30. Functionalisation of Saturated Hydrocarbons

Part 9[1])

Oxidation of Patchouli Alcohol by the 'Gif System': Isolation and Organoleptic Properties of Three New Ketonic Derivatives

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Dedicated to Prof. *Vlado Prelog* on the occasion of his 80th birthday

(17.X.86)

Oxidation of patchouli alcohol (**1**) using the 'Gif system' afforded as major isolated products three new ketonic derivatives **16–18**. The structures of these compounds were established by spectral techniques including 2D-NMR. Ketones **16–18** display interesting organoleptic properties.

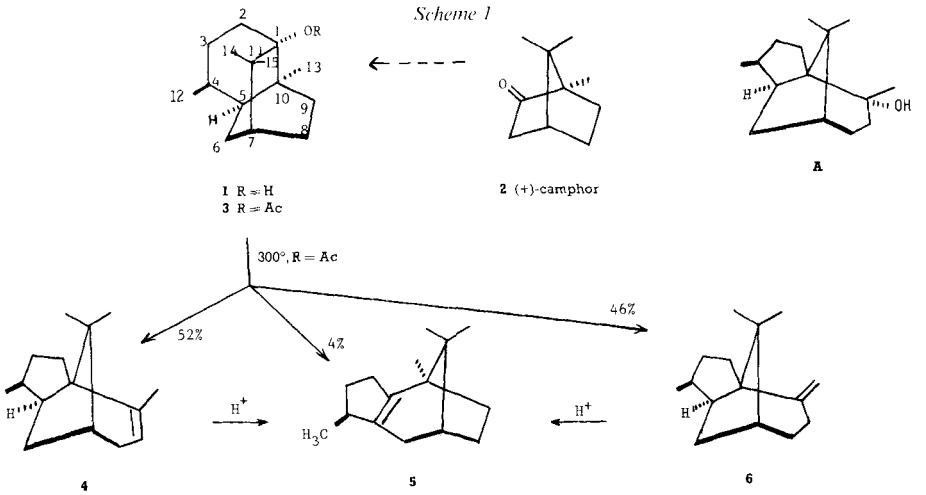
Introduction. – In the preceding parts of this series [2], we described our results on the oxidation of saturated hydrocarbons by the 'Gif system' as well as its extension to more complex molecules such as steroids [3] and the sesquiterpenoid caryolanol [1]. To summarise, this system which comprises an Fe catalyst, molecular O_2, Zn powder, and pyridine/AcOH oxidises simple hydrocarbons at 20° to mainly ketones (yields 20–30%), attack occuring predominantly at secondary positions. In the case of caryolanol and steroids, the same trends are observed. A directing effect of the substituent on the site of oxidation has been demonstrated. Moreover, in the cholestane series, the industrially important side-chain cleavage to the corresponding 20-keto derivatives (major isolated products of the oxidation) was observed and rationalised [4].

In this paper, we wish to report our results concerning the oxidation of the well-known patchouli alcohol (**1**), a conformationally rigid polycyclic sesquiterpenoid. This was studied with the double aim of understanding better the steric requirements of the oxidation process and gaining access to potentially interesting compounds which could display desirable organoleptic properties.

Patchouli alcohol (**1**) was first isolated in the nineteenth century [5] as the major component of patchouli oil (from *Pogostemon cablin* BENTH). It was only in 1963 (a century later) that *Dunitz, Büchi*, and coworkers assign the right structure **1** to patchouli alcohol on the basis of an X-ray analysis [6]. In a following paper [7g], *Büchi* explained the apparently contradictory results of both the chemical elucidation of the structure of patchouli alcohol (**1**) [7h] and of its partial synthesis from (+)-camphor (**2**) [7f]. The structure of patchouli alcohol was indeed first deduced from a series of chemical degradations in which the pyrolysis of patchouli acetate (**3**) to a mixture of α-patchoulene

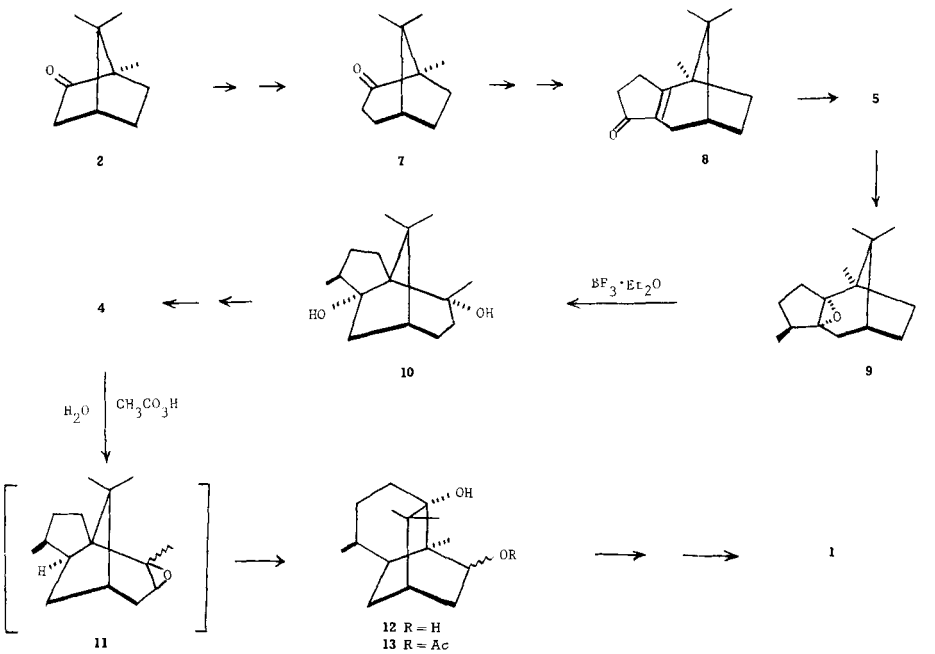
[1]) Part 8: [1].

Scheme 1



(**4**), β-patchoulene (**5**), and γ-patchoulene (**6**) played a key role. The isolation and the structural determination of **4–6** obtained by pyrolysis of the acetate **3** and the formation of β-patchoulene (**5**) by dehydration of patchouli alcohol with H_2SO_4, I_2, or H_3BO_3 led to the conclusion that patchouli alcohol had the tricyclic structure **A** (*Scheme 1*). The occurrence of the skeletal rearrangement initiated by formation of a carbonium ion at C(1) followed by loss of proton was unsuspected at first. With the structure **A** in mind, *Büchi* designed an elegant partial synthesis of patchouli alcohol from (+)-camphor (**2**) as outlined in *Scheme 2*. (+)-Camphor was converted to (−)-homocamphor (**7**) and then *via* **8** to β-patchoulene (**5**). This in turn was epoxidised to **9** which underwent the anticipated

Scheme 2



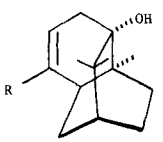
skeletal rearrangement **9**→**10**. The diol **10** was readily converted to α-patchoulene (**4**). Epoxidation of α-patchoulene (**4**) led to a skeletal rearrangement exactly reverse to the one observed in the pyrolysis of patchouli acetate (**3**). Thus α-patchoulene (**4**) gave the diol **12** which was monoacetylated and then readily converted to optically active patchouli alcohol (**1**). The ignorance of this reverse skeletal rearrangement **4** →**12** encouraged *Büchi* in the belief that patchouli alcohol had the structure **A**.

Nowadays, the construction of the tricyclic patchoulane skeleton is still the subject of intensive studies having both an academic interest and an industrial background. Several multistep total or partial syntheses have appeared in the last few years [7] [8]. Most to them give racemic patchouli alcohol (**1**), but syntheses of the optically pure natural (–)-isomer [7a] [7f–h] and of the (+)-isomer [7a] of **1** have been reported.

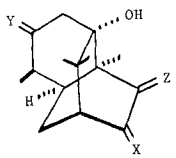
Parallel to the fascinating debate on the real origin of the odour of patchouli oil [9], the syntheses of nor-patchoulenol (**14**), a minor component of the essential oil, which is considered to be the real odour carrier [8] and of patchoulenol (**15**) demonstrated that closely related compounds could exhibit the same odoriferous properties [8]. The biological functionalisation of **1** was also studied. Microbiologial hydroxylations [10] as well as metabolism by rabbits studied by *Ourisson et al.* [11] were shown to give only attack at the 12-methyl group (thus affording an entry to **14**). Other C–H bonds (especially CH_2 groups) remained unaffected.

In the context, it seemed to us that oxidation of **1** using the 'Gif system' might well furnish a new family of ketones of possible odoriferous value. The yields of pure compounds isolated using this system are usually very low. However, the compounds obtained are ketones which are unknown and would be difficult to obtain by total or partial synthesis. Such compounds might indeed be present in natural patchouli oil, but only in trace amounts and so far unidentified.

Results. – The oxidation of patchouli alcohol (**1**), under 'Gif(IV) conditions' [2] (Fe catalyst, Zn powder, aq. pyridine/AcOH, 5.5 h at 20° under air) afforded a mixture which was separated by silica-gel column chromatography into two fractions, the starting material **1** (51%) and the oxidised products (19.5%). The latter fraction was subjected to HPLC (see *Exper. Part*) and gave the new compounds **16** (3.6%, $[\alpha]_D^{20} = -33°$), **17** (1.2%, $[\alpha]_D^{20} = -65°$), and **18** (0.9%, $[\alpha]_D^{20} = -34°$) as major products. The structural determination of the oxidised products **16–18** is mainly based on a detailed NMR study. Analytical, MS and IR data (see *Exper. Part*) as well as CD measurements fully agree with the proposed structures.



14 R = H
15 R = CH_3



16 X = O, Y = Z = H_2
17 Y = O, X = Z = H_2
18 Z = O, X = Y = H_2

NMR Studies[2]). The oxidation sites of compounds **16–18** are determined by 1D- and 2D-NMR spectroscopy (*Figs. 1* and *2*, resp.). Our general strategy has consisted in obtaining partial ^1H assignments from $^1H,^1H$ chemical-shift correlation (COSY), and then, partial ^{13}C assignments from classical 1D techniques and $^1H,^{13}C$ chemical-shift

[2]) The atom numbering of patchouli alcohol (**1**) is retained for **16–18**; for systematic names, see *Exper. Part*.

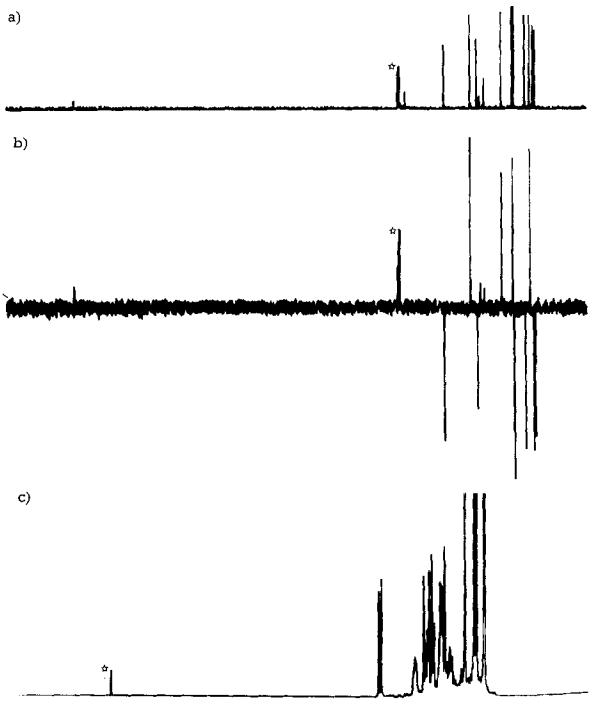
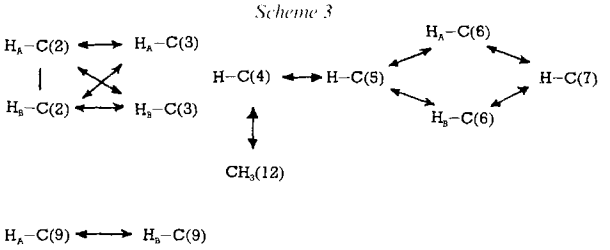


Fig. 1. *1D-NMR Spectra of* **16**. a) ^{13}C-NMR (100 MHz); b) ^{13}C-NMR, *J* modulation of the spin echo (100 MHz); c) ^{1}H-NMR (400 MHz); ☆: $CDCl_3$.

correlation [12]. The remaining ^{1}H and ^{13}C assignments can then be deduced from ^{1}H,^{13}C spectra. We now describe in detail the application of this strategy to the structure elucidation of compound **16**. We noticed, first, that the C skeleton is not modified by oxidation and that only one C=O group is present in the ^{13}C-NMR spectra. Using the known [13] spectral assignments of the starting patchouli alcohol (**1**), the sequences of coupled protons can be proposed *(Scheme 3)* for ketone **16**; these groups of protons, flanked by quaternary C-atoms, can be extracted from the COSY spectrum *(Fig. 2a)*. ^{1}H,^{13}C Correlations examination makes it possible to prove the ^{1}H assignments and identify the corresponding ^{13}C signals *(Fig. 2b)*. It can be seen, from comparison with compound **1**, that the CH_2(8) group is missing in **16**. This indicates that the C=O group is at position 8. The attribution of CH_3(14) and CH_3(15) as well as of the quaternary C(11)

Scheme 3



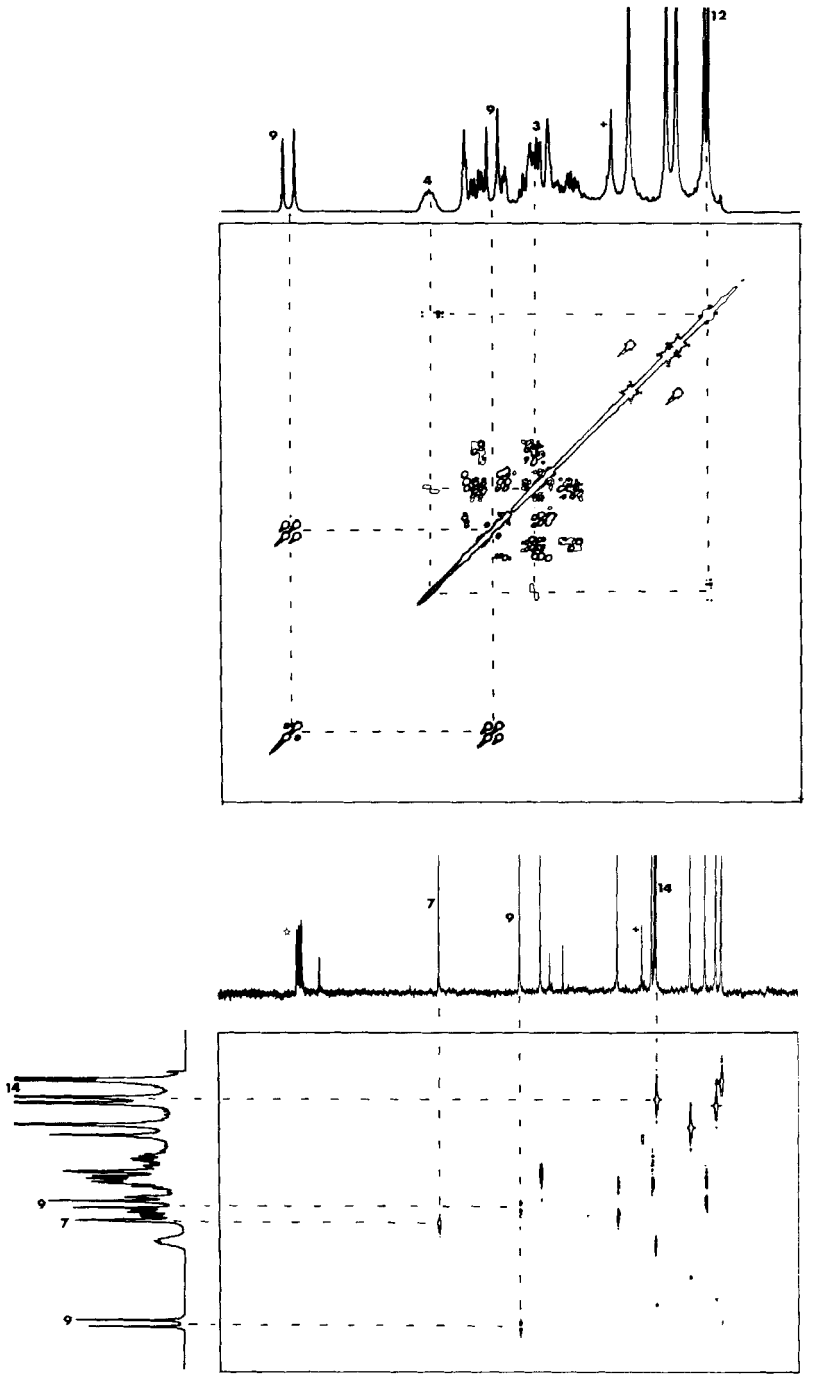


Fig. 2. *2D-NMR Spectra of* **16** *presented as a contour plot.* a) $^1H,^1H$ chemical-shift correlation (COSY, 400 MHz); b) $^1H,^{13}C$ chemical-shift correlation; ☆: $CDCl_3$; + : Impurity.

and C(10) are tentative, since they are obtained from comparison of the compounds **1** and **16–18** and from chemical-shift considerations. Assignments of the carbonyl C-atom and of C(1) are then obvious.

We have applied the same methodology to determine the ^{13}C and ^{1}H assignments and the position of the C=O group for the ketones **17** and **18**. For comparative purposes, spectra of the starting compound **1** have been also studied.

Circular Dichroism. The examination of molecular models shows that, if one leaves out of consideration the substituents $CH_3(12)$, $CH_3(14)$, $CH_3(15)$, and OH–C(1), the C skeleton has a planar symmetry. This plan of symmetry is defined by C(13), C(9), C(8), and C(3). It is noteworthy that in compounds **16–18**, the C=O group is included in this plan. If one brings this observation together with the fact that the framework of these molecules is rigid and spherical (no front-octant effect is to be expected), the interpretation of the CD curves is greatly facilitated. The only contributions to take into account are those coming from the substituents $CH_3(12)$, $CH_3(14)$, $CH_3(15)$, and OH–C(1). It is then obvious that **16–18** should have a positive *Cotton* effect [14], a deduction fully confirmed by the experimental positive $\Delta\varepsilon$ values (see *Exper. Part*).

Conclusion. – Oxidation of patchouli alcohol (**1**) by the 'Gif system' affords in one step new ketonic derivatives **16–18** as major isolated compounds. This confirms the high selectivity previously noted for the oxidation of the CH_2 groups. Although the yields from **1** are rather low, they should be compared with the yields obtained in multistep syntheses of patchouli alcohol; for example 13% of (±)-**1** [8], 8.6% of (±)-**1** [7a], or 2,2% of (+)- or (−)-**1** [7a]. It is also gratifying that chemists can carry out selective syntheses equivalent to the remarkable reactions produced by P_{450} enzymes in the livers of rabbits and dogs. In addition, we do not have to collect and extract urine to perform our practical syntheses. However, rabbits hydroxylated patchouli alcohol at the secondary CH_3 group more efficiently (50–70%) than our accomplishments at the secondary positions (5.7%).

The three isomers **16–18** were all found to have interesting odours. Ketone **18** has an extremely smooth and rich patchouli odour without camphoraceous earthy notes. It is somewhat reminiscent of a note to be found in broom and violet-leaves absolute. The most interesting compound is **17** which has a buttery, orris concrete like note[3]).

Experimental Part

General. HPLC: *Waters Associates* liquid chromatograph equipped with a model *440* absorbance UV detector at 254 nm and a *Jobin-Yvon Iota* differential refractometer; prep. normal-phase *Ultrasphere-Si* and reverse-phase *Ultraphere-ODS* (5μ, 10 mm × 25 cm) columns; *S.D.S.* 'Purex' grade solvents. M.p.: *Reichert Thermovar* hot stage microscope; uncorrected. Optical rotations: *Perkin-Elmer-241* polarimeter, $CHCl_3$ solns., *c* in g/100 ml. CD spectra: MeOH solns., *Jobin-Yvon-Autodichrograph-Mark-V* instrument. NMR spectra: *Bruker AM 400* wide bore spectrometer, $CDCl_3$ solns. with TMS as internal standard. COSY: the applied pulse sequence was: $(\pi/2)$–(t_1)–$(\pi/4)$–(FID, t_2). The spectral width in F_1 and F_2 was 1000 Hz. The number of data points in t_2 was 2048, and 256 increments were recorded. Before *Fourier* transformation, the data were multiplied with unshifted sine bell. Zero filling was applied in F_1. $^{1}H,^{13}C$ chemical-shift correlations: the applied pulse sequence was: $(\pi/2,^{1}H)$–$(t_1/2)$,

[3]) We thank Dr. *B.J. Willis*, Director of Research, PPF, Ashford, for this information and for a generous gift of patchouli alcohol.

(τ_1)–($\pi/2$,^{1}H; $\pi/2$,^{13}C) (τ_2)–(BB,^{1}H; FID, t_2) with $\tau_1 = 0.00357$ s, $\tau_2 = 0.0017$ s. The spectral width in F_1 was 1000 Hz and in F_2 3500 Hz. The number of data points in t_2 was 4096, and 256 increments were recorded. Before *Fourier* transformation, the data was multiplied with $\pi/10$ shifted sine bell in F_2 and *Lorentz-Gauss* in F_1. Zero filling was applied in F_1. *J*-Modulation of the spin echo: the applied pulse sequence was: ($\pi/2$,^{13}C)–(D_1)–(BB,^{1}H; π,^{13}C)–(D_1,BB) (FID,BB^{1}H) with $D_1 = 0.007$ s. MS and HR MS: *Kratos MS 50* instrument.

Oxidation of Patchouli Alcohol (**1**). A mixture of **1** (444 mg, 2 mmol), Zn powder (1.31 g), Fe cluster [2] (8 mg), pyridine/H_2O (28 ml/2 ml, *v/v*), and AcOH (2.3 ml) was stirred at r. t. for 6 h. This was done in 4 parallel runs (4 × 2 mmol). After completion of the reactions (no more Zn), the mixtures were combined, cooled in an ice bath, and carefully acidified with a 25% H_2SO_4 soln. (until pH *ca.* 2). The extracts were washed successively with 1N

Table 1. *^{13}C-NMR Chemical Shifts* (ppm) *of* **1** *and* **16–18** *in* $CDCl_3$

C-Atom[2])	**1**	**16**	**17**	**18**
C(1)	75.29	74.3	78.6	76.9
C(2)	32.63	33.16	50.43	33.02
C(3)	28.58	28.4	216	27.95
C(4)	28.03	28.02	45.78	27.2
C(5)	43.68	43.7	344.27	39.9
C(6)	24.28	21.02	27.5	23.9
C(7)	39.09	57.8	38.3	39.9
C(8)	24.54	216	23.7	42.8
C(9)	28.79	46.6	28.05	216.7
C(10)	37.53[a])	42.0[a])	38.08[a])	54.2
C(11)	40.03[a])	40.0[a])	40.90[a])	41.12
C(12)	18.48	18.7	11.36	18.7
C(13)	20.53	19.5	21.12	12.3
C(14)[b])	26.80	27.8	25.65	26.2
C(15)[b])	24.20	23.11	25.65	24.0

[a])[b]) These assignments could be exchanged.

Table 2. *^{1}H-NMR Chemical Shifts* (ppm) *of* **1** *and* **16–18** *in* $CDCl_3$

H-Atom[2])	**1**	**16**	**17**	**18**
H_A–C(2)	1.5	1.58	2.37	2.41
H_B–C(2)	1.7	1.81	2.71	2.66
H_A–C(3)	1.34	1.41	–	2.36
H_B–C(3)	1.48	1.57	–	2.48
H–C(4)	1.97	2.03	2.67	2.87
H–C(5)	1.44	1.50	1.79	2.53
H_A–C(6)	1.26	1.53	1.05	2.41
H_B–C(6)	1.85	1.70	1.53	2.66
H–C(7)	1.19	1.87	1.15	2.65
H_A–C(8)	1.26		1.29	2.97
H_B–C(8)	1.48	–	1.87	3.58
H_A–C(9)	1.05	1.75	1.25	–
H_B–C(9)	1.85	2.63	1.89	–
CH_3(12)	0.78	0.83	0.99	1.74
CH_3(13)	0.84	1.00	1.05	1.98
CH_3(14)[a])	1.05	0.96	0.89	1.82
CH_3(15)[a])	1.07	1.16	1.08	2.10

[a]) These assignments could be exchanged.

H_2SO_4, H_2O, sat. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated *in vacuo* to yield the crude oxidation mixture. This mixture was chromatographed on a silica-gel column and eluted with hexane/Et_2O (increasing polarity) to give first the unchanged **1** (0.89 g, 51%). Further elution afforded a mixture of ketones which was subjected to further purification by HPLC (normal phase, hexane/AcOEt 85:15 to 80:20, followed by normal-phase HPLC, hexane/i-PrOH 95:5 to 90:10) affording **16–18**. The purity was controlled by reverse-phase chromatography MeOH/H_2O 60:40.

2,3,4,4a,5,6,8,8a-Octahydro-1-hydroxy-4,8a,9,9-tetramethyl-1,6-methanonaphthalen-7(1H)-one (**16**): 70 mg, 3.6% M.p. 122–124° (from hexane). $[\alpha]_D^{20} = -33°$ ($c = 1.6$). CD: $\Delta\varepsilon_{303} = +0.16$. IR ($CH_2Cl_2$): 3600 (free OH), 1710 (CO). NMR: *Table 1* and *2*. MS: 236 ($M^{+\cdot}$), 201, 125, 83. HR-MS: 236.1776 ($C_{15}H_{24}O$, calc. 236.1776).

1,4,4a,5,6,7,8,8a-Octahydro-1-hydroxy-4,8a,9,9-tetramethyl-1,6-methanonaphthalen-3(2H)-one (**17**): 26 mg, 1.2%. M.p. 90–92° (from hexane). $[\alpha]_D^{20} = -65°$ ($c = 0.52$). CD: $\Delta\varepsilon_{296} = +0.365$. IR: 3600 (free OH), 1700 (CO). NMR: *Table 1* and *2*. MS: 236 ($M^{+\cdot}$), 193, 142, 136, 81. HR-MS: 236.1765 ($C_{15}H_{24}O_2$, calc. 236.1776).

1,3,4,4a,5,6,7,8a-Octahydro-1-hydroxy-4,8a,9,9-tetramethyl-1,6-methanonaphthalen-8(2H)-one (**18**): 18 mg, 0.9%. M.p. 106–108° (from hexane). $[\alpha]_D^{20} = -34°$ ($c = 0.5$). CD: $\Delta\varepsilon_{304} = +0.76$. IR: 3600 (free OH), 1710 (CO). NMR: *Table 1* and *2*. Anal. calc. for $C_{15}H_{24}O_2$: C 76.23, H 10.24; found: C 76.23, H 10.28.

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