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10-EPIJUNENOL, A NEW *cis*-EUDESMANE SESQUITERPENOID

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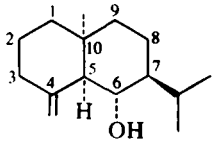
Abstract—An unusual *cis*-eudesmane sesquiterpene alcohol has been isolated from galbanum resin. Some comments about the spectral properties of *cis*-decalins with angular methyl groups are made. A new synthesis of the selinane system is described.

INTRODUCTION

To our knowledge, the only examples of naturally occurring *cis*-eudesmanes are: occidentalol,[1] a sesquiterpene ether isolated from termites,[2] and a group of nor-sesquiterpenes from *Chamaecyparis formosensis*.[3] During an investigation of galbanum resin (from *Ferula galbaniflua*), we isolated an isomer (**1**) of junenol (**2**)[4] having *cis* instead of *trans* fused rings.† Because it seemed that this series would lend itself to synthesis by a route recently described by two of us,[5] we also synthesized the two eudesmanes (**3**, **4**), racemates of the substances to which the new natural product was converted.



10-epijunenol

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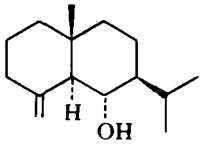

junenol

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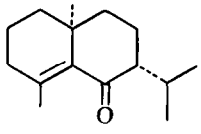

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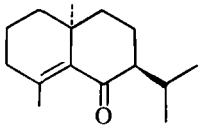

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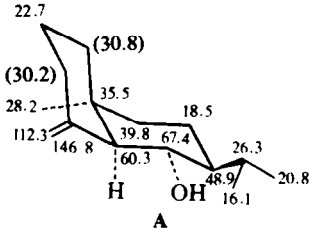
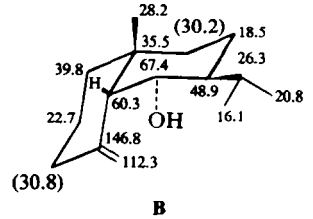
RESULTS AND DISCUSSION

The pentane-soluble part of crude commercial galbanum resin contains a fraction with b.p. 90–105°/0.001 mm. Chromatography on fine silica gel of this enabled a small amount of sesquiterpene alcohol to be eluted at about the same time as geranyl acetate, in a fraction that was notably less polar than guaiol (**5**), a known constituent of the resin.[6]

After further gas chromatographic purification, this alcohol had a sharp m.p. 31°. The PMR spectrum indicated the presence of a carbinol proton, a saturated isopropyl group, a tertiary methyl group, and a methylene group. So far as we could ascertain, the only known secondary alcohol to which the data might be fitted was junenol (**2**),[4] but the optical rotation of the new alcohol was of opposite sign, and the m.p. was 30° lower.‡ Finally, the ^{13}C NMR spectrum showed clearly that it was *cis*-fused, and that two structures had to be taken into consideration (**A** and **B**, in Fig. 1).



A



B

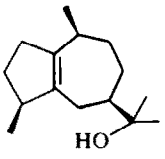
Values in parentheses are alternative attributions.

Fig. 1.

Of the ^{13}C NMR results, particularly notable is the relatively low field shift of the structurally diagnostic methyl group at the ring junction, which in the case of *trans*-10-methyldecalols is less than 20 ppm.[7] Furthermore, the high field shift of the neopentyl methylene C-1 can be rationalized by a 1,3-diaxial interaction in which $H_{1\alpha}$ is involved. In a 6,7-diequatorially substituted

†The sesquterpenoid numbering (as in **1**) is used in this paper for all decalins. The formulae do not necessarily represent the absolute configuration, which is not known in the case of the epijunenol series.

‡Curiously, none of the papers on junenol quote any NMR data except Shaligram *et al.*[4b] who only give figures for the vinyl methylene group. We are indebted to Prof. N. H. Andersen who gave us all that remained of a small sample of junenol, but this was unfortunately insufficient for spectral measurements.



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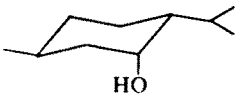

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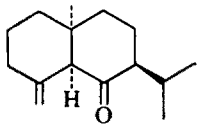

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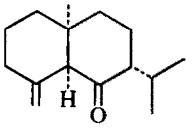

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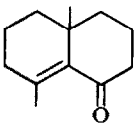


10

10-methyldecalin system, *trans*-fused rings would exhibit two methylene signals in the region 35–40 ppm, corresponding to C-1 and C-9.

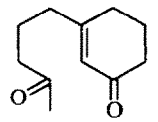
The chemical shift of the methine carbon to which the isopropyl group is attached favours structure **A**. The chemical shift of C-7 (48.9 ppm) in this case should be close to that of C-4 in menthol (**6**) (50.05 ppm[8]). In structure **B**, the chemical shift would be expected to move by about 5–6 ppm upfield with respect to that of C-4 of menthol as a result of the steric compression effect from the C-5 axial substituent in the *cis*-fused system. The chemical shift of the methylene carbon adjacent to the double bond also supports structure **A**. This signal appears at 30.2 or 30.8 ppm (C-3) and is influenced by two major effects. A non-substituted cyclohexane has one signal at 26.8 ppm.[7] The α-effect of the exocyclic double bond is expected to deshield C-3 in **A** by *ca.* +8.5 ppm[9] and the steric compression effect of the C-5 axial substituent should cause a shift of *ca.* −5.5 ppm. The difference of +3 ppm added to 26.8 ppm well explains the C-3 chemical shift of **A**, while for **B**, the only effect influencing C-3 is the α-effect of the exocyclic double bond, and its magnitude (*ca.* +8.5 ppm) is not in agreement with the observed chemical shift.

Further support for structure **A** was obtained by comparison of the PMR spectrum with those of the menthols.[10] The carbinol proton in menthol (**6**, and similar compounds) is at 3.38 ppm and has an axial–axial coupling constant (J_{aa}) of 9.4 Hz, with a signal width of 23 Hz. The corresponding proton in neomenthol (**7**) is at 4.05, its coupling constant is not visible, and the width of the signal is 8.5 Hz. In epijunenol (**1**), the carbinol proton is at 3.53 ppm, its coupling constants are 9 Hz (two J_{aa} giving rise to an apparent triplet), and the signal width is 23 Hz.

The following chemical transformations confirmed the structure of epijunenol (**1**). Chromic oxidation gave a single ketone (**8**), still containing the $\beta\gamma$-unsaturated alkene function. Treatment of this ketone with sodium methoxide in methanol gave a mixture containing unchanged **8**, together with the isomer where only the isopropyl group had epimerized (**9**), and the two isomers (**3**, **4**) of the conjugated ketone.

The stereochemistry of the unconjugated ketone (**8**) was apparent from the unchanged position of the PMR signal of the angular methyl group, which would be at higher field in a *trans*-10-methyldecalone.†[11] Furthermore it has been shown[13] that one of the methylene protons of a *trans*-10-methyldecal-6-one suffers a large anisotropic shift owing to the proximity of the carbonyl group, so that the signals of the methylene group resemble those of a 2-methylenecyclohexanone. In ketones **8** and **9**, there is only a minor displacement from the corresponding signals of epijunenol (**1**), demonstrating the further distance of the carbonyl group in *cis* isomers. The conjugated ketones (**3**, **4**) have been described[14] as rearrangement products from the *trans*-fused isomer (acolamone) of **8** and one of its double bond isomers. A direct comparison of the PMR and IR spectra showed our compounds to be identical with those of the Japanese authors, the small differences between their figures and ours (see experimental section) probably being because of greater accuracy obtained on our 90 MHz instrument.‡

The constitutions of the latter two ketones (**3**, **4**) have been further corroborated by an independent synthesis starting from the octalone (**10**).[5] This was readily accessible by the previously described[5] "methylating cyclization" of the oxo-enone (**11**), followed by dehydration of the β-hydroxyketone intermediate. Ethoxycarbonylation of **10** yielded the largely enolized β-ketoester (**12**)§ which, on treatment with excess methyllithium, was transformed into the hydroxyketone (**13**). Elimination of water (thionyl chloride in pyridine) from the tertiary alcohol (**13**) gave the unstable isopropenyl ketone (**14**) in which the presence of an equatorial isopropenyl group was established by clearly visible couplings in the PMR spectrum of the proton on the ring carbon carrying this group (J_{aa} 10 Hz, J_{ae} 7 Hz). The ketone (**14**) was reduced with hydrogen over platinum in an extremely sluggish reaction to the isopropyl ketone (**3**), identical in all respects with the ketone obtained from the natural



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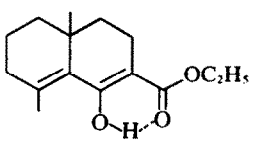

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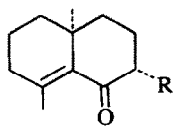


13: R = $C(OH)(CH_3)_2$
14: R = $C(CH_3)CH{=}CH_2$

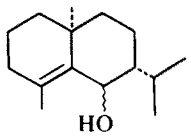
†A substituted (*trans*) junenol has been described by Asakawa *et al.*;[12] it has the PMR signal of the angular methyl group at 0.82 ppm, compared with our value of 0.89 ppm for epijunenol (**1**).

‡We are most grateful to Prof. S. Yamamura for supplying copies of the spectra. The ketones **8** and **9** are reported by Schwartz *et al.* in the course of a synthesis of dihydrojunenol, but without spectral data.[15]

§Traces of the keto form could be detected by bands at 1735 and 1685 cm^{-1} in the IR spectrum.

product. Isomerization of this ketone (3) yielded a mixture (*ca.* 8:2) containing the other stereoisomer (4) as the minor product.

An attempt was made to deconjugate the ketone (3) photochemically;[16] a mixture was obtained that did not contain any of the isomers of the methylene ketones (8, acolamone,[14] etc.) and which was not further examined. Attempts to investigate rearrangement of the alcohol (15), readily obtained by LAH reduction of 3, were frustrated by the very ready dehydration of 15 to δ-selinene (16)† and the diene (17), this occurring on even the mildest treatment of 15.



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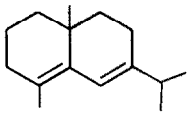

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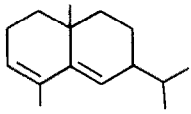

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EXPERIMENTAL

Mass spectra were obtained with an Atlas CH-4 instrument, inlet temp. 150°, with electrons of 70 eV energy. NMR spectra were measured with a Bruker HX-90 instrument in $CDCl_3$, and chemical shifts are given in ppm with tetramethylsilane as 0.00 ppm. IR spectra were recorded on a Perkin–Elmer type 125 spectrophotometer. Gas chromatography (GC) was carried out on a Carlo Erba GT apparatus. The chromatography on silica gel of the galbanum extract was carried out in the Collège de France‡ on the prototype of the Chromatospac-Prep 100 instrument (Jobin Yvon Instruments, S.A.) using Merck silica gel, finer than 220 mesh. Routine silica-gel chromatography was done on Merck silica-gel, 70–325 mesh.

Extraction of galbanum resin. Crude galbanum resin (14.7 kg) was stirred with 5 l. pentane. The filtrate was concentrated to yield about 4.7 kg material, which was distilled. The fraction with b.p. 27–130°/0.1 mm weighed 840 g, and was partitioned between hexane and 95% aqueous MeOH. The less polar phase (upper) was filtered over 1.6 kg of silica gel in a Nylon tube[18] to allow most of the hydrocarbons to be eliminated. The column was washed with ether, thus retaining highly polar substances on the column (acids, polyols, etc.), and the material of medium polarity thus obtained was distilled. At b.p. 60–105°/0.001 mm, 50 g of material distilled, 25 g of which was chromatographed on the fine silica gel in the apparatus described above. With approximately the same R_f value as geranyl acetate (also obtained from this fraction), *ca.* 0.5 g of 10-epijunenol was eluted, and was purified by GC on an OV-17 column. It then had m.p. 31°, $[\alpha]_D^{20}$ +85.7° (6% in EtOH). PMR spectrum: 0.89 (s) superimposed on 0.85 and 0.93 (d, J = 7 Hz), 9H in all; 2.0–2.4 (3H, mult, protons adjacent to C=C); 3.52 (1H, "t", J = 9 Hz); 4.79 (1H, d, J = 1.5 Hz) and 4.93 (1H, mult, J *ca.* 1 Hz, signal width 6 Hz, $C=CH_2$). Mass spectrum, *m/e* (% rel. abundance): 109 (100), 41 (15), 43, 55, 67, 81, 93, 107 (*ca.* 10), 161 (3.5), 189 (5), 204 (M-18°, 5), 22 ($M^{\cdot}$, <1).

Oxidation of epijunenol. Epijunenol (0.1 g) in ether (5 ml) was stirred overnight with chromic acid soln (1 ml, prepared following Brown *et al.*[19]). The mixture was washed with $NaHCO_3$ aq and water, dried, and concentrated. GC on an FFAP column (230°) indicated the presence of *ca.* 18% unchanged epijunenol; the remainder, with a longer retention time, was the corresponding ketone (8). PMR spectrum: 0.86 and 0.90 (6H together, each d, J = 7 Hz); 1.03 (3H, s); 2.74 (1H, s, C=C–CH–C=O); 4.60 and 4.94 (1H each, s + long-range coupling, $C=CH_2$). Mass spectrum: 107 (100), 93 (64), 109 (58), 108 (52), 41 (46), 79 (32), 55 (28), 220 ($M^{\cdot}$, 26).

Base-catalyzed isomerization of epiacolemone (8). The ketone 8 (0.09 g) and NaOMe (0.1 g) in dry MeOH (5 ml) was stirred for 1 hr, then pentane was added and the mixture washed with water until neutral. After concentration, the following substances were identified by GC on an FFAP column (in order of elution):

1. A trace of epijunenol (1).

2. A mixture of the unchanged ketone (8) and two other ketones, which could subsequently be separated by GC on OV-17 into the conjugated *cis*-ketone (3), having identical spectra with those of the synthetic sample (see below), and (9), with PMR spectrum: 0.87 and 0.95 (6H together, each d, J = 6.5 Hz); 1.02 (3H, s); 2.79 (1H, s, C=C–CH–C=O); 4.52 and 4.93 ($C=CH_2$).

3. The conjugated *trans*-ketone (4), identical in retention time and spectra with the synthetic sample (see below).

Ethyl 4a,8-dimethyl - 1 - hydroxy-3,4,5a,5,6,7-hexahydronaphthalen - 2 - oate (12). The octalone 10[4] (14.3 g, 80 mmol) and NaH (7 g, 0.16 mol of a 55% dispersion in mineral oil, washed 3 times with pentane) were heated in glyme (100 ml) at 90° for 5 h. Diethyl carbonate (28.3 g, 0.24 mol) was added at room temp., and the mixture stirred overnight without heating, then 1 hr at 50–60°, and poured into ice-cold dil AcOH. Usual workup (ether) gave 19.1 g of crude product, which was chromatographed on 200 g of silica gel in hexane-ether (98:2). The first fraction yielded, after bulb distillation (b.p. 92–98° and 0.01 mm), 5.52 g of 12, the second fraction yielding 5.6 g of starting material (10) after distillation. The product (12) had the following PMR spectrum: 1.00 (3H, s); 1.33 (3H, t, J = 7 Hz); 2.06 (3H, s, $CH_3C=$); 4.25 (2H, q, J = 7 Hz); 12.82 (1H, s, OH-intramolecular H-bond, unchanged on dilution). IR spectrum (cm^{-1}, in CCl_4): 1735, 1685 (both weak, keto-form); 1637, 1617, 1575 (strong, enolester form with intramolecular H-bond). Mass spectrum: 31 (100), 45 (51), 163 (49), 189 (38), 175 (33), 107 (25), 91 (24), 178 and 79 (21), 250 ($M^{\cdot}$, 10).

11-Hydroxyselin-4-en-6-one (13). A 1.8 N etheral soln of MeLi (49 ml, 88 mmol) was added dropwise to a stirred soln of 12 (5.52 g, 22 mmol) in ether (150 ml) at 0°. The resulting soln was stirred 15 min at 0° then 2 hr at reflux. The cooled mixture was poured onto crushed ice and the product isolated as usual with ether. After concentration, the crude material (*ca.* 5 g) was chromatographed on silica gel (100 g). Elution with hexane–ether (95:5) removed some less polar impurities, then ether elution gave 4.09 g (78%) of 13. PMR spectrum: 0.96, 1.22, 1.27 (each 3H, s); 1.72 (3H, s, $CH_3C=$); 4.63 (1H, s, OH-intramolecular H-bond, unchanged on dilution, disappears on adding D_2O). IR spectrum (CCl_4): 3500, 1665 (strong), 1615 (weak). Mass spectrum: 43 (100), 163 (99), 135 (58), 178 (56), 107 (42), 79 (33), 93 and 91 (32), 236 ($M^{\cdot}$, 1).

Selina-4,11-dien-6-one (14). $SOCl_2$ (0.2 ml, 2.8 mmol) was added dropwise to a cooled soln of 13 (236 mg, 1 mmol) in dry pyridine (5 ml). During the addition, the temp. was allowed to rise from 0° to 15°, then the mixture was stirred for 7 hr at room temp. and poured into ice-water. Work-up in pentane (3 washes with 1N HCl, then sat. $NaHCO_3$ aq and water, drying, and concentrating) gave 148 mg of crude 14 which was used immediately for spectral measurements, and for the following step. PMR spectrum: 1.00 (3H, s); 1.72 (3H, s, $CH_3C=$); 1.81 (3H, s, CH_3 "isopropenyl"); 3.03 (1H, d × d, J_{aa} = 11 Hz, J_{ac} = 7 Hz, isopropenyl –CH–C=O); 4.76 and 4.95 (1H each, s + long-range coupling, $C=CH_2$). IR spectrum (CCl_4): 3075 (med), 1675 (strong), 1645 and 1625 (med), 890 (strong). Mass spectrum: 203 (100), 137 (72), 175 (67), 109 and 41 (60), 218 ($M^{\cdot}$, 54), 91 (49), 79 (46).

(±)-cis-*Selin-4-en-6-one* (3). The crude 14 (2.4 g) in EtOH (20 ml) was shaken with Raney Ni (*ca.* 0.5 g) at room temp. for 1 hr to remove traces of S impurities. The Ni was removed by filtration, and PtO_2 (100 mg) was added, the soln then being shaken in H_2. Two further amounts of catalyst were added (250 and 500 mg) in order to achieve 135 ml of H_2 absorbed (corrected, 55%). The filtered and concentrated soln was bulb distilled (b.p. 85–90° and 0.01 mm) to give 1.55 g of the title compound (*ca.* 90% pure by GC

†Early literature[17a] refers to 16 as "ζ-selinene"; our PMR spectrum fits the meagre data[17b] in the literature. See 17*c* for other leading refs.

‡We are very grateful to Prof. J. Jacques and the staff of the Collège de France for hospitality extended (to A.F.T.) during this separation.

on a 10% silicone oil column at 200°). Chromatography on silica gel (50 g) in hexane–ether (98:2) gave 1.12 g of the pure ketone (**3**, 44% yield based on **13**). PMR spectrum:† 0.89 and 0.94 (6H together, each d, J = 7 Hz); 0.94 (3H, s); 1.68 (3H, s, CH_3C=). λ_{max}^{EtOH} 251 nm, ϵ_{max} 5200. IR spectrum (CCl_4):† 1680 (strong), 1620 (med). Mass spectrum: 205 (100), 178 (92), 149 (79), 220 (M^+, 75), 41 (70), 107 (63), 93 (51), 109 (49), 55 (47), 177 (45).

(±)-trans-*Selin-4-en-6-one* (**4**). The synthetic *cis*- **3** was equilibrated as described above for epiacolemone (**8**). The *trans* isomer (**4**) formed *ca.* 15% of the resulting mixture, and it was purified by GC on OV-17 (200°) when it had a longer retention time than the *cis* isomer. PMR spectrum:† 0.86 and 0.92 (6H together, each d, J = 6 Hz); 1.00 (3H, s); 1.74 (3H, s, CH_3C=). Mass spectrum: 178 (100), 205 (94), 149 (80), 41 (75), 220 (M^+, 62), 107 (58), 55 (52), 109 and 93 (51), 91 (47).

Reduction of cis-*Selin-4-en-6-one* (**3**). The ketone **3** (0.1 g) was added to a soln of excess LAH in ether. After 5 min, the excess reagent was decomposed with water, and the product isolated from the filtered soln. TLC showed that the reduction had occurred with negligible hydrocarbon formation, but on chromatography on silica gel, or on alumina (basic, grade 3), the same mixture was obtained as by GC, and consisted of a 4:6 mixture of δ-selinene (**16**), eluted first from an Apiezon M column, and selina-3,5-diene (**17**). The former (**16**) had PMR spectrum: 0.93 (3H, s); 1.05 (6H, d, J = 6.5 Hz); 1.71 (3H, s, CH_3C=); 6.14 (1H, s, C=C–CH=). Mass spectrum: 189 (100), 161 (87), 204 (M^+, 68), 105 (48), 91 (47), 133 and 41 (42), 119 (32), 95 (29), 81 (25). Selina-3,5-diene (**17**) had PMR spectrum: 0.87 and 0.92 (both d, J = 6.5 Hz), and 0.95 (s), 9H together; 1.78 (3H, s, CH_3–C=); 2.0–2.4 (3H, protons adjacent to C=C); 5.4–5.6 (2H, CH=C–C=CH). Mass spectrum: 161 (100), 81 (30), 105 (29), 41 (24), 91 (22), 119 (20), 204 (M^+, 16), 95, 67 and 55 (15).

Acknowledgement—The authors thank Dr. B. Maurer for valuable discussions.

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†These spectra were identical with those of Yamamura *et al.*[14] although the maxima did not come at identical positions on the scale.