

45. Total Synthesis of ($\pm$)- α -Acoradiene via Intramolecular Photoaddition and Reductive Cyclobutane Cleavage

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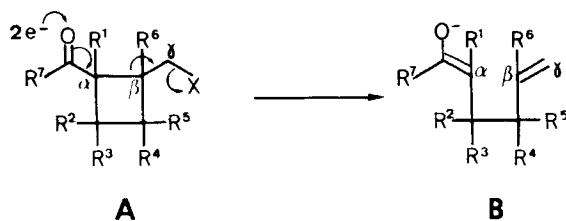
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Summary

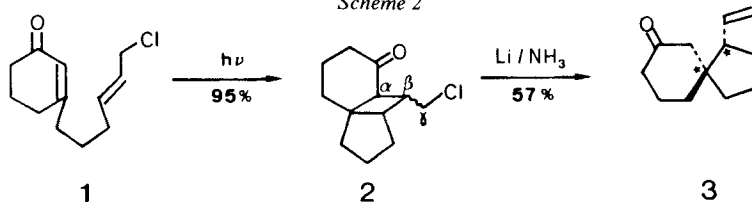
($\pm$)- α -Acoradiene (**4**) has been synthesized from 3-methoxy-2-cyclohexenone by a sequence of 8 steps. The key steps (*Scheme 6*) are the regio- and stereoselective photo[2+2]addition **7** $\rightarrow$ **6** and the reductive fragmentation **6** $\rightarrow$ **5**.

1. Introduction. – The reductive α,β -fragmentation of γ -halocyclobutylketones **A** $\rightarrow$ **B** (*Scheme 1*) has first been described in conjunction with an intramolecular photoaddition reaction: **1** $\rightarrow$ **2** $\rightarrow$ **3**¹⁾ (*Scheme 2*), providing a new, stereoselective approach to the spiro[4.5]decane system [2].

Scheme 1



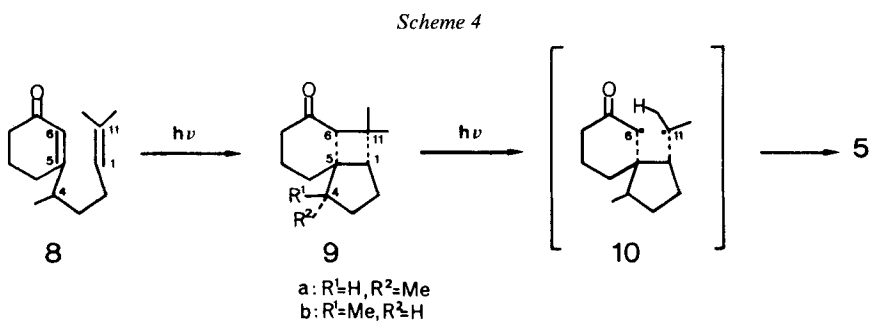
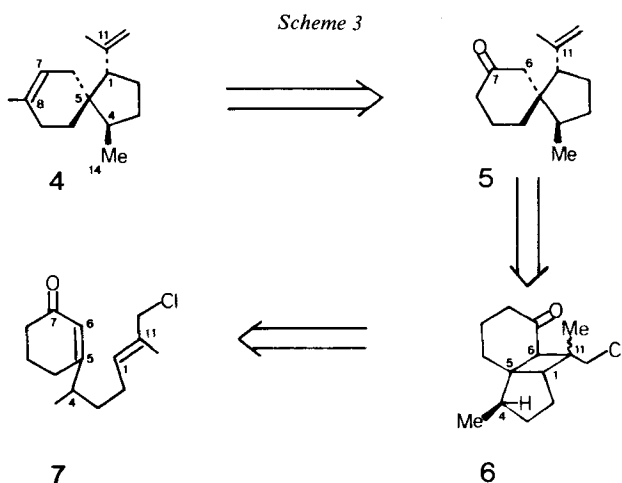
Scheme 2



- ¹⁾ For a recent review on the intramolecular photoaddition/cyclobutane fragmentation sequence in organic synthesis see [1].
- ²⁾ For the structure elucidation of (–)- α -acoradiene see [3]; for alternative syntheses of acorane type sesquiterpenes see a review [4a] and more recent work [4b] [7b] [11].
- ³⁾ The acorane numbering system is used. The systematic names are given in the *Exper. Part*.

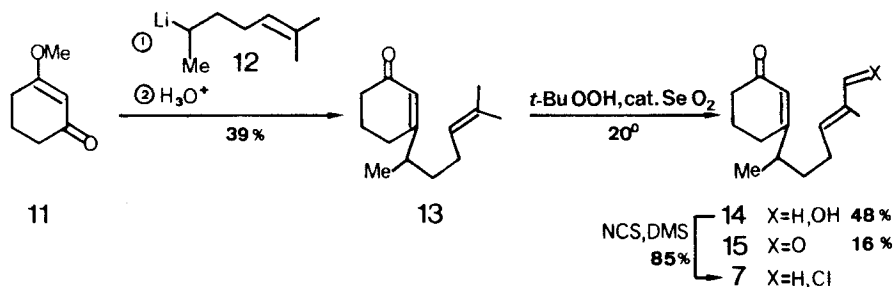
We wish to report here in detail the application of this concept to the synthesis of ($\pm$)-*a*-acoradiene (**4**), recently described in preliminary form [1]² and summarized by the retrosynthetic analysis in *Scheme 3*.

A crucial point of this strategy was the extent to which the chiral center C(4)³ in **7** would induce the configurations of the new centers C(1), C(5) and C(11)³ formed in the addition process **7** $\rightarrow$ **6**. We had little doubt that the addition **7** $\rightarrow$ **6** would be regiocontrolled in the desired sense according to the 'rule of five' [5] and analogous to the reaction **1** $\rightarrow$ **2** [2]. Additionally, after completion of this work, the unidirectional nature of the related photoconversion **8** $\rightarrow$ **9a** + **9b** (1 : 2) (*Scheme 4*) was confirmed [6], thereby disproving a former report [7] which, nevertheless, recorded the interesting photoinduced *Norrish*-type II cleavage **9b** $\rightarrow$ **10** $\rightarrow$ **5**. However, in view of the low efficiency of the process **9b** $\rightarrow$ **5** [1] [6], the reductive fragmentation **6** $\rightarrow$ **5** (*Scheme 3*) seemed to be more promising and more general in preparative terms.



2. Synthesis of the key precursor 7. – We envisaged first the preparation of the known dienone **13** [6] [7], followed by its allylic functionalization (*Scheme 5*). Interestingly, the yield of the transformation **11** + **12** $\rightarrow$ **13** [7], as well as that of the analo-

Scheme 5

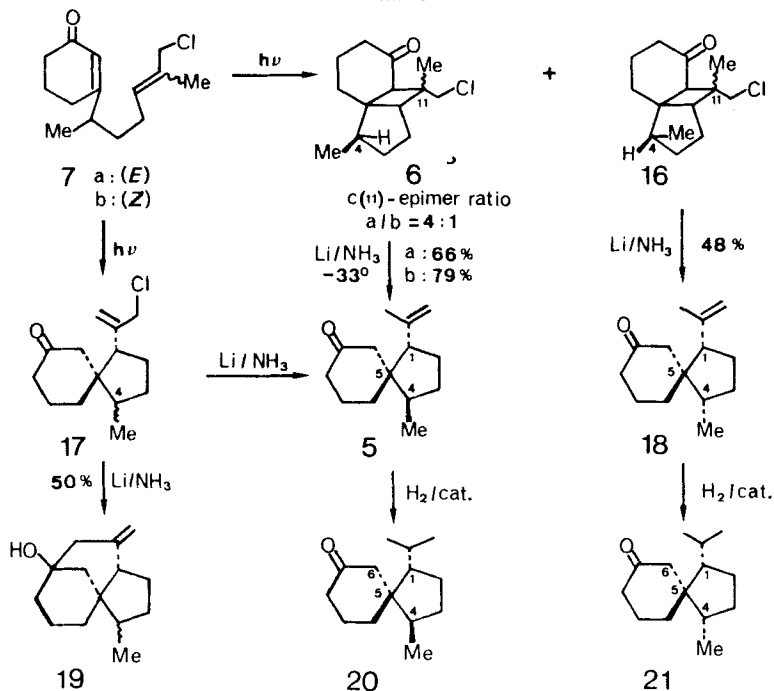


gous addition of **12** to 3-ethoxy-2-cyclopentenone [8], have not been reported. In our hands, metalation of 6-chloro-2-methyl-2-heptene [7] with finely divided lithium/sodium alloy (98:2) in hexane, addition of the resulting organolithium compound **12** to **11**, and acidic hydrolysis of the adduct gave dienone **13** reproducibly in 39% yield. Alternatively, **13** has been obtained in 31% overall yield, starting from *m*-bromoanisole and 6-methyl-5-hepten-2-one [6]. Selenium dioxide catalyzed allylic oxidation [9] of **13** with *t*-butylhydroperoxide furnished the (*E*)-alcohol **14** in 48% yield (84% conversion), together with aldehyde **15** (16%). Longer reaction times led to substantial formation of aldehyde **15**. Treatment of alcohol **14** with *N*-chlorosuccinimide/dimethyl sulfide [10] gave the desired configurationally pure (*E*)-allyl chloride **7a** (85% yield).

3. Irradiation of the dienone 7a and reductive fragmentation of the photo-adducts. – 3.1. *Results.* With the key precursor **7a** in hand, we proceeded to the crucial photocycloaddition step. Irradiation of **7a** in benzene through Pyrex using a high-pressure mercury lamp, followed by rapid chromatography afforded uncyclized **7** (9%), which according to ¹H-NMR., GC. and GC./MS.-evidence was a (2:1)-mixture of the (*E*)- and (*Z*)-isomers **7a** and **7b**. Further elution gave a (1:4:1:3)-mixture (GC.) of the four photoaddition products **6a**, **6b**, **16** and **17** (76% yield, Scheme 6), which on reductive cleavage (Li/NH₃/THF, –33°) furnished the C(4)-epimeric³ spiroketones **5** and **18** (59% yield) as a (10:3)-mixture separable only by capillary-GC.

On the other hand, separation of the photoadducts by medium-pressure chromatography permitted each one to be spectrally characterized and individually subjected to reductive fragmentation. Only the olefinic photoproduct **17** was identified as an inseparable (5:1)-mixture of C(4)-isomers³. Its reduction (Li/NH₃) furnished a (5:1)-mixture of **5** and **18** (29% yield) together with the alcohols **19** (50% yield). Each of the sterically pure [2+2]-adducts **6a**, **6b** and **16** showed a carbonyl band at 1700 cm^{–1} in the IR. spectrum, in agreement with a *cis*-fusion of the cyclobutane to the 5- as well as to the 6-membered ring [1] [2]. Accordingly, the tricyclic adducts differ from each other only with respect to centers C(4)³ and C(11)³. The configurations at C(11)³ were not determined, since this chirality is lost in the subsequent reduction step. Configurational assignment of C(4)³ follows from subsequent reductive fragmentation of the photoproducts: treatment of **6a**

Scheme 6

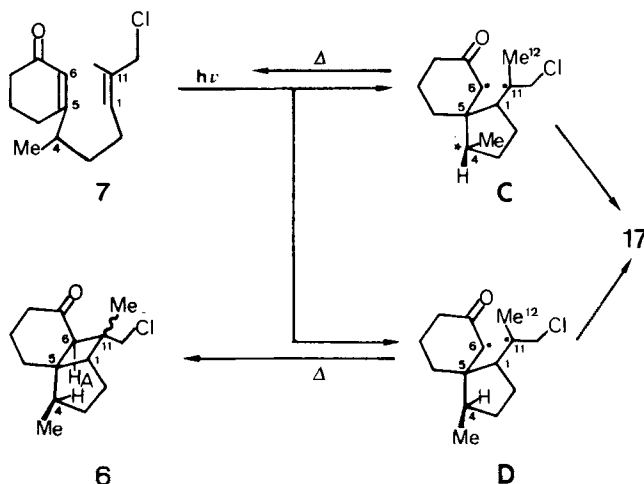


as well as **6b** with $\text{Li}/\text{NH}_3/\text{THF}$ at -33° gave the same spiroketone **5** in 66% and 79% yield, respectively, whereas **16** produced the epimeric spiroketone **18** (48% yield) under identical conditions. To determine structures **5** and **18** each isomer was hydrogenated using *Wilkinson's* catalyst, to give the respective isomers **20** and **21**. Indeed, the $^1\text{H-NMR}$ spectrum of **21**, derived from the minor spiroketone **18**, was identical to that of an unambiguously characterized synthetic precursor of ($\pm$)-acorenone [11]. The most conspicuous differences in the $^1\text{H-NMR}$ (360 MHz) of the epimers **20** and **21** are the signals of the methyl groups (0.8–1.1 ppm) and of the $\text{C}(6)^3$ methylene group; the latter appears as a singlet in **21**, but as an *AB*-system in **20**. Ultimate proof for structure **5** was provided by its conversion to ($\pm$)-*a*-acoradiene (**4**), as described below.

3.2. Discussion. The predominant formation of the sterically less encumbered adducts **6** (in which repulsion between the $\text{C}(4)$ -methyl³ and the $\text{C}(6)$ -H³ is minimized) may be rationalized as depicted in *Scheme 7*. We believe that this substituent crowding is less important during the primary bond formation between $\text{C}(5)^3$ and $\text{C}(1)^3$ ($7 \rightarrow \text{C} + \text{D}$) than in the final cyclobutane ring closure which joins $\text{C}(6)^3$ and $\text{C}(11)^3$. Thus, the diradical intermediate **D** should cyclize smoothly to give the tricyclic adducts **6**. In contrast, the epimeric diradical **C** might revert to **7** rather than form the sterically more encumbered $\text{C}(4)^3$ -epimeric adduct **16**⁴). Evidence

⁴) For other examples of intramolecular photoadditions for which the stereoselectivity has been ascribed to the reversible formation of diradicals, see [1].

Scheme 7



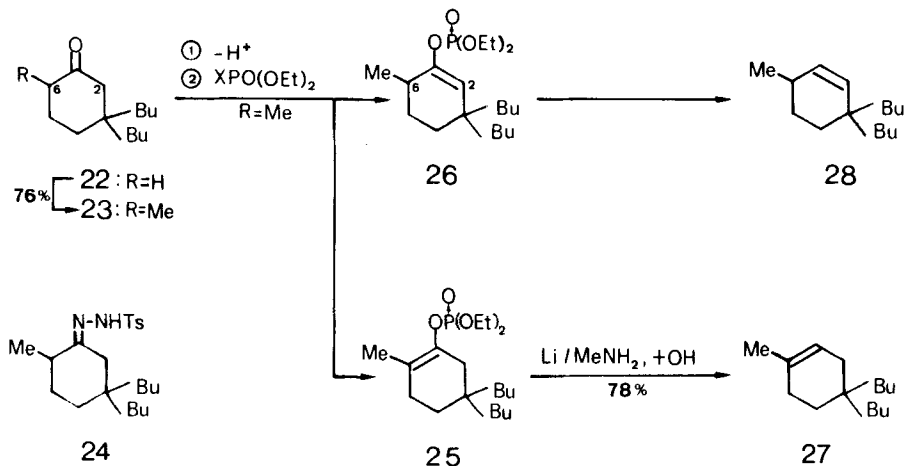
for the reversibility of the first bond formation was provided by the recovery of a mixture **7a/7b** from the reaction mixture obtained on irradiation of stereochemically pure **7a**. Thus, the stereochemical integrity of the isolated trisubstituted olefinic bond in the starting material **7** is lost during the photo-process, apparently *via* the transient diradical(s) **C** (and **D**). In addition, the olefinic spirophtopproducts **17** are obviously derived from the diradical intermediates **D** and **C**, by H-transfer from C(12)³ to C(6)³.

Reductive fragmentation of both C(11)³ epimers **6a** and **6b** furnished the spiroketone **5** in comparable yields under identical reaction conditions. We assume that this process starts with the transfer of one electron from lithium to the carbonyl group, yielding a radical anion which undergoes cleavage of the α,β -cyclobutane bond. In each substrate, **6a** and **6b**, the carbonyl- π -orbital as well as the γ -CH₂-Cl bond may be oriented parallel to the α,β -bond, in accord with the expected requirement for a concerted fragmentation. However, the extent to which this reductive cleavage entails similar stereoelectronic constraints as the classical heterolytic fragmentation processes [12] remains to be clarified.

4. Conversion of the spiroketone **5 to ($\pm$)- α -acoradiene (**4**).** – Having obtained the major spiroketone **5** in pure form and established its structure, we focused our efforts on its final transformation to ($\pm$)- α -acoradiene (**4**). This task required regiochemical control in the introduction of both a methyl group at C(8)³ and an olefinic bond at C(7),C(8). To evaluate possible solutions to this problem, we chose 3,3-dibutylcyclohexanone (**22**) [13] as a model compound and explored its conversion to olefin **27** (Scheme 8).

Monomethylation of **22** at C(6) proceeded efficiently and selectively on successive treatment with lithium tetramethylpiperidide and methyl iodide, affording **23** in 76% yield. Selective olefin formation (**23** $\rightarrow$ **27**) proved to be more difficult, as evident from the results summarized in Tables 1 and 2.

Scheme 8



Since it was the most direct route leading from **23** to **27**, the *Shapiro-Bamford-Stevens* reaction of the tosylhydrazone **24** was studied first. However, treatment of the readily prepared **24** in aprotic and protic media with various bases always led to mixtures of the olefins **27** and **28** (Table 1).

We then examined the option of regioselective enolphosphate formation (Table 2) followed by reduction. In THF at temperatures between -78° and $+20^\circ$, lithium diisopropylamide in the absence or presence of tetramethylethylenediamine showed only non-discriminating deprotonation at C(6) and C(2) (entries a and b). This was also the case with the sterically more demanding lithium di-*t*-butylamide [17] (entry c). In contrast, thermodynamically controlled enolate formation using lithium diisopropylamide and a catalytic amount of *t*-butyl alcohol (entry d), followed by treatment with diethyl chlorophosphate/HMPA at -78° , selectively produced the

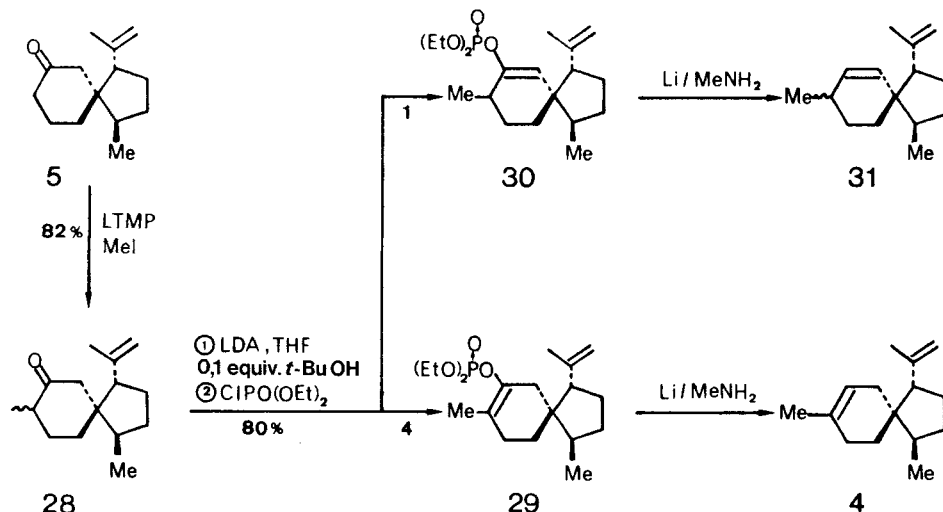
 Table 1. Shapiro-Bamford-Stevens elimination **24** $\rightarrow$ **27** $\rightarrow$ **28**

Entry	Reaction conditions	Total yield 27 + 28 in %	Product ratio 27/28 in %	
a	MeLi, Et ₂ O, r.t., 1.5 h [14]	55	20	80
b	NaO(CH ₂) ₂ ONa, HO(CH ₂) ₂ OH, 150°, 30 min [15]	76	75	25
c	<i>t</i> -BuOK, NMP, 150°, 15 min [16]	94	79	21

 Table 2. Enolate formation and successive trapping with diethyl chlorophosphate: **23** $\rightarrow$ **25** + **26**

Entry	Deprotonation conditions	Total yield 25 + 26 in %	Product ratio 25/26 in %	
a	LDA, THF, 20°, 4 h	81	55	45
b	LDA, TMEDA, -78° , 1 h	68	35	65
c	Li-di- <i>t</i> -butylamide [17], THF, -78° , 2 h	64	34	66
d	LDA (1 equiv.), <i>t</i> -BuOH (0.1 equiv.), THF, 20°, 18 h	83	94	6

Scheme 9



desired enolphosphate **25** in good yield. Reductive removal of the diethyl phosphate group [18] ($\text{Li/MeNH}_2/t\text{-BuOH}$) furnished the trisubstituted olefin **27** in 78% yield and 98.3% purity.

We then proceeded to the analogous transformation **5** $\rightarrow$ **4** (Scheme 9). The spiroketone **5** was readily monomethylated as described above to give a (3:2)-mixture of C(8)-epimers³⁾ **28** in 82% yield. In accord with the model studies summarized in Table 1, the tosylhydrazone derived from **28** gave only complex mixtures on treatment with base. Accordingly, we chose the less direct route to ($\pm$)- α -acoradiene, *via* the enol phosphate **29**. Thermodynamically controlled enol phosphate formation from **28** using the conditions described in Table 2, entry d, gave a (4:1)-ratio of the desired enol phosphate **29** and its regioisomer **30**. Finally, treatment of this mixture with lithium in $\text{CH}_3\text{NH}_2/t\text{-BuOH}$ afforded, together with the olefins **31**, ($\pm$)- α -acoradiene (**4**), which was isolated by preparative gas chromatography (22% yield) and identified by spectral comparison (IR., $^1\text{H-NMR}$.) with authentic ($-$)- α -acoradiene.

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Experimental Part

General. All reactions were carried out under N_2 or Ar. Workup refers to the general procedure of washing an organic phase with H_2O , sat. aq. $NaHCO_3$ - and then sat. aq. $NaCl$ -solution, followed by drying over anhydrous $MgSO_4$, filtration and removal of solvent by distillation *in vacuo* using a rotatory evaporator. Column chromatography was carried out using SiO_2 (Merck Kieselgel 60). For medium-pressure liquid chromatography prepacked columns (Merck, LiChroPrep Si60, 125 m) were used. GC., retention time in min was carried out either A: on a Perkin Elmer 3920, He as carrier gas, quartz capillary column, 25 m, 0.23 mm ID, coated with OV101; or B: on a Hewlett Packard 5790A, H_2 -pressure 12 psi, quartz capillary column 12 m, 0.2 mm ID, coated with OV1; or C: on a Carlo Erba SS 455, N_2 -pressure 1 kg/cm², glass columns 3 m $\times$ 3 mm, packed, stationary phase supported on Chromosorb WAW 80/160. Melting points (m.p.) were determined on a Kofler hot stage and are uncorrected. – IR. spectra: in CCl_4 unless otherwise specified, $\bar{\nu}_{max}$ in cm^{-1} . – 1H -NMR. spectra in $CDCl_3$ at 360 MHz unless otherwise specified, standard tetramethylsilane, δ (ppm) = 0; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz). – Mass spectra (MS.): signals are given in *m/z* (rel.-%).

Synthesis of the key precursor 7a (Scheme 5). – **Preparation of 3-(1,5-dimethyl-4-hexenyl)-2-cyclohexenone (13).** 6-Chloro-2-methyl-2-heptene [7] (3 g, 20.5 mmol) in hexane (30 ml) was added to a suspension of Li/Na-alloy 98:2 (Ventron, 27% suspension in mineral oil, 354 mg, 2 mol-equiv.) in hexane (20 ml) under reflux with vigorous stirring (Vibromix). After stirring the mixture under reflux for 1.1 h the excess of metal and the salts were allowed to settle down. Transfer of the supernatant solution through a syringe needle into another flask, followed by dropwise addition of 3-methoxy-2-cyclohexenone (11) (1.43 g, 10.2 mmol) in hexane (15 ml) at r.t. to the stirred solution, stirring of the reaction mixture at r.t. for 30 min, subsequent acidification with 1N aq. HCl, workup and chromatography (hexane/ether 4:1) yielded pure 13 (oil, 1.655 g, 39% yield). – IR. (film): 1680, 1630. – 1H -NMR. (60 MHz): 1.10 (*d*, *J* = 6.5, 3 H); 1.60 (br. *s*, 3 H); 1.70 (br. *s*, 3 H); 0.8–2.6 (11 H); 5.07 (*m*, 1 H); 5.83 (br. *s*, 1 H). – MS.: 206 (26, $C_{14}H_{22}O^+$), 191 (6), 150 (21), 148 (15), 137 (63), 124 (58), 82 (87), 41 (100).

Preparation of (E)-3-(6-Hydroxy-1,5-dimethyl-4-hexenyl)-2-cyclohexenone (14). The enone 13 (1.59 g, 7.7 mmol) in dry CH_2Cl_2 (18 ml) was added to a stirred mixture of SeO_2 (856 mg, 7.7 mmol) and *t*-butyl hydroperoxide (80%, 2.5 ml, 20 mmol) in dry CH_2Cl_2 (18 ml) at 0° to r.t. While stirring the mixture at r.t., the oxidation 13 $\rightarrow$ 14 was monitored by TLC. to avoid substantial formation of the aldehyde 15. Generally, after a reaction time of 1.5 h, addition of ether and sat. aq. $NaHCO_3$ -solution, washing of the organic layer with Na_2SO_3 , usual workup and chromatography (hexane/ether) furnished the starting enone 13 (251 mg, 16%), the aldehyde 15 (264 mg, 15%) and the desired alcohol 14 (828 mg, 48% yield), oil, b.p. 170° (bath)/0.05 Torr. – IR.: 3650, 3500 br., 1675, 1620. – 1H -NMR. (100 MHz): 1.13 (*d*, *J* = 6.5 Hz, 3 H); 1.66 (*s*, 3 H); 1.3–2.5 (12 H); 4.02 (*s*, 2 H); 5.40 (*t* $\times$ *m*, *J* = 7, 1 H); 5.90 (*s*, 1 H). – MS.: 222 (2, $C_{14}H_{22}O_2^+$), 204 (6), 194 (9), 151 (41), 137 (100), 124 (50).

$C_{14}H_{22}O_2$ (222) Calc. C 75.63 H 9.97% Found C 75.75 H 9.97%

Preparation of (E)-3-(6-Chloro-1,5-dimethyl-4-hexenyl)-2-cyclohexenone (7a). Dimethylsulfide (1.032 g, 16.6 mmol) was added dropwise to a solution of *N*-chlorosuccinimide (1.953 g, 14.6 mmol) in dry CH_2Cl_2 (40 ml). Subsequent addition of the alcohol 13 (800 mg, 3.6 mmol) in CH_2Cl_2 (11 ml) to the resulting suspension at –20°, stirring of the mixture at 0° for 1.1 h, workup and chromatography (hexane/ether 1:1) gave the allylic chloride 7a (oil, 737 mg, 85% yield) distilled at 170° (bath)/0.005 Torr. – GC. (B, 165°): 5.12. – IR. (film): 1670, 1620, 895. – 1H -NMR. (100 MHz): 1.11 (*d*, *J* = 6.5, 3 H); 1.72 (*s*, 3 H); 1.2–2.5 (11 H); 4.01 (*s*, 2 H); 5.51 (*t*, *J* = 7, 1 H); 5.90 (*s*, 1 H). – MS.: 242 (0.4, $C_{14}H_{21}^{37}ClO^+$), 240 (1, $C_{14}H_{21}^{35}ClO^+$), 205 (25), 191 (3), 161 (4), 148 (7), 137 (53), 124 (59), 96 (38), 95 (43), 81 (100).

$C_{14}H_{21}ClO$ (240) Calc. C 69.84 H 8.79 Cl 14.72% Found C 69.77 H 8.87 Cl 14.68%

Irradiation of 7a and reductive fragmentation of the photoadducts (Scheme 6). – A solution of the allylic chloride 7a (102 mg, 0.424 mmol) in benzene (100 ml), through which N_2 was passed slowly, gave on irradiation (Pyrex filter, 125-W high-pressure mercury lamp) for 9 h at r.t. followed by chromatography (hexane/ether 95:5) monocyclic 7 (9 mg, 9%) and a mixture of four photoproducts (77 mg, 76% yield). Analysis by GC. (B, 165°), 1H -NMR. of recovered 7 showed this to be a (2:1)-

mixture of **7a** and **7b**. Isomer **7b** shows the following properties: GC. (B, 165°): 4.55. – ¹H-NMR. (from mixture **7a/7b**): 1.11 (*d*, *J* = 6.5, 3 H); 1.83 (*s*, 3 H); 1.2–2.5 (11 H); 4.01 (*s*, 2 H); 5.35 (*t*, *J* = 7, 1 H); 5.90 (*s*, 1 H). – MS. (GC.-coupling): 242 (0.4, C₁₄H₂₁³⁷ClO⁺), 240 (1, C₁₄H₂₁³⁵ClO⁺), 205 (16), 191 (4), 161 (3), 148 (6), 137 (42), 124 (52), 96 (32), 95 (35), 81 (97), 55 (100).

The photoproduct mixture, which shows in the GC. (C, 5% SE 30, 185°) four peaks 13.8 (1), 15.2 (4), 16.7 (1) and 18.3 (3), was separated by medium-pressure chromatography to yield first the less polar photoproduct **16** (9 mg), m.p. 91–92° (hexane). – GC. (C, 5% SE 30, 185°): 13.8. – IR.: 1700, 1465, 1380. – ¹H-NMR.: 0.93 (*d*, *J* = 6.5, 3 H); 1.20 (*s*, 3 H); 1.3–2.4 (12 H); 2.52 (*s*, 1 H); 3.50 (*d*, *J* = 10, 1 H); 3.62 (*d*, *J* = 10, 1 H). – MS.: 242 (5, C₁₄H₂₁³⁷ClO⁺), 240 (15, C₁₄H₂₁³⁵ClO⁺), 212 (14), 206 (23), 205 (100), 204 (56), 191 (14), 189 (14).

Further elution gave the main product **6a** (oil, 29 mg). – GC. (C, 5% SE 30, 185°): 15.2. – IR.: 1700, 1455, 1380. – ¹H-NMR.: 0.86 (*d*, *J* = 6.5, 3 H); 1.16 (*s*, 3 H); 1.4–2.33 (12 H); 2.34 (*s*, 1 H); 3.55 (*d*, *J* = 10, 1 H); 3.59 (*d*, *J* = 10, 1 H). – ¹³C-NMR. (90.56 MHz): 212.7 (*s*), 57.9 (*d*), 54.3 (*t*), 48.4 (*s*), 48.0 (*d*), 41.4 (*d*), 40.9 (*d*), 39.9 (*t*), 34.3 (*t*), 28.7 (*t*), 24.8 (*t*), 20.9 (*qa*), 20.2 (*t*), 16.2 (*qa*). – MS.: 242 (2, C₁₄H₂₁³⁷ClO⁺), 240 (7, C₁₄H₂₁³⁵ClO⁺), 212 (7), 206 (7), 205 (43), 204 (13), 191 (11), 189 (9), 148 (17), 137 (53), 124 (43), 93 (47), 91 (60), 81 (57), 79 (60), 76 (50), 67 (60), 55 (67), 53 (57), 41 (100), 39 (60).

Further elution provided the most polar cycloadduct **6b** (oil, 10 mg), GC. (C, 5% SE 30, 185°): 16.7. – IR.: 1700, 1460, 1380. – ¹H-NMR.: 0.87 (*d*, *J* = 6.5, 3 H); 1.23 (*s*, 3 H); 1.5–2.5 (12 H); 2.19 (*s*, 1 H); 3.49 (*d*, *J* = 10, 1 H); 3.61 (*d*, *J* = 10, 1 H). – MS.: no *M*⁺, 204 (89), 202 (39), 161 (52), 147 (77), 119 (84), 105 (94), 91 (100).

Further elution gave the olefinic photoproduct **17** (inseparable (5:1)-isomer mixture, oil, 21 mg), GC. (C, 5% SE 30, 185°): 18.3. – IR.: 1715, 1460, 920. – ¹H-NMR.: major signals at 0.93 (*d*, *J* = 7, 3 H); 1.1–2.6 (13 H); 2.71 (*t*, *J* = 8.5, 1 H); 4.03 (br. *s*, 2 H); 5.04 (*s*, 1 H); 5.45 (*s*, 1 H); minor signals at 0.83 (*d*, *J* = 7); 2.93 (*t*, *J* = 8.5); 5.08 (*s*). – MS.: 242 (0.6, C₁₄H₂₁³⁷ClO⁺), 240 (1.8, C₁₄H₂₁³⁵ClO⁺), 204 (8), 134 (14), 120 (46), 119 (37), 105 (100).

Reduction of the unseparated photoproduct mixture with Li/NH₃. A solution of the unseparated mixture obtained on irradiation of **7a** (136 mg, 0.565 mmol) in THF (1 ml) was added dropwise at –33° to a stirred solution of lithium metal (40 mg, 5.65 mmol) in liquid ammonia. After 30 min at –33° addition of solid NH₄Cl, usual workup of the evaporated reaction mixture and chromatography (hexane/ether 85:15) yielded a (10:3)-mixture of the stereoisomeric spiroketones **5** and **18** (69 mg, 59% yield), separable only by capillary GC. (A, 150°): 26.6 (76), 26.9 (23).

Reductive cleavage of the photoadduct 16. Separated pure **16** (17 mg, 0.07 mmol) was treated with lithium in ammonia/THF as described above to give exclusively **18** (7 mg, 48% yield, oil), GC. (A, 150°): 26.9. – IR.: 1718, 1460, 1380, 1232, 895. – ¹H-NMR.: 0.94 (*d*, *J* = 6.5, 3 H); 1.2–2.35 (11 H); 1.76 (*s*, 3 H); 2.14 (*d*, *J* = 15, 1 H); 2.21 (*d*, *J* = 15, 1 H); 2.33 (*t*, *J* = 9.5, 1 H); 4.77 (*s*, 1 H); 4.97 (*s*, 1 H). – MS.: 206 (24, C₁₄H₂₂O⁺), 164 (12), 163 (100), 150 (21), 92 (17), 91 (61).

Reductive cleavage of the major photoadduct 6a. Separated product **6a** (300 mg, 1.25 mmol) was treated with lithium in NH₃/THF as described above to give **5** (169 mg, 66% yield, oil), GC. (A, 150°): 26.60. – IR.: 1715, 1450, 1230, 895. – ¹H-NMR.: 0.90 (*d*, *J* = 7, 3 H); 1.2–2.1 (9 H); 1.76 (*s*, 3 H); 2.13 (*d*, *J* = 14, 1 H); 2.17 (*d*, *J* = 14, 1 H); 2.30 (*t*, *J* = 6, 2 H); 2.53 (*t*, *J* = 9, 1 H); 4.73 (*s*, 1 H); 4.97 (*s*, 1 H). – ¹³C-NMR. (90.561 MHz): 212.1 (*s*), 144.9 (*s*), 113.6 (*t*), 52.4 (*d*), 52.1 (*s*), 47.9 (*t*), 41.0 (*t*), 39.2 (*d*), 30.5 (*t*), 30.0 (*t*), 26.9 (*t*), 23.7 (*qa*), 22.4 (*t*), 16.0 (*qa*). – MS.: 206 (16, C₁₄H₂₂O⁺), 191 (6), 163 (58), 150 (45), 137 (45), 124 (68), 121 (77), 68 (94), 67 (100).

Reductive cleavage of the photoproduct 6b. Separated pure **6b** (231 mg, 0.96 mmol) was treated with lithium in NH₃/THF as described above to provide exclusively **5** (156 mg, 79% yield), identified by GC. (A, 150°) and by ¹H-NMR.

Reduction of the olefinic photoproduct 17. The (1:5)-mixture of **17**-isomers (8 mg, 0.03 mmol) was treated with lithium in NH₃/THF as described above to give after chromatography a (1:5)-mixture of **5** and **18** (2 mg, 29%), identified by GC. (A, 150°) and by ¹H-NMR. Further elution afforded the alcohol **19** (4 mg, 50%). – IR. (CHCl₃): 3610, 3450 br., 910. – ¹H-NMR. (100 MHz): 0.88 (*d*, *J* = 7, 3 H); 0.9–2.7 (17 H); 4.73 (br. *s*, 2 H). – MS.: 206 (88, C₁₄H₂₂O⁺), 163 (14), 150 (38), 137 (100), 124 (91), 97 (66).

Preparation of (1R,4R*,5R*)-1-Isopropyl-4-methylspiro[4.5]decan-7-one (21)*. A solution of the minor spiroketone **18** (7 mg, 0.034 mmol) and tris(triphenylphosphine)chlororhodium(I) (3 mg, 0.0032 mmol) in benzene (0.5 ml) was stirred under H₂ (1 atm) for 16 h. A solution of the evaporated

mixture in pentane/ether 4:1 was filtered through SiO_2 to give **21** (oil, 6 mg, 84%), GC. (A, 150°): 25.33. – IR.: 1712, 1470, 1230. – $^1\text{H-NMR}$. (100 MHz): 0.89 (*d*, $J=6.5$, 3 H); 0.93 (*d*, $J=6.5$, 3 H); 1.03 (*d*, $J=6.5$, 3 H); 1.2–2.1 (11 H); 2.22 (*s*, 2 H); 2.34 (*m*, 2 H). This $^1\text{H-NMR}$ spectrum is identical to that of independently prepared **21** [11].

Preparation of (1R*,4S*,5R*)-1-Isopropyl-4-methylspiro[4.5]decan-7-one (20). A solution of the major spiroketone **5** (10 mg, 0.0485 mmol) and tris(triphenylphosphine)chlororhodium(I) (7 mg, 0.0077 mmol) in benzene (0.8 ml) was stirred under H_2 (1 atm) for 40 h. A solution of the evaporated mixture in pentane/ether afforded after filtration through SiO_2 the ketone **20** (oil, 6 mg, 59% yield), GC. (A, 150°): 25.01. – IR.: 1712, 1462, 1230. – $^1\text{H-NMR}$. (100 MHz): 0.86 (*d*, $J=6.5$, 6 H); 0.99 (*d*, $J=6.5$, 3 H); 1.2–2.5 (11 H); 2.15 (*d*, $J=14$, 1 H); 2.32 (*d*, $J=14$, 1 H); 2.3 (*m*, 2 H).

Model Studies: Conversion of 3,3-dibutylcyclohexanone (22) to 4,4-dibutyl-1-methylcyclohexene (27) (Scheme 8, Tables 1 and 2). – **Preparation of 3,3-dibutylcyclohexanone (22)** [13]. A BuLi -solution in THF (1.55N, 51.6 ml, 80 mmol) was added dropwise to a stirred solution of $\text{CuBr} \cdot \text{Me}_2\text{S}$ (8.22 g, 40 mmol) in Me_2S (80 ml) at -78° . After 15 min at -78° 3-thiobutyl-2-cyclohexenone (3.68 g, 20 mmol) in THF (10 ml) was added. The mixture was stirred at -78° for 30 min, then allowed to warm up to 0° , and then quenched with sat. aq. NH_4Cl -solution. Workup and bulb-to-bulb distillation at 100° (bath)/0.1 Torr furnished the ketone **22** (4.10 g, 98% yield, oil), GC. (C, 5% SE 30, 190°): 8.12. – IR.: 1715, 1470, 1230, 1220. – $^1\text{H-NMR}$. (100 MHz): 0.91 (*t*, $J=6$, 6 H); 1.0–2.0 (16 H); 2.16 (*s*, 2 H); 2.29 (*t*, $J=7$, 2 H). – MS.: no M^+ -peak, 167 (1), 153 (79), 135 (15), 97 (27), 83 (16), 69 (37), 55 (100).

Preparation of 3,3-dibutyl-6-methylcyclohexanone (23). A solution of CH_3Li in ether (1.75N, 5 ml, 8.75 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.63 ml, 9.6 mmol) in THF (24 ml) at 0° . To the resulting solution the solution of ketone **22** (1.68 g, 8 mmol) in THF (4 ml) was added at -78° . Warming up of the mixture to 0° , rapid injection of CH_3I (2.2 ml, 35 mmol) and additional stirring at 0° , workup and chromatography (hexane/ether 39:1) furnished the methylated ketone **23** (1.365 g, 76% yield, oil), GC. (C, 5% SE 30, 180°): 10.77. – IR.: 1715, 1465, 1380. – $^1\text{H-NMR}$. (100 MHz): 0.89 (*m*, 6 H); 1.01 (*d*, $J=6.5$, 3 H); 1.0–2.5 (17 H); 2.16 (*s*, 2 H). – MS.: no M^+ -peak, 167 (87), 149 (11), 97 (16), 83 (35), 69 (53), 55 (100).

Preparation of 3,3-dibutyl-6-methylcyclohexanone N-p-tolylsulfonylhydrazone (24). A mixture of the ketone **23** (112 mg, 0.5 mmol), *p*-tolylsulfonylhydrazine (130 mg, 0.7 mmol) and *p*-tolylsulfonic acid hydrate (5 mg) in CHCl_3 (25 ml) was heated under reflux while the condensate was passed continuously over molecular sieves (3 Å, 5 ml). Washing of the solution with an aq. NaHCO_3 -solution, workup, chromatography (CH_2Cl_2) and crystallization (pentane) furnished the hydrazone **24** (165 mg, 84% yield), m.p. $102\text{--}104^\circ$. – IR. (CH_2Cl_2): 3280, 1375, 1330, 1165, 810. – $^1\text{H-NMR}$. (100 MHz): 0.8–2.5 (19 H); 0.87 (*t*, $J=6$, 6 H); 1.05 (*d*, $J=7$, 3 H); 2.44 (*s*, 3 H); 7.12 (br. *s*, 1 H); 7.32 (*d*, $J=8$, 2 H); 7.86 (*d*, $J=8$, 2 H). – MS.: 392 (2, $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2\text{S}^+$), 336 (7), 335 (28), 238 (20), 237 (100), 207 (19).

Treatment of 24 with methylolithium in ether (Table 1, entry a). A solution of CH_3Li in ether (1.6N, 0.22 ml, 0.35 mmol) was added to a solution of the hydrazone **24** (34 mg, 0.09 mmol) in ether (1 ml). After 1.5 h at r.t., workup and rapid chromatography (hexane) yielded a (1:4)-mixture of the olefins **27** and **28** (10 mg, 55% yield), GC. (C, 10% OV-225, 140°): 6.86 (80), 8.20 (20); (C, 3% Apiezon, 180°): 10.1 (80), 11.6 (20). – $^1\text{H-NMR}$. (60 MHz): 0.8–1.8 (23 H); 0.97 (*d*, $J=6$, 3 H); 5.38 (*s*, 1.6 H).

Treatment of 24 with disodium ethylene glycolate in ethylene glycol (Table 1, entry b). The hydrazone **24** (80 mg, 0.2 mmol) was added to a solution of Na (46 mg, 2 mmol) in dry ethylene glycol (2 ml). The mixture was heated to 150° for 30 min to give after workup a (3:1)-mixture of the olefins **27** and **28** (35 mg, 84%) analyzed by GC. (C, 10% OV-225, 140°): 6.8 (25), 8.2 (67.68); (C, 3% Apiezon, 180°): 10.0 (21.6), 11.6 (68.4).

Treatment of 24 with potassium *t*-butoxide in N-methylpyrrolidone (Table 1, entry c). A mixture of the hydrazone **24** (60 mg, 0.153 mmol), *t*-BuOK (22 mg, 0.19 mmol) and dry *N*-methylpyrrolidone (1.5 ml) was heated at 150° for 15 min to give after workup a (79:21)-mixture of the olefins **27** and **28** (30 mg, 94%), GC. (C, 10% OV-225, 140°): 7.0 (21), 8.4 (79). – $^1\text{H-NMR}$. of the major isomer: 0.89 (*t*, $J=7$, 6 H); 1.0–1.5 (14 H); 1.63 (*s*, 3 H); 1.75 (*s*, 2 H); 1.85 (br. *s*, 2 H); 5.27 (br. *s*, 1 H). – $^1\text{H-NMR}$. of the minor isomer: 0.95 (*d*, $J=7$); 5.37 (*d*, $J=10$); 5.45 ($d \times d$, $J=2$ and 10).

Preparation of 5,5-dibutyl-2-methyl-1-cyclohexenyl diethyl phosphate (25) and 3,3-dibutyl-6-methyl-1-cyclohexenyl diethyl phosphate (26) (Table 2). – **Entry a:** A solution of lithium diisopropylamide in THF (0.9N, 0.3 ml, 0.27 mmol) was added to a stirred solution of the ketone **23** (67 mg, 0.3 mmol) in THF (0.2 ml). The mixture was stirred at r.t. for 4 h. Then a solution of diethyl chlorophosphate (44 μl , 0.3 mmol) in hexamethylphosphoramide (44 μl) was added at -78° . The mixture was stirred

at -78° for 1 h and subsequently allowed to warm up to r.t. Workup gave a (1:1)-mixture of the enolphosphates **25** and **26** (87 mg, 81%), GC. (C, 5% SE 30, 220°): 11.2 (45), 12.7 (54.3). – $^1\text{H-NMR}$. (100 MHz): 0.7–2.5 (29.5 H); 1.10 (*d*, $J=7$, 1.5 H); 1.68 (br. s, 1.5 H); 4.17 (*qi*, $J=7$, 4 H); 5.30 (br. s, 0.5 H).

Entry b. A solution of the ketone **23** (67 mg, 0.3 mmol) in THF (0.2 ml) was added to a mixture of a Ip_2NLi -solution in THF (0.9N, 0.6 ml, 0.54 mmol) and dry tetramethylethylene diamine (0.4 ml) at -78° . After stirring the solution at -78° for 1 h, diethyl bromophosphate (130 mg, 0.6 mmol) was added at -78° . The mixture was allowed to warm up to r.t. to give after workup a (3:65)-mixture of the enolphosphates **25** and **26** (73 mg, 68%), GC. (C, 5% SE 30, 220°): 11.4 (65), 12.8 (35).

Entry c. A solution of BuLi in hexane (1.45N, 0.28 ml, 0.4 mmol) was added to (*t*-Bu) $_2\text{NH}$ [17] (52 mg, 0.4 mmol) in THF (0.2 ml) at 0° . Then a solution of the ketone **23** (67.3 mg, 0.3 mmol) in THF (0.2 ml) was added at -78° . The mixture was stirred at -78° for 2 h and treated with diethyl chlorophosphate and hexamethylphosphoramide as described above to give a (34:66)-mixture of **25** and **26** (69 mg, 64%), GC. (C, 5% SE 30, 220°): 11.0 (66), 12.4 (34).

Entry d. A solution of Ip_2NLi in THF (0.9N, 0.33 ml, 0.3 mmol) was added at 0° to a solution of the ketone **23** (67 mg, 0.3 mmol) in THF (0.2 ml). After addition of 0.1N *t*-BuOH in THF (0.3 ml, 0.03 mmol) the mixture was stirred at r.t. for 18 h and then treated with diethyl chlorophosphate and hexamethylphosphoramide at -78° as described above to give a (94:6)-mixture of the enolphosphates **25** and **26** (89 mg, 83%), GC. (C, 5% SE 30, 220°): 11.0 (6), 12.4 (94). – IR.: 1710, 1270, 1040, 970. – $^1\text{H-NMR}$. (100 MHz): 0.91 (*t*, $J=6$, 6 H); 1.0–2.2 (24 H); 1.70 (br. s, 3 H); 4.16 (*qi*, $J=7.5$, 4 H). – MS.: 360 (6, $\text{C}_{15}\text{H}_{37}\text{O}_4\text{P}^+$), 304 (16), 303 (100), 120 (35), 115 (34).

Preparation of 4,4-dibutyl-1-methyl-1-cyclohexene (27). A mixture of the enolphosphate **25** (contaminated with 6% of **26**, 36 mg, 0.1 mmol), *t*-BuOH (37 μl , 0.4 mmol) and THF (0.2 ml) was added to a solution of lithium (10 mg, 1.5 mmol) in methylamine (2 ml) at -78° . The mixture was stirred at -78° for 30 min and then quenched at -78° with solid NH_4Cl . Workup and chromatography (pentane) gave the olefin **27** (oil, 16 mg, 78%), GC. (C, 10% OV-225, 140°): 7.11 (1.7), 8.55 (98.3). – IR.: 1465, 1455, 1375. – $^1\text{H-NMR}$. (100 MHz): 0.92 (*t*, $J=6$, 6 H); 0.9–2.4 (21 H); 5.30 (br. s, 1 H). – MS.: 208 ($\text{C}_{15}\text{H}_{28}^+$), 179 (7), 165 (21), 152 (20), 151 (100), 138 (12).

Conversion of the major spiroketone 5 to ($\pm$)- α -acoradiene (4) (Scheme 9). – *Preparation of (1R*,4S*,5R*)-1-isopropenyl-4,8-dimethylspiro[4.5]decan-7-ones (28).* A solution of the major spiroketone **5** (99 mg, 0.481 mmol) in THF (2 ml) was added dropwise to a stirred solution of lithium tetramethylpiperidide (0.5N, 1.15 ml, 1.2 mol-equiv., freshly prepared from tetramethylpiperidine and BuLi) in THF/hexane 2:1 at -70° . After stirring the mixture at -70° for 30 min and then at 0° for 10 min, MeI (336 mg, 2.38 mmol) was added. Stirring of the reaction mixture at 0° for 30 min, followed by workup and filtration through SiO_2 (hexane/ether 7:3) produced a (3:2)-mixture of the C(8)-epimers **28** (87 mg, 82% yield). For their characterization the epimers **28** were chromatographed (hexane/ether 95:5) to furnish the less polar isomer **28a**, oil, GC. (A, 160°): 25.95. – IR.: 1715, 1460, 1380, 898. – $^1\text{H-NMR}$: 0.87 (*d*, $J=6.5$, 3 H); 1.02 (*d*, $J=6.5$, 3 H); 1.0–2.25 (10 H); 1.38 (*d* $\times$ *qi*, $J=3.5$ and 12.5, 1 H); 1.76 (*s*, 3 H); 2.32 (*septulet*, $J=6.5$, 1 H); 2.47 (*t*, $J=10$, 1 H); 4.72 (*s*, 1 H); 5.01 (*s*, 1 H). – MS.: 220 (41, $\text{C}_{15}\text{H}_{24}\text{O}^+$), 177 (16), 164 (42), 163 (60), 151 (31), 138 (43), 135 (32), 121 (60), 109 (62), 95 (60), 82 (60), 81 (63), 68 (100).

Further elution furnished the more polar isomer **28b**, m.p. $66\text{--}67^{\circ}$ (hexane). – GC. (A, 160°): 27.47. – IR.: 1715, 1460, 1380, 896. – $^1\text{H-NMR}$: 0.94 (*d*, $J=7$, 3 H); 1.06 (*d*, $J=6.5$, 3 H); 1.2–2.05 (9 H); 1.7 (*s*, 3 H); 2.11 (*d*, $J=14$, 1 H); 2.22 (*d* $\times$ *d*, $J=2$ and 14, 1 H); 2.24 (*m*, 1 H); 2.52 (*t*, $J=7$, 1 H); 4.66 (*s*, 1 H); 4.86 (*s*, 1 H). – MS.: 220 (40, $\text{C}_{15}\text{H}_{24}\text{O}^+$), 177 (20), 164 (36), 163 (39), 151 (34), 138 (42), 135 (30), 121 (51), 109 (49), 95 (51), 82 (54), 81 (59), 68 (100).

Preparation of (1R,4S*,5R*)-1-isopropenyl-4,8-dimethylspiro[4.5]dec-7-en-7-yl diethyl phosphate (29) and (1R*,4S*,5R*)-1-isopropenyl-4,8-dimethylspiro[4.5]dec-6-en-7-yl diethyl phosphate (30).* A solution of Ip_2NLi in THF (0.9N, 0.33 ml, 0.30 mmol, freshly prepared) was added dropwise to a stirred solution of the epimer-mixture **28** (33 mg, 0.15 mmol) at 0° . After addition of 0.1N *t*-BuOH in THF (0.3 ml, 0.03 mmol) the mixture was stirred at r.t. for 18 h. Subsequently a mixture of diethyl chlorophosphate (30 μl , 0.2 mmol) and hexamethylphosphoramide (30 μl , 0.17 mmol) was added at -78° . Then the mixture was warmed up to r.t. to afford after workup and rapid chromatography (hexane/ethylacetate) the enolphosphates **29** and **30** in a ratio of 4:1 ($^1\text{H-NMR}$ analysis, 43 mg, 80% yield, oil). – IR.: 1270, 1050, 1040, 975, 893. – $^1\text{H-NMR}$. of the main isomer (100 MHz): 0.89 (*d*, $J=7$, 3 H); 1.0–2.5 (14 H); 1.37 (*d* $\times$ *t*, $J=0.7$ and 7, 6 H); 1.75 (br. s, 3 H); 2.45 (*t*, $J=8$, 1 H); 4.16 (*d* $\times$ *qi*, $J=0.7$ and 7,

4 H); 4.68 (br. s, 1 H); 4.90 (m, 1 H). – $^1\text{H-NMR}$. of the minor isomer (100 MHz): 0.79 (d, $J=7$); 4.82 (m); 5.17 (m). – MS.: 356 (50, $\text{C}_{19}\text{H}_{33}\text{O}_4\text{P}^+$), 287 (75), 274 (69), 271 (44), 220 (26), 202 (100).

Preparation of (1R,4S*,5R*)-1-isopropenyl-4,8-dimethylspiro[4.5]dec-7-ene (4) ($\equiv (\pm)$ -a-acoradiene) and (1R*,4S*,5R*)-1-isopropenyl-4,8-dimethylspiro[4.5]dec-6-ene (31).* A solution of the (4:1)-mixture **29/30** (14 mg, 0.04 mmol) and *t*-BuOH (15 μl , 0.16 mmol) was added dropwise to a stirred solution of Li (5 mg, 0.7 mmol) in methylamine (1 ml) at -78° under Ar. Stirring of the mixture for further 30 min at -78° , followed by addition of solid NH_4Cl at -78° , evaporation, workup and fast chromatography (pentane) gave a mixture (5.5 mg, 67% yield) of ($\pm$)-a-acoradiene (**4**) and the spiro[4.5]dec-6-enes **31**. GC. (C, 10% OV-225, 155°): 7.0 (60), 9.1 (40). Prep. GC. (glass column, $2\text{ m} \times 13\text{ mm}$, 10% OV-225, 155°) furnished pure ($\pm$)-a-acoradiene (**4**) (1.8 mg, 22%), GC. (C, 10% OV-225, 155°): 7.0. – IR.: 1643, 1468, 1450, 1440, 1380, 890. – $^1\text{H-NMR}$.: 0.88 (d, $J=6.5$, 3 H); 1.2–2.1 (9 H); 1.43 (t, $J=6.5$, 2 H); 1.64 (s, 3 H); 1.72 (s, 3 H); 2.45 (t, $J=7$, 1 H); 4.62 (s, 1 H); 4.83 (s, 1 H); 5.32 (br. s, 1 H). – MS.: 204 (3, $\text{C}_{15}\text{H}_{24}^+$), 186 (3), 147 (5), 143 (4), 133 (3), 121 (7), 119 (11), 105 (9), 93 (6), 72 (8), 57 (15), 44 (100), 43 (81). – The IR. and $^1\text{H-NMR}$. spectra are identical to those of authentic (–)-a-acoradiene. Further elution gave the spiro[4.5]dec-6-ene **31** (2.4 mg, 29%, (2:1)-mixture of **31**-stereoisomers by $^1\text{H-NMR}$. analysis), GC. (C, 10% OV-225, 155°): 9.1. – IR.: 1643, 1455, 1374, 1218, 910, 890. – $^1\text{H-NMR}$. of the major isomer: 0.84 (d, $J=7$, 3 H); 0.96 (d, $J=7$, 3 H); 1.2–2.4 (10 H); 1.72 (s, 3 H); 2.42 (m, 1 H); 4.67 (s, 1 H); 4.79 (s, 1 H); 5.22 (m, 1 H); 5.54 (m, 1 H). – $^1\text{H-NMR}$. of the minor isomer: 0.88 (d, $J=7$); 0.97 (d, $J=7$); 1.72 (s); 2.35 (t, $J=7.5$); 4.69 (s); 4.79 (s); 5.36 (m); 5.54 (m). – MS.: 204 (2, $\text{C}_{15}\text{H}_{24}^+$), 189 (1), 170 (3), 169 (2), 156 (4), 141 (5), 105 (4), 93 (4), 77 (3), 72 (4), 57 (9), 44 (100).

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