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

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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 entropy 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* strategy[1]).

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

1 **2**

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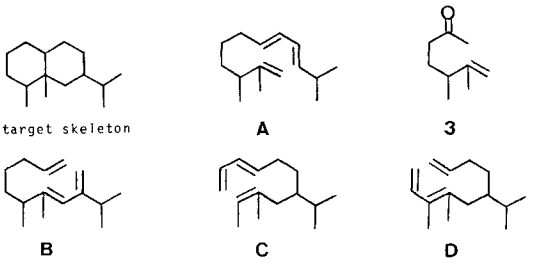
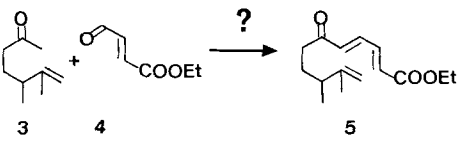
In this work we describe an intramolecular *Diels-Alder* route to eudesmane and valencane sesquiterpenes[2])[3]) *via* an acyclic triene precursor which is readily accessible from industrial starting materials.

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 C_{15}-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 fumaraldehydate **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**).

Scheme 1[4])



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 fumaraldehydate (**4**) furnished, in 29% yield, the expected aldol ester **7** which, however, was resistent to dehydration (*e.g.* distillation over $KHSO_4$,

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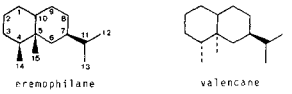
[2]) The definition of the valencane and eremophilane skeleton used in this paper is, in accord with *Marshall & Warne* [4], as follows:

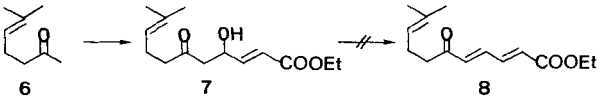


For simplicity, the eremophilane/valencane numbering is retained in the general part of this paper for all hydronaphthalene derivatives. Systematic names are given in the *Exper. Part.*

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

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

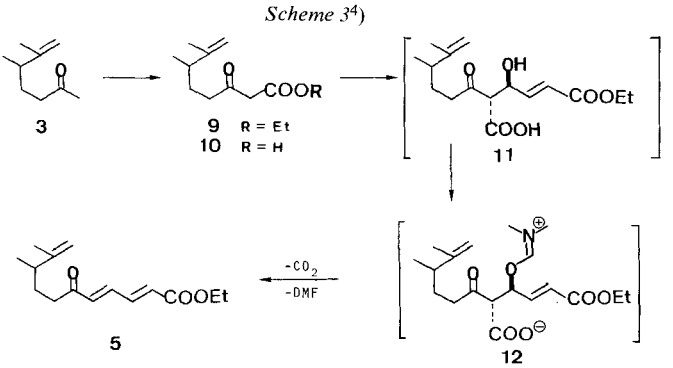
Scheme 2[4])



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 CO_2. 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 CO_2, 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.* $O-CH=N(CH_3)_2^+$) 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)*.

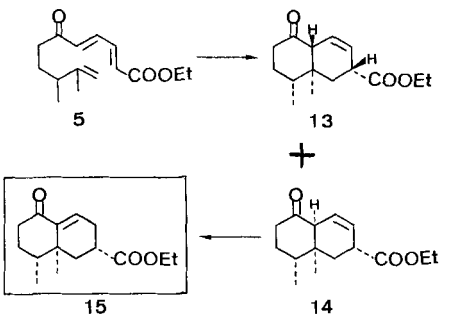
Scheme 3[4])



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*-

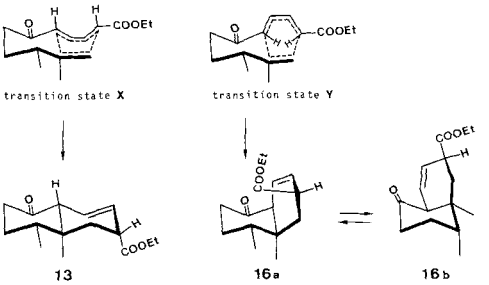
fused **13** and its *cis*-isomer **14**, or only *cis*-isomer **14** by rapid C(10)-epimerization of the unstable primary *Diels-Alder* product **13**.

Scheme 4[4])



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** (→ **16**) or other alternatives.

The secondary methyl group of **X** is thereby in the more stable equatorial position, avoiding the 1,3-diaxial H,CH_3-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** → **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** → **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]).

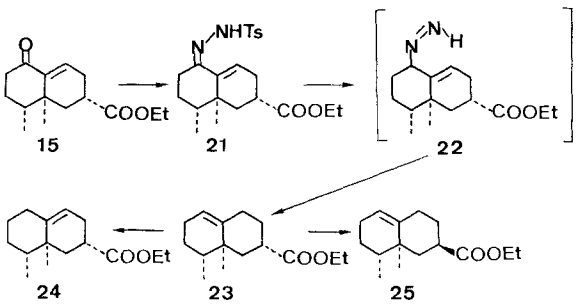
Scheme 5[4])

[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 $NaBH_4$ 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 6[4])

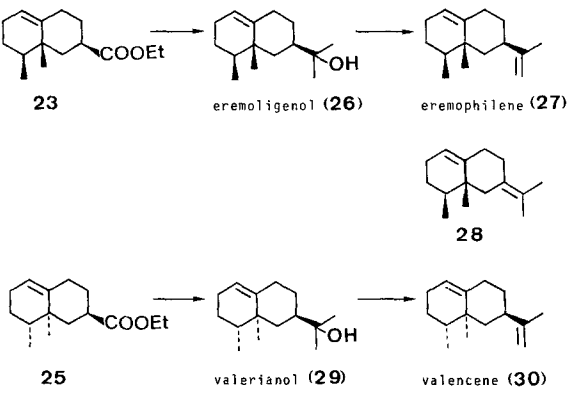


Finally, **23** was transformed, as described by *Coates & Shaw* [20], into racemic eremoligenol (**26**) [24], eremophilene (**27**) [25], its double-bond isomer **28** [20], valerianol (**29**) [26], and valencene (**30**) [27][7]) (*Schemes 6* and *7*). The spectral data of racemic valerianol (**29**) 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 methyllithium followed by $SOCl_2$/pyridine dehydration, into the

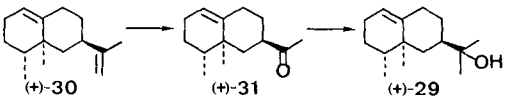
[6]) Identical in all respects with a sample kindly supplied by Professor *Coates*.
[7]) For an alternative synthesis, see [28].
[8]) For racemic **31**, see [28].
[9]) For an alternative synthesis of (+)-**29**, see [29].

Scheme 7[4])

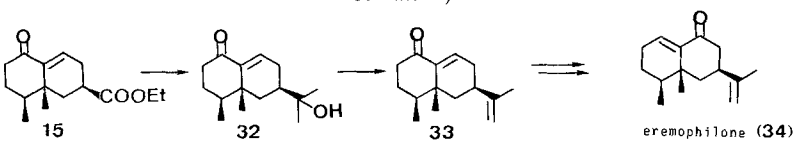


known eremophilone intermediate **33** [31] as main product (50% yield based on **15**, see *Scheme 9*). Since **33** had already been transformed in three steps by *Ziegler et al.* [31] into racemic eremophilone (**34**) (first total synthesis), our access to **33** also opened a new route to racemic eremophilone[10]).

Scheme 8[4])



Scheme 9[4])



5. NMR. data of the bicyclic intermediates. – The ^{13}C-NMR. shift assignments of the bicyclic structures **13**–**15**, **23**, and **25**–**39** (see *Table*) are based on the proton-noise-decoupled (PND) and the single-frequency off-resonance-decoupled (SFORD) spectra, selective proton-decoupling technique, deuterium labelling [2-$^2H_2$]-**15**, and chemical shift correlations between our substances and related compounds[11]).

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*-methyldecalin **35** [34a] and **36** [34c], *Table*), the β-deshielding effect imposed by $H_3C(14)$

[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)	CH_3–CH_2–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[a])	–	–	20.1[a'])	16.0[a])[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	27.2	29.3	45.8	–	–	15.7	–	–	–	–
36	[34c][e])	28.4	21.8	22.8	30.3	33.1	42.3	22.8	27.8	28.0	41.8	–	–	28.3	–	–	–	–
37	[34d][e])	119.2	26.0	19.1	40.2	34.8	42.3	22.5	28.7	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[a'])	20.1[a'])
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	109.3

[a])[a']) Similar values may be inversed. [b]) Deuterium labelling. [c]) Assigned by selective proton decoupling technique. [d]) Not observed. *e*) Shift values taken from the reference given.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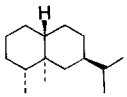
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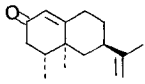
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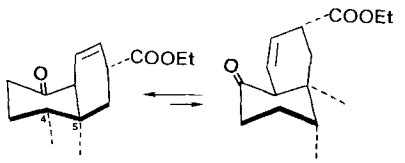
upon $H_2C(3)$ ($\Delta\delta = +9$ ppm) as well as the *γ-gauche*-shielding effect ($\Delta\delta = -5$ ppm) by $H_3C(14)$ upon $H_3C(15)$ (*Table, e.g.* **35** and **38**). On these grounds the relative configuration at the centres C(4), C(5), and C(10) of **13** and **14** (conformation **14a** preferred), and the relative configuration at the centers C(4) and C(5) of **15**, **32**, and **33** could be rigorously assigned. ^{1}H-NMR. spectroscopy (360 MHz) further corroborated the *cis*-configuration of the vicinal methyl groups in **14** (conformation **14a** preferred) showing, after irradiation at $H_3C(14)$, the typical couplings for an



14a 14b

axial hydrogen atom at C(4) ($J(ax, ax) = 13$ Hz; $J(ax, eq) = 4$ Hz). The ^{1}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 ^{1}H- and ^{13}C-NMR. spectra could be given, these configurations were established by chemical correlation with compounds of known configuration (*i.e.* **23**, eremoligenol (**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. ($H_2O \leq 0.1\%$) 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 (2*E*)-4-oxo-2-butenoate (**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): 3450*s*, 1715 *S*, 1705*s*, 1655 *S*. – ^{1}H-NMR.: 1.29 (*t*, $J = 7$, CH_3CH_2O); 1.61 and 1.68 (2 br. *s*, 2 H_3C–C(10)); 2.26 (*d*×*t*, $J_1 = 7$, $J_2 = 7$, 2 H–C(8)); 2.47 (*t*, $J = 7$, 2 H–C(7)); 2.62 (*d*×*d*, $J_1 = 18$, $J_2 = 8.6$, 1 H–C(5)); 2.71 (*d*×*d*, $J_1 = 18$, $J_2 = 3.6$, 1 H–C(5)); 4.20 (*qa*, $J = 7$,

CH_3CH_2O); 4.74 (*m*, H–C(4)); 5.04 (br. *t*, J = 7, H–C(9)); 6.11 (*d*×*d*, J_1 = 16, J_2 = 2, H–C(2)); 6.87 (*d*×*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 anh. 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): 1715*s*, 1625 *S*. – ^{1}H-NMR.: 1.02 (*d*, *J* = 7, H_3C–C(6)); 1.27 (*t*, *J* = 7, CH_3CH_2O); 1.63 (br. *s*, H_3C–C(7)); 1.62 (*d*×*t*, J_1 = 7.5, J_2 = 7.5, 2 H–C(5)); 2.16 (*t*×*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, CH_3CH_2O); 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): 2930*s*, 1700*s*. – ^{1}H-NMR.: 1.03 (*d*, *J* = 7, H_3C–C(6)); 1.63 (br. *s*, H_3C–C(7)); 1.65 (*d*×*t*, J_1 = 7.5, J_2 = 7.5, 2 H–C(5)); 2.16 (*t*×*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 (2*E*)-4-oxo-2-butenoate (**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° (±3°) (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): 3060*w*, 1715*s*, 1690*s*, 1595*s*, 997*s*, 890*m*. – ^{1}H-NMR.: 1.04 (*d*, *J* = 7, H_3C–C(9)); 1.32 (*t*, *J* = 7.5, CH_3CH_2O); 1.65 (*s*, H_3C–C(10)); 1.68 (*d*×*t*, J_1 = 7, J_2 = 7.5, 2 H–C(8)); 2.19 (*t*×*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, CH_3CH_2O); 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*×*d*, J_1 = 15, J_2 = 11, H–C(3)); 7.31 (*d*×*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-*(2*R*,4a*R*,8*R*,8a*S*)- and* rel-*(2*R*,4a*S*,8*R*,8a*S*)-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), anh. 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}C-NMR.).

A solution of 0.6% **5** in anh. toluene in the presence of hydroquinone, heated at 250° for 6 h in a stainless steal autoclave, gave 93% of pure **14**. **13**: ^{1}H-NMR.: 0.57 (*s*, H_3C–C(8a)). – ^{13}C-NMR.: see *Table*[2]). **14**: IR. (neat): 1730*s*, 1710*s*. – ^{1}H-NMR.: 0.88 (*s*, H_3C–C(8a)); 0.94 (*d*, *J* = 7, H_3C–C(8)); 1.29 (*t*, *J* = 7.5, CH_3CH_2O); 2.74 (narrow *m*, H–C(4a)); 3.17 (br. *m*, H–C(2)); 4.18 (*qa*, *J* = 7.5, CH_3CH_2O); 5.48 (*m*, H–C(3)); 5.94 (*m*, H–C(4)). Irrad. at 0.94 ppm → 2.03 (*d*×*d*, *J*(*ax*,*ax*) = 13, *J*(*ax*,*eq*) = 4, H–C(8)). – ^{13}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-*(2*R,*8*S,*8a*R*)-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 ($NaHCO_3$, H_2O), dried ($MgSO_4$), concentrated and bulb-to-bulb distilled at 120–130°/0.01 Torr yielding 226 mg (90%) of **15**. – IR. (neat): 1725*s*, 1688*s*. – ^{1}H-NMR.: 0.88 (*s*, H_3C–C(8a)); 0.98 (*d*, J = 6.5, H_3C–C(8)); 1.28 (*t*, J = 7, CH_3CH_2O); 4.15 (*qa*, J = 7, CH_3CH_2O); 6.26 (*d*×*d*, J_1 = 3, J_2 = 5, H–C(4)). Irrad. at 0.98 ppm → 1.89 (*d*×*d*, *J(ax,ax)* = 12, *J(ax,eq)* = 4, H–C(8)). – ^{13}C-NMR.: see *Table*[2]). – 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-*(2*R,*8*S,*8a*R*)- and* rel-*(2*R,*8*R,*8a*S*)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-2-carboxylate* (**23** *and* **25** [22], *resp.*), *and ethyl* rel-*(2*R,*8*S,*8a*R*)-8,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-2-carboxylate* (**24**) via *ethyl* rel-*(2*R,*8*S,*8a*R*)-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 $NaBH_4$ (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, $NaHCO_3$, H_2O), dried ($MgSO_4$) 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 ^{1}H-NMR. of the first peak showed it to consist of **23** and **24**, and the second peak was identified as **25**. **23**: IR. (neat): 1730*s*, 1460*m*, 1376*m*, 1370*m*. – ^{1}H-NMR.: 0.83 (*s*, H_3C–C(8a)); 0.88 (*d*, J = 6, H_3C–C(8)); 1.28 (*t*, J = 7, CH_3CH_2O); 4.16 (*qa*, J = 7, CH_3CH_2O); 5.33 (br. *m*, H–C(5)). – ^{13}C-NMR.: see *Table*[2]). – 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**: ^{1}H-NMR.: 0.92 (*d*, J = 7, H_3C–C(8)); 1.01 (*s*, H_3C–C(8a)); 1.27 (*t*, J = 7, CH_3CH_2O); 4.16 (*qa*, J = 7, CH_3CH_2O); 5.38 (br. *m*, H–C(4)). **25**: IR. (neat): 1730*s*, 1457*m*. – ^{1}H-NMR.: 0.88 (*d*, J = 6, H_3C–C(8)); 0.93 (*s*, H_3C–C(8a)); 1.25 (*t*, J = 7, CH_3CH_2O); 2.58 (*d*×*d*×*d*×*d*, J_1 = 13, J_2 = 13, J_3 = 3.25, J_4 = 3.25, H–C(2)); 4.12 (*qa*, J = 7, CH_3CH_2O); 5.35 (*m*, H–C(5)). – ^{13}C-NMR.: see *Table*[2]). – 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 $CHCl_3$ (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 · 3 H_2O (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, $NaHCO_3$, drying ($MgSO_4$) 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**.

*(+)-(2*R,*8*R,*8a*S*)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2-naphthyl methyl ketone (+)-***31** *from natural valencene (=(+)-(2*R,*8*R,*8a*S*)-2-isopropenyl-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalene; (+)-***30**). Natural valencene ((+)-**30**, $[\alpha]_D^{20} = +91.3°$ (c = 1.55, $CHCl_3$), 10.2 g (50 mmol) in CH_2Cl_2 (100 ml)) was ozonolyzed (1 equiv. of O_3) 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 ($NaHCO_3$, H_2O), dried ($MgSO_4$) 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, $[\alpha]_D^{20} = +106°$ (c = 1.22, $CHCl_3$). – IR. (neat): 1710*s*. – ^{1}H-NMR.: 0.88 (*d*, J = 6.5, H_3C–C(8)); 0.94 (*s*, H_3C–C(8a)); 2.15 (*s*, CH_3CO–C(2)); 2.64 (*d*×*d*×*d*×*d*, J_1 = 12.5, J_2 = 12.5, J_3 = 3.25, J_4 = 3.25, H–C(2)); 5.35 (*m*, H–C(5)). – ^{13}C-NMR.: see *Table* [2]). – 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 etheral methyllithium (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, $NaHCO_3$, H_2O), dried ($MgSO_4$) 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**, $[\alpha]_D^{20} = +151.4°$ ($c = 1.2$, $CHCl_3$). – IR. (neat): 3350*s*. – ^{1}H-NMR.: 0.88 (*d*, $J = 7$, $H_3C-C(8')$); 0.92 (*s*, $H_3C-C(8a')$); 1.16 and 1.17 (2 *s*, 2 $H_3C-C(1)$); 5.32 (*m*, H–C(5')). – ^{13}C-NMR.: see *Table*[2]). – 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-*(4* R, *4a* S, *6* S)*-6-(1'-Hydroxy-1'-methylethyl)-4, 4a-dimethyl-3, 4, 4a, 5, 6, 7-hexahydronaphthalen-1(2*H*)-one* (**32**) *from keto ester* **15**. A solution of 1.3N ethereal methyllithium (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, $NaHCO_3$, H_2O), dried ($MgSO_4$) 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): 3460*s*, 1680*s*, 1630*s*. – ^{1}H-NMR.: 0.92 (*s*, $H_3C-C(4a)$); 0.95 (*d*, $J = 7$, $H_3C-C(4a)$); 1.21 and 1.215 (2 *s*, 2 $H_3C-C(1')$); 2.33 ($d \times d \times d$, $J_1 = 17$, $J_2 = 12$, $J_3 = 8$, $H_{ax}-C(2)$); 2.5 ($d \times d \times d$, $J_1 = 17$, $J_2 = 6$, $J_3 = 2$, $H_{eq}-C(2)$); 6.15 ($d \times d$, $J_1 = 6.5$, $J_2 = 2$, H–C(8)). – ^{13}C-NMR.: see *Table*[2]). – 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-*(4* R, *4a* S, *6* S)*-6-Isopropenyl-4, 4a-dimethyl-3, 4, 4a, 5, 6, 7-hexahydronaphthalen-1(2*H*)-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, $NaHCO_3$, H_2O), dried ($MgSO_4$) 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]. – ^{1}H-NMR.: 0.92 (*s*, $H_3C-C(4a)$); 0.95 (*d*, $J = 7$, $H_3C-C(4)$); 1.76 (br. *s*, $CH_2=C(CH_3)$); 2.34 ($d \times d \times d$, $J_1 = 17$, $J_2 = 12$, $J_3 = 7.5$, $H_{ax}-C(2)$); 2.5 ($d \times d \times d$, $J_1 = 17$, $J_2 = 6$, $J_3 = 2$, $H_{eq}-C(2)$); 4.72 and 4.77 (2 br. *s*, $CH_2=C(CH_3)$); 6.19 ($d \times d$, $J_1 = 6$, $J_2 = 2$, H–C(8)). – ^{13}C-NMR.: see *Table*[2]). – 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).

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