

216. A Stereocontrolled Entry to Racemic Eremophilane and Valencane Sesquiterpenes *via* an Intramolecular *Diels-Alder* Reaction

by Ferdinand Näf, René Decorzant and Walter Thommen

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

(18. VIII. 82)

Summary

A stereocontrolled route to racemic eremophilane and valencane sesquiterpenes is described *via* a common intermediate **15**, accessible from an intramolecular *Diels-Alder* reaction. ^{13}C -NMR.-shift assignments of the bicyclic intermediates and products are presented.

1. Introduction. – The *Diels-Alder* reaction [1] occupies a central position in organic synthesis: it allows the simultaneous formation of two new σ -bonds in conjunction with a high degree of stereochemical control and is ideally suited for the synthesis of complex natural products possessing 6-membered rings. Besides the numerous applications of the intermolecular case, the intramolecular variant [2] has been exploited only over the last decade, although with exponentially growing activity. The merits of an intramolecular reaction with respect to an intermolecular reaction are (i) relatively lower activation energies for entropic reasons, and (ii) increased stereochemical control through additional conformational interactions in the transition state.

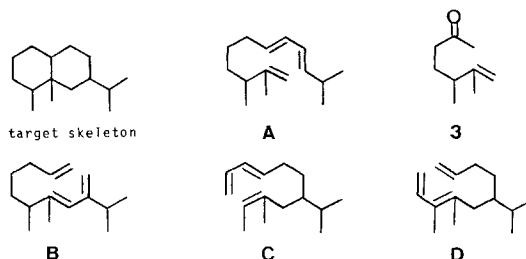
However, the structural and steric problems so elegantly overcome by an intramolecular *Diels-Alder* reaction are not actually solved, but merely transferred to the preparation of the appropriate precursor, a substituted triene. Despite recent considerable progress, stereospecific olefin synthesis [3] is still troublesome and therefore overshadows the elegance of many syntheses based on an intramolecular *Diels-Alder* strategy¹⁾.

¹⁾ For polyene synthesis by fragmentation of cyclic compounds, a strategy which is exactly the reverse of polyene cyclization, see e.g. **1** \rightarrow **2** [4].

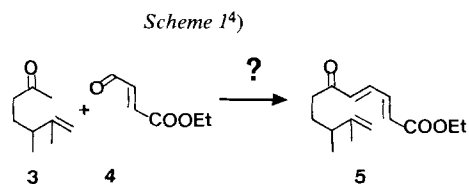


In this work we describe an intramolecular *Diels-Alder* route to eudesmane and valencane sesquiterpenes²⁾) *via* an acyclic triene precursor which is readily accessible from industrial starting materials.

In view of an intramolecular *Diels-Alder* approach, all possible precursors **A–D** of our target skeleton were critically inspected for their feasibility. A triene of type **A**, already containing the C-skeleton of the industrial 5,6-dimethyl-6-hepten-2-one (**3**) [6] (an irone precursor), and, in principle, easily accessible from **3** was given preference over **B–D**.

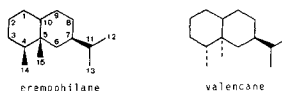


2. Preparation of the acyclic triene 5. – Instead of constructing an acyclic C₁₅-triene of type **A**, we opted for the triene keto ester **5**. Firstly, **5** seemed to be directly accessible by (a formal) condensation of **3** with the known ethyl fumaraldehyde **4** [7] (prepared by ozonolysis of ethyl sorbate (= ethyl (*E,E*)-2,4-hexadienoate) [7b]); secondly, the compounds derived from **5** would allow epimerization at C(7) if necessary (see *Scheme 6*, **23** → **25**).



Kinetic deprotonation of model compound **6** (*Scheme 2*) with lithium diisopropylamide in THF at -5° (to give the less substituted lithium enolate) followed by addition of ethyl fumaraldehyde (**4**) furnished, in 29% yield, the expected aldol ester **7** which, however, was resistant to dehydration (*e.g.* distillation over KHSO_4 ,

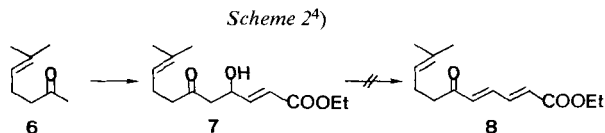
²⁾ The definition of the valencane and eremophilane skeleton used in this paper is, in accord with *Marshall & Warne* [4], as follows:



For simplicity, the eremophilane/valencane numbering is retained in the general part of this paper for all hydronaphthalene derivatives. Systematic names are given in the *Exper. Part*.

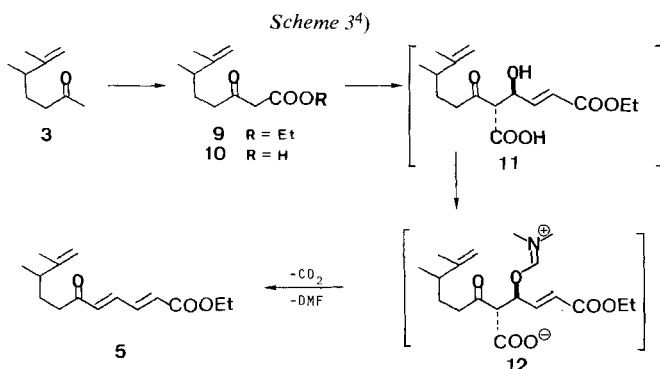
³⁾ For a preliminary note of this work, see [5].

⁴⁾ Without the sign of optical rotation all formulas refer to racemic compounds.



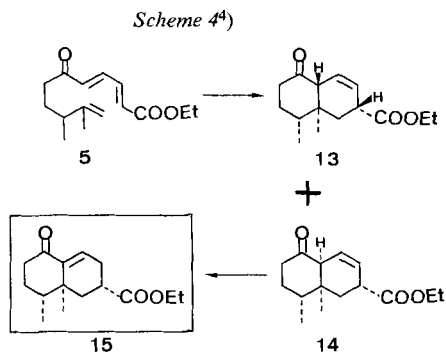
methanesulfonyl chloride/‘collidine’ (= 2,4,6-trimethylpyridine), dicyclohexylcarbodiimide/(heat)). Probably the instability of both the aldol intermediate **7** and the product **8** is the limiting factor. A milder reaction sequence using a variation of the *Knoevenagel* condensation [8] was thus tried with keto acid **10**, prepared from ketone **3** via keto ester **9** (Scheme 3). Indeed, heated with ester **4** in DMF at 50° for 2 h, **10** gave directly the triene keto ester **5** in 23% yield with evolution of CO₂. A further improvement of this step was realized by virtue of a decarboxylative dehydration method via β -hydroxy acids using dimethylformamide acetals. a method recently developed by *Eschenmoser et al.* [9] and others [10] [11]. Accordingly, keto acid **10** was allowed to react with **4** (4–5 h at RT., no solvent) to give the hypothetical hydroxy acid **11** which, after addition of dimethylformamide diethyl acetal (1 equiv.) in petroleum ether (15 min at RT., and 1 h at 50°), furnished, with evolution of CO₂, crystalline (*E,E*)-triene keto ester **5** (49% yield, m.p. 39–40°). The effect of dimethylformamide acetal in this reaction is assumed [9] [11] to be dual. Firstly, it involves transformation of the OH-group of the aldol into a better leaving group (*i.e.* O–CH=N(CH₃)₂⁺) with concomitant suppression of the *retro*-aldol reaction, and secondly it activates the intermediate carboxyl function (by base catalysis), leading to a zwitterion such as **12** which undergoes a stereocontrolled decarboxylative *anti*-elimination.

Based on (i) the (*E,E*)-configuration of product **5**, and (ii) the known stereospecificity of this elimination reaction, the intermediates **11** and **12** are thus tentatively assigned the structures shown (*cf.* Scheme 3).



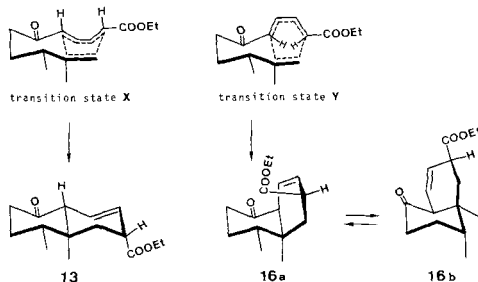
3. The intramolecular *Diels-Alder* reaction and key intermediate **15.** – A degassed solution of triene **5** in toluene (~0.6%) was heated 6 h at 250° to give in 93% yield (depending on the purity of the starting material) either a 1:1 mixture of the *trans*-

fused **13** and its *cis*-isomer **14**, or only *cis*-isomer **14** by rapid C(10)-epimerization of the unstable primary *Diels-Alder* product **13**.



The observed stereoselectivity of the intramolecular *Diels-Alder* reaction is mechanistically rationalized by assuming that transition state **X** which leads to the *trans*-isomer **13** is preferred to **Y** (\rightarrow **16**) or other alternatives.

The secondary methyl group of **X** is thereby in the more stable equatorial position, avoiding the 1,3-diaxial H,CH₃-interactions in the alternative axial position. The preference of transition state **X** over **Y** is in agreement with a similar case recently reported by Roush & Hall [12a] (**17** \rightarrow **18**; Scheme 5).



In order to account for the observed stereochemistry they invoked coplanarity of the keto group to the adjacent diene, a conformation that leads to *trans*-fused product **18**. However, a purely steric argument was proposed by Wilson *et al.* [13] to rationalize the *trans*-selectivity of their reaction **19** \rightarrow **20**.

On the other hand, *cis*-fused hydronaphthalene derivatives, or *cis/trans*-mixtures have also been reported to result from the thermolysis of 1,3,9-decatrienes whose substitution pattern differs from **5**, **17**, and **19** [2b] [14]⁵⁾.

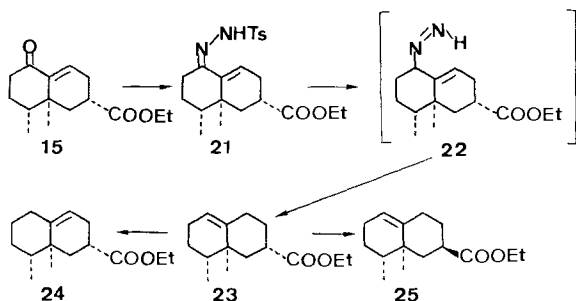
Scheme 5⁴⁾



⁵⁾ For some leading references dealing with the stereochemistry of intramolecular *Diels-Alder* reactions, see [2b] [2c] [12–19].

The instability of **13** under our reaction conditions leading to epimerization at C(10) to give the more stable *cis*-isomer **14** is most probably due to the unfavorable 1,3-diaxial interaction between the angular methyl group and the ester substituent. The bicyclic intermediates **13** and **14** were further isomerized by acid catalysis (0.2% *p*-toluenesulfonic acid monohydrate in toluene, 3 h under reflux) into one single product, our key intermediate **15** (90% yield). The configurational assignments of **13**–**15** are based on NMR. arguments (*Section 5*) and chemical correlations with known products (*Section 4*).

4. Eremophilane and valencane sesquiterpenes from key intermediate 15. – Intermediate **15** was first correlated with the known **23** [20] (*Scheme 6*). For the critical transformation **15** → **23** several variants of the hydride reduction of α, β -unsaturated tosylhydrazones were available [21–23]. Application of a recent, simple procedure [22], heating tosylhydrazone **21** in AcOH with NaBH₄ at 70° for 3 h, gave *via* the intermediate **22** a mixture of **23**–**25**. The suspicion that this mixture might arise from an acid-catalyzed isomerization of the primary product **23** led us to try the extremely mild variant of *Kabalka et al.* [23] using ‘catecholborane’ (= 2*H*-1,3,2-benzodioxaborole) at 40° under quasi neutral conditions, which indeed afforded pure **23**⁶⁾ (55% yield based on **15**).

Scheme 6⁴⁾

Finally, **23** was transformed, as described by *Coates & Shaw* [20], into racemic eremoligenol (**26**) [24], eremophilene (**27**) [25], its double-bond isomer **28** [20], valerianol (**29**) [26], and valencene (**30**) [27]⁷⁾ (*Schemes 6 and 7*). The spectral data of racemic valerianol (**29**) were identical with those of optically active valerianol ((+)-**29**) prepared by partial synthesis from natural valencene ((+)-**30**) *via* (+)-**31**⁸⁾ (*Scheme 8*)⁹⁾.

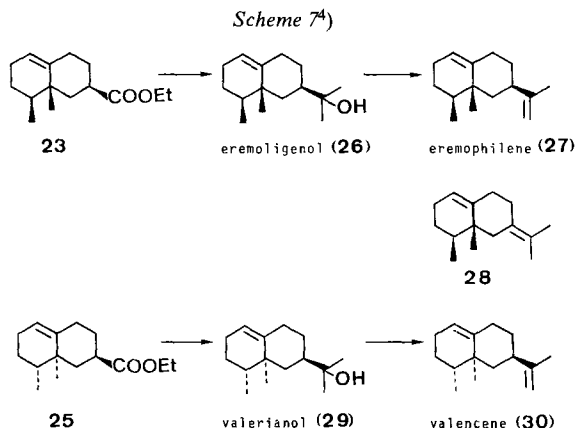
Moreover, our key intermediate **15** proved very useful for a short total synthesis of racemic eremophilone (**34**) [30]. Accordingly, **15** was transformed, by treatment with methyl lithium followed by SOCl₂/pyridine dehydration, into the

⁶⁾ Identical in all respects with a sample kindly supplied by Professor *Coates*.

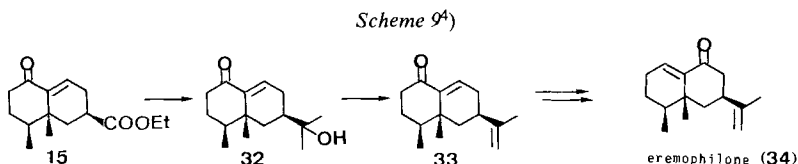
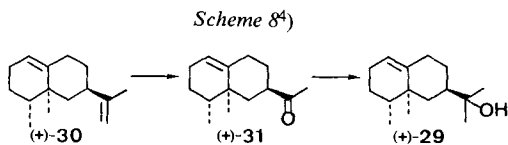
⁷⁾ For an alternative synthesis, see [28].

⁸⁾ For racemic **31**, see [28].

⁹⁾ For an alternative synthesis of (+)-**29**, see [29].



known eremophilone intermediate **33** [31] as main product (50% yield based on **15**, see Scheme 9). Since **33** had already been transformed in three steps by Ziegler *et al.* [31] into racemic eremophilone (**34**) (first total synthesis), our access to **33** also opened a new route to racemic eremophilone¹⁰⁾.



5. NMR. data of the bicyclic intermediates. – The ¹³C-NMR. shift assignments of the bicyclic structures **13–15**, **23**, and **25–39** (see Table) are based on the protonoise-decoupled (PND) and the single-frequency off-resonance-decoupled (SFORD) spectra, selective proton-decoupling technique, deuterium labelling [²⁻²H₂]-**15**, and chemical shift correlations between our substances and related compounds¹¹⁾.

Among the characteristic features in support of the configurational assignments given, we particularly used the marked shift difference of the angular methyl group between *trans*- and *cis*-fused hydronaphthalenes (see, *e.g.* *trans*- and *cis*-methyl-decalin **35** [34a] and **36** [34c], Table), the β-desielding effect imposed by H₃C (14)

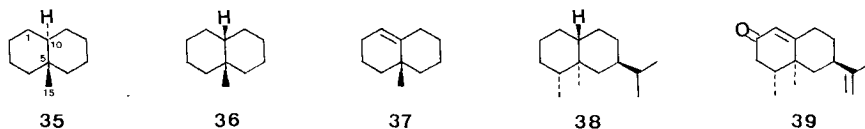
¹⁰⁾ For alternative syntheses, see [32].

¹¹⁾ See [33] (general), and [34] (for shielding effects).

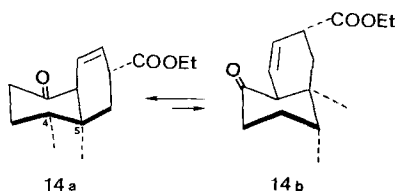
Table. ^{13}C -NMR. *shifts* (at 90.55 MHz, in ppm rel. to TMS, ca. 20% in CDCl_3)²

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(14)	C(15)	$\text{CH}_2\text{-CH}_2\text{-O}$	C(12)	C(13)
13	209.1	40.7	31.4	41.2	39.8	35.7	38.9	124.5 ^{a)}	123.6 ^{a)}	56.1	174.9	14.6	11.3	14.1	60.8	-
14	212.7	39.3	30.1	30.1	38.1	35.6	39.5	126.0 ^{a)}	126.4 ^{a)}	59.7	173.5	14.8	20.8	14.2	60.8	-
15	203.4	39.9 ^{b)}	28.5	38.4 ^{c)}	39.0	36.9 ^{c)}	36.3 ^{c)}	26.9	128.7	146.5	174.9	15.4	19.8	14.5	60.3	-
32	205.7	40.1	29.1	41.6	40.6	35.3	36.5	27.2	128.5	148.2	71.9	15.3	21.2	-	26.9 ^{a)}	27.2 ^{a)}
33	205.5	40.3	29.3	38.1	40.7	39.5	37.3	30.9	128.9	147.9	148.8	15.6	21.1	-	21.2	109.6
25	120.9	25.8	27.2	40.8	37.4	41.8	39.8	30.4	31.7	141.7	176.1	15.6	18.1	14.2	60.2	-
29	119.8	25.9	27.3	41.2	37.7	40.6	44.5	29.0	32.7	143.2	72.3	15.7	18.5	-	27.0 ^{a)}	27.1 ^{a)}
30	120.1	25.9	27.2	41.0	37.8	45.0	41.0	33.2	32.8	142.9	150.4	15.7	18.4	-	20.8	108.3
31	121.1	25.9 ^{c)}	27.2 ^{c)}	40.9 ^{c)}	37.6	41.3	47.8 ^{c)}	30.0 ^{c)}	31.9 ^{c)}	141.7	211.5	15.6	18.2	-	27.8	-
28	119.7	25.9	27.6	40.2	d)	42.5	d)	33.9	31.5	d)	d)	15.6	17.6 ^{d)}	-	20.1 ^{a)}	16.0 ^{a)}
23	120.4	25.7 ^{c)}	27.0 ^{c)}	40.6 ^{c)}	38.0	40.0	38.0 ^{c)}	27.8 ^{c)}	29.1 ^{c)}	143.0	175.8	15.7 ^{c)}	18.7 ^{c)}	14.2	60.2	-
26	120.6	25.2	27.2	42.0	37.8	35.4	34.3	26.4	28.1	143.9	72.6	16.0	21.0	-	26.4 ^{a)}	27.5 ^{a)}
27	120.5	25.5	27.3	38.6	38.1	39.9	37.0	28.5	30.1	143.9	150.0	16.0	21.4	-	20.3	108.2
34	134.9	25.6	26.6	38.9 ^{a)}	d)	43.3	39.2 ^{a)}	41.5	203.1	147.6	144.4	16.0	24.8	-	20.6	110.0
35	[34a] ^{e)}	29.3	27.2	22.1	42.1	33.9	42.1	22.1	29.3	45.8	-	-	15.7	-	-	-
36	[34c] ^{e)}	28.4	21.8	22.8	30.3	33.1	42.3	22.8	28.0	41.8	-	-	28.3	-	-	-
37	[34d] ^{e)}	119.2	26.0	19.1	40.2	34.8	42.3	22.5	32.8	143.6	-	-	24.4	-	-	-
38	[27b]	29.3 ^{a)}	26.9	31.1	43.7	36.8	42.6	39.1	30.1 ^{a)}	29.2 ^{a)}	46.8	33.3	15.3	11.4	-	19.6 ^{d)}
39	[27b]	124.7	199.2	42.2	40.5	39.4	44.1	40.6	31.8	33.1	170.1	149.0	14.9	16.9	-	20.8

^{a)} Similar values may be inverted. ^{b)} Deuterium labelling. ^{c)} Assigned by selective proton decoupling technique. ^{d)} Not observed. ^{e)} Shift values taken from the reference given.



upon $\text{H}_2\text{C}(3)$ ($\Delta\delta = +9$ ppm) as well as the γ -*gauche*-shielding effect ($\Delta\delta = -5$ ppm) by $\text{H}_3\text{C}(14)$ upon $\text{H}_3\text{C}(15)$ (Table, e.g. **35** and **38**). On these grounds the relative configuration at the centres C(4), C(5), and C(10) of **13** and **14** (conformation **14a** preferred), and the relative configuration at the centers C(4) and C(5) of **15**, **32**, and **33** could be rigorously assigned. $^1\text{H-NMR}$. spectroscopy (360 MHz) further corroborated the *cis*-configuration of the vicinal methyl groups in **14** (conformation **14a** preferred) showing, after irradiation at $\text{H}_3\text{C}(14)$, the typical couplings for an



axial hydrogen atom at C(4) ($J(ax, ax) = 13$ Hz; $J(ax, eq) = 4$ Hz). The $^1\text{H-NMR}$. spectrum (360 MHz) of **23** displays the typical signal of an equatorial hydrogen atom at C(7) (relatively narrow multiplet with two eq,eq- and two eq,ax-couplings), and **25** shows the axial H-C(7) as a triplet of a triplet by two identical ax,ax- and ax,eq-couplings with the H-atoms at C(6) and C(8) ($J(ax, ax) = 12.5$, $J(ax, eq) = 3$ Hz), both spectra being in full agreement with the structures assigned earlier [20]. Since no configurational assignment of C(7) in **13**–**15**, **32**, and **33** by way of their ^1H - and ^{13}C -NMR. spectra could be given, these configurations were established by chemical correlation with compounds of known configuration (*i.e.* **23**, eremolignol (**26**), eremophilene (**27**), **33**, eremophilone (**34**) as outlined above).

Experimental Part

General Remarks. See [35].

Ethyl (2E)-4-hydroxy-10-methyl-6-oxoundeca-2,9-dienoate (7). Anh. ($\text{H}_2\text{O} \leq 0.1\%$) diisopropylamine (11.1 g, 0.11 mol) in anh. ether (100 ml) was treated with 1.5N BuLi in hexane (67 ml, 0.1 mol) at -5° . After stirring at 0° for 20 min, 6-methyl-5-hepten-2-one (**6**) (12.6 g, 0.1 mol) in anh. ether (20 ml) was added at -20 to -30° . After stirring at 0° for 10 min, the yellowish mixture was treated with ethyl (2E)-4-oxo-2-butenate (**4**) [7b] (12.8 g, 0.1 mol) in anh. ether (20 ml) at -50° (exothermic reaction). The resulting mixture was stirred at -50 to -20° for 1 h and at 0° for 1 h more, before decomposing by pouring onto a mixture of crushed-ice/ NH_4Cl solution. Extraction with ether (twice), washing (1N HCl, Na_2CO_3 , H_2O), drying (MgSO_4) and concentration gave 21 g of crude **7**. Of this crude material 10 g were chromatographed on silica gel (100 g) using hexane/ethyl acetate 4:1 to give 3.49 g (29%) of pure **7**. - IR. (CCl_4): 3450s, 1715 S, 1705s, 1655 S. - $^1\text{H-NMR}$.: 1.29 (t, $J = 7$, $\text{CH}_3\text{CH}_2\text{O}$); 1.61 and 1.68 (2 br. s, 2 $\text{H}_3\text{C}-\text{C}(10)$); 2.26 ($d \times t$, $J_1 = 7$, $J_2 = 7$, 2 H-C(8)); 2.47 (t, $J = 7$, 2 H-C(7)); 2.62 ($d \times d$, $J_1 = 18$, $J_2 = 8.6$, 1 H-C(5)); 2.71 ($d \times d$, $J_1 = 18$, $J_2 = 3.6$, 1 H-C(5)); 4.20 (qa, $J = 7$,

$\text{CH}_3\text{CH}_2\text{O}$): 4.74 (*m*, H–C(4)); 5.04 (br. *t*, $J=7$, H–C(9)); 6.11 ($d \times d$, $J_1=16$, $J_2=2$, H–C(2)); 6.87 ($d \times d$, $J_1=16$, $J_2=4.2$, H–C(3)).

Ethyl 6,7-dimethyl-3-oxo-7-octenoate (**9**). Sodium hydride dispersion (80% by weight) in oil (33 g, 1.1 mol) was degreased with pentane, suspended in anhyd. ether (300 ml) and allowed to stir at 25° overnight (increases the reactivity of the hydride). Ethyl carbonate (118 g, 1 mol) was added and the mixture heated to reflux temp. From 70 g (0.5 mol) of 5,6-dimethyl-6-hepten-2-one (**3**) [6] in a dropping funnel one quarter was added. Heating was continued until hydrogen evolution started. At this point, the rest of **3** was added at such a rate that gentle reflux was maintained. After the addition was complete, heating was continued for 4 h. The mixture was then poured onto a mixture of crushed-ice/acetic acid (*ca.* 100 g), and extracted twice with ether. The ethereal phase was washed (water), dried (MgSO_4) and concentrated to give *ca.* 120 g of crude **9**. Four identical runs (a total of *ca.* 470 g) were distilled together using a *Vigreux* column to give 30.7 g of a forerun (b.p. *ca.* 89°/0.1 Torr), 296 g (70%) of pure **9** (b.p. 89–96°/0.1 Torr), and 87 g of residue. – IR. (CCl_4): 1715s, 1625s. – $^1\text{H-NMR}$.: 1.02 (*d*, $J=7$, $\text{H}_3\text{C-C}(6)$); 1.27 (*t*, $J=7$, $\text{CH}_3\text{CH}_2\text{O}$); 1.63 (br. *s*, $\text{H}_3\text{C-C}(7)$); 1.62 ($d \times t$, $J_1=7.5$, $J_2=7.5$, 2 H–C(5)); 2.16 ($t \times qa$, $J_1=7.5$, $J_2=7$, H–C(6)); 2.47 (*t*, $J=7.5$, 2 H–C(4)); 3.42 (*s*, 2 H–C(2)); 4.2 (*qa*, $J=7$, $\text{CH}_3\text{CH}_2\text{O}$); 4.68 and 4.72 (2 br. *s*, 2 H–C(8)). – MS.: 212 (1, M^+), 55 (100), 42 (70), 41 (66), 125 (65), 69 (55), 119 (55), 82 (53), 88 (43), 97 (30), 108 (30), 143 (10), 194 (10).

6,7-Dimethyl-3-oxo-7-octenoic acid (**10**). Keto ester **9** (53 g, 0.25 mol) was added dropwise to a solution of KOH (84% content, 25 g, 0.37 mol) in water (120 ml) at 10° during 10 min. After stirring overnight at 20°, the solution was acidified at –10 to 0° with 10% HCl solution (120 ml), extracted twice with ether, washed (water), dried (MgSO_4) and concentrated below 20° to yield 40 g of crude **10**. – IR. (CCl_4): 2930s, 1700s. – $^1\text{H-NMR}$.: 1.03 (*d*, $J=7$, $\text{H}_3\text{C-C}(6)$); 1.63 (br. *s*, $\text{H}_3\text{C-C}(7)$); 1.65 ($d \times t$, $J_1=7.5$, $J_2=7.5$, 2 H–C(5)); 2.16 ($t \times qa$, $J_1=7$, $J_2=7.5$, H–C(6)); 2.5 (*t*, $J=7.5$, 2 H–C(4)); 3.49 (*s*, 2 H–C(2)); 4.68 and 4.73 (2 br. *s*, 2 H–C(8)).

Ethyl (2E,4E)-9,10-dimethyl-6-oxoundeca-2,4,10-trienoate (**5**). The keto acid **10** was mixed with ethyl (2E)-4-oxo-2-butenate (**4**; 44.8 g, 0.35 mol) and stirred at 20° for 5 h to give the crude, extremely labile hydroxy-oxo acid **11**. After addition of petroleum ether 50–70° (200 ml) at 20° (to give a non-homogeneous solution), this was treated dropwise with dimethylformamide dimethyl acetal (35.7 g, 0.3 mol) at 0° ($\pm 3^\circ$) (slight evolution of CO_2). The resulting solution was then heated to 25° (vigorous evolution of CO_2). After stirring at reflux temp. (48°) for 2 h, the mixture was poured on ice, extracted with ether, washed (2N HCl, NaHCO_3 , H_2O), dried (MgSO_4), concentrated (yielding 41 g), and bulb-to-bulb distilled, bath temp. 160–170°/0.005 Torr, giving 29.5 g of semicrystalline material and 5.5 g of residue. Crystallization from pentane, chromatographic purification (silica gel, hexane/ether 9:1) of the mother liquors followed by crystallization gave a total of 24.7 g (39% overall yield based on **2**) of pure crystalline **5**, m.p. 39–40°. – IR. (neat): 3060w, 1715s, 1690s, 1595s, 997s, 890m. – $^1\text{H-NMR}$.: 1.04 (*d*, $J=7$, $\text{H}_3\text{C-C}(9)$); 1.32 (*t*, $J=7.5$, $\text{CH}_3\text{CH}_2\text{O}$); 1.65 (*s*, $\text{H}_3\text{C-C}(10)$); 1.68 ($d \times t$, $J_1=7$, $J_2=7.5$, 2 H–C(8)); 2.19 ($t \times qa$, $J_1=7$, $J_2=7.5$, H–C(9)); 2.53 (*t*, $J=7.5$, 2 H–C(7)); 4.24 (*qa*, $J=7.5$, $\text{CH}_3\text{CH}_2\text{O}$); 4.69 and 4.73 (2 *s*, 2 H–C(11)); 6.23 (*d*, $J=15$, H–C(2), *trans*); 6.44 (*d*, $J=15$, H–C(3), *trans*); 7.16 ($d \times d$, $J_1=15$, $J_2=11$, H–C(3)); 7.31 ($d \times d$, $J_1=15$, $J_2=11$, H–C(4)). – MS.: 250 (3, M^+), 95 (100), 41 (89), 55 (73), 29 (58), 67 (51), 117 (49), 122 (47), 81 (40), 139 (18), 153 (15), 177 (12), 168 (10).

Ethyl rel-(2R,4aR,8R,8aS)- and rel-(2R,4aS,8R,8aS)-8,8a-dimethyl-5-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxylate (**13** and **14**, *resp.*). A solution of **5** (12.5 g, 50 mmol), anhyd. toluene (250 ml) and hydroquinone (500 mg) was degassed and then heated in a sealed Pyrex glass tube for 6 h at 250°. Concentration and bulb-to-bulb distillation at 115–130°/0.01 Torr gave 9.3 g (74%) of a 1:1 mixture of **13** and **14** (determined by $^{13}\text{C-NMR}$).

A solution of 0.6% **5** in anhyd. toluene in the presence of hydroquinone, heated at 250° for 6 h in a stainless steel autoclave, gave 93% of pure **14**. **13**: $^1\text{H-NMR}$.: 0.57 (*s*, $\text{H}_3\text{C-C}(8a)$). – $^{13}\text{C-NMR}$.: see *Table*². **14**: IR. (neat): 1730s, 1710s. – $^1\text{H-NMR}$.: 0.88 (*s*, $\text{H}_3\text{C-C}(8a)$); 0.94 (*d*, $J=7$, $\text{H}_3\text{C-C}(8)$); 1.29 (*t*, $J=7.5$, $\text{CH}_3\text{CH}_2\text{O}$); 2.74 (narrow *m*, H–C(4a)); 3.17 (br. *m*, H–C(2)); 4.18 (*qa*, $J=7.5$, $\text{CH}_3\text{CH}_2\text{O}$); 5.48 (*m*, H–C(3)); 5.94 (*m*, H–C(4)). Irrad. at 0.94 ppm \rightarrow 2.03 ($d \times d$, $J(ax,ax)=13$, $J(ax,eq)=4$, H–C(8)). – $^{13}\text{C-NMR}$.: see *Table*². – MS.: 250 (45, M^+), 177 (100), 204 (83), 93 (97), 43 (75), 29 (41), 55 (33), 121 (29), 107 (28), 77 (26), 159 (23), 69 (19), 235 (18).

Isomerization of a mixture 13/14 into 14. A 1:1 mixture **13/14** (2 g) was passed through a column of silica gel (60 g) in hexane/ether 9:1. After evaporation of the solvent, 1.6 g of pure **14** was collected.

Isomerization of a mixture 13/14 into ethyl rel-(2R, 8S, 8aR)-8, 8a-dimethyl-5-oxo-1, 2, 3, 5, 6, 7, 8, 8a-octahydronaphthalene-2-carboxylate (15). a) Upon chromatography of a 1:1 mixture **13/14** (1 g) on neutral aluminium oxide (activity III; 50 g) in hexane/ether 97:3, 0.51 g of pure **15** was obtained. b) A 1:1 mixture **13/14** (250 mg, 1 mmol), toluene (2.5 ml) and *p*-toluenesulfonic acid monohydrate (5 mg) was heated at reflux for 3 h. The mixture was taken up in ether, washed (NaHCO₃, H₂O), dried (MgSO₄), concentrated and bulb-to-bulb distilled at 120–130°/0.01 Torr yielding 226 mg (90%) of **15**. - IR. (neat): 1725s, 1688s. - ¹H-NMR.: 0.88 (s, H₃C-C(8a)); 0.98 (d, J=6.5, H₃C-C(8)); 1.28 (t, J=7, CH₃CH₂O); 4.15 (qa, J=7, CH₃CH₂O); 6.26 (d×d, J₁=3, J₂=5, H-C(4)). Irrad. at 0.98 ppm → 1.89 (d×d, J(ax, ax)=12, J(ax, eq)=4, H-C(8)). - ¹³C-NMR.: see Table²). - MS.: 250 (48, M⁺), 177 (100), 31 (58), 43 (43), 121 (34), 55 (26), 161 (25), 105 (22), 77 (19), 135 (16), 235 (13), 69 (12).

Mixture of ethyl rel-(2R, 8S, 8aR)- and rel-(2R, 8R, 8aS)-8, 8a-dimethyl-1, 2, 3, 4, 6, 7, 8, 8a-octahydronaphthalene-2-carboxylate (23 and 25 [22], resp.), and ethyl rel-(2R, 8S, 8aR)-8, 8a-dimethyl-1, 2, 3, 5, 6, 7, 8, 8a-octahydronaphthalene-2-carboxylate (24) via ethyl rel-(2R, 8S, 8aR)-8, 8a-dimethyl-5-(tosylhydrazono)-1, 2, 3, 5, 6, 7, 8, 8a-octahydronaphthalene-2-carboxylate (21). Keto ester **15** (1 g, 4 mmol), tosylhydrazine (0.84 g, 4.5 mmol) and anh. ethanol (20 ml) were stirred at reflux temp. for 1 h. Evaporation of the solvent gave 1.65 g of non-crystalline crude **21**. Crude **21** (0.43 g) was dissolved in glacial acetic acid (5 ml), and NaBH₄ (0.38 g, 10 mmol) was added portionwise at 20° with external cooling. The resulting mixture was stirred at 70° for 1 h, poured onto ice, made alkaline by addition of 10% NaOH-solution, and extracted with ether. The extract was washed (1N HCl, NaHCO₃, H₂O), dried (MgSO₄) and concentrated. The resulting crude product (240 mg) was chromatographed on silica gel (12 g) with hexane/ether 95:5 yielding 86 mg of an oil. GLC. (10% Carbowax, 200°) showed two peaks close together. The ¹H-NMR. of the first peak showed it to consist of **23** and **24**, and the second peak was identified as **25**. **23**: IR. (neat): 1730s, 1460m, 1376m, 1370m. - ¹H-NMR.: 0.83 (s, H₃C-C(8a)); 0.88 (d, J=6, H₃C-C(8)); 1.28 (t, J=7, CH₃CH₂O); 4.16 (qa, J=7, CH₃CH₂O); 5.33 (br. m, H-C(5)). - ¹³C-NMR.: see Table²). - MS.: 236 (33, M⁺), 147 (100), 162 (85), 120 (67), 95 (65), 41 (43), 105 (40), 29 (34), 55 (30), 79 (30), 67 (24), 221 (12), 190 (10). **24**: ¹H-NMR.: 0.92 (d, J=7, H₃C-C(8)); 1.01 (s, H₃C-C(8a)); 1.27 (t, J=7, CH₃CH₂O); 4.16 (qa, J=7, CH₃CH₂O); 5.38 (br. m, H-C(4)). **25**: IR. (neat): 1730s, 1457m. - ¹H-NMR.: 0.88 (d, J=6, H₃C-C(8)); 0.93 (s, H₃C-C(8a)); 1.25 (t, J=7, CH₃CH₂O); 2.58 (d×d×d×d, J₁=13, J₂=13, J₃=3.25, J₄=3.25, H-C(2)); 4.12 (qa, J=7, CH₃CH₂O); 5.35 (m, H-C(5)). - ¹³C-NMR.: see Table²). - MS.: 236 (35, M⁺), 197 (100), 162 (95), 163 (56), 120 (50), 93 (39), 105 (38), 41 (34), 221 (30), 79 (25), 69 (24), 29 (23), 55 (22).

Ester 23 [23] from tosylhydrazono ester 21. The crude **21** (1.65 g) (see above) was dissolved in CHCl₃ (10 ml), 'catecholborane' (0.56 ml, 5 mmol) was added at 0° and the mixture stirred at 0° for 2 h. After addition of NaOAc·3H₂O (1.63 g, 12 mmol), the mixture was stirred at reflux temp. (60°) for 1 h, allowed to cool, poured onto ice-water, and extracted with ether. Washing (1N HCl, NaHCO₃, drying (MgSO₄) and concentration of the extract gave 2.15 g of crude material which was chromatographed on silica gel (40 g) using hexane/ether 9:1, and bulb-to-bulb distilled (90–100°/0.01 Torr) to give 518 mg (55% based on **15**) of pure **23**.

(+)-(2R, 8R, 8aS)-8, 8a-Dimethyl-1, 2, 3, 4, 6, 7, 8, 8a-octahydro-2-naphthyl methyl ketone (+)-**31** from natural valencene (= (+)-(2R, 8R, 8aS)-2-isopropenyl-8, 8a-dimethyl-1, 2, 3, 4, 6, 7, 8, 8a-octahydronaphthalene; (+)-**30**). Natural valencene ((+)-**30**, [α]_D²⁰ = +91.3° (c=1.55, CHCl₃), 10.2 g (50 mmol) in CH₂Cl₂ (100 ml) was ozonolyzed (1 equiv. of O₃) at -30° for 1 h. Dimethylsulfide (7.75 g, 125 mmol) was added at -20 to -10°, the mixture was stirred at +20° for 1 h, washed (NaHCO₃, H₂O), dried (MgSO₄) and concentrated. Since a test for peroxides (KI, thiosulfate titration) was still positive the mixture was reduced again by stirring with triphenylphosphine (157 g, 60 mmol) in toluene (50 ml) at 20° overnight (peroxide test negative). The solution was concentrated, diluted with pentane (50 ml) and filtered. The filtrate was cooled to -30° (2 h) and filtered again. After concentration, the crude material was bulb-to-bulb distilled at 100–120°/0.01 Torr to give 8.41 g of volatile material which was chromatographed on silica gel (85 g) with hexane/ether 99:1 to 9:1. Pure ketone (+)-**31** (1.81 g, 17.6%) was obtained, [α]_D²⁰ = +106° (c=1.22, CHCl₃). - IR. (neat): 1710s. - ¹H-NMR.: 0.88 (d, J=6.5, H₃C-C(8)); 0.94 (s, H₃C-C(8a)); 2.15 (s, CH₃CO-C(2)); 2.64 (d×d×d×d, J₁=12.5, J₂=12.5, J₃=3.25, J₄=3.25, H-C(2)); 5.35 (m, H-C(5)). - ¹³C-NMR.: see Table²). - MS.: 206 (51, M⁺), 43 (100), 121 (56), 91 (46), 107 (38), 135 (31), 163 (31), 79 (27), 55 (25), 71 (23), 191 (17), 29 (15), 147 (14).

*Valerianol (= (+)-(2'R, 8'R, 8a'S)-1-[8', 8a'-Dimethyl-1', 2', 3', 4', 6', 7', 8', 8a'-octahydro-2'-naphthyl]-1-methylethanol; (+)-**29**) from ketone (+)-**31**.* A solution of 0.85N ethereal methylolithium (6 ml,

5.1 mmol) was added at 0° to a solution of (+)-**31** (0.3 g, 5 mmol) in anh. ether (20 ml). After stirring for 2 h at 20°, the mixture was poured onto ice, extracted with ether, washed (1N HCl, NaHCO₃, H₂O), dried (MgSO₄) and concentrated (0.98 g). Chromatography on silica gel (30 g) with hexane/ether 9:1, followed by bulb-to-bulb distillation at 100–110°/0.05 Torr gave 325 mg (29%) of pure (+)-**29**, [α]_D²⁰ = +151.4° (*c* = 1.2, CHCl₃). – IR. (neat): 3350s. – ¹H-NMR.: 0.88 (*d*, *J* = 7, H₃C–C(8')); 0.92 (*s*, H₃C–C(8a')); 1.16 and 1.17 (2 *s*, 2 H₃C–C(1)); 5.32 (*m*, H–C(5')). – ¹³C-NMR.: see Table². – MS.: 222 (1, M⁺), 161 (100), 59 (99), 204 (42), 135 (28), 41 (37), 93 (28), 105 (27), 81 (25), 189 (22), 149 (18), 67 (17), 29 (12).

rel-(4R, 4aS, 6S)-6-(1'-Hydroxy-1'-methylethyl)-4, 4a-dimethyl-3, 4, 4a, 5, 6, 7-hexahydronaphthalen-1(2H)-one (**32**) from keto ester **15**. A solution of 1.3N ethereal methylolithium (38 ml, 50 mmol) was added at 10–20° to a solution of **15** (2.5 g, 10 mmol) in anh. ether (25 ml). After stirring for 3 h at 20°, the mixture was poured onto ice, extracted with ether, washed (1N HCl, NaHCO₃, H₂O), dried (MgSO₄) and concentrated (2.55 g). Chromatography on silica gel (50 g) with hexane/ether 9:1 gave 1.63 g (69%) of pure **32**. – IR. (neat): 3460s, 1680s, 1630s. – ¹H-NMR.: 0.92 (*s*, H₃C–C(4a)); 0.95 (*d*, *J* = 7, H₃C–C(4a)); 1.21 and 1.215 (2 *s*, 2 H₃C–C(1)); 2.33 (*d* × *d* × *d*, *J*₁ = 17, *J*₂ = 12, *J*₃ = 8, H_{ax}–C(2)); 2.5 (*d* × *d* × *d*, *J*₁ = 17, *J*₂ = 6, *J*₃ = 2, H_{eq}–C(2)); 6.15 (*d* × *d*, *J*₁ = 6.5, *J*₂ = 2, H–C(8)). – ¹³C-NMR.: see Table². – MS.: 236 (0, M⁺), 43 (100), 59 (72), 91 (59), 119 (57), 175 (46), 105 (43), 161 (38), 77 (29), 145 (22), 218 (17), 133 (17).

rel-(4R, 4aS, 6S)-6-Isopropenyl-4, 4a-dimethyl-3, 4, 4a, 5, 6, 7-hexahydronaphthalen-1(2H)-one (**33**) [31] by dehydration of **32**. Thionyl chloride (0.3 ml or 0.48 g, 4 mmol) was added at –10° to a stirred solution of **32** (0.54 g, 2–3 mmol) in anh. pyridine (5 ml). The resulting mixture was stirred at 0° for 15 min, poured onto ice, extracted with ether, washed (1N HCl, NaHCO₃, H₂O), dried (MgSO₄) and concentrated (0.37 g). Chromatography on silica gel (50 g) with hexane containing 2 → 5% ether gave 76 mg (15%) of pure **33** [31]. – ¹H-NMR.: 0.92 (*s*, H₃C–C(4a)); 0.95 (*d*, *J* = 7, H₃C–C(4)); 1.76 (*br. s.*, CH₂=C(CH₃)); 2.34 (*d* × *d* × *d*, *J*₁ = 17, *J*₂ = 12, *J*₃ = 7.5, H_{ax}–C(2)); 2.5 (*d* × *d* × *d*, *J*₁ = 17, *J*₂ = 6, *J*₃ = 2, H_{eq}–C(2)); 4.72 and 4.77 (2 *br. s.*, CH₂=C(CH₃)); 6.19 (*d* × *d*, *J*₁ = 6, *J*₂ = 2, H–C(8)). – ¹³C-NMR.: see Table². – MS.: 218 (100, M⁺), 175 (74), 55 (67), 105 (67), 119 (67), 161 (65), 91 (63), 41 (63), 203 (54), 133 (50), 147 (42), 79 (42), 67 (26).

REFERENCES

- [1] K. Alder & M. Schumacher, in 'Progress in the Chemistry of Organic Natural Products', L. Zechmeister, ed., Vol. 10, Springer-Verlag, Wien 1953, p. 1; K. Alder, in «Neuere Methoden der präparativen organischen Chemie», W. Foerst, ed., Vol. 1, Verlag-Chemie, Weinheim 1963, p. 251; H. Wollweber, «Diels-Alder-Reaktion», Georg Thieme Verlag, Stuttgart 1972.
- [2] a) R. G. Carlson, Annu. Rep. Med. Chem. 9, 270 (1974); b) W. Oppolzer, Angew. Chem. Int. Ed. 16, 10 (1977); c) G. Brieger & J. N. Bennett, Chem. Rev. 80, 63 (1980).
- [3] a) «Houben-Weyl, Methoden der organischen Chemie», Vol. V/1b, E. Müller, ed., Georg Thieme Verlag, Stuttgart 1972, p. 1; b) Annual Reports in Organic Synthesis 1979, L. G. Wade, jr. & M. J. O'Donnell, eds., Academic Press 1980; and earlier volumes in this series.
- [4] J. A. Marshall & T. M. Warne, jr., J. Org. Chem. 36, 178 (1971).
- [5] F. Näf, R. Decorzant & W. Thommen, Helv. Chim. Acta 62, 114 (1979).
- [6] a) H. Pommer, H. Mueller & H. Overwein (BASF AG), S. Afr. Pat. 6707,415 (25.4.1968); Chem. Abstr. 70, 87041f (1969); b) J. M. Conia, F. Leyendecker & C. Dubois-Faget, Tetrahedron Lett. 1966, 129.
- [7] a) H.-D. Scharf & J. Janus, Chem. Ber. 111, 2741 (1978); b) P. L. Stotter & J. B. Eppner, Tetrahedron Lett. 1973, 2417.
- [8] G. Jones, Org. React. 15, 204 (1967).
- [9] A. Rüttimann, A. Wick & A. Eschenmoser, Helv. Chim. Acta 58, 1450 (1975); E. Vogel, Diss. ETH Nr. 6123 (1978).
- [10] S. Hara, H. Taguchi, H. Yamamoto & H. Nozaki, Tetrahedron Lett. 1975, 1545.
- [11] a) J. Mulzer, U. Kühl & G. Brüntrup, Tetrahedron Lett. 1978, 1545; b) J. Mulzer & G. Brüntrup, Tetrahedron Lett. 21, 1909 (1979).

- [12] a) *W. R. Roush & St. E. Hall*, *J. Am. Chem. Soc.* **103**, 5200 (1981); b) *W. R. Roush & St. M. Peseckis*, *ibid.* **103**, 6696 (1981); c) *W. R. Roush, J. I. Ko & H. R. Gillis*, *J. Org. Chem.* **45**, 4264 (1980).
- [13] *S. R. Wilson & D. T. Mao*, *J. Am. Chem. Soc.* **100**, 6289 (1978).
- [14] *S. R. Wilson & D. T. Mao*, *J. Org. Chem.* **44**, 3093 (1979).
- [15] *S. R. Wilson & J. C. Huffmann*, *J. Org. Chem.* **45**, 560 (1980).
- [16] *J. D. White & B. G. Sheldon*, *J. Org. Chem.* **46**, 2273 (1981); *J. D. White, B. G. Sheldon, B. A. Solheim & J. Clardy*, *Tetrahedron Lett.* **1978**, 5189.
- [17] *D. F. Taber, C. Campbell, B. P. Gunn & I. Chin*, *Tetrahedron Lett.* **1981**, 5141.
- [18] *R. K. Boeckman, jr. & D. M. Demko*, *J. Org. Chem.* **47**, 1789 (1982).
- [19] *T. Takebayashi, N. Iwasawa & T. Mukaiyama*, *Chem. Lett.* **1982**, 579.
- [20] *R. M. Coates & J. E. Shaw*, *J. Org. Chem.* **35**, 2597 (1970).
- [21] *R. O. Hutchins, C. A. Milewski & B. E. Maryanoff*, *J. Am. Chem. Soc.* **95**, 3662 (1973); *R. O. Hutchins, M. Kacher & L. Rua*, *J. Org. Chem.* **40**, 923 (1975); *E. J. Taylor & C. Djerassi*, *J. Am. Chem. Soc.* **98**, 2275 (1976).
- [22] *R. O. Hutchins & N. R. Natale*, *J. Org. Chem.* **43**, 2299 (1978).
- [23] a) *G. W. Kabalka & J. D. Baker, jr.*, *J. Org. Chem.* **40**, 1834 (1975); b) *G. W. Kabalka, D. T. C. Yang & J. D. Baker, jr.*, *ibid.* **41**, 574 (1976); c) *G. W. Kabalka, D. T. C. Yang, J. H. Chandler & J. D. Baker, jr.*, *Synthesis* **1977**, 124.
- [24] *H. Ishi, T. Tozoy & H. Minato*, *J. Chem. Soc. C* **1966**, 1545.
- [25] *J. Krepinský, O. Motl, L. Dolejš, L. Novotný, V. Herout & R. B. Bates*, *Tetrahedron Lett.* **1968**, 3315; *J. Hochmannová & V. Herout*, *Collect. Czech. Chem. Commun.* **29**, 2369 (1964); *E. Piers & R. J. Kezieve*, *Tetrahedron Lett.* **1968**, 583.
- [26] *G. Jommi, J. Krepinský, V. Herout & F. Sorm*, *Collect. Czech. Chem. Commun.* **34**, 593 (1969); *H. Hikino, N. Suzuki & T. Takemoto*, *Chem. Pharm. Bull.* **16**, 832 (1968).
- [27] a) *G. L. K. Hunter & W. B. Brogden, jr.*, *J. Food Sci.* **30**, 1 (1965); b) *W. D. MacLeod, jr.*, *Tetrahedron Lett.* **1965**, 4779.
- [28] a) *H. M. McGuire, H. C. Odom, jr. & A. R. Pinder*, *J. Chem. Soc., Perkin Trans. I*, 1879 (1974); b) *S. Torii, T. Inokuchi & K. Handa*, *Bull. Chem. Soc. Jpn.* **55**, 887 (1982).
- [29] *H. C. Odom, jr. & A. R. Pinder*, *J. Chem. Soc., Perkin Trans. I*, 2193 (1972).
- [30] *A. E. Bradfield, A. R. Penfold & J. L. Simonsen*, *J. Chem. Soc.* **1932**, 2744; *A. R. Penfold & J. L. Simonsen*, *ibid.* **1939**, 87; *C. Djerassi, R. Mauli & L. H. Zalkow*, *J. Am. Chem. Soc.* **81**, 3424 (1959); *L. H. Zalkow, F. X. Markley & C. Djerassi*, *ibid.* **81**, 2914 (1959); *idem*, *ibid.* **82**, 6354 (1960).
- [31] *F. E. Ziegler, G. R. Reid, W. L. Studt & P. A. Wender*, *J. Org. Chem.* **42**, 1991 (1977); *F. E. Ziegler & P. A. Wender*, *Tetrahedron Lett.* **1974**, 449.
- [32] *J. E. McMurry, J. H. Musser, M. S. Ahmad & L. C. Blaszcak*, *J. Org. Chem.* **40**, 1829 (1975); *J. Ficini & A. M. Touzin*, *Tetrahedron Lett.* **1977**, 1081.
- [33] *F. W. Wehrli & T. Wirthlin*, 'Interpretation of Carbon-¹³NMR. Spectra', Heyden, London, New York 1977.
- [34] a) *W. A. Ayer, L. M. Browne, S. Fung & J. B. Stothers*, *Org. Magn. Reson.* **11**, 73 (1978); b) *S. H. Grover, D. H. Marr, J. B. Stothers & C. T. Tan*, *Can. J. Chem.* **53**, 1351 (1975); c) *D. K. Dalling, D. M. Grant & E. G. Paul*, *J. Am. Chem. Soc.* **95**, 3718 (1973); d) *B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert & F. Näf*, *Helv. Chim. Acta* **58**, 1567 (1975).
- [35] *B. Maurer, A. Hauser, W. Thommen, K.-H. Schulte-Elte & G. Ohloff*, *Helv. Chim. Acta* **63**, 293 (1980).