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CONFIRMATION OF STRUCTURE AND ABSOLUTE STEREOCHEMISTRY OF 9-EPI-β-CARYOPHYLLENE FROM *DACRYDIUM CUPRESSINUM*

SIMON F. R. HINKLEY, NIGEL B. PERRY and REX T. WEAVERS†

Plant Extracts Research Unit, Crop & Food Research, Department of Chemistry, University of Otago, New Zealand

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Key Word Index—*Dacrydium cupressinum*; Podocarpaceae; rimu; absolute stereochemistry; molecular modelling; sesquiterpene; 9-epi-β-caryophyllene; β-caryophyllene.

Abstract—The structure of the rare sesquiterpene 9-epi-β-caryophyllene, isolated from the foliage of the New Zealand rimu tree, *Dacrydium cupressinum* was verified by 2D NMR techniques and the relative stereochemistry determined by NOE studies. The absolute stereochemistry was determined by conversion of both β-caryophyllene and 9-epi-β-caryophyllene into the same known [7,2,$0^{1,6}$,$0^{1,9}$] tricyclic compound. Molecular modelling results on the lowest energy conformations of β-caryophyllene and 9-epi-β-caryophyllene were in agreement with experimental results.

INTRODUCTION

We have previously reported that the unusual sesquiterpene, 9-epi-β-caryophyllene (**1**) is found at high levels in the foliage of some specimens of the New Zealand rimu tree, *Dacrydium cupressinum* Lamb. [1]. This compound differs from the widely distributed β-caryophyllene (**2**) only at the ring junction where the [7,2,0]bicyclo undecane ring system is *cis*-fused rather than *trans*-fused [2]. Compound **1** was reported previously by Bohlmann and Zdero [3] who isolated it from *Euryops brevipapposus* (Compositae, Tribus Senecioneae). Their structural assignment was on the basis of a comparison of the ^{1}H and ^{13}C NMR spectra of **1** and its monoepoxide (**3**) with the spectra of β-caryophyllene (**2**) and its oxide (**4**). An earlier report of a 'sesquiterpene of the caryophyllene type' from *Abies magnifica* (Pinaceae), which had spectral data (IR, MS, ^{1}H NMR) matching those of **1**, may have been the first reported isolation of this compound [4]. Bohlmann and Ziesche [5] have also reported the isolation of the epoxide (**3**) from the roots of *Senecio crassissimus* (Compositae).

Barrero, Sánchez and Ferrol [6, 7] have more recently reported 15-hydroxy-9-epi-β-caryophyllene (**5**) from the wood of *Juniperus oxycedrus* (Cupressaceae). This compound was clearly distinct from 15-hydroxy-β-caryophyllene (**6**) which was synthesized from β-caryophyllene (**2**) by oxidation with selenium dioxide. It seemed strange that our NMR data for the geminal dimethyl grouping of **1** [1] were quite different to those quoted by Barrero *et al.* [6] for this group in **5**. Comparison of NMR data for the related epoxides and keto epoxides derived from the parent hydrocarbons **1** and **2** seemed to reinforce this anomaly (Table 1). A further point of difference was that the ^{1}H NMR spectrum of **5** recorded at room temperature showed two conformations, present in approximately equal proportions [6]. Spectra of **1** had shown no evidence of more than one conformation [1]. These differences between **1** and **5** suggested that the structure of **1** should be re-examined.

None of the studies so far have determined the absolute stereochemistry for **1** or **5**. However, optical rotation values indicate that the 9-epi-β-caryophyllene (**1**) found in *D. cupressinum* was the same enantiomer as that found in *E. brevipapposus*. No optical rotation data were reported for the hydrocarbon from *A. magnifica*. The naturally occurring epoxide **3** isolated from *S. crassismus* is also of the same stereochemical series.

In this paper we report further spectroscopic evidence for the structure of **1** and describe experiments that show (+)-9-epi-β-caryophyllene (**1**) is of the same absolute stereochemistry at C-1 as (−)-β-caryophyllene (**2**). The conformations of caryophyllenes with both *cis*- and the *trans*-fused ring junctions are also examined by molecular modelling.

RESULTS AND DISCUSSION

Diene **1** was isolated from *D. cupressinum* foliage as described previously [1]. Proton chemical shift values were determined by the use of homonuclear-2D-*J*-resolved spectra, and a one-bond heteronuclear correlation experiment (HETCOR) was used to inter-relate proton signals with carbon signals. Carbon–carbon bond connectivities were established by the use of proton–proton homonuclear (COSY) and long-range heteronuclear correlation (LRHETCOR) experiments. The DEPT sequence was used to confirm carbon multiplicities. It was possible to determine non-ambiguous substructures from the LRHETCOR spectra even though

†Author to whom correspondence should be addressed.

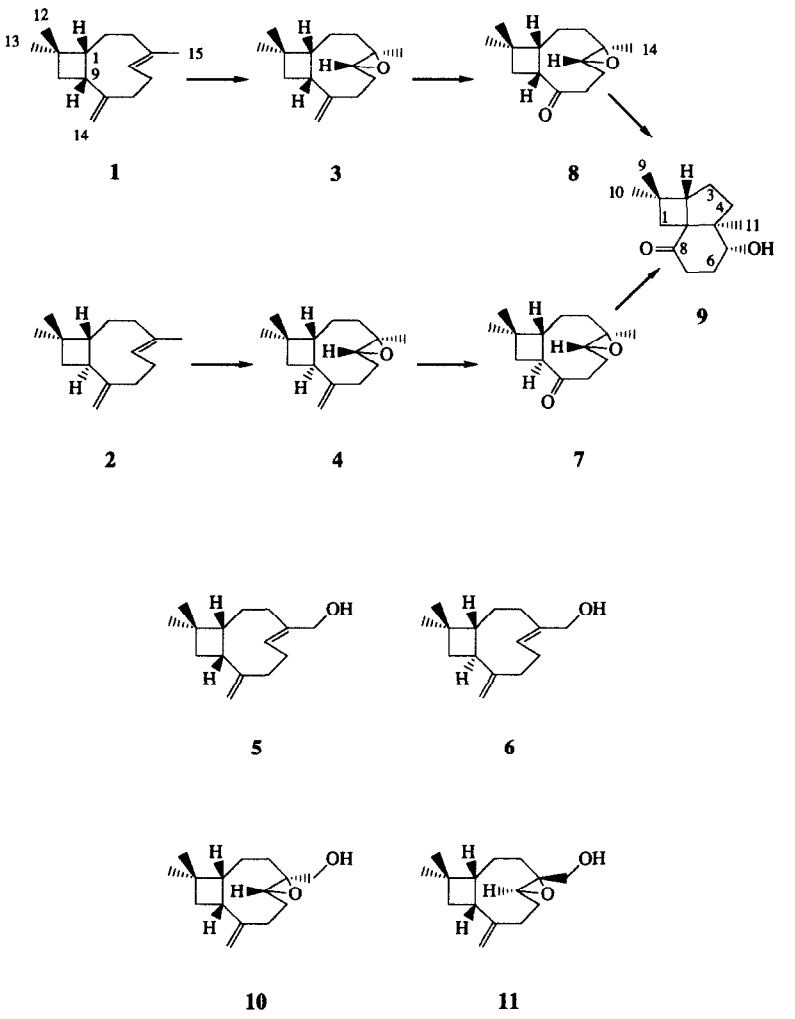


Table 1. NMR data for *gem*-dimethyl groupings of β-caryophyllenes and 9-epi-β-caryophyllenes

	β-Caryophyllenes			9-epi-β-Caryophyllenes	
	^{1}H NMR	^{13}C NMR		^{1}H NMR	^{13}C NMR
2*	0.97, 0.99	22.6, 30.1	1	0.90, 1.19	25.5, 29.9
6†	0.96, 0.98	22.8, 30.0	5†	0.98, 0.99, 1.00	22.1, 21.9, 29.8, 30.0
4	0.97, 0.99	21.5, 29.8	3	0.90, 1.19	25.2, 29.8
7	1.04, 1.04	22.3, 29.4	8	0.99, 1.16	24.0, 30.2

*Ref. [8].
†Ref. [6].

both two- and three-bond correlations were present. Complete NMR data for **1** are given in Table 2.

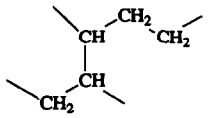
Correlations from the COSY spectrum (Table 2) established two sequences of protonated carbons as **1a** and **1b**. Although the picture was complicated by peak overlaps in the δ1.4–1.5 region, single-frequency decoupling experiments and LRHETCOR correlations removed any ambiguities. Union of these two substructures at two points was enabled based on long-range COSY and LRHETCOR correlations involving the allylic methyl (C-15) and the exocylic methylene (C-14) groupings. This completed a nine-membered ring. Further correlations involving the remaining methyl groups established that these were geminally related. The quaternary carbon which bore these methyl groups was attached as shown in substructure **1c**. This structure, on connection of the remaining two unfilled valencies led to the gross features of **1**.

NOE experiments confirmed the key stereochemical points (Fig. 1). Evidence for a *cis*-ring junction was shown by an enhancement of the H-1 resonance upon irradiation of H-9, while the *trans*-geometry of the tri-substituted double bond was evident from an enhancement of one of the H-6 signals upon irradiation of H-15. NOE enhancements observed from H-12 to both ring junction methine protons enabled the assignment of the *gem*-dimethyl resonances, while the mutual enhancements of H-5 and H-9 demonstrated the orientation of the tri-substituted double bond within the nine-membered ring. The sequence of enhancements involving H-13, H-10α, the two C-14 protons and H-15 showed that the exocyclic

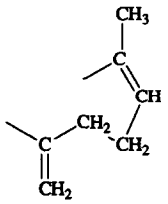
Table 2. ^1H and ^{13}C NMR data for **1**

C	^{13}C	Chemical shifts (δ) ^1H*	Correlations LRHETCOR	COSY
1	53.8	2.12 *m*	25.2, 41.6	1.47, 2.89
2	25.2	1.44 *m*	—	2.07
		1.47 *m*	—	2.12
3	41.6	1.88 *ddd* (*J* = 3, 12, 12) β	18.7	1.53, 2.07
		2.07 *m* α	—	1.44, 1.88
4	136.6	—	—	—
5	121.9	5.10 *ddd* (*J* = 1, 3, 12) β	18.7, 27.4, 41.6	1.53, 1.97, 2.32
6	27.4	1.97 *m* β	—	1.74, 2.32, 5.10
		2.32 *m* ($W_{1/2}$ = 13) α	—	1.74, 1.97, 2.45, 5.10
7	39.2	1.74 *m* β	27.4, 112.8, 149.8	1.97, 2.32, 2.45, 4.79
		2.45 *dd* (*J* = 7, 12) α	27.4	1.74, 2.32
8	149.7	—	—	—
9	43.0	2.89 *ddd* (*J* = 8, 8, 12)	25.2, 112.8, 149.8	1.55, 1.70, 2.12
10	38.2	1.70 *dd* (*J* = 11, 11) α	25.5, 29.9, 32.9	1.19, 1.55, 2.89
		1.55 *m* β	—	1.70, 2.89
11	32.9	—	—	—
12	29.9	1.19 *s*	25.5	0.90, 1.70
13	25.5	0.90 *s*	32.9	1.19
14	112.8	4.86 *d* (*J* = 1)	43.0	4.79
		4.79 *br s*	39.2	1.74, 4.86
15	18.7	1.53 *br s*	41.6, 136.6	1.88, 5.10

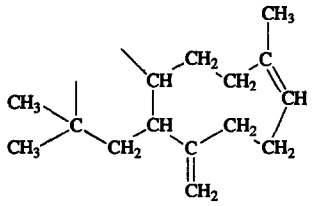
*Proton δ values for overlapping peaks were deduced from HOMO-2D-*J* resolved spectra.



1a



1b



1c

methylene grouping projects downwards. Thus the dominant conformation of **1** is that described as αα [8], with both the exocyclic methylene and the allylic methyl groups below the plane of the nine-membered ring.

The strategy used to determine the absolute stereochemistry of **1** was to convert both 9-epi-β-caryophyllene (**1**), of unknown absolute stereochemistry, and (−)-β-caryophyllene (**2**), whose absolute stereochemistry has been determined [9], into a common chiral target compound. The success of this method depended critically on the direction by which an attacking reagent approached the tri-substituted double bond in **1** and **2**. To achieve the same chirality at C-4 in each case required that the same face of this π-system be exposed.

Selective epoxidation of **2** by *m*-chloroperoxybenzoic acid (*m*-CPBA) gave the known β-epoxide (**4**). Although Warnoff and Srinivasan had generated both the α- and β-epoxides by using ethereal monoperphthalic acid at 5° [10], no α-epoxide formation was observed in our work (GLC, ^1H NMR). NOE experiments on **1** (discussed above) had shown that its tri-substituted double bond was also disposed favourably to induce attack on the *re*-face of C-4 to give the β-epoxide. Thus, epoxidation of **1**, as previously described [3], gave epoxide **3**. NOE experiments confirmed that the relative configuration was as expected with similar enhancements to those summarized for **1** in Fig. 1.

Ozonolysis of **4** generated the previously reported epoxy ketone, kobusone (**7**) which has been isolated from the essential oil of *Cyperus rotundus* (Cyperaceae) [11]. In a similar fashion, ozonolysis of **3** generated the new norsesquiterpene 9-epi-kobusone (**8**).

As Corey [12] has shown that the *cis*-caryophyllene ring junction is more strained than the *trans*-arrangement, it was hoped that epimerization at C-9 could be achieved in **8** to generate compound **7**. Investigation of enolate formation in **7** by using NaOD–D_2O–D_1-ethanol showed that the C-7 methylene ring protons were quickly exchanged. Although a longer reaction time did result in deprotonation at C-9, this led to formation of the

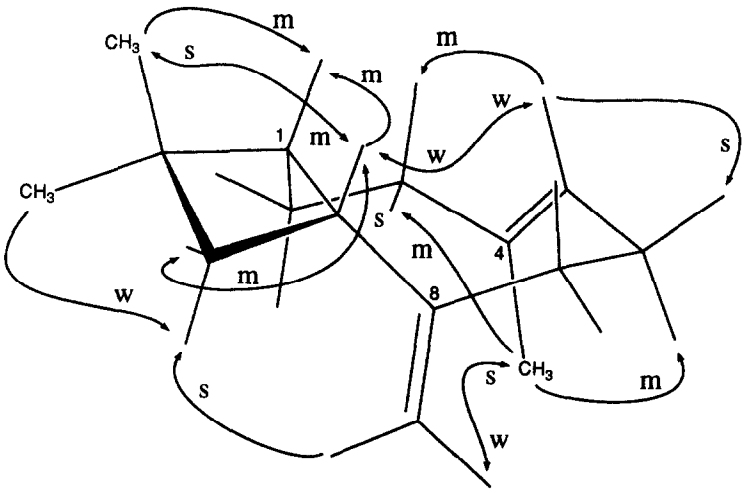


Fig. 1. Important observed NOEs for 1. w, Weak (1–2%); m, medium (2–5%); s, strong (5–10%).

tricyclic compound **9**, di-deuterated at C-7. Under non-deuterating conditions, the previously reported tricycle (**9**) was obtained as the major product [11, 13]. Similar treatment of **8** also gave **9**. Spectral data for the two samples were identical and specific rotations at five different wavelengths were very similar. Thus, the sample of **1** from *D. cupressinum* is (1*R*,4*Z*,9*R*)-(+)-9-epi-*β*-caryophyllene. This absolute configuration is consistent with biosynthesis of **1** by cyclization to the *si*-face of the 10,11-double bond of farnesyl pyrophosphate, as for the other rimu sesquiterpenes [1] and indeed for all the sesquiterpenes of higher plants [14]. The absolute stereochemistry of the sample of **1** from *E. brevipapposus* [3] and of the epoxide **3** from *Senecio crassissimus* [5], follows from this result.

The only reported molecular modelling study on the caryophyllene ring system is that by Shirahama *et al.* [8] on *β*-caryophyllene (**2**). *β*-Caryophyllene is known to exist as a mixture of two major conformations in solution at room temperature. The results of hydroboration [15] and epoxidation [10] experiments require the presence of at least one conformation with the allylic methyl group below the plane of the nine-membered ring, and at least one with it above. Shirahama *et al.* [8] later detailed the existence of two exchanging conformations from inspection of the ^{13}C NMR spectrum at different temperatures. Molecular models indicated four strain minimum conformations (*βα*, *ββ*, *αα*, and *αβ*), distinguished by the positions of the exocyclic methylene (listed first) and the allylic methyl groups relative to the plane of the nine-membered ring [8]. Molecular modelling (MMI force field) on these suggested that the *βα* and *ββ* conformations would predominate in solution [8].

We now report molecular modelling studies on the caryophyllene and 9-epi-caryophyllene system using the systematic variant of the Monte Carlo search procedure, which has been reported as the most effective for searching cyclic flexible molecules [16]. These studies made use of MM2 force field parameters [17].

When this method was applied to *β*-caryophyllene (**2**), the results (Table 3) were in agreement with previous findings [8, 10, 15]. This MM2 modelling indicated that the *βα* and *ββ* conformations would predominate in solution, but the predicted populations (roughly 50:50) do not match the ^{13}C NMR data as closely as those predicted previously by MMI [8].

Conformational searches on 9-epi-*β*-caryophyllene (**1**) predict that an *αα* conformation would be followed, 6.4 kJ mol^{-1} higher in energy, by an *αβ* conformation (Table 3). This corresponds to a Boltzmann population distribution of 93:7 *αα*:*αβ* (at 300 K). The prediction of a dominant *αα* conformation of **1** in solution is in agreement with the results from the NOE experiments (Fig. 1), with the production of only epoxide **3** by *m*-CPBA oxidation, and with the observation of only 15 peaks in

Table 3. Molecular modelling on *β*-caryophyllene and derivatives

	Conformer	Energy (kJ mol^{-1})
1	*αα*	223.34
	*αβ**	229.71
	αβ	229.89
2	*ββ*	202.56
	βα	202.64
	αα	208.21
	αβ	221.18
5	*αα*†	230.49
	αα†	232.37
	αα†	233.68
	αα†	235.95
	*αβ**	237.03
	αβ	237.30

*Planar cyclobutane ring [20].

†These conformations are C4-C15 rotamers.

the ^{13}C NMR spectrum over a temperature range of −60 to +70°.

Alcohol **5** has been reported to be a mixture of two major conformations at room temperature in approximately equal proportions. As two mono epoxides, **10** and **11**, were produced in the ratio 7:3 when **5** was epoxidized with *m*-CPBA [7], the major conformations of **5** were assigned as αα and αβ. Molecular modelling on alcohol **5** resulted in many discrete conformations (Table 3). The four lowest energy conformations were all αα, differing only in the orientation of the hydroxyl group. An αβ-conformation was predicted to occur 6.5 kJ mol^{-1} higher in energy above the global minimum. This energy difference corresponds to an αβ-population of 7%. This failure of the modelling to match reported experimental observations for **5** may indicate that some factor which is not recognized in the MM2 force field is at play. A possibility is intramolecular hydrogen bonding between the hydroxyl group and the exocyclic double bond [18].

We have thus confirmed that the sesquiterpene isolated from rimu foliage has the gross structure and absolute stereochemistry depicted in **1**. NMR studies on **1** show that it exists as one major conformation in solution at room temperature, this being an αα form. Modelling studies on **1** and on β-caryophyllene (**2**) relate well to both the chemistry and to the NMR spectra, but fail to provide any insight into the discrepancies between the observed spectral data for **1** and its 15-hydroxy derivative **5**.

EXPERIMENTAL

Molecular modelling. These studies were carried out on a Silicon Graphics Personal Iris computer using Macromodel V3.1X [19] with MM2 force field parameters [17]. Conformations were generated by opening the C2-C3 bond and varying torsions C10-C9-C8-C7, C9-C8-C7-C6, C8-C7-C6-C5 and C7-C6-C5-C4. Further C3-C4-C15-O and C4-C15-O-H torsions were included for compound **5** which contained a C-15 hydroxyl moiety. Five hundred conformations were generated and filtered to exclude geometries with energies greater than 50 kJ mol^{-1} above the global (current) energy minimum, then minimized using the Polak-Ribiere conjugate gradient minimization procedure with the stopping criteria of 0.05 kJ mol^{-1}Å. All minimized conformations were compared and only unique conformations within 50 kJ mol^{-1} of the global (final) minimum were stored. Searches were repeatable, with search results independent of starting geometry or solvent treatment. Identical conformations were produced if the search was completed with $CHCl_3$ solvent treatment rather than *in vacuo*.

Diene **2**. A β-caryophyllene sample (ex BDH) was purified on a silica column with hexane elution to remove humulene and oxidized material. Pure **2** was collected; ^1H NMR identical to an authentic sample; $[\alpha]^{24}$ −13.0° (589 nm); −13.8° (578 nm); −15.2° (546 nm); −17.5° (436 nm); −5.7° (365 nm) ($CHCl_3$; *c* 6.96).

Kobusone (**7**). Compound **7** was prepared from **2** by the published methods [3, 11]. Recrystallization from Et_2O gave crystals; mp 52–54° (lit. [11]: mp 60°); IR ν_{max}^{KBr} cm^{-1}: 1693 (C=O); ^1H NMR (299.99 MHz, $CDCl_3$): δ 0.95 (1H, *m*, H-3), 1.04 (6H, *s*, H-12, 13), 1.31 (3H, *s*, H-14), 1.43 (1H, *m*, H-6), 1.52 (1H, *m*, H-2), 1.62 (1H, *m*, H-2), 1.67 (1H, *m*, H-10), 1.94 (1H, *ddd*, *J* = 1, 10, 10 Hz, H-1), 2.07 (1H, *dd*, *J* = 10, 10 Hz, H-10), 2.16 (1H, *ddd*, *J* = 4, 4, 13 Hz, H-3), 2.40 (1H, *m*, $W_{1/2}$ = 30 Hz, H-6), 2.56 (2H, *m*, $W_{1/2}$ = 15 Hz, H-7), 2.69 (1H, *dd*, *J* = 5, 10 Hz, H-5), 3.06 (1H, *ddd*, *J* = 9, 9, 9 Hz, H-9); ^{13}C NMR (74.9 MHz, $CDCl_3$): δ 16.3 (*q*, C-14), 22.3 (*q*, C-13), 24.9 (*t*, C-6), 26.6 (*t*, C-2), 29.4 (*q*, C-12), 34.5 (*s*, C-11), 35.4 (*t*, C-10), 37.8 (*t*, C-7), 39.1 (*t*, C-3), 51.4 (*d*, C-1), 52.7 (*d*, C-9), 58.0 (*s*, C-4), 61.7 (*d*, C-5), 214.3 (*s*, C-8).

Deuterated **7**. Na metal (0.3 g) was dissolved in EtOD (5 ml) and the resultant soln added dropwise with vigorous stirring to a suspension of **7** (51.6 mg) in D_2O (5 ml) under a N_2 atmosphere. EtOD (3 ml) was added to effect complete dissolution. After stirring at room temp. for 6.5 hr, H_2O (10 ml) was added. Et_2O extraction (3 × 10 ml), drying ($MgSO_4$) and evapn yielded di-deuterated **7** (54.5 mg). A portion was chromatographed on basic Al_2O_3 to give the pure compound; ^1H NMR (299.99 MHz, $CDCl_3$): δ 1.43 (*dd*, *J* = 10, 13 Hz, H-6), 2.40 (*dd*, *J* = 5, 13 Hz, H-6), 2.56 (no peak, H-7); ^2H NMR (46.04 MHz, $CHCl_3$): δ 2.6 (*s*, D-7); ^{13}C NMR (74.9 MHz, $CDCl_3$): δ 37.2 (*quin*, *J* = 20 Hz, C-7), 37.8 (no peak); MS *m/z* 224.1798 $[M]^+$, $C_{14}H_{20}D_2O_2$ requires 224.1745.

9-epi-β-Caryophyllene (**1**). 9-epi-β-Caryophyllene was isolated by extraction of rimu foliage as described in ref. [1]. The ^1H and ^{13}C NMR data are summarized in Table 2; $[\alpha]^{24}$ +186° (589 nm); +188° (578 nm); +193° (546 nm); +211° (436 nm); +275° (365 nm) ($CHCl_3$; *c* 0.75).

9-epi-β-Caryophyllene oxide (**3**). Epoxidation of diene **1** as described in ref. [3] gave epoxide **3**; ^1H NMR (299.99 MHz, $CDCl_3$): δ 0.90 (3H, *s*, H-13), 1.16 (3H, *s*, H-15), 1.19 (3H, *s*, H-12), 1.35 (1H, *m*, H-6), 1.52 (2H, *m*, H-2), 1.65 (1H, *ddd*, *J* = 3, 11, 11 Hz, H-10), 1.75 (1H, *dd*, *J* = 11, 11 Hz, H-10), 1.91 (1H, *ddd*, *J* = 2, 6, 13 Hz, H-7), 2.01 (1H, *dd*, *J* = 11, 11 Hz, H-6), 2.07 (1H, *m*, H-1), 2.12 (1H, *m*, H-3), 2.20 (1H, *m*, H-3), 2.61 (1H, *m*, $W_{1/2}$ = 27 Hz, H-7), 2.64 (1H, *dd*, *J* = 2, 11 Hz, H-5), 3.02 (1H, *ddd*, *J* = 8.5, 8.5, 11 Hz, H-9); ^{13}C NMR (74.9 MHz, $CDCl_3$): δ 18.5 (*q*, C-15), 21.3 (*t*, C-2), 25.2 (*q*, C-13), 27.2 (*t*, C-6), 29.8 (*q*, C-12), 33.0 (*s*, C-11), 36.5 (*t*, C-7), 38.2 (*t*, C-10), 41.4 (*t*, C-3), 42.3 (*d*, C-9), 53.5 (*d*, C-1), 60.1 (*s*, C-4), 61.8 (*d*, C-5), 114.5 (*t*, C-14), 148.4 (*s*, C-8).

9-epi-Kobusone (**8**). A soln of epoxide **3** (255 mg) in MeOH was treated with O_3 at −78° until a persistent blue colour remained. Dimethylsulphide (5 ml) was added after excess O_3 had been removed by purging with N_2, and the reaction mixt. was stirred for 12 hr. Evapn, followed by washing with NaCl soln then chromatography (basic Al_2O_3) and recrystallization from Et_2O gave [1*R*-(1*R**,4*R**,6*R**, 10*R**)]-4,12,12-trimethyl-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-one (**8**) as crystals (101 mg); mp < 50°; (found: C, 75.5; H, 9.7. $C_{14}H_{22}O_2$ requires: C, 75.6; H, 10.0%); IR ν_{max}^{KBr} cm^{-1}: 1698 (C=O); ^1H NMR (299.99 MHz, $CDCl_3$): δ 0.91 (1H, *m*, H-3), 0.99 (3H, *s*, H-13), 1.14 (3H, *s*, H-14), 1.16 (3H, *s*, H-12), 1.52 (1H, *dddd*, *J*

=2, 2, 7, 15 Hz, H-2), 1.59 (1H, *m*, H-10), 1.63 (1H, *m*, H-6), 1.76 (1H, *m*, H-2), 2.09 (1H, *m*, H-10), 2.14 (1H, *m*, H-6), 2.18 (1H, *dd*, *J*=7, 7 Hz, H-3), 2.27 (1H, *br dd*, *J*=9, 9 Hz, H-1), 2.42 (1H, *m*, H-7), 2.79 (1H, *m*, H-7), 2.80 (1H, *dd*, *J*=6, 6 Hz, H-5), 3.67 (1H, *ddd*, *J*=8, 9, 9 Hz, H-9); ^{13}C NMR (74.9 MHz, $CDCl_3$): δ17.3 (*q*, C-14), 21.1 (*t*, C-2), 23.8 (*t*, C-6), 24.0 (*q*, C-13), 30.2 (*q*, C-12), 34.1 (*s*, C-11), 35.1 (*t*, C-10), 40.4 (*t*, C-3), 41.5 (*t*, C-7), 45.7 (*d*, C-9), 52.5 (*d*, C-1), 60.0 (*s*, C-4), 61.0 (*d*, C-5), 213.4 (*s*, C-8).

Tricyclic keto alcohol **9**. (*a*) Kobusone (**7**) (496 mg) was heated under reflux with KOH–EtOH (10%, 300 ml) for 2 hr. The mixt. was cooled and H_2O (500 ml) was added. Et_2O extraction and chromatography (basic Al_2O_3) followed by recrystallization (2× from Et_2O) gave **9** (247 mg); mp 148° (lit. [13]: 148–149°); IR ν_{max}^{KBr} cm^{-1}: 3504 (O–H), 1684 (C=O); ^{1}H NMR (299.99 MHz, $CDCl_3$): δ0.83 (3H, *s*, H-11), 0.89 (3H, *s*, H-10), 0.96 (3H, *s*, H-9), 1.38 (1H, *d*, *J*=12 Hz, H-1), 1.64 (1H, *m*, $W_{1/2}$=28 Hz, H-4), 1.77 (1H, *m*, H-3), 1.82 (1H, *m*, H-6), 2.00 (2H, *m*, H-3 and H-6), 2.05 (1H, *m*, H-4), 2.30 (1H, *m*, H-2a), 2.36 (1H, *m*, H-7), 2.48 (1H, *m*, H-1), 2.54 (1H, *ddd*, *J*=6, 14, 14 Hz, H-7), 3.87 (1H, *dd*, *J*=4, 12 Hz, H-5); ^{13}C NMR (74.9 MHz, $CDCl_3$): δ11.9 (*q*, C-11), 24.6 (*q*, C-10), 25.3 (*t*, C-3), 29.9 (*q*, C-9), 30.5 (*t*, C-6), 31.3 (*s*, C-2), 33.3 (*t*, C-1), 36.4 (*t*, C-7), 37.5 (*t*, C-4), 53.3 (*s*, C-4a), 55.0 (*d*, C-2a), 58.2 (*s*, C-8a), 70.4 (*d*, C-5), 212.3 (*s*, C-8); $[\alpha]^{24}$ −32.4° (589 nm); −33.4° (578 nm); −36.6° (546 nm); −35.9° (436 nm); +77.4° (365 nm) ($CHCl_3$; *c* 1.16).

(*b*) Treatment of 9-epi-kobusone (**8**) (35.3 mg) in an identical manner gave **9** (15.5 mg); identical mp and spectral data to those from **7**; $[\alpha]^{24}$ −33.5° (589 nm); −33.8° (578 nm); −36.7° (546 nm); −36.4° (436 nm); +80.4° (365 nm) ($CHCl_3$; *c* 1.16).

(*c*) Treatment of kobusone (**7**) with NaOD–EtOD–D_2O as described for the preparation of deuterated **7**, with a reaction time of 72 hr, gave a sample of **9** which was di-deuterated at C-3; ^{1}H NMR (299.99 MHz, $CDCl_3$): δ2.34 (no peak, H-7), 2.54 (no peak, H-7); ^{2}H NMR (46.04 MHz, $CHCl_3$): δ2.33 (1D, *s*, D-7), 2.54 (1D, *s*, D-7); ^{13}C NMR (74.9 MHz, $CDCl_3$): $\delta\sim$35.6 (*m*, C-7), 36.4 (no peak, C-7); MS *m/z* 224.1745 $[M]^+$, $C_{14}H_{20}D_2O_2$, requires 224.1745.

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