269. Macrocycles by Olefination of Dialdehydes with 1,3-Bis(dimethylphosphono)-2-propanone

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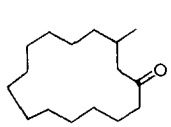
(27.IX.79)

Summary

Conjugated cyclic divinyl ketones containing fifteen and seventeen membered rings have been prepared in a single step by condensation of 1,3-bis(dimethylphosphono)-2-propanone (**10**) with the dialdehydes **14**, **17**, **20**, and **42** in the presence of hydrogencarbonate in aqueous *t*-butyl alcohol at reflux without using high dilution techniques. The more highly unsaturated aldehydes give better yields and ketones **34** and **36**, or mixtures of the two, were transformed to muscone (**1**) and Exaltone® by standard procedures. Civetone (**2**) was prepared by hydrogenation of **43** in pyridine solution. Dienone **29** appears to be the first α,β-unsaturated ketone in which one of the β-vinyl proton resonates at higher field than the corresponding α-proton.

Since the recognition of muscone (**1**) *(Moschus moschiferus)* and civetone (**2**) *(Viverra zibetha)* as macrocyclic ketones, by *Ruzicka* in 1926, much effort has been expended on the discovery and development of industrially practicable syntheses of these, and related macrocycles, which remain critical raw materials in the hands of creative perfumers. Traditionally, macrocyclic ketones were prepared by cyclization of α,ω-bifunctional, saturated aliphatic precursors [1]. More recently, the readily available and inexpensive cyclododecanone has become an attractive starting material. Among the several newly developed methods for ring expansion, *via* bicyclic intermediates, the epoxyketone tosylhydrazone fragmentation deserves special mention, because it is practiced on an industrial scale [2].



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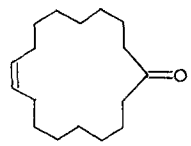

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While surveying existing methods [3] [4] for the synthesis of macrocyclic ketones we noticed that no attempts seem to have been made to put the 'rigid group principle' [5] to use in this area. This appeared to be a serious

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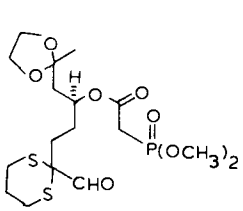
omission considering past successes in the preparation of highly unsaturated macrocycles, such as salicylides, phthalocyanins, annulenes, porphyrins and corrins.

We have explored a new route to cyclopentadecanone (Exaltone®), muscone (**1**) and civetone (**2**) which begins with the elaboration of polyunsatured cyclic ketones, and terminates with the catalytic hydrogenation of some, or where needed, all of the olefinic bonds. The *Horner-Emmons* modification of the *Wittig* reaction [6] was chosen for irreversible cycloolefination. This reaction was used previously to prepare the unsaturated 16-membered dilactone **4** from phosphonate **3** and sodium hydride in a highly dilute tetrahydrofuran solution [7]. Somewhat earlier cyclododecenone **6** was prepared, although in only 20–30% yield, by cyclization of the phosphonium ylide **5** [8].



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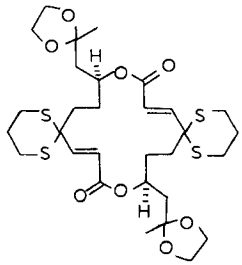

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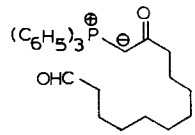

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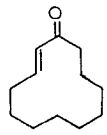

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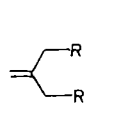
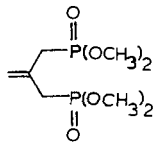
Of the several phosphonates considered in the synthetic planning the ketodiphosphonate **10** was selected because condensation with α,ω-dicarbonyl compounds should lead to $\alpha,\beta,\alpha',\beta'$-diunsaturated cyclic ketones in a single operation. Indeed, this particular diphosphonate **10** had been used successfully, not for the preparation of cyclic ketones, but that of aliphatic dienones by condensation with aldehydes and ketones in the presence of sodium hydride [9]. A five step procedure starting with 2,3-dibromopropene gave the ketodiphosphonate **10** in low yield [9] [10], and two more efficient methods for its preparation have now been developed. The crystalline diiodide **7** [11] easily synthesized from methallyl chloride in two known operations, underwent a smooth *Arbusov* reaction, when heated with trimethyl phosphite, to afford the diphosphonate **9** in 92% yield[1]). Oxidation of the olefin **9** to the ketone **10** was best accomplished by ozonization in methanol at $-20°$, followed by reduction of intermediates with trimethyl phosphite at room temperature. Parenthetically, aqueous work-up had to be avoided, and the crude product was submitted to vacuum distillation giving the water-soluble ketodiphosphonate **10** in 87% yield.

An alternate synthesis starts with the condensation of methallyl chloride with trimethyl phosphite. This reaction, because of the low boiling points of both components, was very slow in the absence of a catalytic amount of nickel bromide [13], but in its presence it proceeded rapidly at 87–140° affording phosphonate **11** in 66% yield. Bromination of **11** with *N*-bromosuccinimide followed by condensation of the crude bromide **12** with trimethyl phosphite furnished the

[1]) According to a German patent claim the less expensive dichloride **8** serves equally well in the preparation of **9** [12].



7 R = I
8 R = Cl



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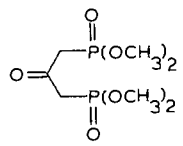

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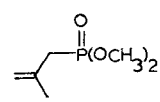

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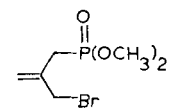

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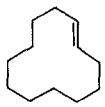
diphosphonate **9**, which was separated from lower boiling by-products by rapid distillation under reduced pressure. Ozonization produced **10** in 40% overall yield from dimethyl methallylphosphonate.

The now readily available diphosphonate **10** became an even more attractive reagent when it was found that anion formation necessary for olefination could be induced by inexpensive bases such as hydrogencarbonates and carbonates in protic solvents.

1,12-Dodecanedial (**14**), the other structural moiety needed for the projected synthesis of Exaltone®, was prepared by ozonization of cyclododecene (**13**) in methanol/methylene chloride at $-20°$ followed by reduction with trimethyl phosphite. The yield of dialdehyde **14** never exceeded 50%, but when the methanol solution was treated with dimethyl sulfide [14] at room temperature during 18–24 h the tetramethyl diacetal **15** was formed in 88% yield. The partial formation of acetals under these conditions was noted previously [15] and we have now found that methylcyclododecene (**22**) [16], 1,5-cyclooctadiene (**24**), 1,5,9-cyclododecatrienes (**16**), (**19**) and 1-octene (**26**) all gave acetals **23**, **25**, **18**, **21** and **27** in good yields. The mechanisms of these transformations is obscure at present, but experiments that may help to clarify the situation are planned.



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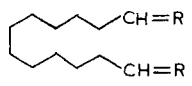
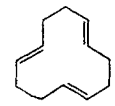


14 R = O
15 R = $(OCH_3)_2$



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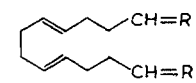
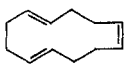


17 R = O
18 R = $(OCH_3)_2$



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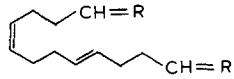
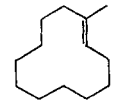


20 R = O
21 R = $(OCH_3)_2$



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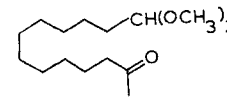

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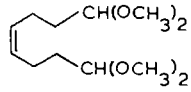

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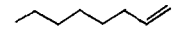

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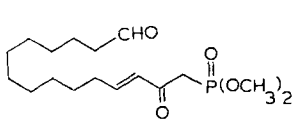
Horner-Emmons condensation of dialdehyde **14** with the diphosphonate in aqueous *t*-butyl alcohol containing potassium hydrogencarbonate at room temperature afforded 42% of the monoolefin **28**, which when heated at reflux in the same solvent-base combination was transformed to a mixture of C_{15}-dienones **29**, **31** (51%), and the C_{30}-tetraenone **30** (5%). Not surprisingly, when the condensation of dialdehyde **14** with diphosphonate **10** was performed at reflux the dienones **29** and **31** were formed in 20–25% yield in a single operation. Individual isomers were isolated by chromatography. The major diastereomer **31** (93%) with (*E*, *E*)-configuration displayed the anticipated spectral properties. The most striking characteristic of the minor isomer **29** (7%) with (*E*, *Z*)-configuration was its 270-MHz-^{1}H-NMR. spectrum ($CDCl_3$): while the α- and β-protons at the (*E*)-double bond gave rise to the anticipated doublet at δ 6.29 ($J = 16$ Hz) and doublet of triplets at δ 6.89 ($J = 7$ and 16 Hz), the olefinic protons at the (*Z*)-double bond appeared as a doublet of doublets at δ 6.23 ($J = 12$ and 2 Hz) and a doublet of triplets at 5.97 ($J = 12$ and 8 Hz). Shielding by the polymethylene chain causes the β-proton of the (*Z*)-double bond to appear at higher field than the α-proton. To our knowledge this situation has no precedent, although a decrease in the difference in chemical shift between the downfield β-proton and the upfield α-proton in going from cyclopentenone to cyclononenone had been noted earlier [17]. Both (*E*, *E*)- **31** and (*E*, *Z*)-dienone **29** are the result of a rate, rather than a thermodynamically controlled process, as demonstrated by the following isomerization experiments. Exposure of the (*E*, *E*)-isomer **31** to *p*-toluenesulfonic acid in refluxing toluene for 2 h gave an equilibrium mixture of dienones containing 8% starting material **31**, 78% of the α,β-β',γ'-dienone **32**, and 14% of the doubly deconjugated ketone **33**. That equilibrium had indeed been reached was verified by converting isomers **32** and **33** to the same mixture. Catalytic reduction of all four isomeric cyclopentadecadienones **29**, **31**, **32** and **33** gave Exaltone®.



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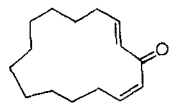

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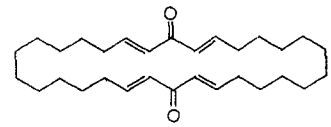

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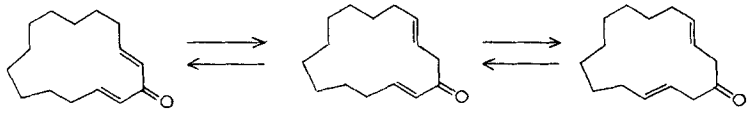
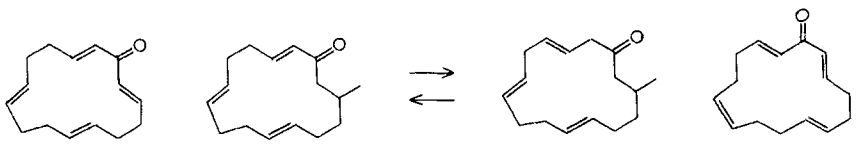


31 **32** **33**

These early experiments on the formation of macrocyclic ketones by *Horner-Emmons* olefination were thus encouraging, and at this stage 1,12-dodecanedial (**14**) was replaced with the less flexible dialdehydes **17** and **20** which according

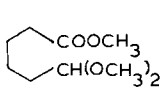
to the 'rigid group principle' were expected to undergo cycloolefination more efficiently. Condensation of the (*E,E*)-isomer **17**, prepared by ozonization of commercial (*E,E,E*)-1,5,9-cyclododecatriene (**16**), was investigated next [18]. When a solution of the dialdehyde **17** and the diphosphonate **10** in 90% *t*-butyl alcohol/water was added with a motor driven syringe through the reflux condenser of a vigorously refluxing 'solution' of 2.5 equivalents of potassium hydrogencarbonate in the same solvent mixture, in the course of 4 h, the all (*E*)-cyclopentadecatetraenone **34**, m.p. 51–53°, was produced reproducibly in 60–65% yield. Examination of the contents of the reaction vessel revealed the presence of two layers. The upper, organic phase containing both unreacted dialdehyde **17** and tetraenone **34** was essentially neutral, thus providing an environment for these substances in which they were protected against unwanted base catalyzed alterations. The lower, aqueous phase, on the other hand, was found to be basic due to the presence of hydrogencarbonate and/or carbonate. Whether the *Horner-Emmons* condensation occurs at the interphase or in the organic layer is not known. Addition of tetraalkylammonium salts as phase transfer catalysts had no effect on the yield of cyclized product. Catalytic reduction of **34** gave Exaltone®, while condensation with lithium dimethylcuprate in ether at −20° afforded trisdehydromuscone **35** in 81% yield. The α,β-unsaturated isomer **35** was found to be more stable than its deconjugated counterpart **37**, and the mixture of isomers obtained by equilibrating either **37** or **35** contained 14% of the former and 86% of the latter. Catalytic hydrogenation was used to transform **35** to racemic muscone (**1**). Cyclopentadecatetraenone **36**, m.p. 34–35°, was available from the (*E,Z*)-dienedial **20** (ex(*E,E,Z*)-1,5,9-cyclododecatriene **19** [18]) and the diphosphonate **10** in 55% yield. In preparative runs mixtures of the dialdehydes **17** and **20** were used routinely, and the overall yields of muscone (**1**) and Exaltone® were the same as those using pure diastereomers. This new approach to these odor principles thus allows their preparation from a common, late intermediate [19].



34 **35** **37** **36**

For the synthesis of civetone (**2**) aldehyde **42** was required, and prepared as followed. Acetal ester **38** [20] available by ozonization of cyclohexanone enolacetate in methanol followed by treatment with dimethyl sulfide and with methyl orthoformate [15] was reduced with lithium aluminum hydride. The resulting alcohol **39** was transformed to the acetylenic acetal **40** by a known high yield sequence [21], involving consecutive treatment with tosyl chloride, sodium iodide and acetylene. The monosubstituted acetylene **40** was alkylated with the same iodoacetal that served in its preparation to afford the disubstituted, symmetrical acetylene **41**. Acetal hydrolysis, followed by condensation of the dialdehyde **42** with the

ketodiphosphonate **10**, using the previously described conditions, gave the C_{17}-cyclic ketone **43** in 56% yield. The synthesis of civetone (**2**) was completed by a highly selective hydrogenation of **43** in pyridine solution over a barium sulfate supported catalyst that furnished pure material in 99% yield. Incidentally, the two C_{15}-ketones **44** and **45** were prepared similarly by hydrogenation of **34** and **36**.



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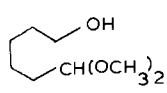

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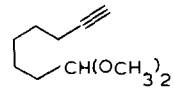

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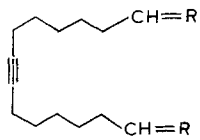
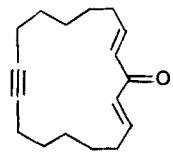


41 R = $(OCH_3)_2$
42 R = O



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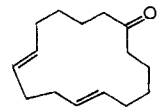

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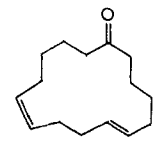
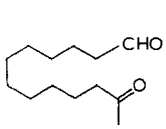
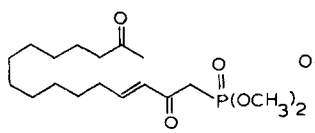


45

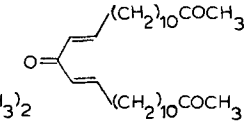
To our surprise, an effort to use ketoaldehyde **46**, prepared by hydrolysis of acetal **23**, as a partner in a *Horner-Emmons* cyclization failed. Condensation with diphosphonate **10** under standard conditions at room temperature afforded the monoolefin **47** (65% yield) that was recovered unchanged after exposure to the same conditions at 80°. The behavior of **47** towards stronger bases was not examined. When performed at 80° the reaction of the diphosphonate **10** with the ketoaldehyde **46** produced the *aliphatic* dienone **48** in 42% yield, but cyclized products were not detected.



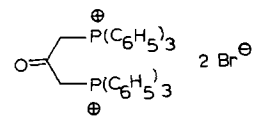
46



47



48



49

In conclusion it should be mentioned that efforts were made to replace the diphosphonate **10** with the bis(phosphonium)bromide **49**. Although the corresponding bis-phosphorane has been prepared [22], and condensed successfully with carbonyl compounds, we failed to isolate cyclic products from its condensation with dialdehyde **14**.

We are indebted to *Firmenich SA* Geneva for generous financial support of this investigation. Dr. *G. Ohloff*, Director of Research, deserves special thanks for a lively exchange of ideas, and for gifts of many valuable chemicals. The high field NMR. experiments were performed at the Facility for Biomolecular Research at M.I.T. which is supported by Grant No. RR 00995 from the Division of Research Resources of the *NIH* and by the *NSF* under Contract No. C-670.

Experimental Part

Gas liquid chromatography was performed on a *Perkin-Elmer* 3920 instrument using rubber gum SE-30 and cyclohexanedimethanol succinate columns. Melting points were determined on a hot-stage microscope. The following spectrometers and solvents were used: IR., *Perkin-Elmer* 247 ($CHCl_3$; bands are given in cm^{-1}); ^{1}H-NMR., *Varian* T-60, *Hitachi Perkin-Elmer* R24B, and *Bruker* HX-270 (CCl_4, unless otherwise stated; chemical shifts are reported in ppm relative to TMS as internal standard and coupling constants are in Hz); UV., *Perkin-Elmer Hitachi* 200 (EtOH, absorptions are given in nm); MS., *Varian* Mat 44 (results are quoted as *m/z*). Microanalyses were performed by the *Robertson Laboratory,* Florham Park, N.J.

1,3-Bis(dimethylphosphono)-2-methylidene propane (**9**). Trimethyl phosphite (400 ml; 3.4 mol) was placed into a 2-l flask equipped with an addition funnel, a gas inlet tube, and a *Vigreux* column with distilling head. The phosphite was heated at reflux, then a solution of 131 g (0.425 mol) of diiodide **7** [11] in 200 ml of benzene was added dropwise over a period of 2 h, followed by an additional 100 ml of trimethyl phosphite within 30 min. The reaction was run under a steady flow of argon, and *ca.* 150 ml of distillate (iodomethane, benzene) was allowed to collect. Distillation of the reaction mixture afforded 106 g (92%) of diphosphonate **9**, b.p. 125–127°/0.08 Torr. – IR.: 1650, 1250, 1050, 900. – ^{1}H-NMR.: 2.75 (*d* with fine splitting, $J=24$, 4 H); 3.65 (*d*, $J=10$, 12 H); 5.00 (*t*, $J=5$, 2 H). – MS.: 272 (M^+, 6), 163 (100).

$C_8H_{18}O_6P_2$ (272.18) Calc. C 35.30 H 6.67 P 22.76% Found C 35.02 H 6.64 P 22.91%

1,3-Bis(dimethylphosphono)-2-propanone (**10**). A solution of 27.2 g (0.10 mol) of **9** in 250 ml of methanol was ozonized at −10 to −20° until appearance of a blue color. Trimethyl phosphite (35 ml) was then added dropwise at −10° and the mixture was left overnight at RT. The solvent was removed i.V. *(in vacuo),* and the residue was distilled to give 24.5 g (90%) of keto-diphosphonate **10**, b.p. 156–158°/0.08 Torr. – IR.: 1720, 1250. – ^{1}H-NMR. ($CDCl_3$): 3.35 (*d*, $J=23$, 4 H); 3.75 (*d*, $J=11$, 12 H). – MS.: 274 (M^+, 5), 124 (100).

$C_7H_{16}O_7P_2$ (274.15) Calc. C 30.67 H 5.88 P 22.60% Found C 30.43 H 5.99 P 22.32%

1-Dimethylphosphono-2-methyl-2-propene (**11**). A stirred mixture of 90.5 g (1 mol) of methallyl chloride, 150 g (1.2 mol) of trimethyl phosphite, 4 g of anhydrous nickel bromide and 1 g of hydroquinone was heated at reflux for 7 h under argon, during which time the temperature rose from 87° to 140°. Distillation of the reaction mixture through a *Vigreux* column afforded 108 g (66%) of phosphonate **11**, b.p. 95–98°/15 Torr. – IR.: 1650, 1250, 1050, 900, 870. – ^{1}H-NMR.: 1.75–1.95 (*m*, 3 H); 2.35 (*d*, $J=23$, 2 H); 3.65 (*d*, $J=11$, 6 H); 4.7–4.95 (*m*, 2 H). – MS.: 164 (M^+, 17), 79 (100).

$C_6H_{13}O_3P$ (164.14) Calc. C 43.91 H 7.98 P 18.87% Found C 43.60 H 8.09 P 18.78%

Keto-diphosphonate **10** *from methallyl phosphonate* **11**. A mechanically stirred mixture of 122 g (0.75 mol) of **11**, 147 g (0.82 mol) of *N*-bromosuccinimide, and 0.5 g of azo-bis(isobutyronitrile) in 1 l of CCl_4 was heated at reflux for 2.5 h. It was cooled to 5°, suction filtered, and evaporated to give crude bromide **12** (230 g). An analytical sample was obtained by chromatography on silica gel: b.p. 91°/0.1 Torr. – IR.: 1640, 1250, 1050, 920, 905. – NMR.: 2.68 (*d*, $J=22$, 2 H); 3.72 (*d*, $J=11$, 6 H); 4.10 (*d*, $J=2$, 2 H); 5.12 (*d* with fine splitting, $J=5$, 1 H); 5.33 (*d* with fine splitting, $J=5$, 1 H). – MS.: 243 (M^+, 2), 245 (M^{+2}, 2), 163 (100).

Crude **12** was dissolved in 120 ml of toluene, 140 ml of trimethyl phosphite and 0.2 g of hydroquinone were added, and after 1.5 h of heating at reflux the reaction mixture was submitted to a rapid distillation. The product distilling at 120–155°/0.05 Torr (167 g; GLC. indicated the presence of *ca.* 50% of **9**) was ozonized in 1 l of methanol and reduced with 100 ml of trimethyl phosphite as described above. Distillation yielded 79.8 g (39%, based on **11**) of ketodiphosphonate **10**, b.p. 158–162°/0.08 Torr.

1,12-Dodecanedial tetramethyl acetal (**15**). A solution of 16.6 g (0.10 mol) of cyclododecene (**13**) in 150 ml of methanol and 50 ml of methylene chloride was ozonized at −10 to −20°.

Methyl sulfide (20 ml) was added, and the mixture was left for 24 h at RT. Most of the solvent was removed i.V., then water was added, and the mixture was extracted with pentane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 24.5 g (84%) of diacetal **15**, b.p. 120–124°/0.1 Torr. – IR.: 1130, 1060. – ^{1}H-NMR.: 1.1–1.6 (*m*, 20 H); 3.15 (*s*, 12 H); 4.15 (br., 2 H).

$C_{16}H_{34}O_4$ (290.45) Calc. C 66.17 H 11.80% Found C 66.34 H 11.92%

1,12-Dodecanedial (**14**). Diacetal **15** (18.4 g; 63 mmol) was dissolved in 150 ml of tetrahydrofuran and 0.3 ml of 70% perchloric acid. Water (130 ml) was added in portions over a period of 48 h at RT. in such a manner that the solution remained homogeneous. The reaction mixture was poured into water, extracted with ether, washed with brine containing sodium hydrogencarbonate, dried (Na_2SO_4), and evaporated. Distillation yielded 12.0 g (96%) of dial **14**, b.p. 106–108°/0.3 Torr ([23]: 128–130°/4 Torr); solidifies. A sample was crystallized from hexane: m.p. 35–36°. – IR.: 2840, 2730, 1725. – ^{1}H-NMR.: 1.2–1.8 (*m*, 16 H); 2.2–2.5 (*m*, 4 H); 9.7 (*t*, J = 1.5, 2 H).

Dimethyl(2,15-dioxo-3-pentadecen-1-yl)phosphonate (**28**). A solution of 6 g (60 mmol) of $KHCO_3$ in 250 ml of water was added to 9.9 g (50 mmol) of dial **14** and 16.4 g (60 mmol) of keto-diphosphonate **10** in 250 ml of *t*-BuOH, and the mixture was stirred for 6 h at 25°. After addition of water the mixture was extracted with ether, washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue with ethyl acetate on silica gel gave 3.2 g of impure **14** and 7.3 g (42%) of **28**, which was dried at 30°/0.05 Torr. – IR.: 2740, 1730, 1700, 1670, 1630, 1250, 1050, 980. – ^{1}H-NMR.: 1.1–1.8 (*m*, 16 H); 2.0–2.5 (*m*, 4 H); 3.05 (*d*, J = 22, 2 H); 3.70 (*d*, J = 11, 6 H); 6.12 (*d*, J = 16, 1 H); 6.85 (*d*×*t*, J = 6.5 and 16, 1 H); 9.55 (*t*, J = 1.5, 1 H). – MS.: 346 (M^+, 4), 41 (100).

Cyclization of monoolefin **28**. A 500 ml-round bottom flask equipped with an efficient magnetic stirrer, reflux condenser, and a gas-inlet tube was charged with 5 g (50 mmol) of $KHCO_3$ and 200 ml of 9:1 *t*-butyl alcohol/water. The stirred mixture was heated at vigorous reflux under a steady flow of argon, while a solution of 7.3 g (21 mmol) of **28** in 40 ml of 9:1 *t*-butyl alcohol/water was added through the condenser at a constant rate over a period of 5 h. The solvent was removed i.V., brine was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and distilled to give 4.0 g (51%) of a 7:93 mixture of isomers **29** and **31**. Separation was achieved by chromatography on silica gel, using hexane + 2% AcOEt as eluant.

(2Z,14E)-2,14-Cyclopentadecadien-1-one (**29**): b.p. 120° (bath temp.)/0.1 Torr. – IR.: 1660, 1620, 980. – ^{1}H-NMR. ($CDCl_3$; 270 MHz): 1.1–1.7 (*m*, 16 H); 2.3–2.5 (*m*, 4 H); 5.97 (*d*×*t*, J = 12 and 8, 1 H); 6.23 (*d*×*d*, J = 12 and 2, 1 H); 6.29 (*d*, J = 16, 1 H); 6.89 (*d*×*t*, J = 16 and 7, 1 H). – MS.: 220 (M^+, 2), 41 (100). – UV.: 239 (ε = 12,300).

$C_{15}H_{24}O$ (220.36) Calc. C 81.76 H 10.98% Found C 81.98 H 10.84%

(E,E)-2,14-Cyclopentadecadien-1-one (**31**): b.p. 105°/0.1 Torr. – IR.: 1670, 1620, 980. – ^{1}H-NMR. ($CDCl_3$; 270 MHz): 1.2–1.7 (*m*, 16 H); 2.3–2.4 (*m*, 4 H); 6.28 (*d*, J = 16.5, 2 H); 6.70 (*d*×*t*, J = 16.5 and 7.2 H). – MS.: 220 (M^+, 5), 41 (100). – UV.: 236 (ε = 15,600).

$C_{15}H_{24}O$ (220.36) Calc. C 81.76 H 10.98% Found C 81.54 H 11.22%

The residue (2.0 g) from above distillation was chromatographed on silica gel. Hexane/AcOEt 9:1 eluted 0.42 g (4.5%) of *(E,E,E,E)-2,14,17,29-cyclotriacontatetraene-1,16-dione* (**30**), which was crystallized from ether/hexane: m.p. 88–89°. – IR.: 1675, 1640, 1615, 890. – ^{1}H-NMR.: 1.1–1.7 (*m*, 32 H); 1.9–2.4 (*m*, 8 H); 6.17 (*d*, J = 16, 4 H); 6.75 (*d*×*t*, J = 16 and 6.5, 4 H). – MS.: 440 (M^+, 3), 55 (100). – UV.: 248 (ε = 37,900).

$C_{30}H_{48}O_2$ (440.72) Calc. C 81.76 H 10.98% Found C 81.95 H 10.83%

Isomerization of dienone **31**. A mixture of 1 g of **31**, 50 mg of *p*-toluenesulfonic acid and 25 ml of toluene was heated under reflux for 2 h. The mixture was diluted with ether, washed with 5%

$NaHCO_3$-solution, dried (Na_2SO_4), and evaporated. Distillation of the remaining oil at ~ 110°/0.1 Torr gave 0.68 g of a mixture of compounds **31** (8%), **32** (78%) and **33** (14%). Pure samples were obtained by silica gel chromatography with hexane + 2% AcOEt.

(E,E)-2,13-Cyclopentadecadien-1-one (**32**). IR.: 1690, 1665, 1620, 980, 970. – ^{1}H-NMR.: 1.1–1.8 (*m*, 14 H); 1.9–2.5 (*m*, 4 H); 2.9–3.2 (*m*, 2 H); 5.1–5.8 (*m*, 2 H); 6.10 (*d*, J = 16, 1 H); 6.70 (*d* × *t*, J = 16 and 7, 1 H). – MS.: 220 (M^+, 5), 81 (100). – UV.: 229 (ε = 11,900).

$C_{15}H_{24}O$ (220.36) Calc. C 81.76 H 10.98% Found C 82.01 H 11.22%

(E,E)-3,13-Cyclopentadecadien-1-one (**33**). IR.: 1710, 970. – ^{1}H-NMR.: 1.1–1.7 (*m*, 12 H); 1.8–2.3 (*m*, 4 H); 2.9–3.3 (*m*, 4 H); 5.1–5.9 (*m*, 4 H). – MS.: 220 (M^+, 7), 67 (100).

Equilibration of pure **32** and **33** under the same conditions led to the same mixture of isomers.

(E,E,E,E)-2,6,10,14-Cyclopentadecatetraen-1-one (**34**). A solution of 3.10 g (16 mmol) of dial **17** and 4.40 g (16 mmol) of keto-diphosphonate **10** in 25 ml of 9:1 *t*-butyl alcohol/water was added over a period of 4.5 h to a refluxing mixture of 4.0 g (40 mmol) of $KHCO_3$ in 125 ml of 9:1 *t*-butyl alcohol/water. For details see under cyclization of monoolefin **28**. Work-up gave 2.15 g (62%) of **34**, b.p. 101–105°/0.05 Torr, which solidified and was crystallized from hexane: m.p. 51–53°. – UV.: 235 (ε = 13,700). – IR.: 1660, 1640, 1615, 975, 965. – ^{1}H-NMR.: 2.1–2.6 (*m*, 12 H); 5.2–5.6 (*m*, 4 H); 6.05 (*d*, J = 16, 2 H); 6.62 (partially resolved *d* × *t*, J = 16 and 7, 2 H). – MS.: 216 (M^+, 1), 79 (100).

$C_{15}H_{20}O$ (216.32) Calc. C 83.29 H 9.32% Found C 83.24 H 9.37%

(2E,6Z,10E,14E)-2,6,10,14-Cyclopentadecatetraen-1-one (**36**). Condensation of dial **20** with keto-diphosphonate **10** was carried out as above and gave 55% of **36**: b.p. 110°/0.1 Torr; m.p. 34–35°. – IR.: 1665, 1640, 1615, 980. – ^{1}H-NMR.: 2.0–2.5 (*m*, 12 H); 5.0–5.6 (*m*, 4 H); 6.00 (*d*, J = 16, 1 H); 6.12 (*d*, J = 16, 1 H); 6.2–6.9 (*m*, 2 H). – MS.: 216 (M^+, 2), 49 (100). – UV.: 237 (ε = 13,300).

$C_{15}H_{20}O$ (216.32) Calc. C 83.29 H 9.32% Found C 83.60 H 9.39%

Cyclopentadecanone (Exaltone®). A solution of 0.89 g (4.1 mmol) of tetraenone **34** in 20 ml of ethanol was hydrogenated in the presence of 0.1 g of 10% Pd/C (75 min, 20°). Filtration, evaporation and distillation yielded 0.90 g (98%) of Exaltone®, b.p. 85°/0.05 Torr; m.p. 65–67°. – IR.: 1710. – ^{1}H-NMR. ($CDCl_3$): 1.2–1.9 (*m*, 24 H); 2.43 (*t*, J = 6, 4 H). – MS.: 224 (M^+, 6), 41 (100).

(E,E)-6,10-Cyclopentadecadien-1-one (**44**). A mixture of 1.58 g (7.3 mmol) of tetraenone **34** and 0.1 g of 5% Pd/$BaSO_4$ in 40 ml of pyridine was hydrogenated at 20°/760 Torr until absorption ceased (3 h). The mixture was filtered, poured into water and extracted with pentane. The organic layer was washed with water, dried (Na_2SO_4), evaporated, and distilled to afford 1.57 g (98%) of **44**, b.p. 97°/0.07 Torr. – IR.: 1700, 970. – ^{1}H-NMR.: 1.2–1.8 (*m*, 8 H); 1.8–2.5 (*m*, 12 H); 5.0–5.7 (*m*, 4 H). – MS.: 220 (M^+, 1), 41 (100).

(6Z,10E)-6,10-Cyclopentadecadien-1-one (**45**). Hydrogenation of tetraenone **36** under the same conditions gave 98% of **45**, b.p. 98°/0.07 Torr. – IR.: 1700, 970. – ^{1}H-NMR.: 1.2–1.8 (*m*, 8 H); 1.9–2.5 (*m*, 12 H); 5.0–5.6 (*m*, 4 H). – MS.: 220 (M^+, 1), 41 (100).

Trisdehydromuscone (= E,E,E-14-Methyl-2,6,10-cyclopentadecatrien-1-one) (**35**). To a stirred suspension of 0.86 g (4.5 mmol) of cuprous iodide in 25 ml of dry ether under argon was added 4.7 ml (9 mmol) of 1.9M methyllithium/ether at – 10°. Tetraenone **34** (0.89 g; 4.1 mmol) in 10 ml of ether was then added at – 10° over a period of 10 min, and stirring was continued for 30 min at – 10° to 0°. The reaction mixture was poured into cold, dilute sulfuric acid and extracted with ether. The organic layer was washed with water, 5% $NaHCO_3$-solution, dried (Na_2SO_4), evaporated and distilled to give 0.77 g (81%) of **35**, b.p. 95–98°/0.05 Torr. – UV.: 226 (ε = 9300). – IR.: 1685, 1660, 1625, 970. – ^{1}H-NMR.: 0.85 (*d*, J = 5, 3 H); 1.1–2.9 (*m*, 15 H); 5.2–5.5 (*m*, 4 H); 5.82 (*d*, J = 16, 1 H); 6.6 (partially resolved *d* × *t*, 1 H). – MS.: 232 (M^+, 1), 41 (100).

$C_{16}H_{24}O$ (232.37) Calc. C 82.70 H 10.41% Found C 82.70 H 10.67%

Acid catalyzed isomerization of **35** (*p*-toluenesulfonic acid, toluene, 2 h reflux) led to a mixture of **35** (86%) and **37** (14%). The latter was isolated by chromatography on silica gel and had b.p. ~120° (bath)/0.05 Torr. – IR.: 1700, 970. – ^{1}H-NMR.: 0.87 (*d*, J=5.5, 3 H); 1.1–3.1 (*m*, 15 H); 5.2–5.7 (*m*, 6 H). – MS.: 232 (M^+, 1), 79 (100).

$C_{16}H_{24}O$ (232.37) Calc. C 82.70 H 10.41% Found C 82.88 H 10.62%

Muscone (**1**). Hydrogenation of 0.77 g (3.3 mmol) of trisdehydromuscone **35** in 20 ml of ethanol and 0.1 g of 10% Pd/C (1 h, 20°) gave, after filtration, evaporation and distillation, 0.77 g (98%) of muscone (**1**), b.p. 95°/0.05 Torr. – IR.: 1700. – ^{1}H-NMR.: 0.92 (*t*, J=6, 3 H); 1.1–2.5 (*m*, 27 H). – MS.: 238 (M^+, 6), 41 (100).

Methyl 6,6-dimethoxyhexanoate (**38**). Cyclohexanone enolacetate (56 g; 0.4 mol) in 500 ml of methanol was ozonized in a dry-ice/acetone bath until the solution turned blue. Dimethyl sulfide (60 ml) was added, and the cooling bath was removed. The temperature rose slowly to 48°, and after it had returned to RT., 40 ml of trimethyl orthoformate and 1 ml of acetyl chloride were added. The mixture was then left for 48 h at RT.

Three identical batches were combined and the solvent was removed i.V. The residue was dissolved in ether, washed with brine containing a small amount of $NaHCO_3$, dried (Na_2SO_4), and distilled to give 193 g of product, b.p. 56–69°/0.1 Torr. – ^{1}H-NMR. indicated the presence of *ca.* 20% of methyl-6-oxo-hexanoate. The product was mixed with 100 ml of trimethyl orthoformate, 20 ml of methanol, and 0.5 g of *p*-toluene sulfonic acid. The mixture was left for 48 h at RT., then worked up as above yielding 201 g (88%) of **38**, b.p. 61°/0.1 Torr ([20]: 83°/2.2 Torr).

6,6-Dimethoxy-1-hexanol (**39**). A solution of 201 g (1.06 mol) of **38** in 500 ml of dry ether was added at reflux temperature within 1 h to a stirred suspension of 30 g (0.75 mol) of $LiAlH_4$ in 750 ml of ether. Stirring was continued for 1 h at RT., then 100 ml of 5 N NaOH was added slowly with external cooling. Stirring became difficult, but improved towards the end. After completion of the addition stirring was continued for 1 h, then the suspension was suction filtered, washed with ether, and evaporated. Distillation afforded 169 g (98%) of **39**, b.p. 78°/0.1 Torr ([20]: 83–88°/0.9 Torr).

1,1-Dimethoxy-6-iodohexane. Alcohol **39** (81.0 g; 0.50 mol) was added to an ice-cooled mixture of 99.3 g (0.52 mol) of *p*-toluenesulfonyl chloride and 72 ml (0.9 mol) of pyridine at such a rate that the temperature remained below 15°. Stirring was continued for 2 h at 5–10°, then cold water was added and the mixture was extracted with ether. The organic layer was washed with 5% aq. AcOH-solution, cold 2% NaOH, dried (Na_2SO_4), and evaporated at 20°. The residue (190 g) was dissolved in 500 ml of acetone, then a solution of 97.5 g (0.65 mol) of NaI in 500 ml of acetone was added, and the mixture was stirred for 24 h at RT. Most of the solvent was removed i.V., then ether was added. The mixture was washed with water, dried (Na_2SO_4), evaporated and distilled to give 124.9 g (92%) of 1,1-dimethoxy-6-iodohexane, b.p. 76–78°/0.05 Torr ([21]: 77–78°/0.5 Torr).

1,1-Dimethoxy-7-octyne (**40**). Acetylene was bubbled through *ca.* 300 ml of liquid ammonia while 8.1 g (0.35 atom) of sodium was added in small pieces. After the disappearance of the blue color, dimethylsulfoxide (150 ml) was added cautiously. 1,1-Dimethoxy-6-iodohexane (81.6 g; 0.3 mol) was then added over a period of 10 min while acetylene was bubbled through the stirred mixture. The ammonia was allowed to evaporate and was replaced with ether. When the mixture had reached 0°, dilute NH_4Cl solution was added. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave 48.9 g (96%) of **40**, b.p. 91°/8 Torr ([21]: 65–68°/1.5–2 Torr).

1,1,14,14-Tetramethoxy-7-tetradecyne (**41**). To a stirred suspension of lithium amide, prepared from 1.45 g (0.21 atom) of lithium in *ca.* 200 ml of liquid ammonia, was added 30.6 g (0.18 mol) of **40** over a period of 10 min. Dimethylsulfoxide (100 ml) was then added, followed by 62.5 g (0.23 mol) of 1,1-dimethoxy-6-iodohexane within 10 min. Work-up as above gave an oil, from which low-boiling impurities were removed by heating at 100°/0.05 Torr. Crude **41** (40.8 g, 72% yield) was used without further purification. A sample was submitted to a rapid distillation: b.p. 140°/0.05 Torr. – IR.: 1125, 1070, 1050. – ^{1}H-NMR.: 1.1–1.8 (*m*, 16 H); 1.9–2.3 (*m*, 4 H); 3.25 (*s*, 12 H); 4.35 (*t*, J=6, 2 H).

$C_{18}H_{34}O_4$ (314.47) Calc. C 68.75 H 10.90% Found C 69.10 H 10.53%

7-Tetradecynedial (**42**). A mixture of 31.4 g (0.10 mol) of diacetal **41**, 300 ml of tetrahydrofuran, 100 ml of water, and 0.5 ml of 70% perchloric acid was stirred at RT. under argon. After 8 h a further 75 ml of water was added, and stirring was continued overnight. The mixture was poured into water, extracted with ether, washed with brine containing Na_2CO_3, dried (Na_2SO_4), and evaporated. Distillation afforded 21.1 g (95%) of **42**, b.p. 125–127°/0.05 Torr. – IR.: 2725, 1720. – ^{1}H-NMR.: 1.1–1.8 (*m*, 12 H); 1.9–2.6 (*m*, 8 H); 9.65 (*t*, $J \sim 2$, 2 H).

$C_{14}H_{22}O_2$ (222.33) Calc. C 75.62 H 9.99% Found C 75.89 H 9.96%

(E,E)-2,16-Cycloheptadecadien-9-yn-1-one (**43**). A solution of 4.44 g (20 mmol) of dial **42** and 6.03 g (22 mmol) of keto-diphosphonate **10** in 30 ml of 9:1 *t*-butyl alcohol/water was added to a refluxing mixture of 5 g (50 mmol) of $KHCO_3$ and 200 ml of *t*-butyl alcohol/water 9:1 over a period of 6.5 h. For further details and work-up see under cyclization of monoolefin **28**. Distillation gave 2.75 g (56%) of **43**, b.p. 128°/0.05 Torr, which solidified and was crystallized from hexane: m.p. 55–56°. – UV.: 240 ($\varepsilon = 15{,}100$). – IR.: 1660, 1640, 1615, 980. – ^{1}H-NMR.: 1.3–1.9 (*m*, 12 H); 2.0–2.6 (*m*, 8 H); 6.25 (*d*, $J = 17$, 2 H); 6.80 (*d*×*t*, $J = 17$ and 6.5, 2 H). – MS.: 244 (M^+, 1), 41 (100).

$C_{17}H_{24}O$ (244.38) Calc. C 83.55 H 9.90% Found C 83.59 H 9.90%

Civetone (**2**). Dienone **43** (2.60 g; 10.6 mmol) in 75 ml of pyridine was hydrogenated at 20°/760 Torr in the presence of 0.2 g of 5% $Pd/BaSO_4$ until absorption ceased (3.5 h). The mixture was filtered, evaporated, and distilled to yield 2.64 g (99%) of civetone (**2**), b.p. 103°/0.05 Torr. – IR.: 1700. – ^{1}H-NMR.: 1.0–2.5 (*m*, 28 H); 5.1–5.6 (*m*, 2 H). – MS.: 250 (M^+, 7), 41 (100).

Identity with authentic civetone was established by comparison of spectra and retention times on GLC.

13,13-Dimethoxy-2-tridecanone (**23**). Ozonization of 17.5 g (97 mmol) of olefin **22** in 150 ml of methanol and 50 ml of methylene chloride, followed by reduction with 20 ml of dimethyl sulfide and work-up as described previously gave 21.7 g (95%) of **23**, b.p. 108–112°/0.05 Torr. – IR.: 1710. – ^{1}H-NMR.: 1.1–1.7 (*m*, 18 H); 2.04 (*s*, 3 H); 2.32 (*t*, $J = 7$, 2 H); 3.10 (*s*, 6 H); 4.23 (*t*, $J = 6$, 1 H).

12-Oxo-tridecanal (**46**). Ketoacetal **23**, when hydrolyzed by the method described above (THF, H_2O, $HClO_4$; 48 h at RT.), yielded **46** (82%), m.p. 33°. – IR.: 2730, 1710. – ^{1}H-NMR.: 1.0–1.9 (*m*, 16 H); 2.00 (*s*, 3 H); 2.1–2.5 (*m*, 4 H); 9.70 (*t*, $J \sim 2$, 1 H).

Dimethyl(2,15-dioxo-3-hexadecen-1-yl)phosphonate (**47**). A mixture of 1.50 g (7 mmol) of keto-aldehyde **46**, 1.92 g (7 mmol) of keto-diphosphonate **10**, 2 g (20 mmol) of $KHCO_3$, 90 ml of *t*-butyl alcohol, and 20 ml of water was stirred for 20 h at RT. After addition of water, the mixture was extracted with ether, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the remaining oil with ethyl acetate on silica gel gave 1.64 g (65%) of **47** as a viscous oil. – IR.: 1710, 1665, 1625, 1250, 1050, 975. – ^{1}H-NMR.: 0.9–1.8 (*m*, 16 H); 2.00 (*s*, 3 H); 1.9–2.4 (*m*, 4 H); 3.00 (*d*, $J = 22$, 2 H); 3.64 (*d*, $J = 11$, 6 H); 6.05 (*d*, $J = 16$, 1 H); 6.82 (*d*×*t*, $J = 16$ and 7, 1 H).

Attempted cycloolefination with ketoaldehyde **46**. Similar to the procedure described above, a solution of 1.70 g (8 mmol) of **46** and 2.20 g (8 mmol) of keto-diphosphonate **10** in 15 ml of 9:1 *t*-butyl alcohol/water was added within 3 h to a refluxing mixture of 2 g (20 mmol) of $KHCO_3$ and 100 ml of *t*-butyl alcohol/water 9:1. Work-up, followed by chromatography on silica gel gave 0.75 g (42%) of triketone **48**, m.p. 76–78° (from ether). – IR.: 1705, 1660, 1635, 1610, 980. – ^{1}H-NMR. ($CDCl_3$): 1.1–1.8 (*m*, 32 H); 2.12 (*s*, 6 H); 2.0–2.5 (*m*, 8 H); 6.25 (*d*, $J = 16$, 2 H); 6.87 (*d*×*t*, $J = 16$ and 6, 2 H). – MS.: 446 (M^+, 4), 43 (100).

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