261. Construction of Large Carbocyclic Rings by *Ireland-Claisen* Rearrangement of *O*-Silylated Lactone Enolates: Synthesis of (±)-Muscone [1]

by **Rudolf K. Brunner** and **Hans-Jürg Borschberg***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, Universitätsstrasse 16, CH-8092 Zürich

(22. IX. 83)

Summary

(±)-Muscone (**5**) has been synthesized from methyl 13-(chloroformyl)tridecanoate (**6**) in nine steps in an overall yield of 24%. The key steps involve an efficient transformation of the readily accessible 14-hydroxy-15-methyl-15-hexadecenoic acid (**9**) into the tetradecanolide **1** and a subsequent *Ireland-Claisen* rearrangement of its triethylsilyl enolate **2** to a 8:1-mixture of the stereoisomeric 15-membered carbocycles **4** and **10** *(Scheme 4)*.

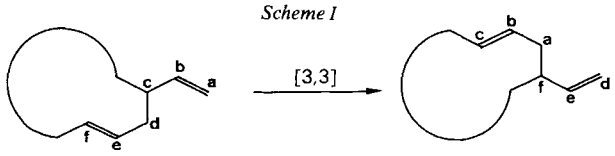
The increasing number of isolated natural products containing large carbocycles has led to a considerable synthetic interest in the construction of such systems. Most of the published approaches, however, suffer from certain limitations such as *a*) harsh reaction conditions incompatible with the presence of sensitive functional groups (*cf. e.g.* the classical acyloin condensation), *b*) lack of stereoselectivity (*cf. e.g. Corey's* Ni-catalyzed coupling of bis-allylic dibromides [2] or his intramolecular *Diels-Alder* methodology [3]), and *c*) the highly demanding stereoselective construction of the bi- or polycyclic precursors required for the fragmentation approach (see *e.g.* [4] and references therein).

One way to circumvent some of these problems is to use [3,3]-sigmatropic rearrangements of 1,5-diene units grafted on to an existing macrocyclic skeleton. Depending upon the location of the double bonds involved, three topologically different situations arise: *a*) when none of them forms part of the cyclic perimeter, ring expansion by four atoms is observed (*cf. e.g.* [5] [6]), *b*) a four-atom ring contraction occurs when both double bonds are incorporated in the ring, *c*) when one of them is endocyclic a [3,3]-sigmatropic shift leads to a rearranged product of the same ring size as the starting material (the oxy-*Cope* version of this process has been studied extensively by *Thies & Bolesta*, see [7] and references therein).

[1]) Presented in preliminary form at the 'Herbstversammlung der Schweizerischen Chemischen Gesellschaft', October 15, 1982 in Bern. Taken in part from the doctoral thesis of *R.K.B.* [1].

We were attracted by the prospect of applying the general scheme below to the conversion of heterocyclic into carbocyclic systems. This can, in principle, be accomplished by placing a heteroatom in position **d** or **e** in compounds of the general formula **I** *(Scheme 1)*[2]).

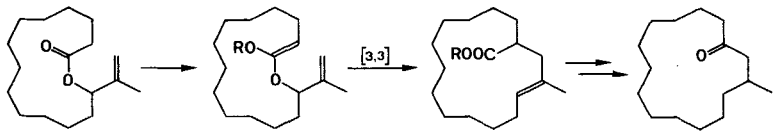
Scheme 1



I **II**

We focused our interest on the possible placement of an O-atom in position **d** *(Scheme 1)* mainly because macrocyclic lactones have become readily available (for reviews see [9]) and the pioneering work of *Ireland et al.* [10] has shown that *Claisen* rearrangement of allyl silyloxyvinyl ethers proceed in high yield and under very mild conditions (mostly at or below room temperature). To check the feasibility of this approach we chose the 15-membered carbocycle (±)-muscone (**5**) *(Scheme 2)* as our synthetic target[3])[4]).

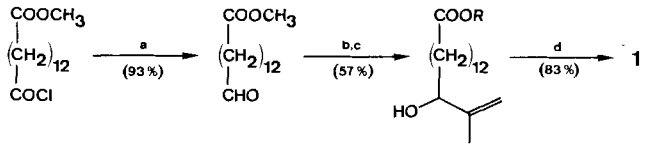
Scheme 2



1 **2** R = $SiEt_3$ **3** R = $SiEt_3$ **4** R = H **5**

The lactone **1** required for the synthesis of **5** *via* **2** and **3** was prepared in a straightforward manner as shown in *Scheme 3*.

Scheme 3



6 **7** **8** R = CH_3 **9** R = H

Reagents: a) H_2, Pd/C, 2,6-dimethylpyridine, b) isopropenylmagnesium bromide, THF, c) KOH, CH_3OH/H_2O, d) Ph_3P, 2,2′-dipyridyl disulfide, $AgClO_4$, CH_3CN.

---

[2]) A ring-contracting version of this approach has been explored independently by *Funk et al.* [8] who transformed a ten-membered lactone with an endocyclic double bond into a cyclohexane derivative *via* an *Ireland-Claisen* rearrangement of its *O*-trimethylsilyl-enolate.

[3]) A similar scheme has been investigated independently by *Danishefsky et al.* [11] who concentrated their interest on the *Ireland-Claisen* rearrangement of allylic 5-, 6- and 7-membered lactones. Their findings culminated in an elegant synthesis of (±)-widdrol [12].

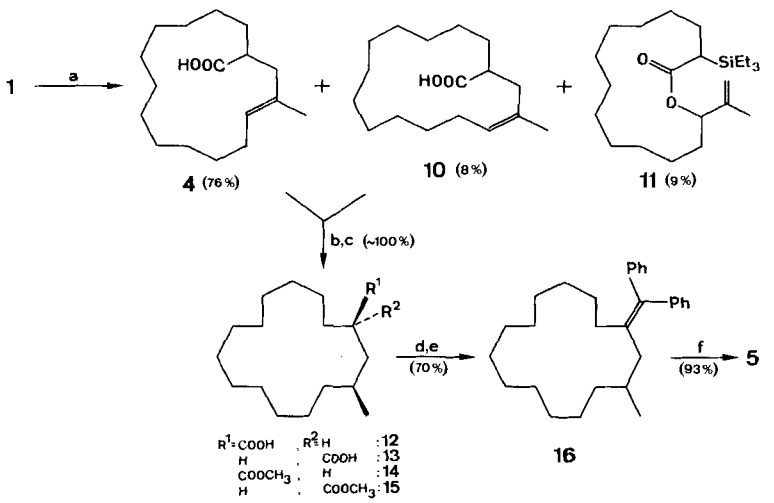
[4]) For a recent compilation of existing syntheses of this natural product see [1].

Rosenmund reduction (modified method [13]) of the readily available methyl 13-(chloroformyl)tridecanoate (**6**) [14] led to the aldehyde **7**[5]), which was treated with the *Grignard* reagent prepared from 2-bromopropene to give the allylic alcohol **8.** The free acid **9** was obtained by hydrolysis with aqueous base in an overall yield of 53%. Lactonization of this hydroxy acid proceeded smoothly[6]) under the reaction conditions worked out by *Gerlach et al.* [16] resulting in reproducible 80–88% yields of purified lactone **1** *(Scheme 2)*.

The *Ireland-Claisen* rearrangement was achieved by treating the Li-enolate of lactone **1** (prepared by reaction of **1** with a slight excess of lithium cyclohexylisopropylamide in THF) with triethylsilyl trifluoromethylsulfonate followed by gentle heating overnight. Work up with aqueous acid gave an acidic fraction containing a mixture of two products in the ratio of *ca.* 8:1 with spectroscopic properties consistent with the expected carbocyclic structures **4** and **10** *(Scheme 4)*, respectively. The IR, ^{1}H-NMR and mass spectra of the two isomers are very similar; their ^{13}C-NMR data, however, show substantial differences. The chemical shifts of their corresponding CH_3-groups (15.4 ppm for the major *vs.* 23.8 ppm for the minor isomer) differ considerably and thus allow an unambiguous assignment of the (*E*)-configuration to the main (**4**) and of the (*Z*)-configuration to the minor (**10**) component [17]. The stereoselectivity of this sigmatropic rearrangement is disappointingly low when compared to acyclic systems [10a]; this is, however, of no consequence for our synthesis of (±)-muscone (**5**).

The neutral part (*ca.* 10% of the above crude reaction mixture) consisted essentially of a single product which, according to its spectroscopic properties, must be the

Scheme 4



Reagents: a) Li *N*-cyclohexylisopropylamide, THF, $CF_3SO_2OSiEt_3$, 16 h, 65°, b) H_2, Pt, EtOH, c) CH_2N_2, Et_2O, d) PhMgBr, Et_2O, e) H^+, CCl_4/reflux/30 min, f) RuO_2, $NaIO_4$, H_2O/CCl_4.

---

[5]) This compound has already been obtained by *Ruzicka et al.* [15] by a different route.

[6]) In view of the numerous published procedures for effecting macrolactonization *via* carboxyl activation [9] it is surprising that they have been used only seldom in connection with allylic alcohols. There is, to our knowledge, only one recent report by *Funk et al.* [8] concerning the cyclization of several long-chain hydroxy acids containing primary allylic OH-groups.

C-triethylsilylated lactone **11**. The presence of only 23 signals in its wide-band ^{1}H-decoupled ^{13}C-NMR spectrum shows that this compound is a single stereoisomer. It is not clear, however, which of the two possible diastereomeric formulae should be assigned to the isolated product.

The further transformation of the mixture of unsaturated acids **4** and **10** into (±)-muscone (**5**) was straightforward: hydrogenation with *Adam's* catalyst followed by esterification with etheral CH_2N_2 led to a 3:1 mixture of the two diastereomeric esters **14** and **15** *(Scheme 4)*. These were subjected to a *Barbier-Wieland* degradation modified according to the procedure of *Stork et al.* [18]. The purified product **5** (obtained in 65% yield) proved to be identical (DC, GLC, IR, ^{1}H-NMR) with a racemic reference sample kindly provided by *Firmenich SA* (Geneva).

The conclusion that can be drawn from the linear nine-step synthesis of (±)-muscone (**5**) described here, which proceeds with an overall yield of 24% (average yield per step: 85.3%) and thus represents an efficient synthesis for this compound, is that the high yields and the remarkably mild reaction conditions for the key steps **9**→**1**→**4** *(Scheme 3 and 4)* suggest that this approach to macrocycles might prove useful for the construction of more elaborate natural products containing large rings.

We are grateful to Prof. Dr. *D. Arigoni* for his support of this work.

Experimental Part

General. Abbreviations: RV, rotatory evaporator; r.t., room temperature; h.v., high vacuum; TLC, thin layer chromatography. Solvents and reagents: THF: *Fluka puriss, p.a.*, redistilled from K; CH_3CN, benzene and CCl_4: all *Fluka, puriss p.a.*, redistilled from P_2O_5; Mg: *Ventron m4 N, 'chips for Grignard'*; 2,2'-dipyridyl disulfide: *Fluka, puriss, p.a.*, recrystallized from $CHCl_3$/hexane. Melting points (m.p.) were determined on a *Büchi* melting point apparatus and are not corrected. TLC: precoated TLC, plates *'silica gel 60 F254' (Merck)* were used. For medium-pressure column chromatography [19] *'silica gel 60'* (0.04–0.063 mm, *Merck*) was used. Gas chromatography (GLC): *Fractovap 2150 (Carlo Erba)*; capillary columns and temp. as specified; H_2 as carrier gas. UV: *Perkin-Elmer PE402;* λ_{max} in nm; log ε in parentheses. IR: *Perkin-Elmer PE297*; 2–3% solutions in CCl_4; cm^{-1}; relative intensities, where *s*, *m* and *w* denote strong, medium and weak, respectively. ^{1}H-NMR: *Varian HA-100* (100 MHz) or *Bruker WM-300* (300.13 MHz); in $CDCl_3$; TMS as internal standard; chemical shifts in ppm (δ-values); *s*, *d*, *t*, *q* and *m* denote singlet, doublet, *etc.*; coupling constants *J* in Hz. ^{13}C-NMR: *Varian XL-100* (25.2 MHz) or *Bruker WM-300* (75.4 MHz); in $CDCl_3$ with TMS as internal standard; chemical shifts in ppm as determined by wide-band ^{1}H-decoupling; *s*, *d*, *t* and *q* denote singlet doublet, *etc.* as displayed in the off-resonance ^{1}H-decoupled spectrum. MS: *Hitachi-Perkin-Elmer RMU-6A;* relative peak intensities in % of the base peak (= 100%); the samples were introduced indirectly and ionized at 70 eV/120–200°.

Methyl 13-formyltridecanoate (**7**) [15]. To a well-agitated suspension of 353 mg Pd/C (*Fluka, puriss*, 10% Pd) in 100 ml of dry THF were added 3.032 g (28.3 mmol) 2,6-lutidine *(Fluka, purum)*. After saturation with H_2 at atmospheric pressure in a hydrogenation apparatus *(Kühner-Roche)* a solution of 9.693 g (33.3 mmol) *methyl 13-chloroformyltridecanoate* (**6**) [14] in 10 ml THF was added. When the H_2-uptake had stopped (*ca.* 3 h at r.t.) the catalyst was removed by filtration under N_2. The filtrate was evaporated (RV) and extracted with Et_2O (3 × 100 ml). Filtration and evaporation led to an oily residue which was distilled in a *Büchi Kugelrohr* apparatus (120°/0.01 Torr to yield 7.95 g (31 mmol, 93%) of **7**. The distillate solidified on cooling, m.p. 46–48°. IR: 2715 *w*, 1744 *s*. ^{1}H-NMR (100 MHz): 9.74 (*t*, *J* = 1.7, 1H); 3.62 (*s*, 3H); 2.39 (*dt*, *J* = 1.7 and 7, 2H); 2.29 (*t*, *J* = 7, 2H); 1.8–1.1 (*m*, 20H). MS: 185 (13; $M^+ - 71$), 166 (14), 157 (18), 125 (32), 87 (46), 74 (100).

Methyl 14-hydroxy-15-methyl-15-hexadecenoate (**8**). A *Grignard* reagent, prepared from 1.289 g (53 mmol) Mg and 6.412 g (53 mmol) 2-bromopropene *(Fluka, purum)* in 50 ml THF was added slowly *via* a stainless steel double-ended needle *(Aldrich)* to a well-stirred solution of 12.36 g (48.2 mmol) aldehyde **7** in 100 ml THF under Ar at r.t. After stirring for 4 h at r.t. 50 ml of a sat. aq. NH_4Cl-solution were added. Partition between Et_2O and H_2O, followed by drying the combined org. extracts over $MgSO_4$, filtration and evaporation resulted in 13.58 g of crude

product. Chromatography (hexane/Et_2O 2:3) led to 10.38 g (34.8 mmol; 72.2% yield) of crystalline **8**. M.p. 39°. IR: 3620*w*, 3080*w*, 1746*s*, 904*m*. ^{1}H-NMR: 4.90 (*m*, 1H); 4.80 (*m*, 1H); 4.03 (*t*, J = 6.2, 1H); 3.62 (*s*, 3H); 2.28 (*t*, J = 7, 2H); 1.70 (*d*, J = 1, 3H); 1.7–1.1 (*m*, 23H, including 1.61 (br. *s*, 1H, exchangeable with D_2O)). MS: 298 (1; M^+), 280 (2), 266 (12), 228 (17), 143 (17), 98 (33), 87 (79), 71 (100).

$C_{18}H_{34}O_3$ (298.47) Calc. C 72.44 H 11.48% Found C 72.42 H 11.55%

14-Hydroxy-15-methyl-15-hexadecenoic Acid (**9**). The ester **8** (5.97 g, 20 mmol) was dissolved in a mixture of 50 ml MeOH and 50 ml aq. 2N KOH. After a reflux period of 90 min the mixture was worked up with Et_2O/aq. phosphate buffer (pH 4) to give 6 g of crude material which was purified by chromatography (hexane/Et_2O 1:3). Yield: 4.50 g (15.82 mmol; 79.1%) of crystalline **9**. M.p. 66–68°. IR: 3620*w*, 3500–2300 *br. m*, 1716*s*, 904*m*. 1H-NMR: 6.1–5.3 (br. *s*, 2H, exchangeable with D_2O); 4.90 (*m*, 1H); 4.80 (*m*, 1H); 4.04 (*t*, J = 7, 1H); 2.32 (*t*, J = 7, 2H); 1.9–1.1 (*m*, 25H, including 1.70 (*d*, J = 1, 3H)). MS: 266 (10, M^+ – 18), 233 (4), 181 (4), 82 (27), 71 (100).

$C_{17}H_{32}O_3$ (284.44) Calc. C 71.79 H 11.34% Found C 71.66 H 11.52%

14-Isopropenyl-14-tetradecanolide (**5**). A mixture of 1.555 g (6.98 mmol) 2,2'-dipyridyl disulfide, 1.91 g (7.28 mmol) Ph_3P (*Fluka, puriss, p.a.*) and 1.656 g (5.82 mmol) of **9** was dried overnight at r.t./10^{-2} Torr. After addition of 4 ml benzene the mixture was allowed to stand at r.t. for 1 h. Then it was diluted with 20 ml of dry CH_3CN and added subsequently within 4 h to a mixture of 35 ml 0.5 M $AgClO_4$ (*Fluka, puriss p.a.*) in toluene [16] and 400 ml of CH_3CN (motordrive syringe) which was kept stirring at 65° with exclusion of O_2 and light. After completion of the addition the mixture was agitated at the same temp. for an additional 30 min. Then most of the solvent was removed (RV) and the residue was treated with 100 ml aq. 1N NaCN and extracted with benzene (3 × 100 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated down to a volume of *ca.* 3 ml. Chromatography (benzene) furnished 1.287 g (4.83 mmol; 83% yield) of pure **1** as a colorless liquid. IR: 3080*w*, 1738*s*, 902*m*. ^{1}H-NMR (100 MHz): 5.20 (*t*, J = 6.5, 1H); 4.90 (*m*, 1H); 4.80 (*m*, 1H); 2.46–2.06 (*m*, 2H); 1.9–1.1 (*m*, 25H, including 1.70 (*d*, J = 1, 3H)). ^{13}C-NMR (25.2 MHz): 173.0 (*s*); 144.3 (*s*); 111.2 (*t*); 76.3 (*d*); 33.9 (*t*); 33.4 (*t*); 27.8 (*t*); 27.0 (*t*); 26.9 (*t*); 26.7 (*t*); 26.6 (*t*); 26.4 (*t*); 26.2 (*t*); 25.0 (*t*); 24.6 (*t*); 24.4 (*t*); 18.8 (*q*). MS: 266 (16, M^+), 223 (4), 210 (4), 195 (5), 109 (16), 95 (48), 83 (20), 82 (100).

$C_{17}H_{30}O_2$ (266.42) Calc. C 76.64 H 11.36% Found C 76.47 H 10.62%

Ireland-Claisen *Rearrangement of Lactone* **1**. To 0.404 ml (2.41 mmol) *N*-cyclohexylisopropylamine (*Fluka, pract.*, redistilled from CaH_2) in 5 ml THF were added 1.6 ml 1.5N BuLi in hexane (*EGA*) at 0° under Ar. After 15 min this mixture was cooled to – 78° and then combined with a solution of 583 mg (2.19 mmol) of **1** in 5 ml THF. After 15 min 0.338 ml HMPT (*Fluka, purum*, redistilled from CaH_2 under h.v.) and 0.545 ml (2.41 mmol) triethylsilyl trifluoromethanesulfonate (*Fluka, purum*) were added at – 78°. The resulting mixture was allowed to warm up (r.t.) within 1 h and was then heated at reflux for 16 h. After cooling to r.t. it was worked up by addition of crushed ice and 0.5 M H_2SO_4 until pH 2 was reached [7]. Partition between Et_2O and aq. base resulted in a neutral fraction (90 mg), from which 71.5 mg (0.27 mmol; 9% yield) of the oily *C*-silylated compound **11** were isolated by chromatography (hexane/Et_2O 9:1) [8]. IR: 3080*w*, 1710*s*, 1652*w*, 912*m*. ^{1}H-NMR (100 MHz): 5.34–5.16 (*m*, 1H); 4.97 (*m*, 1H); 4.82 (*m*, 1H); 1.72 (*d*, J = 1, 3H); 1.7–1.1 (*m*, 23H); 1.05–0.85 (*m*, 9H); 0.75–0.55 (*m*, 6H). ^{13}C-NMR (25.2 MHz): 174.1 (*s*); 144.0 (*s*); 112.9 (*t*); 76.8 (*d*); 37.0 (*d*); 34.0 (*t*); 32.2 (*t*); 31.0 (*t*); 27.4 (*t*); 27.3 (*t*); 27.0 (*t*); 26.6 (*t*); 26.2 (*t*); 25.0 (*t*); 24.4 (*t*); 24.2 (*t*); 18.4 (*q*); 7.3 (3*q*); 2.7 (3*t*). MS: 380 (9, M^+), 351 (100), 159 (20), 157 (37), 115 (44), 103 (94), 87 (68).

The basic extracts of the workup described above were acidified (pH 3) and extracted with $CHCl_3$ (3 × 150 ml) to give 520 mg of crude acidic material. Chromatography (hexane/AcOEt 7:3) resulted in 445 mg (1.67 mmol; 76.2% yield) of pure (E)-*3-methyl-3-cyclopentadecenoic acid* (**4**). IR: 3500–2300 br. *m*, 1707*s*. ^{1}H-NMR (100 MHz): 5.18 (*t*, J = 7.5, 1H); 2.64–1.1 (*m*, 28H, including 1.59 (*s*, 3H)). ^{13}C-NMR (25.2 MHz): 183.5 (*s*); 132.3 (*s*); 128.2 (*d*); 42.9 (*d*); 41.8 (*t*); 29.2 (*t*); 29.0 (*t*); 27.0 (4*t*); 26.8 (2*t*); 26.5 (*t*); 25.5 (*t*); 25.2 (*t*); 15.9 (*q*). MS: 266 (71; M^+), 248 (8), 220 (11), 123 (19), 121 (32), 119 (96), 117 (100), 82 (89).

$C_{17}H_{30}O_2$ (266.42) Calc. C 76.64 H 11.35% Found C 76.51 H 11.34%

A roughly equimolar mixture of **4** and (*Z*)-isomer **10** could be isolated from the chromatogramme above when the first fraction containing **4** was processed separately. A ^{13}C-NMR spectrum (25.2 MHz) of this mixture showed

---

[7]) A GLC analysis (*SE54*, 155°) of an aliquot of the org. layer, esterified with etheral CH_2N_2, revealed the presence of three main components: **4**, (78%), **10** (11%) and **11** (11%) (of unknown stereochemistry).

[8]) Since the spectra showed the presence of several minor impurities no combustion analysis was attempted.

additional bands which were not present in the spectrum of pure **4**: 132.0 (*s*); 128.8 (*d*); 113.4 (*d*); 33.9 (*t*); 30.4 (*t*); 28.5 (*t*); 26.2 (*t*); 25.9 (*t*); 25.3 (*t*); 23.8 (*q*). (The peaks in the region between 28.3 and 26.5 ppm were not sufficiently well-resolved to permit an unambiguous assignment).

Hydrogenation of **4**. PtO_2 (5 mg, *Engelhard*, 82.3% Pt) suspended in 5 ml EtOH containing 0.01 ml AcOH was reduced with H_2 at atmospheric pressure in a hydrogenation apparatus. Then 426 mg (1.6 mmol) of the unsaturated acid **4** were added. When the H_2-uptake had stopped, the catalyst was removed by filtration and the filtrate was evaporated to give 429 mg (1.6 mmol) of a 3:1 mixture[9]) of the two saturated diastereomeric acids **12** and **13**. IR: 3500–2300 br. *m*; 1710 *s*. ^{1}H-NMR: 2.43 (*m*, 1H); 1.8–1.1 (*m*, 27H); 0.88 (*d*, $J = 6$, 3H). MS: 268 (56; M^+), 250 (20), 114 (38), 113 (32), 97 (34), 69 (59), 55 (100).

$C_{17}H_{32}O_2$ (268.43) Calc. C 76.06 H 12.02% Found C 75.91 H 11.98%

1-(Diphenylmethylidene)-3-methylcyclopentadecane (**16**). 3-Methylcyclopentadecanoic acid (537 mg, 2 mmol) (mixture of diastereomers **12** and **13**) was dissolved in 15 ml Et_2O and treated with a slight excess of freshly distilled etheral CH_2N_2 during 10 min at r. t. After removal of solvent and excess reagent the oily residue was dissolved in 3 ml of dry Et_2O and added to 0.01 mol phenylmagnesium bromide in 20 ml Et_2O. The resulting solution was stirred overnight at r. t. and then heated at reflux for an additional 7 h. Workup with 2 N H_2SO_4 gave 934 mg of a colorless oil which was dissolved in 10 ml CCl_4 together with 10 mg mesitylenesulfonic acid dihydrate (*Fluka, purum*) and refluxed for 30 min. Chromatography (hexane) of the evaporated mixture furnished 542 mg (1.395 mmol; 69.7% yield based on unsaturated acid **4**) of crystalline **16**. A sample which had been recrystallized three times from Et_2O/MeOH had m.p. 91.5–92°. UV (95% EtOH): max. 245 (4.04). IR: 3080 *w*, 3058 *w*, 3025 *w*, 2930 *s*, 2875 *s*, 1597 *w*, 697 *s*. ^{1}H-NMR (100 MHz): 7.3–7.0 (*m*, 10H); 2.3–1.0 (*m*, 27H); 0.76 (*d*, $J = 6.5$, 3H). ^{13}C-NMR (25.2 MHz): 143.8 (*s*); 139.1 (*s*); 138.5 (2*s*); 129.7 (2*d*); 129.3 (2*d*); 127.9 (4*d*); 125.9 (2*d*); 38.4 (*t*); 36.3 (*t*); 31.2 (*t*); 29.5 (*d*); 27.9 (*t*); 27.0 (2*t*); 26.8 (2*t*); 26.7 (4*t*); 25.4 (*t*), 19.8 (*q*). MS: 388 (100; M^+), 206 (25), 205 (77), 193 (17), 192 (21), 191 (11), 180 (12), 105 (29), 91 (28).

$C_{29}H_{40}$ (388.64) Calc. C 89.63 H 10.37% Found C 89.61 H 10.24%

(±)-Muscone (**5**). To a solution of 1.71 g (8 mmol) $NaIO_4$ (*Fluka, puriss, p.a.*) in 40 ml H_2O were added 20 mg (0.15 mmol) RuO_2 (*Engelhard*, 54.7% Ru) and then a solution of 389 mg (1 mmol) of **16** in 30 ml CCl_4 at r. t. The vigorously stirred mixture turned from black to yellow after *ca.* 70 min. The org. layer was separated and combined with two CH_2Cl_2-extracts of the aq. phase. Evaporation at normal pressure to a volume of *ca.* 3 ml was followed by chromatography (Et_2O/pentane 1:6) to give 221 mg (0.93 mmol; 93% yield) of pure **5**, identical (TLC, GLC, IR, ^{1}H-NMR) with an authentic racemic sample kindly provided by *Firmenich SA* (Geneva).

REFERENCES

[1] *R.K. Brunner*, Dissertation ETH Zürich, No. 7256 (1983).

[2] a) *E.J. Corey & E.K.W. Wat*, J. Am. Chem. Soc. *89*, 2757 (1967); b) *E.J. Corey & E. Hamanaka*, J. Am. Chem. Soc. *89*, 2758 (1967); c) *W.G. Dauben, G.H. Beasley, M.D. Broadhurst, B. Muller, D.J. Peppard, P. Pesnelle & C. Suter*, J. Am. Chem. Soc *97*, 4973 (1975); d) *L. Crombie, G. Kneen & G. Pattenden*, J. Chem. Soc., Chem. Commun. *1976*, 66.

[3] *E.J. Corey & M. Petrzilka*, Tetrahedron Lett. *1975*, 2575.

[4] a) *P.S. Wharton & G.A. Hiegel*, J. Org. Chem. *30*, 3254 (1965); b) *J.A. Marshall*, Synthesis *1971*, 229; c) *D. Sternbach, M. Shibuya, F. Jaisli, M. Bonetti & A. Eschenmoser*, Angew. Chem. *91*, 670 (1979).

[5] *R.C. Cookson & P. Singh*, J. Chem. Soc. (C) *1971*, 1477.

[6] *K. Gubernator & R. Gleiter*, Angew. Chem. *94*, 710 (1982).

[7] *R.W. Thies & R.E. Bolesta*, J. Org. Chem. *41*, 1233 (1976).

[8] *M.M. Abelmann, R.L. Funk & J.D. Munger, Jr.*, J. Am. Chem. Soc. *104*, 4030 (1982).

[9] a) *S. Masamume, G.S. Bates & J.W. Corcoran*, Angew. Chem. *89*, 602 (1977); b) *K.C. Nicolaou*, Tetrahedron *33*, 683 (1977); c) *T.G. Back*, Tetrahedron *33*, 3041 (1977).

[10] a) *R.E. Ireland & R.H. Mueller*, J. Am. Chem. Soc. *94*, 5897 (1972); b) *R.E. Ireland, R.H. Mueller & A.K. Willard*, J. Am. Chem. Soc. *98*, 2868 (1976).

---

[9]) According to a GLC analysis (*PL64*, 180°) of the corresponding methyl esters **14** and **15**. It is not known whether the major isomer has structure **12** or **13**.

[11] *S. Danishefsky, R.L. Funk & J.F. Kerwin, Jr.*, J. Am. Chem. Soc. *102*, 6889 (1980).
[12] *S. Danishefsky & K. Tsuzuki*, J. Am. Chem. Soc. *102*, 6891 (1980).
[13] *A.W. Burgstahler, L.O. Weigel & C.G. Shaefer*, Synthesis *1976*, 167.
[14] *Å. Ellin, S. Orrenius, Å. Pilotti & C.-G. Swahn*, Arch. Biochem. Biophys. *158*, 597 (1973).
[15] *L. Ruzicka, M. Stoll, W. Scherrer, H. Schinz & C.F. Seidel*, Helv. Chim. Acta *15*, 1459 (1932).
[16] *H. Gerlach, K. Oertle & A. Thalmann*, Helv. Chim. Acta *59*, 755 (1976).
[17] a) *D.F. Wiemer, J. Meinwald, G.D. Prestwich & I. Miura*, J. Org. Chem. *44*, 3950 (1979); b) *F. Miyamoto, H. Naoki, T. Takomoto & Y. Naya*, Tetrahedron *35*, 1913 (1979).
[18] *G. Stork, A. Meisels & J.E. Davies*, J. Am. Chem. Soc. *85*, 3419 (1963).
[19] *W.C. Still, M. Cahn & A. Mitra*, J. Org. Chem. *43*, 2923 (1978).