A Total Synthesis of Cadin-4, 10(15)-dien-3α-ol: Structure of Khusinol

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A total synthesis of cadin-4,10(15)diene-3α-ol, one of the structures proposed for khusinol, is described. Neither this compound nor its C_3-epimer was identical with khusinol.

La synthèse totale du cadindiène-4,10(15)ol-3α, une des structures proposées pour le khusinol est décrite. Ce composé et son épimère au niveau du C_3 ne sont pas identifiés au khusinol.

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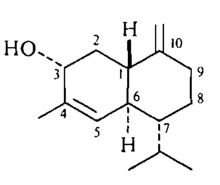
The isolation of khusinol from the oil of *Vitiveria zizanioides* (L). Nash was first reported in 1963 and at that time structure **1** (title compound) was assigned to this sesquiterpene alcohol (1). It was also shown, by conversion to (−) γ-cadinene, that khusinol belongs to the naturally occurring antipodal series of cadalenic compounds and is therefore of interest from the point of view of biogenesis (1).

Structure **1** for khusinol was adduced from chemical evidence and, apparently, without the benefit of n.m.r. spectroscopy. More recently, however, a revised structure **2** for khusinol has been proposed (2). The latter proposal was based on further chemical evidence and high resolution n.m.r. spectroscopy. The validity of neither of these structures has been verified by synthesis.



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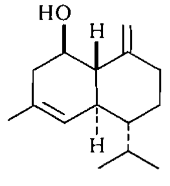
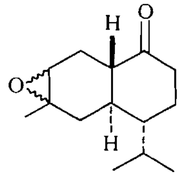


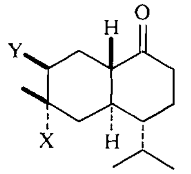
2

Before the proposal of structure **2** for khusinol, we were prompted by the availability in our laboratories of the convenient intermediate **3** to complete a synthesis of **1**. We now wish to give an account of the details of this synthesis (see Scheme 1) and to report that, since neither **1** nor its C_3-epimer (**12**) were identical with khusinol, these structures need no longer be considered for this sesquiterpenoid.[1]

The totally synthetic enone **3** (3) was converted into the crystalline epoxide **4** by treatment with *m*-chloroperbenzoic acid.[2] The assignment of structure **4**, rather than the alternative structure **5**, to the epoxide is based on the following evidence. The epoxide was converted, in 92% yield, into a crystalline bromohydrin in which the bromine atom and the hydroxyl group are *trans* diaxially oriented (4). The n.m.r. signal for the methyl group at C-4 appeared at δ 1.87 in agreement with the presence of the group CH_3—C—Br. Acetylation of the bromohydrin under conditions which could not be expected to acetylate a tertiary alcohol such as **7** and which gave only a monoacetate when applied to the diol **8** (*vide supra*), did, in fact, give a crystalline acetate. Furthermore, the downfield shift (1.17 p.p.m.) of the n.m.r. signal for the C-3 proton as a result of acetylation of the bromohydrin is characteristically associated with the acetylation of a secondary alcohol such as **6** (5). The above evidence establishes structure **6** for the bromohydrin to the exclusion of **7**. Therefore, in accordance with the well established stereospecific manner in



4 β-Epoxide (as in Scheme 1)
5 α-Epoxide



6 Y = OH; X = Br
7 Y = Br; X = OH

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[1] The numbering system shown in **1** is used throughout.

[2] The i.r. and n.m.r. spectra of all compounds were consistent with assigned structures; spectral data are given in the Experimental.

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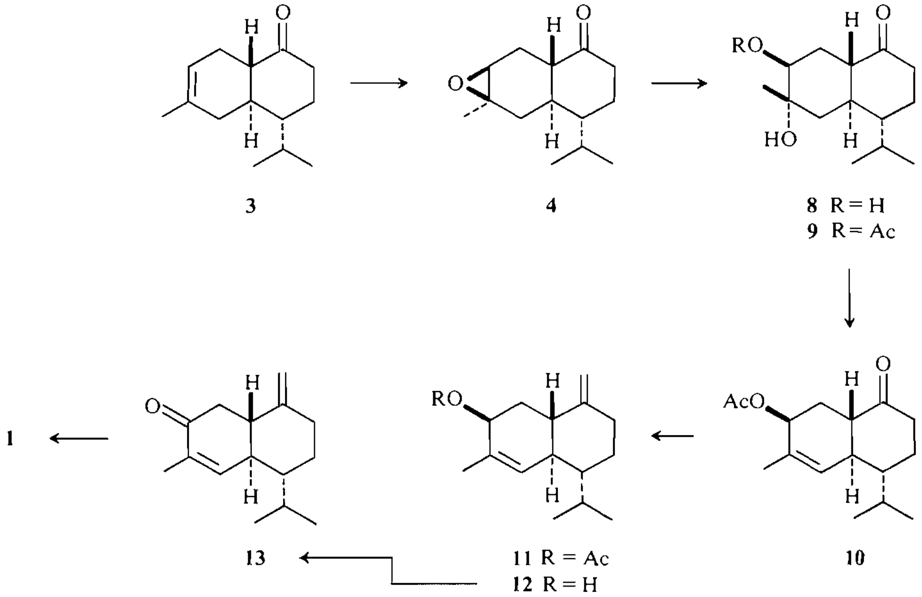

SCHEME 1

which epoxides are cleaved (4), the epoxide which is the precursor of **6** must be assigned structure **4** rather than **5**.

Hydrolysis of the epoxide **4** afforded the crystalline diaxially oriented diol **8** (4). Acetylation of the latter and treatment of the resulting monoacetate **9** with phosphorus oxychloride in pyridine gave the olefin **10**. The fact that the n.m.r. signal for the vinylic proton in **10** appeared as a singlet is proof that the double bond was introduced into the assigned position (3).

The acetate **10** was converted into the diene **11** in 79% yield via a modified Wittig reaction (6). Several cases have been reported where decalones and octalones having the keto group adjacent to a ring junction (such as in **10**), when subjected to the Wittig reaction, have yielded olefins in which the angular carbon atom originally adjacent to the ketone had undergone epimerization (7). This phenomenon has been observed only in the case of *cis*-fused systems. The possibility of this type of epimerization happening in the case of **10** to give a *cis*-fused diene is ruled out by the fact that, in the n.m.r. spectrum of the diene, the signal at δ 5.83 for the vinylic proton at C-5 appeared as a singlet. This requires that the dihedral angle between the C-5 and -6 protons be approximately 90°, a requirement satisfied by the *trans*-fused structure **11** but not by any reasonable conformation of the *cis*-fused diene corresponding to **11**.

Reduction of the acetate **11** with lithium aluminum hydride afforded the alcohol **12** which is the C_3-epimer of the desired compound (**1**).

Oxidation of **12** with activated manganese dioxide (8) gave, in 75% yield, the α,β-unsaturated ketone **13** which, on reduction with lithium aluminum hydride, afforded **1** as a crystalline compound in 98% yield. The broadening of the n.m.r. signal for the C-3 proton by 13 Hz ($w_{1/2}$) as a result of the transformation $\mathbf{12} \rightarrow \mathbf{1}$ is consistent with the conversion of a quasi axial hydroxyl into a quasi equatorial hydroxyl group (5). Comparison of the spectral properties and behavior on t.l.c. of the newly acquired dienol with the corresponding properties of the precursor dienol **12** showed that the two compounds were distinctly different.

Experimental

General

The n.m.r. spectra were determined in deuteriochloroform ($CDCl_3$) solutions with a Varian T-60 instrument. Chemical shifts are expressed in p.p.m. (δ values) downfield from the tetramethylsilane signal as internal standard.

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Reaction products were isolated by the following procedure. The product was extracted into the specified solvent and the extract was washed two or three times with appropriate aqueous solutions as indicated. The original aqueous layer (if any) and the aqueous washings were extracted three times with the solvent and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated *in vacuo* on a rotary evaporator.

Brine refers to a saturated solution of sodium chloride.

Petroleum ether refers to the fraction with boiling point range 30–60°.

Keto Epoxide **4**

A solution of 411 mg of the enone **3** and 454 mg of *m*-chloroperbenzoic acid in 37 ml of chloroform was stirred at room temperature for 1 h. The solution was then treated with 28 ml of 10% aqueous sodium bisulfite solution and stirred for a further 15 min. The reaction mixture was extracted with chloroform and the extract was worked-up in the usual manner by washing with 5% sodium bicarbonate solution and water. The oily residue, on crystallization from pentane afforded 245 mg (55%) of **4**, m.p. 71–73°; ν_{max} (Nujol) 1705 cm^{-1} (ketone); n.m.r. δ 0.75 and 1.00 (doublets, 3H each, $J = 7.0$ Hz, isopropyl group),[3] 1.28 (s, 3H, CH_3—C—O), 3.05 (m, 1H, H—C—O).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C, 75.44; H, 9.82.

Keto Bromohydrin **6** *and its Acetate*

A solution of 33 mg of the epoxide **4** in 2 ml of glacial acetic acid was treated, with cooling in an ice bath, with 0.5 ml of 24% hydrobromic acid in acetic acid. The reaction solution was kept at 0° for 45 min then diluted with 30 ml of methylene chloride. The resulting solution was worked-up in the usual manner by washing with water. The residue, an oil, was crystallized from pentane to give 42 mg (92%) of **6**, m.p. 123–125°; ν_{max} (Nujol) 3420 (OH) and 1685 cm^{-1} (ketone); n.m.r. δ 1.87 (s, 3H, CH_3—C—Br), 4.03 (m, $w_{1/2} = 6.5$ Hz, 1H, H—C—OH).

The *acetate* was prepared in 72% yield in the usual manner with acetic anhydride in pyridine at room temperature. Crystallized from pentane, it melted at 143–145°, ν_{max} (Nujol) 1740 (acetate) and 1705 cm^{-1} (ketone); n.m.r. δ 1.71 (s, 3H, CH_3—C—Br), 2.00 (s, 3H, acetate), 5.20 (m, $w_{1/2} = 6.5$ Hz, 1H, H—C—OAc).

Anal. Calcd. for $C_{16}H_{25}OBr$: Br, 23.14. Found: Br, 23.02.

Keto Diol **8**

A mixture of 445 mg of the epoxide **4**, 60 ml of acetone, and 60 ml of water was refluxed for 15 h. The acetone was evaporated *in vacuo* and the remaining aqueous solution was saturated with sodium chloride and extracted with ether. The ether extracts were worked-up in the usual manner by washing with brine. The crude product, an oil, was chromatographed on a column of 15.0 g of silica gel in benzene–ether (1:1). The eluate, on crystallization from ethyl acetate–petroleum ether afforded 237 mg of **8**, m.p. 134°; ν_{max} (Nujol) 3550 and 3350 (hydroxyls) and 1680 cm^{-1} (ketone); n.m.r. δ 1.28 (s, 3H, CH_3—C—OH), 3.63 (m, $w_{1/2} = 6.5$ Hz, 1H, H—C—OH).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.54; H, 10.06. Found: C, 70.20: H, 10.28.

Acetate **9**

Treatment of the diol **8** in the usual manner with acetic anhydride in pyridine afforded, in 95% yield, the acetate **9**, m.p. 137°; ν_{max} (Nujol) 3410 (OH) and 1700 cm^{-1} (broad band, ketone and acetate); n.m.r. δ 1.30 (s, 3H, CH_3—C—OH), 2.06 (s, 3H, acetate). 4.82 (m, $w_{1/2} = 6.5$ Hz, 1H, H—C—OAc).

Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.38; H, 9.40.

Enone Acetate **10**

A solution of 2.03 g of the acetate **9** in 75 ml of pyridine was treated, with cooling on an ice-salt bath, with 16.5 ml of phosphorus oxychloride then left at room temperature for 12 h. The reaction was poured into a mixture of 500 g of ice and water and the resulting cold solution was extracted with ether. The ether extract was worked-up in the usual manner by washing, in the order mentioned, with cold 1 *N* hydrochloric acid, cold saturated sodium bicarbonate solution, and ice water. Evaporation of the ether extracts yielded 2.00 g of yellow oil which was combined with 450 mg of similar material from another run. The oil was chromatographed on a column of 120 g of silica gel impregnated with 20% of silver nitrate. Elution of the column with 25% of ether in petroleum ether, evaporation of the effluent *in vacuo* and crystallization of the residue from pentane afforded 1.40 g (61%) of **10**, m.p. 108–109°; ν_{max} (Nujol), no hydroxyl bands, 1735 (acetate) and 1710 cm^{-1} (ketone); n.m.r. δ 1.71 (s, 3H, vinylic CH_3), 2.03 (s, 3H, acetate), 5.17 (m, $w_{1/2} = 9.5$ Hz; 1H, H—C—OAc), 5.81 (s, 1H, vinylic proton).

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.56; H, 8.96.

Dienol Acetate **11**

The Wittig reaction was carried out in an atmosphere of dry, oxygen-free nitrogen as follows. A stirred suspension of 393 mg of the ketone **10** in 3 ml of dimethyl sulfoxide was treated with 3.75 ml of a 0.5 *M* solution of methylenetriphenylphosphorane (6) whereupon a mildly exothermic reaction occurred and the ketone was completely dissolved. The yellow reaction solution was stirred at room temperature for 11 h then poured into 35 ml of water. The aqueous solution was worked-up in the usual manner by extraction with ether, and washing the ether extracts with water. Evaporation of the ether extracts *in vacuo* gave 446 mg of oil which was chromatographed on a column of 15.0 g of silica gel impregnated with 20% of silver nitrate. Elution of the column with 5% of ether in pentane yielded an oil which, after crystallization from pentane, afforded 309 mg (79%) of **11**, m.p. 53–54°; ν_{max} (Nujol) 1740 (acetate), 1684 (olefin), and 890 cm^{-1} with overtone at 1780 cm^{-1} (exocyclic CH_2); n.m.r. δ 1.72 (s, 3H, vinylic CH_3), 2.03 (s, 3H, acetate), 4.47 and 4.63 (singlets, 1H each, exocyclic CH_2), 5.17 (m, $w_{1/2} = 7.0$ Hz, 1H, H—C—OAc), 5.83 (s, 1H, vinylic proton).

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 78.01; H, 9.97.

Dienol **12**

A solution of 519 mg of the dienol acetate **11** in 25 ml of ether was added dropwise to a stirred mixture of 250 mg of lithium aluminum hydride in 25 ml of ether. After stirring for 16 h at room temperature, the reaction mixture was refluxed for 2 h, cooled, and treated with 0.4 ml of brine

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[3] This pair of doublets appears in the n.m.r. spectra of all succeeding compounds.

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and stirred for a further period of 1 h. Removal of the solid material by filtration and evaporation of the filtrate *in vacuo* gave 550 mg of oil. Chromatography of the crude product on 25 g of silica gel impregnated with 20% of silver nitrate using 25% of ether in petroleum ether as solvent gave an oil which, on crystallization from petroleum ether, afforded 348 mg of **12**, m.p. 96°; ν_{max}(Nujol), no carbonyl absorption, 3225 (OH), 1648 (olefin), 880 with overtone at 1760 cm^{-1} (exocyclic CH_2); n.m.r. δ 1.78 (s, 3H, vinylic CH_3), 3.97 (m, $w_{1/2}$ = 7.0 Hz, 1H, H—C—OH), 4.50 and 4.63 (singlets, 1H each, exocyclic CH_2), 5.70 (s, 1H, vinylic proton).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.63; H, 10.71.

Dienone 13

A suspension of 251 mg of the dienol **12** and 5.0 g of activated manganese dioxide (8) in 75 ml of pentane was stirred at room temperature for 6 h. Removal of the solid material by filtration and evaporation of the filtrate *in vacuo* afforded an oil which crystallized from pentane to afford 186 mg (74%) of **13**, m.p. 62.5–63°; λ_{max} (EtOH) 238 nm (ε, 9700); ν_{max} (Nujol), no hydroxyl band, 1675 (ketone), 1647 (olefin), 880 with overtone at 1760 cm^{-1} (exocyclic CH_2); n.m.r. δ 1.78 (s, 3H, vinylic CH_3), 4.50 and 4.71 (singlets, 1H each, exocyclic CH_2), 6.81 (s, 1H, vinylic proton).

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.84; H, 10.06.

Dienol 1 (Cadin-4, 10(15)-diene-3α-ol)

A solution of 130 mg of the dienone **13** in 10 ml of ether was added dropwise to a refluxing mixture of 200 mg of lithium aluminum hydride and 10 ml of ether. The reaction mixture was refluxed for 18 h then cooled and treated with 0.4 ml of brine. After stirring for 2 h, the solid material was removed by filtration and the filtrate was evaporated *in vacuo*. Crystallization of the residue from ether – petroleum ether afforded 129 mg of **1**, m.p. 115.5–116.5°; ν_{max} (Nujol) 3350(OH), 1647 (olefin), 880 with overtone at 1760 cm^{-1} (exocyclic CH_2); n.m.r. δ 1.77 (s, 3H, vinylic CH_3), 4.15 (m, $w_{1/2}$ = 20 Hz, 1H, H—C—OH), 4.50 and 4.62 (singlets, 1H each, exocyclic CH_2), 5.57 (s, 1H, vinylic proton).

This compound was separated from authentic khusinol and from the dienol **12** by t.l.c. on silica gel with chloroform as solvent.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.56; H, 11.20.

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