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Alcohol from *Juniperus oxycedrus* is Reassigned as 15-Hydroxy-β-caryophyllene

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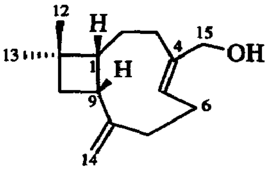
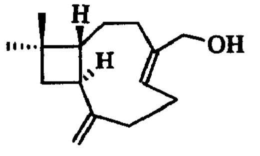
Abstract - The sesquiterpene from Juniperus oxycedrus L. (Cupressaceae), previously assigned as 15-hydroxy-9-epi-β-caryophyllene with the unusual cis-ring junction, has been shown to be the trans-fused isomer, 15-hydroxy-β-caryophyllene. The absolute stereochemistry for this compound has been determined by synthesis from (-)-β-caryophyllene.

A sesquiterpene alcohol, isolated from the essential oil of *J. oxycedrus* by Barrero *et.al.*, has been reported as 15-hydroxy-9-epi-β-caryophyllene (1)[1]. Initially, the structure 15-hydroxy-β-caryophyllene (2) was mooted, and the synthesis of this compound was attempted by direct selenium dioxide oxidation of β-caryophyllene (3). The product of this reaction was deemed to be (2) and, as the spectroscopic features of the synthetic alcohol and the natural product were significantly different, the natural product was assigned structure (1). NMR experiments on two epoxides synthesised from the natural product confirmed the caryophyllene skeleton and an NOE interaction between H-1 and H-9 in one of the epoxides appeared to confirm the *cis*-ring junction[2].



(1)



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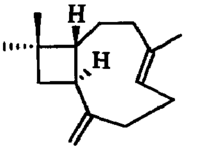

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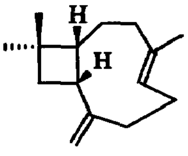


(4)

We have isolated 9-epi-β-caryophyllene (4), a compound with a very similar structure to (1), from the essential oil of the New Zealand rimu tree, *Dacrydium cupressinum* Sol. *ex* Lamb, (Podocarpaceae)[3]. The structure of (4) has recently been verified by the use of various 2D NMR experiments, the relative stereochemistry has been determined by obtaining a full set of consistent NOE interactions, and the absolute stereochemistry has been deduced as (1*R*, 9*R*) by conversion of both (4) and (-)-β-caryophyllene (3) into the same compound[4].

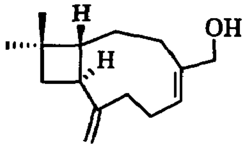
We noted that the ^{13}C NMR chemical shifts for the metabolite from *J. oxycedrus* matched those of the *trans*-fused hydrocarbon (3) much more closely than those of the *cis*-fused (4) (Table 1). Complication of the ^{13}C NMR spectrum due to conformational mobility was also more like the behaviour of (3) than that of (4). These observations suggested that the naturally occurring alcohol might be (2) as originally believed. A further consequence would be that the product of selenium dioxide oxidation of (3) had been incorrectly assigned as (2)[1].

Allylic oxidation of (3) with SeO_2 impregnated silica gel has been reported to proceed with geometric isomerisation of the endocyclic double bond to form alcohol (5) with the less strained *cis*-double bond configuration[5]. We repeated this oxidation and verified the *cis* arrangement for the endocyclic double bond by NOE experiments[6]. Further evidence for the *cis*-geometry was provided by oxidation of this alcohol (5) with NDC[7] to the previously reported aldehyde (7)[8]. Spectral data for compound (5) were identical to those quoted for the product of direct SeO_2 oxidation of (3) which had been assigned structure (2)[1].

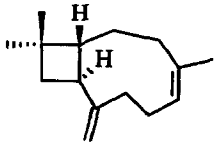
Table 1. **Selected NMR data for β-caryophyllene and related compounds.**

Compound	^{1}H NMR		^{13}C NMR	
	H-12	H-13	C-12	C-13
Alcohol *ex J. oxycedrus*[†]	0.99	0.97	29.8, 30.0	21.8, 22.1
(3)[†]	1.00	0.97	29.9, 30.1	22.0, 22.7
(4)	1.19	0.90	29.9	25.5
(5)	1.00	0.97	30.0	22.8
(6)	1.00	0.98	30.1	23.2
(7)	0.94	0.98	30.0	22.7

[†] Two conformations are observed in the ^{13}C NMR spectra at 25°C.



(5)



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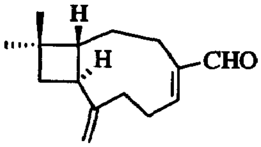

(7)

As the supposition that the natural product reported as **(1)** was in fact 15-hydroxy-β-caryophyllene **(2)** now seemed very probable, photoisomerisation of **(5)** to produce this compound was investigated. Benzene (0.5 M) sensitised photolysis (254 nm) of **(5)** in pentane[9,10] gave a maximum photostationary *trans/cis* ratio of 0.28. The *trans* isomer was separated from **(5)** by column chromatography[11], and was found to have identical spectroscopic properties to the natural product from *J. oxycedrus*[1]. As **(2)** was prepared from (-)-β-caryophyllene **(3)** and had the same optical rotation as the natural product, the full stereochemistry is (-)-(1*R*,9*S*,4*Z*)-15-hydroxy-β-caryophyllene.

In conclusion, we have proved that the compound previously isolated from *J. oxycedrus* was 15-hydroxy-β-caryophyllene **(2)**, with the absolute stereochemistry as shown. This structural assignment leads to a consistent set of NMR data (Table 1). In addition, the major product from the reaction of **(3)** with selenium dioxide is not **(2)**, but rather its isomer **(5)**, with a *cis*-double bond.

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