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Sesquiterpenoids. LIV.[1] Absolute Configuration of Eudesma-4(14),7(11)-dien-8-one

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Synopsis. (+)-Eudesma-4(14),7(11)-dien-8-one (**1**) isolated from *Atractylodes* rhizomes has been degraded with basic alumina to the trisnor ketone (**3**). From the CD spectra of **1** and **3**, the absolute configuration of **1** has been established to be 5*S*, 10*R*, which has so far been allocated to the (−)-enantiomer.

During the course of our study on the physiologically active constituents of Oriental medicines, it was found that a methanol extract of *Atractylodes japonica* rhizomes showed a significant antiinflammatory activity. Fractionation of the extract monitored by a pharmacological assay afforded active fractions from which an oily substance was isolated. The mass spectrum of the substance ($[\alpha]_D$+92.6°) showed it to be a sesquiterpenoid having the composition of $C_{15}H_{22}O$. The spectral data, in particular a UV absorption maximum at 246 nm and IR bands at 1676 and 1620 cm^{-1} demonstrated the presence of a conjugated enone system in a six- or larger-membered ring. In the IR and ^1H NMR spectra, peaks compatible with one tertiary methyl (δ 0.73), two vinyl methyls (δ 1.78 and 1.90) and an exo-methylene (1640 and 882 cm^{-1}, δ 4.56 and 4.80) were observed. These structural characteristics indicated that this compound was (+)-eudesma-4(14),7(11)-dien-8-one (**1**) obtained recently from the same plant.[2] The conclusion was substantiated by direct comparison with an authentic specimen.

The substance (**1**) is very unstable when subjected to alumina chromatography. A ketonic compound (**3**) was isolated from the decomposition products in varying yields. The compound (**3**) exhibited in its mass spectrum the molecular ion peak at *m/e* 178 corresponding to the composition $C_{12}H_{18}O$. The presence of a saturated carbonyl (1710 cm^{-1}), a tertiary methyl (δ 0.70) and an exo-methylene (1643 and 886 cm^{-1}, δ 4.48 and 4.77) was observed. The structure of the ketone (**3**) was assigned to 1-methyl-7-methylenebicyclo[4.4.0]decan-3-one, the structure being confirmed by direct comparison with an authentic specimen.[3]

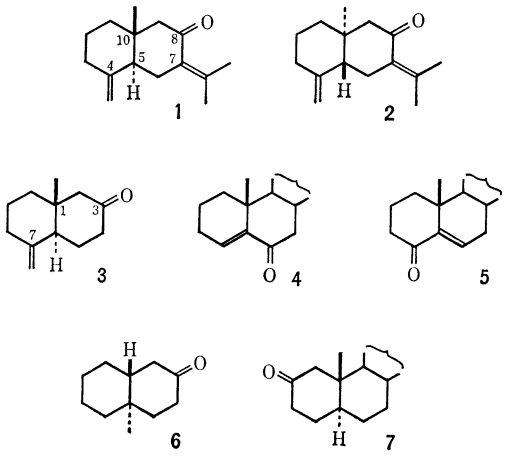
Eudesma-4(14),7(11)-dien-8-one was first isolated in the laevorotatory form ($[\alpha]_D$−55.6°) from *Asarum caulescens*, and was assigned to the stereochemistry **1** although no evidence for it was described.[4] The laevorotatory enantiomer ($[\alpha]_D$−87.4°) was also recently isolated from *Peteravenia schultzii* and assigned to the same stereochemistry (**1**),[5] where specific rotations at 589, 578, 546, and 436 nm were recorded, but no evidence for the assignment was given.

When (+)-eudesma-4(14),7(11)-dien-8-one was isolated from *Atractylodes japonica*, the enantiomeric stereostructure (**2**) was first allocated for it,[6] since its CD curve was found to be enantiomeric with that of the (−)-isomer from *Asarum caulescens* which had been reported to possess the stereostructure **1**. The proposed stereochemistry of the (+)-isomer from *A. japonica* was later altered to **1**, no evidence being reported.[2]

As a result, the same stereostructure **1** is now attributed to both of the (+)- and (−)-isomers with no evidence for the stereochemistry.

The substance (**1**) with the dextrorotatory activity isolated from *A. japonica* exhibited a negative Cotton effect for the n-π^* transition in the ORD and CD curves. The A/B ring fusion of the substance (**1**) was considered to be *trans* by the transformation of germacrone to the *trans*-fused selinane,[4,7] and is now substantiated by the transformation of the substance (**1**) into the trisnor ketone (**3**) having the *trans* ring fusion. The observed negative Cotton effect indicated that the chiral situation of the cisoid enone system is anticlockwise, identical with that of cholest-4-en-6-one (**4**)[8] and enantiomeric with that of cholest-5-en-4-one (**5**).[8] Furthermore, the ketone (**3**) showed a negative Cotton effect at 290 nm for the n-π^* transition in the CD curve. Inspection of the octant diagram demonstrated the absolute configuration of the ketone (**3**) to be 5*S*, 10*R*, identical with the decalone (**6**)[9] and enantiomeric with cholestan-2-one (**7**).[8] These observations led to the conclusion that the absolute configuration of the (+)-enantiomer corresponds to **1**, and consequently that of the (−)-enantiomer to **2**.

Although the reasons for the previous assignments for the absolute stereochemistry are unknown, the ORD curve of the (−)-isomer from *P. schultzii* measured in the range 589—436 nm might be considered as part of a negative Cotton curve but is in fact composed of a positive Cotton curve on a negative plane curve.



Experimental

The homogeneity of each compound was ascertained dy

silica gel thin layer chromatography (Merck Kieselgel GF_{254} with various solvent systems, the spots being visualized by heating with dil. sulfuric acid), and by gas-liquid chromatography with 10% Silicone SE-30 on Chromosorb-W (Φ 3 mm × 1 m glass column). In the ^1H NMR spectra, chemical shifts (δ) are expressed in ppm downfield from internal TMS. Abbreviations: s=singlet, br=broad.

Isolation of (+)-Eudesma-4(14),7(11)-dien-8-one from Atractylodes japonica *Rhizomes.* The crude drug (435 g), the dried rhizomes of *Atractylodes japonica*, was extracted 6 times with refluxing MeOH (1 liter) for 5 h (each extraction). The MeOH solutions were combined and concentrated to dryness to afford an extract (118 g). The MeOH extract (104 g) was diluted with water and extracted with light petroleum, yielding a petroleum soluble portion (27 g) and a water soluble portion (77 g). The former was applied to a column of silica gel (300 g) and eluted with benzene to give an antiinflammatory active fraction (2.7 g) which was again chromatographed over silica gel (100 g). An eluate (1.0 g) with AcOEt–hexane (1: 49) was purified by repeated silica gel chromatography to give (+)-eudesma-4(14),7(11)-dien-8-one (**1**) as a colorless oil: $[\alpha]^{20}$ +92.6° (*c* 0.034, MeOH); ORD (*c* 0.0113, MeOH) $[\alpha]_D^{20}$ +90.8° (589), +110° (546), +181° (436), +187° (414), +57.2° (356) (trough), +3420° (300) (peak), and +4240° (290 nm); CD (*c* 0.0004, MeOH) $[\theta]^{24}$ -3.56×10^3 (320 nm) (negative maximum); MS *m/e* 218 (M^+); UV_{max} (hexane) 246 nm (log ε 3.90); IR (liquid) 1676 (conj. C=O), 1640 (C=C), and 882 ($C=CH_2$); ^1H NMR (100 MHz, CCl_4) δ 0.73 (3H, s, CH_3), 1.78 (3H, s, CH_3), 1.90 (3H, s, CH_3), 4.56 and 4.80 ppm (1H each, br s, $C=CH_2$). These spectral data are in line with those reported.[2,4] The substance showed identical behavior on thin layer chromatography and gas-liquid chromatography with that of an authentic **1**.

*Alumina Treatment of (+)-Eudesma-4(14),7(11)-dien-8-one to (−)-*trans*-1-Methyl-7-methylenebicyclo[4.4.0]decan-3-one.* The compound **1** (1.0 g) was applied to a column of basic alumina (300 g). Elution with AcOEt–hexane (3: 97) (300 ml) afforded the unchanged **1** (0.4 g). Further elution with AcOEt–hexane (1: 1) (130 ml) afforded an oily product (449 mg), which was purified by repeated chromatography over silica gel to furnish (−)-*trans*-1-methyl-7-methylenebicyclo[4.4.0]decan-3-one (**3**) as a colorless oil: $[\alpha]_D^{20}$ −6.6° (*c* 0.0085, MeOH); CD (*c* 0.001, MeOH) $[\theta]^{24}$ -6.74×10^3 (290 nm) (negative maximum); MS *m/e* 178 (M^+); IR (CCl_4) 1710 (C=O), 1643 (C=C), and 886 cm^{-1} ($C=CH_2$); ^1H NMR (60 MHz, CCl_4) δ 0.70 (3H, s, CH_3), 4.48 and 4.77 ppm (1H each, br s, $C=CH_2$). The IR spectrum was superimposable with that of a synthetic (±)-**3**.

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