76. Photosensitized Oxygenation of Abieta-7,9(11)-dien-13β-ol

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Summary

Dehydration of abiet-8-ene-7β,13β-diol (ibozol, **1**) leads to abieta-7,9(11)-dien-13β-ol (**2**) which aromatizes slowly to the known abieta-8,11,13-triene (**3**). Photosensitized oxygenation of the heteroannular diene **2** yields a mixture from which three compounds were identified: abiet-7-ene-9α,11α,13β-triol (**4**), abieta-8,11,13-trien-7-one (**5**), and abieta-8,11,13-trien-7α-ol (**6**).

Introduction. – There is considerable interest in the potent anti-leukemic activity and cytotoxicity of certain naturally occurring oxygenated diterpenes [1–3] and various synthetic approaches have been recently described [4]. In view of our interest in potential anti-tumoral agents, we report on the photosensitized oxygenation of the previously unknown heteroannular diterpene, abieta-7,9(11)-dien-13β-ol (**2**), prepared from ibozol (**1**, abiet-8-ene-7β,13β-diol) a diterpene isolated from the Labiatae *Iboza riparia* NE BROWN [5]. The photosensitized oxygenation of simpler substrates is well known [6] but few examples are documented in the diterpenoid series [7].

Results. – Ibozol (**1**) dehydrates in refluxing toluene in the presence of a catalytic amount of *p*-toluenesulfonyl chloride to give abieta-7,9(11)-dien-13β-ol (**2**; 81%) and abieta-7,11,13-triene (**3**; 15%) which were separated by column chromatography. The diene **2** was shown to be the primary product in a separate experiment during which compound **2** aromatized slowly to **3** under the conditions used for the dehydration of ibozol (**1**).

The new heteroannular diene **2** ($M^+ = 288$, $C_{20}H_{32}O$) exhibits UV. absorption at 248 nm (ε 14'100) in agreement with data on similar chromophores [8]. Its structure was substantiated by ^{13}C-NMR. *(Table 1);* the multiplicities of the olefinic carbon resonances confirm the existence of two trisubstituted double bonds.

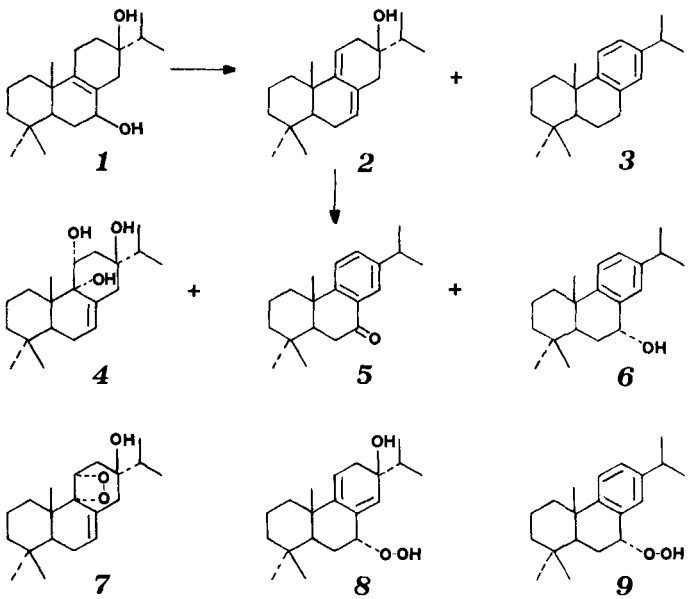
The aromatic abietatriene **3** ($M^+ = 270$, $C_{20}H_{30}$) known as 'dehydroabietane' [9] has UV. absorption in the 240–280 nm range similar to that observed for dehydroabietic acid [10] and the ^{1}H-NMR. spectrum shows 3 aromatic protons with the expected *ABX*-coupling pattern.

Table 1. *^{13}C-NMR. chemical shifts*[a]) *of ibozol* (**1**), *abietadienol* (**2**) *and abieteneiriol* (**4**)[b])

Assignments	1[c])	2	4	Assignments	1[c])	2	4
C(1)	37.1	37.3	37.7	C(11)	21.0	115.1	68.8
C(2)	18.9	19.0	18.7	C(12)	31.8	36.1[f])	39.9[i])
C(3)	41.4	41.0	41.1	C(13)	72.2	72.2	73.9
C(4)	33.0	33.2	33.0	C(14)	36.5	42.2[f])	41.7[i])
C(5)	49.7	49.2	43.4	C(15)	34.4	35.0	34.6
C(6)	30.1	24.0	24.3	C(16)	16.7[d])	16.7[g])	16.7[k])
C(7)	72.1	125.8	130.6	C(17)	16.8[d])	16.9[g])	16.8[k])
C(8)	126.8	130.0[e])	134.2	C(18)	33.0	33.1	33.8
C(9)	141.8	147.8[e])	76.0	C(19)	21.6	22.2[h])	22.6
C(10)	38.4	37.3	42.1	C(20)	20.2	22.0[h])	17.2

[a]) In ppm relative to TMS.
[b]) In $CDCl_3$ at 31°; concentrations were 0.1M.
[c]) Values comparable to those in [5].
[d])–[k])Signals with the same letter may be interchanged.

The photooxygenation of the heteroannular diene **2** in methanol, in the presence of Rose Bengal, proceeded slowly and yielded at least 11 products (TLC.). Filtration on a silica gel column furnished the main fraction (76%) from which the triol **4** (9%) crystallized in acetone. Several spots on TLC. of the mother-liquors reacted with 2,4-dinitrophenylhydrazine. The main component, the aromatic ketone **5** (22%) [11] [12], was separated by repeated chromatographies. From the more polar fractions the benzylic alcohol **6** [12] was retrieved (5%); its structure was established by its oxidation to ketone **5** with pyridinium chlorochromate and from spectroscopic data. Abietatriene **3** did not react under the same photooxygenation conditions.



Structures. – *Triol* **4**. Elemental analysis, UV., IR. and MS. data *(Exper. Part)* are consistent with the structure of **4** which was established by NMR. spectrometry.

In the ^{1}H-NMR. spectrum *(Fig. 1)* the methyl resonances are similar to those of ibozol (**1**) [5]. Exchange with D_2O proved the existence of two tertiary hydroxyl protons (disappearance of *s* at 1.12 and 2.29 ppm) and a secondary hydroxyl proton (disappearance of *d* at 1.61 ppm, $J = 6.5$ Hz).

The analysis of the proton spin systems in rings B and C *(Fig. 2)* were made by double irradiation experiments, the chemical shifts and coupling constants being

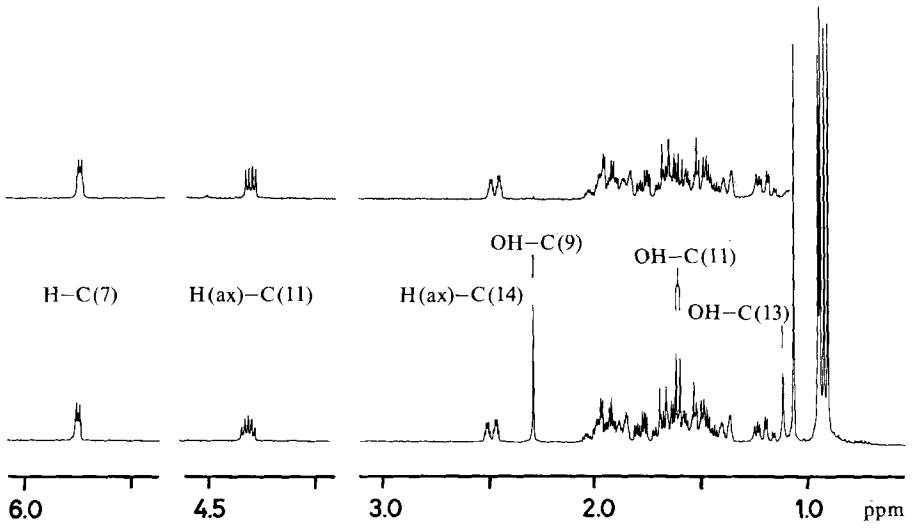


Fig. 1. *360 MHz ^{1}H-NMR. spectrum of a solution of abiet-7-ene-9a,11a,13β-triol* (**4**) (10 mM in $CDCl_3$, at 24°). Upper trace: spectrum after addition of D_2O.

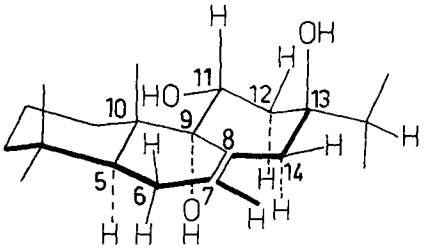


Fig. 2. *Numerical assignment of the protons in rings B and C of abiet-7-ene-9a,11a,13β-triol* (**4**)

refined by iterative spectral simulation *(Fig. 3, Table 2)*. The proton appearing at 4.32 ppm is assigned to H–C(11). This led to the consecutive structure elucidation in rings B and C. By decoupling, or after exchange with D_2O, the multiplet of H–C(11) simplifies to a $d \times d$ ($J = 11.1$ and 5.4 Hz), indicating the presence of two vicinal protons, geminally coupled, on C(12). The proton at C(11) must

Table 2. *^{1}H-NMR. parameters of the coupled protons in rings B and C of abietenetriol* (**4**)[a])

Assignments	Chemical shifts[b])	Coupling constants[c])							
H(ax)–C(5)	1.52	^3J(5ax,6ax)	= 12.6	^3J(5ax,6eq)	= 4.5				
H(ax)–C(6)	1.91	^2J(6ax,6eq)	= –18.3	^3J(6ax,5ax)	= 12.6	^3J(6ax,7)	= 2.0	^5J(6ax,14ax)	= 3.5
H(eq)–C(6)	2.01	^2J(6eq,6ax)	= –18.3	^3J(6eq,5ax)	= 4.5	^3J(6eq,7)	= 5.7	^5J(6eq,14ax)	= 3.3
H–C(7)	5.76	^3J(7,6ax)	= 2.0	^3J(7,6eq)	= 5.7	^4J(7,14ax)	= –2.2		
H(ax)–C(14)	2.49	^2J(14ax,14eq)	= –14.9	^4J(14ax,7)	= –2.2	^5J(14ax,6eq)	= 3.3	^5J(14ax,6ax)	= 3.5
H(eq)–C(14)	1.95	^2J(14eq,14ax)	= –14.9	^4J(14eq,12eq)	= 3.0				
H(ax)–C(12)	1.67	^2J(12ax,12eq)	= –12.8	^3J(12ax,11ax)	= 11.1				
H(eq)–C(12)	1.78	^2J(12eq,12ax)	= –12.8	^3J(12eq,11ax)	= 5.4	^4J(12eq,14eq)	= 3.0		
H(ax)–C(11)	4.32	^3J(11ax,12ax)	= 11.1	^3J(11ax,12eq)	= 5.4	^3J(11ax,OH)	= 6.5		
HO–C(11)	1.61	^3J(OH,11ax)	= 6.5						

[a]) In $CDCl_3$ at 24°; concentration 0.01 M. [b]) In ppm relative TMS. [c]) In Hz;the digital resolution (0.2 Hz/point) is the practical error of the coupling constants.

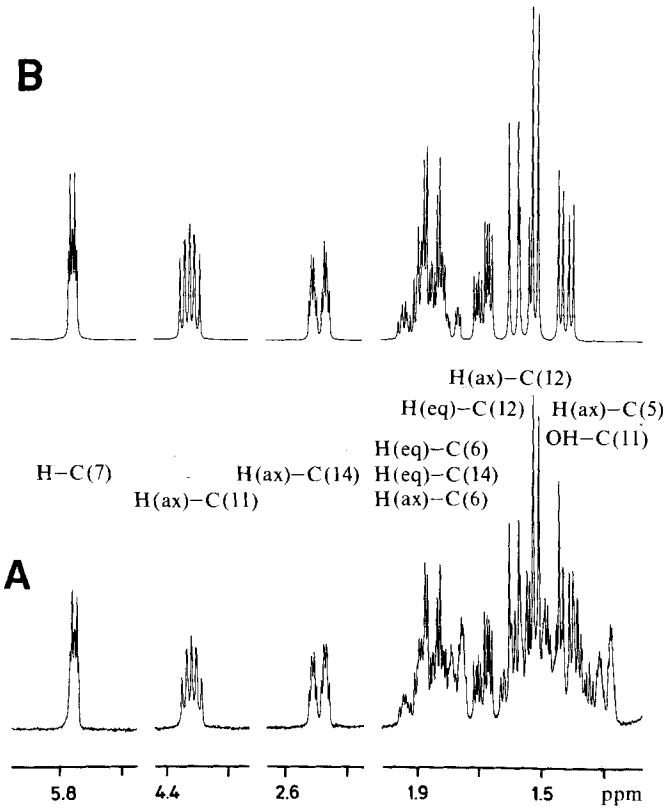


Fig. 3. *Part of the 360-MHz-^{1}H-NMR. spectrum of abiet-7-ene-9a,11a,13β-triol* (**4**). (A) Experimental. (B) Spectrum computed for the ten coupled protons in rings B and C *(cf. Fig. 2)* with the chemical shifts and coupling constants of *Table 2* assuming a line width of 1.2 Hz. The simulation (iterative program PANIC) was performed in two steps: first a seven-spin system (H–C(15), 2 H–C(6), H–C(7), 2 H–C(14), H(eq)–C(12)) was calculated and the incomplete multiplet of H(eq)–C(12) eliminated. Then, a five-spin system (H(eq)–C(14), 2 H–C(12), H(ax)–C(11) and HO–C(11)) was determined and the multiplet of H(eq)–C(14) eliminated. (B) Represents the sum of the two partial spectra.

be axial having the large vicinal coupling (11.1 Hz) with H_a(ax)–C(12). This orientation can also be inferred from the large H–C–OH coupling constant (6.5 Hz) [14].

From the absence of an additional coupling of H_a(ax)–C(12) the adjacent C(13) must be tetrasubstituted. H_β(eq)–C(12) exhibits a long-range W-coupling of 3.0 Hz with the β-equatorial proton at C(14); such a large value usually occurs in rather strained molecules [15]. H_a(ax)–C(14) is allylically coupled ($J = -2.2$ Hz) to the olefinic proton at C(7) (5.76 ppm); this implies a nearly perpendicular orientation of H_a(ax)–C(14) to the plane of the double bond [16]. The deshielding of H_a(ax)–C(14) (2.49 ppm) compared to all other axial protons, in particular the similarly positionned H_a(ax)–C(12) (1.67 ppm), must be attributed to the anisotropy of the C(7), C(8)-double bond. The position of this double bond is further con-

firmed by the deshielding of the neighboring protons at C(6) and by their large geminal coupling (−18.3 Hz) [17]. H_α(ax)–C(14) also undergoes a homoallylic coupling with both protons at C(6) (3.3 and 3.5 Hz). H_β–C(6) can be distinguished by its coupling constant with the H_α(ax)–C(5) (12.6 Hz).

In the ^{13}C-NMR. spectrum, assignments were facilitated by comparison with those of **1** [5] *(Table 1)*. The shifts of C(1), C(2), C(4), C(18), C(19) and those of the isopropyl moiety are identical for both compounds **1** and **4**. The ^{13}C-shift of C(6) is identical to that of the corresponding ^{13}C-resonance in isopimaradiene [13]. The multiplicities of the olefinic carbon resonances agree with the presence of a trisubstituted double bond.

The shielding of C(5) by 6.3 ppm with respect to that in **1** is consistent with a γ-gauche effect [18] exerted by the hydroxy group at C(9); this group is also responsible for the shielding by 3.0 ppm of the C(20) (γ-*trans* effect [18]). The deshielding of C(10) by 4.3 ppm appears to be a combination of a β-effect from the hydroxyl group at C(9) and a γ-effect from that at C(11).

Ketone **5**. The presence of an aryl ketone is supported by the UV. (255, 303 nm) and IR. spectra (1678, 1610 cm^{-1}) [11]. The ^{1}H-NMR. spectrum displays the characteristic *ABX* coupling pattern for the aromatic protons at C(11), C(12) and C(14). The strong deshielding of H–C(14) indicates the proximity of the carbonyl group at C(7). The methylene protons at C(6) adjacent to the carbonyl group appear at 2.64 and 2.73 ppm as the *AB*-part of an *ABX*-system coupled to H–C(5) (1.88 ppm). H_β(eq)–C(1) is deshielded (2.34 ppm) from the complex region of the other methylene protons in ring A (1.5–1.8 ppm) which indicates the near coplanarity of this proton with the aromatic ring C. The ^{13}C-NMR. was described by *Wenkert et al.* [19].

Alcohol **6**. The molecular ion $M^+ = 286$ ($C_{20}H_{30}O$) accompanied by the more intense $(M-18)^+$ fragment supports the presence of a hydroxy group. In the ^{1}H-NMR. spectrum, the aromatic protons at C(11) and C(14) (7.20 and 7.19 ppm, respectively) are both coupled to H–C(12) at 7.11 ppm; compared to the corresponding pattern of the protons in abietatriene **3** H–C(12) and H–C(14) are deshielded by 0.13 and 0.31 ppm, respectively, an effect attributed to the hydroxyl group at C(7). The isopropyl protons appear at the same positions as in **5** (see *Exper. Part*) and the signal of H_β(eq)–C(1) (2.28 ppm) is distinguished from the other protons of ring A (1.3–1.8 ppm).

Discussion. – Double bonds in 'locked' *trans*-dienes react independently with singlet oxygen to yield either 1,2-dioxetanes or allylic hydroxyperoxides, whereas in *cis*-dienes both bonds react rapidly to form endoperoxides [20].

The 9,11-*cis*-diol **4** may result from a [2+2]-cycloaddition of singlet oxygen to the C(9),C(11)-double bond of **2** from the less bulky α-side of the molecule and formation of an intermediate 1,2-dioxetane **7** which undergoes a sensitized photoreduction to the diol **4**. This sequence has been recently proposed as an experimental probe for dioxetane intermediates [21].

The main event appears to be an 'ene-reaction' of singlet oxygen with the C(7),C(8)-double bond and H_α(ax)–C(14), this atom being in optimal, nearly perpendicular conformation to the plane of the double bond. The resulting allylic

hydroperoxide **8** must undergo readily aromatization to **9** rather than addition with singlet oxygen to the homoannular diene (*cf.* hydroperoxycyclohexadiene [22]). Surprisingly, the hydroperoxyde **9** is not among the products identified but ketone **5** and alcohol **6** appear instead, obviously because of a disproportionation. The eventuality that such a reaction could have taken place during chromatography cannot be evinced completely though hydroperoxides or dioxetanes may be separated on silica gel without harm [23]. The formation of the alcohol **6** from **9** could be explained by a photoreduction similar to that encountered with dioxetanes [21] but dehydration of hydroperoxides to form ketones takes place in presence of strong bases, acids or metal ions [24]. It is known, moreover, that hydroperoxides may undergo radical induced dimerisation to form tetroxides which decompose to give each one molecule of alcohol, ketone and oxygen [25].

Alternatively the formation of **5** and **6** by oxidation of intermediary abietatriene **3** (as *e.g.* [7a]) can be excluded. This is further documented by the similar case of dehydroabietic acid which is inert to photooxygenation [7b].

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Experimental Part

The technical assistance of *E. Outon-Alonso* and *K. K. Gaeta* is appreciated.

General remarks. – Materials: column chromatography silica gel *Merck 60* (70–230 mesh); TLC. (thin layer chromatography) *Merck 60 F254.*

Instrumentation. UV.: *Unicam SP1800* $\lambda_{max}(\varepsilon)$. IR. ($cm^{-1}$): *Beckman IR 4230* and *Perkin-Elmer 727 B.* MS.: *Hewlett Packard 5980 A* (Chemical ionization CI., and Electron impact EI.). ^1H- and ^{13}C-NMR.: *Bruker WH-360* (360 and 90.5 MHz), chemical shifts in ppm relative to internal TMS (*J* Hz).

Dehydration of ibozol (**1**, *abiet-8-ene-7β,13β-diol*). Ibozol (**1**, 1 g, 3.27 mmol) and *p*-toluenesulfonyl chloride (30 mg, 0.15 mmol) were refluxed in 15 ml anhydrous toluene for 15 min. Chromatography of the viscous residue on silica gel (30 g) with hexane (100 ml) afforded 147 mg (15%) of *abietatriene* (**3**). – UV. (MeOH): 276 (1020), 268 (950), 261 *S* (690); min. 272 (730). – IR. (CH_2Cl_2): 3050, 2980, 2960, 2940, 2900, 2890, 2870, 2850, 1500, 1475, 1460, 1435, 1420, 1385, 1375, 1370, 1360, 890, 825. – ^1H-NMR. ($CDCl_3$): 7.17 (*d*, $J=9$, 1 H, H–C(11)); 6.98 (*d*×*d*, $J=9$ and 1.5, 1 H, H–C(12)); 6.88 (*d*, $J=1.5$, 1 H, H–C(14)); 2.8–2.9 (*m*, 3 H, 2 H–C(7) and H–C(15)); 2.27 (br. *d*, $J=12.5$, 1 H, H_β(eq)–C(1)) 1.87 (*m*, 1 H, H–C(5)); 1.75, 1.69, 1.60, 1.47, 1.36 (5 *m*, 7 H, H(ax)–C(1), 2 H–C(2), 2 H–C(3); 2 H–C(6)); 1.23 (*d*, $J=6.5$, 6 H, 3 H–C(16) and 3 H–C(17)); 1.18 (*s*, 3 H, 3 H–C(18)); 0.95 (*s*, 3 H, 3 H–C(19)); 0.94 (*s*, 3 H, 3 H–C(20)). – MS. (EI.): 270 (M^+; 37); 255 ($M-15^+$, 100); 173 (48); 159 (50).

Further elution with hexane/ethyl acetate 10:1 (100 ml) furnished 768 mg (81%) of *abieta-7,9(11)-dien-13β-ol* (**2**). – UV. (MeOH): 242 (14100). – IR. (film): 3480, 1650, 1470, 1390, 1375, 1050, 800. – ^{13}C-NMR. ($CDCl_3$) see *Table 1.* – MS. (EI.): 288 (M^+).

Formation of abietatriene *3* from *2*. – Compound **2** (200 mg) was refluxed 90 min in toluene (5 ml) in the presence of *p*-toluenesulfonyl chloride (19 mg). After concentration and chromatography of the residue on silica gel, elution from hexane afforded 165 mg (88%) of abieta-7,11,13-triene (**3**).

Photooxygenation of *2*. A solution of **2** (1 g, 3.47 mmol) and Rose Bengal (20 mg, 0.02 mmol) in methanol (200 ml) was irradiated in a water-cooled borosilicate tube reactor with 3×60 W bulbs while oxygen was internally circulated. The reaction was followed by TLC. for 50 h until the starting material had disappeared. By rapid chromatography on silica gel (30 g) with hexane/ethyl acetate 2:1 (100 ml) 763 mg of a mixture was collected (see below). Further elution with hexane/ethyl acetate 1:1 afforded another 155 mg of more polar products.

The main fraction crystallized partially from acetone to give 100 mg (9%) of *abiet-7-ene-9α,11α,13β-triol* (**4**), m.p. 220–224°; Rf (hexane/ethyl acetate 3:1) 0.15. – UV.: no absorption above 210 nm. – IR. (KBr): 3500, 3420, 1650, 1470, 1380, 1220, 1040, 990 and 790. – ^{1}H-NMR. ($CDCl_3$): 1.2–1.8 (*m*, 6 H, 2 H–C(1), 2 H–C(2), 2 H–C(3)); 1.6 (*hept.*, J=6.8, 1 H, H–C(15)); 1.07 (*s*, 3 H, 3 H–C(20)); 0.95 (*s*, 3 H, 3 H–C(19)); 0.93 (*d*, J=6.8, 6 H, 3 H–C(16) and 3 H–C(17)); 0.91 (*s*, 3 H, 3 H–C(18)); the signals of the protons on C(5), C(6), C(7), C(11), C(12) and C(14) are in *Table 2*. – ^{13}C-NMR.: *Table 1*. – MS. (CI.): 304 $(M-18)^+$.

$C_{20}H_{34}O_3$ Calc. C 74.48 H 10.62% Found C 74.41 H 10.54%

By TLC. of the mother liquors of crystallization (663 mg) (hexane/ethyl acetate 3:1) 11 spots were detected by UV. and iodine. Rf: 0.66, 0.62, 0.56, 0.49, 0.41, 0.27, 0.25, 0.22, 0.18, 0.13 and 0.1, the most intense in UV. being 0.56, 0.22 and 0.18. On spraying with dinitrophenylhydrazine (2%, acid ethanol), zones 0.56 [UV. (MeOH): 255, 303] and 0.18 [UV. (MeOH): 249] turned yellow-orange; the other zones gradually darkened to brown.

The mixture (93 mg) was re-chromatographed on silica gel (20 g) (hexane/ethyl acetate 3:1). *Fraction 1:* 2 mg (18 ml), Rf 0.66 and 0.62; *fraction 2:* 34 mg (20 ml), 0.66, 0.62, 0.56 (**5**), 0.49, 0.41; *fraction 3:* 4 mg (10 ml), 0.49, 0.41 and 0.30; *fraction 4:* 7 mg (42 ml), 0.30; *fraction 5:* 20 mg (40 ml), 0.27, 0.25, 0.22, 0.18 and 0.14; *fraction 6:* 11 mg (20 ml), 0.15 (containing some **4**); *fraction 7:* 6 mg (83 ml), 0.09 and 0.06.

Fraction 2 (30 mg) was separated by prep. TLC. (hexane/ethyl acetate 3:1) in 3 zones: *A*) Rf 0.66 (1 mg), *b*) Rf 0.60 (identical with previous 0.56 (20 mg)), and *c*) Rf 0.40–0.50 (8 mg). *Zone b*) contained one product identified as abietatrienone **5** (see below). *Zone c*) was combined with previous *fraction 3* (total 12 mg) and chromatographed on a *Merck Lobar* column (size B) with hexane/ethyl acetate 3:1. Compounds Rf 0.50–0.55 eluted first (3 mg, 30 ml) followed by pure **6** (Rf 0.42; 7 mg; 50 ml).

Abieta-8,11,13-trien-7-one (**5**). – UV. (MeOH): 255 and 303 (rel. OD. 1:0.2); min. 281 (rel. OD. 0.1). – IR. (CH_2Cl_2): 3000 *S*, 2970, 2930, 2910, 1678, 1610, 1560*m*, 1490, 1460, 1410*m*, 1395, 1385, 1375, 1365, 1340, 1325, 1300 br., 1200, 1170*m*, 1140*m*, 1080 br., 1055, 1038, 978*m*, 940*m*, 920*m*, 900 br. *m*, 865*m*, 835*s*. – ^{1}H-NMR. ($CDCl_3$): 7.87 (*d*, J=2, 1 H, H–C(14)); 7.39 (*d*×*d*, J=8 and 2, 1 H, H–C(12)); 7.30 (*d*, J=8, 1 H, H–C(11)); 2.92 (*hept.*, J=7, 1 H, H–C(15)); 2.73 (*d*×*d*, J=18 and 4.5, 1 H, H_α(eq)–C(6)); 2.64 (*d*×*d*, J=18 and 13.5, 1 H, H_β(ax)–C(6)); 2.34 (br. *d*, J=14, 1 H, H_β(eq)–C(1)); 1.88 (*d*×*d*, J=13.5 and 4.5, 1 H, H_α–C(5)); 1.83–1.55 (*m*, 5 H, H_α(ax)–C(1), 2 H–C(2), 2 H–C(3)); 1.26 (*d*, J=7, 6 H, 3 H–C(16) and 3 H–C(17)); 1.25 (*s*, 3 H, 3 H–C(18)); 1.0 (*s*, 3 H, 3 H–C(19)); 0.94 (*s*, 3 H, 3 H(ax)–C(20)). – MS. (EI.): 284 (M^+; 36), 269 (100), 227 (25), 201 (47), 199 (50).

Abieta-8,11,13-trien-7-ol (**6**). – IR. (CH_2Cl_2): 3500, 1608. – ^{1}H-NMR. ($CDCl_3$): 7.2 (*d*, J=8, 1 H, H–C(11)); 7.19 (*d*, J=2, 1 H, H–C(14)); 7.11 (*d*×*d*, J=8 and 2, 1 H, H–C(12)); 4.8 (br., 1 H, H–C(7)); 2.88 (*hept.*, J=6, 1 H, H–C(15)); 2.28 (br. *d*, J=12, 1 H, H_β(eq)–C(1)); 1.98 (*m*, 2 H, H–C(5) and H_β(ax)–C(6)); 1.36–1.8 (structurated *m*, 6 H, H_α(ax)–C(1), 2 H–C(2), 2 H–C(3), H_α(eq)–C(6)); 1.22 (*d*, J=6, 6 H, 3 H–C(16) and 3 H–C(17)); 1.13 (*s*, 3 H, 3 H–C(18)); 0.98 and 0.93 (2 *s*, 2×3 H, 3 H–C(19) and 3 H–C(20)). – MS. (EI.): 286 (M^+), 268 $(M-18)^+$.

Oxidation of alcohol *6* to ketone *5*. Compound **6** (3 mg) and pyridinium chlorochromate (4 mg) in CH_2Cl_2 (1 ml) were left for 2 h at RT. TLC. (development with dinitrophenylhydrazine) showed formation of **5** (Rf of **5** 0.54, of starting material 0.42).

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