 H). – MS.: 238 (M^+, <1), 210 (<1), 195 (11), 141 (11), 122 (4), 105 (9), 99 (41), 79 (31), 73 (100), 55 (21), 45 (47).

11-(1,3-Dioxolan-2-yl)-undecanal (**26**). Yield: ~35%. – IR.: 2710, 1725 (CHO). – ^{1}H-NMR.: 2.1–2.6 (*m*, 2 H); 3.6–4.1 (*m*, 4 H); 4.83 (*t*, *J*=4, 1 H); 9.75 (*t*, *J*=2, 1 H). – MS.: 242 (M^+, <1), 113 (<1), 95 (1), 81 (<1), 73 (32), 62 (4), 43 (13), 31 (100) (cf. lit. [12]).

9-(1,3-Dioxolan-2-yl)-5-nonenal (**27**; ~1:9 mixture of (*E*) and (*Z*) isomer). Yield: ~75%, b.p. 92–94°/0.1 Torr. – IR.: 2710, 1725 (CHO). – ^{1}H-NMR.: 1.3–1.8 (*m*, 6 H); 1.9–2.2 (*m*, 2 H); 2.5 (*m*, 4 H); 3.85 (*m*, 4 H); 4.85 (*t*, *J*=4, 1 H); 5.4 (*m*, 2 H); 9.7 (*m*, 1 H). – MS.: 212 (M^+, <1), 183 (1), 169 (2), 124 (5), 99 (20), 80 (35), 73 (100), 55 (20), 41 (35).

(Z)-7-(1,3-Dioxolan-2-yl)-4-heptenal (**28**). Yield: ~70%, b.p. 55–57°/0.1 Torr. – IR.: 2720, 1710 (CHO). – ^{1}H-NMR.: 1.5–1.8 (*m*, 2 H); 2.0–2.55 (*m*, 8 H); 3.8–4.1 (*m*, 4 H); 4.86 (*t*, *J*=4, 1 H); 5.4 (*m*, 2 H); 9.75 (*m*, 1 H). – MS.: 184 (M^+, <1), 155 (1), 141 (1), 99 (20), 73 (100), 45 (28), 41 (22).

[1]) Strongly acidic catalyst from *Filtrol Inc.*, Los Angeles, USA.

Data of the diacetals **29–33**: *(Z,E)-1,10-Bis(1,3-dioxolan-2-yl)-3,7-decadiene* (**29**). – IR.: 965 (CH=CH, *E*). – ^{1}H-NMR.: 0.5–0.9 (*m*, 4 H); 2.0–2.2 (*m*, 8 H); 3.8–4.1 (*m*, 8 H); 4.85 (2 *t*, superimposed, $J=4$, 2 H); 5.3–5.6 (*m*, 4 H). – MS.: 282 (M^+, < 1), 205 (1), 141 (3), 133 (6), 99 (35), 79 (20), 73 (100), 55 (20), 45 (75).

(E,E)-1,10-Bis(1,3-dioxolan-2-yl)-3,7-decadiene (**30**). – IR.: 968 (CH=CH, *E*). – ^{1}H-NMR.: 1.5–1.85 (*m*, 4 H); 1.9–2.2 (*m*, 8 H); 3.6–4.0 (*m*, 8 H); 4.84 (*t*, superimposed, $J=4$, 2 H); 5.3–5.55 (*m*, 4 H). – MS.: 282 (M^+, < 1), 141 (1), 119 (3), 86 (70), 84 (100), 83 (16), 47 (25), 35 (10), 31 (25).

1,10-Bis(1,3-dioxolan-2-yl)decane (**31**). – ^{1}H-NMR.: 1.25–1.35 (*m*, 20 H); 3.8–3.9 (*m*, 4 H); 4.85 (*t*, $J=4$, 2 H).

1,8-Bis(1,3-dioxolan-2-yl)-4-octene (**32**; ~1:9 mixture of (*E*) and (*Z*) isomer; GC.-analysis). – ^{1}H-NMR.: 1.3–1.9 (*m*, 8 H); 2.0–2.3 (*m*, 4 H); 3.8–4.0 (*m*, 8 H); 4.85 (*t*, $J=4$, 2 H); 5.38 (*m*, 2 H). – MS.: 256 (M^+, < 1), 204 (1), 122 (3), 99 (12), 87 (6), 81 (6), 75 (40), 73 (100), 55 (8), 45 (22), 31 (45).

(Z)-1,6-Bis(1,3-dioxolan-2-yl)-3-hexene (**33**). – ^{1}H-NMR.: 1.5–1.9 (*m*, 4 H); 2.0–2.4 (*m*, 4 H); 3.8–4.1 (*m*, 4 H); 4.8–5.0 (*t*, $J=5$, 2 H); 5.3–5.55 (*m*, 2 H). – MS.: 228 (M^+, < 1), 202 (3), 113 (6), 99 (50), 86 (15), 73 (100), 45 (35), 27 (36).

3. Saponification of the diacetals 29–33. – *General procedure.* To a stirred mixture of diacetal (0.1 mol), tetrahydrofuran (100 ml) and $HClO_4$-solution (70%; 0.5 ml), water (80 ml) was added dropwise during 12–15 h at RT. The end of the reaction was monitored by GC. Then water (500 ml) was added, and the dialdehydes formed were isolated by extraction with pentane and distilled at 0.1 Torr. Yield: > 90%.

4. Preparation of the homoallyl alcohols 5, 7, 9, 11 and 13. – *General procedure.* To a stirred mixture of Mg-turnings (1.3 mol) and abs. ether (50 ml) under N_2 methallyl chloride (2 ml; freshly distilled) was added. After the reaction had started, a solution of mono acetals **4**, **25–28** (1 mol), methallyl chloride (1.4 mol) in abs. ether (1000 ml) and abs. tetrahydrofuran (250 ml) was introduced dropwise, maintaining the temperature < 15° by external cooling. Stirring was continued 3 h longer, when NH_4Cl/ice was added, the organic layer separated and the aqueous phase extracted with ether (3 × 300 ml). The combined organic fractions were washed with water and dried (Na_2SO_4). Evaporation and distillation of the residue at 0.1 Torr gave the homoallyl alcohols **5**, **7**, **9**, **11** and **13** in yields between 90–98%.

2-Methyl-14-(1,3-dioxolan-2-yl)-1,7,11-tetradecatrien-4-ol (**5**; ~1:1 mixture of (*E,Z*) and (*Z,E*) isomer). Yield: 95% from **4**, b.p. ~150°/0.1 Torr (bulb). – IR.: 3345, 3080, 1642, 890. – ^{1}H-NMR.: 1.74 (*s*, 3 H); 3.5–4.1 (*m*, 5 H); 4.7–5.0 (*m*, 2 H); 5.2–5.6 (*m*, 4 H). – MS.: 294 (M^+, < 1), 222 (1), 208 (< 1), 195 (9), 177 (3), 159 (4), 147 (7), 141 (13), 129 (12), 119 (13), 109 (18), 99 (40), 93 (39), 79 (49), 73 (100), 67 (36), 55 (39), 43 (96), 31 (83).

(E,E)-2-Methyl-14-(1,3-dioxolan-2-yl)-1,7,11-tetradecatrien-4-ol (**7**). Yield: 86%, b.p. ~150°/0.1 Torr (bulb). – IR.: 3485, 3100, 1650, 885. – ^{1}H-NMR.: 1.78 (*s*, 3 H); 3.6–4.1 (*m*, 5 H); 4.7–5.0 (*m*, 3 H); 5.4 (*m*, 4 H). – MS.: 294 (M^+, 0), 222 (< 1), 150 (56), 135 (27), 121 (36), 107 (37), 93 (28), 79 (19), 71 (62), 55 (25), 43 (48), 31 (100).

2-Methyl-14-(1,3-dioxolan-2-yl)-1-tetradecen-4-ol (**9**). Yield: 95%. – IR.: 3500 (OH), 3130, 1655, 890 (C=CH_2). – ^{1}H-NMR.: 1.75–2.3 (*m*, 6 H); 2.1 (*s*, 1H, disappeared with D_2O-addition); 3.5–4.1 (*m*, 5 H); 4.7–5.0 (*m*, 3 H). – MS.: 298 (M^+, < 1), 200 (< 1), 180 (< 1), 163 (1), 144 (2), 124 (10), 109 (7), 89 (28), 81 (6), 73 (22), 63 (13), 56 (100), 43 (70), 31 (56).

(Z)-2-Methyl-12-(1,3-dioxolan-2-yl)-1,8-dodecadien-4-ol (**11**). Yield: 87%, b.p. ~150°/0.1 Torr (bulb). – IR.: 3450 (OH), 3080, 1645, 885 (C=CH_2). – ^{1}H-NMR.: 1.2–1.6 (*m*, 8 H); 1.83 (*s*, 3 H); 1.9–2.3 (*m*, 6 H); 4.7 (*m*, 1H); 3.85 (*m*, 4 H); 4.85 (*m*, 2 H); 5.38 (*t*, $J=5$, 2 H). – MS.: 268 (M^+, < 1), 232 (1), 151 (3), 133 (5), 99 (22), 81 (12), 73 (100), 55 (22), 45 (35).

(Z)-2-Methyl-10-(1,3-dioxolan-2-yl)-1,7-decadien-4-ol (**13**). Yield: 91%. – IR.: 3450 (OH), 3080, 1640, 885 (C=CH_2). – ^{1}H-NMR.: 1.3–1.85 (*m*, 4 H); 1.75 (*m*, 3 H); 2.0–2.35 (*m*, 6 H); 3.7 (*m*, 1H); 3.8–4.0 (*m*, 4 H); 4.8–4.95 (*m*, 2 H); 5.3–5.5 (*m*, 2 H). – MS.: 240 (M^+, 1), 185 (3), 155 (3), 141 (3), 123 (6), 99 (30), 79 (15), 73 (100), 45 (35), 41 (30).

5. Cyclization of homoallylic alcohols 5, 7, 9 and 11; formation of bicyclic ethers 6, 8, 10 and 12. – *General procedure.* A special, recently described apparatus *(Pyrex)* [13] for performing reactions in higher dilutions was additionally equipped with a water separator. Therein a solution of *p*-toluenesulfonic acid (1 g) in toluene (500 ml) was refluxed, while a solution of the homoallyl alcohols **5**, **7**, **9** or **11** (15 g) and *p*-toluolsulfonic acid (1 g) in toluene (300 ml) was added dropwise over 3 h. The

cyclization was followed by GC. and by the quantity of ethylene glycol eliminated. In general, the reaction is complete after another 3–4 h[2]). The reaction mixture was cooled to RT., washed twice with water and sat. aq. $NaHCO_3$-solution, then dried (Na_2SO_4) and evaporated. The residue upon distillation (0.1 Torr) gave the bicyclic ethers **6**, **8**, **10** and **12**[3]).

14-Methyl-16-oxabicyclo[10.3.1]hexadeca-4,8,13-triene (**6**; ~1:1 mixture of (*E,Z,Z*) and (*Z,E,Z*) isomer). Yield: 75%, b.p. 68–71°/0.1 Torr. – ^{1}H-NMR.: 1.66 (*d*, *J*=2, 3 H); 3.2–3.6 (*m*, 1 H); 3.7–4.1 (*m*, 1 H); 4.15–6.9 (*m*, 5 H). – MS.: 232 (M^+, 48), 217 (6), 203 (11), 189 (19), 175 (7), 163 (24), 147 (36), 135 (38), 121 (86), 109 (75), 95 (100), 79 (73), 67 (73), 55 (57), 41 (99).

(E,E,Z)-14-Methyl-16-oxabicyclo[10.3.1]hexadeca-4,8,13-triene (**8**). Yield: 50%, b.p. 70–72°/0.1 Torr. – ^{1}H-NMR.: 1.3–2.4 (*m*, 17 H); 3.1–3.55 (*m*, 1 H); 3.7–4.0 (*m*, 1 H); 4.9–5.6 (*m*, 5 H). – MS.: 232 (M^+, 29), 214 (15), 203 (5), 189 (9), 175 (3), 163 (12), 147 (22), 135 (27), 121 (59), 109 (69), 95 (86), 79 (74), 67 (78), 55 (44), 41 (100).

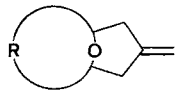
(Z)-14-Methyl-16-oxabicyclo[10.3.1]hexadec-13-ene (**10**). Yield: 20%,. b.p. 68–70°/0.1 Torr. – ^{1}H-NMR.: 1.1–2.2 (*m*, 25 H); 3.2–3.65 (*m*, 1 H); 3.8–4.2 (*m*, 1 H); 5.24 (*m*, 1 H). – MS.: 236 (M^+, 17), 221 (11), 207 (<1), 194 (4), 178 (5), 163 (2), 149 (4), 135 (8), 121 (22), 109 (34), 95 (100), 81 (43), 67 (39), 55 (54), 41 (59), 29 (20). The same bicyclic ether **10** was obtained in 95% yield by hydrogenation of **6** with *Lindlar* catalyst in 2-propanol under normal pressure.

(Z,Z)-12-Methyl-14-oxabicyclo[8.3.1]tetradeca-5,11-diene (**12**). Yield: 40%, b.p. 90–100°/0.1 Torr (bulb). – ^{1}H-NMR.: 1.45 (*m*, 8 H); 3.1–4.2 (*m*, 2 H); 5.51–5.5 (2 *m* overlapped, 3 H). – MS.: 206 (M^+, 25), 191 (4), 163 (10), 149 (8), 135 (10), 121 (40), 109 (30), 55 (100), 81 (40), 67 (40), 55 (35), 41 (55).

6. Pd/C-catalyzed isomerization of 10. Formation of 14-methyl-16-oxabicyclo[10.3.1]hexadec-1(15)-ene (17)[4]). – Pd/C-catalyst (0.3 g) in abs. dioxane (15 ml) was activitated by heating in a H_2-atmosphere at 100° during 1 h. Then H_2 was replaced by N_2/H_2 9:1, the ether **10** (0.5 g) was added and heating to 100° continued. After 3 h GC. indicated complete transformation. The mixture was cooled to RT., filtered and evaporated i.V. Bulb distillation (120°/0.1 Torr) of the residue yielded 0.45 g of product, containing ~80% of **17** (GC.). Purified **17** showed: IR.: 1668 (OC=C). – ^{1}H-NMR.: 0.95 (*d*, *J*=7, 3 H); 1.3–1.5 (*m*, 20 H); 1.8–2.2 (*m*, 3 H); 3.8–4.1 (*m*, 1 H); 4.2–4.32 (*m*, 1 H). – MS.: 236 (M^+, 45), 221 (40), 194 (20), 178 (20), 135 (35), 95 (75), 81 (60), 69 (100), 55 (90), 41 (90).

7. Pd/C-catalyzed hydrogenation of 6, 8 and 10. Formation of 14-methyl-16-oxabicyclo[10.3.1]hexadecene (18, mixture of isomers). – The ethers **6**, **8** and **10** (1 g) were perhydrogenated by shaking them in ethanol solution (50 ml) together with Pd/C-catalyst (0.2 g) in an H_2-atmosphere at RT. Ether **18** was formed in all cases in >80% yield. – ^{1}H-NMR.: 0.9 (*d*, *J*=7, 3 H); 1.35 (*m*, 13 H); 3.1–3.6 (*m*, 2 H). – MS.: 238 (M^+, 50), 223 (12), 194 (30), 112 (35), 99 (55), 81 (66), 69 (70), 55 (100), 41 (95). – Compound **18** is identical with the ether obtained previously [14] by acid-catalyzed dehydration of 3-methyl-cyclopentadecane-1,5-diol (5-hydroxymuscol; comparison of spectra [15]).

8. (*R,S*)-Muscone (1). – a) *From ethers* **6**, **8** *and* **10**. Pd/C-catalyst (5 g) was activated by refluxing in xylene (175 ml) under H_2 for 30 min. Then the H_2-flow was reduced to ~30–40 ml H_2/min and ethers **6**, **8** or **10** (20 g) were added while maintaining the temperature at 135°. Monitoring by GC. indicated complete transformation after 10–12 h and formation of *ca.* 20% of **18** and 80% of (*R,S*)-muscone (**1**) as final products. Three compounds, appearing as major intermediates during the reaction, were isolated by GC. from a half-transformed mixture and could be identified as the unsaturated ketones **19** (*E* and *Z*) and **20** (see below). For product isolation the reaction mixture was cooled to RT., filtered and distilled using first a *Vigreux*-column (solvent evaporation) and then a *Fischer* 'spaltrohr' column. Together with ether **18** (3.2 g; b.p. 88–90°/0.1 Torr), 15.1 g of (*R,S*)-muscone (**1**; b.p. 85°/0.1 Torr) was obtained (75%); it had spectra identical with an authentic sample.



A

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2) The unstable by-products of type **A** are thus transformed into the more stable isomer with the endocyclic double bond.

3) The ring junction configuration of the bicyclic ethers **6**, **8**, **10** and **11** is unknown, but there is probably a mixture of isomers.

4) Compound **17** mixed with its isomer, 14-methyl-16-oxabicyclo[10.3.1]hexadec-1-ene, has been prepared by another route [14].

b) *From the saturated ether* **18**[5]). A solution of ether **18** (50 g) in petrol ether (50 ml; b.p. 60–80°) and Pd/C-catalyst (5 g), freshly saturated with H_2, was heated in a 1-l autoclave under N_2 at 260–270°. After 10–14 h the reaction was complete (GC.). After cooling to RT., filtration and evaporation the residue upon distillation (0.1 Torr) gave 45 g (90%) of almost pure (*R,S*)-muscone (**1**).

9. 3-Methylcyclotridecanone (34). – A solution of bicyclic ether **12** (20.6 g) in xylene (100 ml) was treated as described under 8a) at 135° with H_2-activated Pd/C-catalyst (1 g) in a stream of *ca.* 30 ml of H_2/min. After 10 h the reaction was complete (GC.). Work-up as described previously (filtration, evaporation of solvent, *Vigreux*-distillation at 0.1 Torr) gave 0.8 g of a lower distilling fraction and 1.2 g of the practically pure ketone **34**. – IR.: 1710 (C=O). – ^{1}H-NMR.: 0.98 (*d*, J=7, 3 H); 1.3 (*m*, 18 H); 1.4–1.9 (*m*, 1 H); 2.0–2.8 (*m*, 4 H). – MS.: 210 (M^+, 25), 195 (7), 152 (14), 135 (8), 125 (22), 111 (18), 97 (48), 85 (85), 69 (75), 55 (100), 41 (90); (*cf.* lit. [16]).

10. Dehydromuscones 19 (*E* and *Z*) and 20. – Isolated by preparative GC. *(Carbowax)* from the reaction mixture described under 8a) after halftransformation **19** and **20** had a higher retention time on these columns than muscone.

3-Methylcyclopentadec-3-en-1-one (**19**; 2:1 mixture of (*E*) and (*Z*) isomer). – IR.: 1710 (C=O). – ^{1}H-NMR.: 1.25–1.4 (*m*, 18 H); 1.65 (*s*, CH_3 for (*E*)-**19**); 1.98 (*d*, J=2, CH_3 for (*Z*)-**19**); 3.02 (*s*, CH_2 for (*E*)-**19**); 3.15 (*s*, CH_2 for (*Z*)-**19**); 5.2–5.4 (*m*, 1 H). – MS.: 236 (M^+, 45), 221 (15), 137 (12), 109 (55), 95 (90), 82 (75), 69 (75), 55 (100), 41 (99); (cf. lit. [10] [16]).

3-Methylcyclopentadec-2-en-1-one (**20**). – IR.: 1605, 1680 (CO=CH). – ^{1}H-NMR.: 1.25–1.4 (*m*, 20 H); 2.18 (*d*, J=2, 3 H); 2.15–2.5 (*m*, 4 H); 6.15 (*m*, 1 H). – MS.: 236 (M^+, 25), 221 (8), 123 (15), 109 (35), 98 (85), 95 (95), 83 (85), 69 (50), 55 (75), 41 (100); (*cf.* lit. [9] [16]).

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[5]) Results obtained in collaboration with Dr. *W. Schenk, Firmenich SA*.