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Base Treatment of Kobusone Revisited

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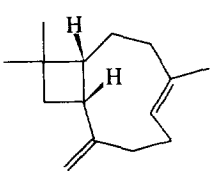
Abstract. The caryophyllene derived epoxy ketone, kobusone, is transformed by treatment with ethanolic potassium hydroxide, into two ketols. Although the published structure of the major compound is correct, the minor product is now shown to contain a *trans* fused cyclopropane ring rather than the previously reported *cis* junction. This cyclopropyl keto alcohol shows an unusual propensity for reduction, being converted to a diol by prolonged treatment with ethanolic KOH.

INTRODUCTION

A key step in our verification of the structure and absolute stereochemistry of the natural product 9-*epi*-β-caryophyllene (**1**)[1], which had been isolated previously from the New Zealand podocarp, *Dacrydium cupressinum*, was the transannular cyclisation of the β-caryophyllene (**2**) derived epoxy ketone (**3**) into the tricyclic compound (**4**) induced by heating with potassium hydroxide in ethanol[2].



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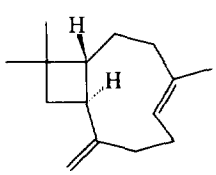

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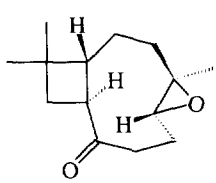

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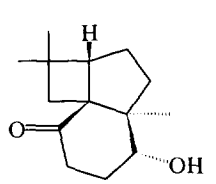
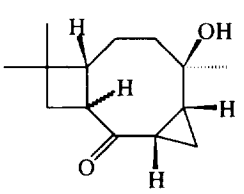


(**4**)

Epoxy ketone (**3**) is a natural product isolated from nutgrass, *Cyperus rotundus*[3], and has been given the name kobusone. During its structural elucidation, it was found to convert to two keto alcohols upon base treatment. One of these was compound (**4**), while the other was not characterised. Some time later, the structure of this second product was reported as (**5**)[4]. The stereochemistry of (**5**) at C-1 was not determined, but it was proposed that the cyclopropane ring was *cis* fused and pointing towards the α-face of the cyclooctane ring on the basis of assumed concerted opening of the epoxide by the more stable enolate. Here we report the revised structure (**6**) for this minor product from the base treatment of kobusone, and discuss some of its chemistry.



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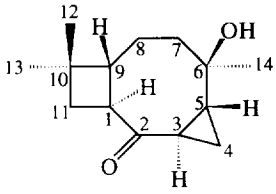


(6)

RESULTS AND DISCUSSION

As expected, microanalysis of compound (**6**) gave data consistent with a molecular formula, $C_{14}H_{22}O_2$. Furthermore, the IR spectrum indicated ketone (1699 cm^{-1}) and alcohol functionalities (3419 cm^{-1}) as previously noted. Some ^1H NMR data had been reported previously and these closely matched those for our sample. Full ^1H and ^{13}C NMR assignments were obtained by homonuclear and heteronuclear correlation experiments.

Comparison of the ^{13}C NMR chemical shifts for the geminal methyl groups (δ 19.3, 28.3) with those of other *cis* and *trans* fused caryophyllene derivatives[5] suggested that the *trans* fusion of the cyclobutane ring had been retained. Corey[6] made use of the fact that the *trans* fused arrangement is more stable in (**3**) when he synthesised it by isomerisation of the *cis*-fused epimer under basic conditions *en route* to a total synthesis of β-caryophyllene. This suggested that (**6**), which was also formed under basic conditions, would retain *trans*-fusion of the cyclobutane ring. However, some doubt about this ring junction stereochemistry was aroused by the fact that the H-1 signal showed a similar pattern to that observed for the *cis*-fused 9-*epi*-β-caryophyllene (**1**)[1], implying that epimerisation may have taken place. To clarify this stereochemical point, NOE experiments were undertaken (Figure 1[7]). Irradiation of H-1 produced enhancements of both the C-6 methyl singlet (H-14), and the H-3 signal. Likewise, irradiation of H-9 led to enhancement of the H-5 peak. No enhancements between H-1 and H-9 were observed. Although the absence of NOE does not prove that the ring junction is *trans*, it should be noted that in all other *cis* fused derivatives studied[2], such an enhancement has always been observed. These results are consistent with structure (**6**) where both the cyclopropane and cyclobutane rings are *cis*-fused and with a 6α-methyl stereochemistry (Figure 1).

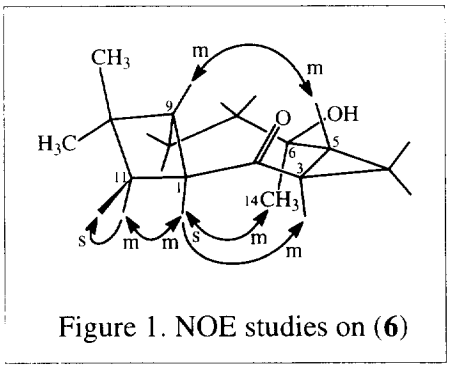


Figure 1. NOE studies on (**6**)

On mechanistic grounds, a solvolytic opening of the epoxide ring of (**3**) is unlikely as caryophyllene epoxide is unchanged by reaction under similar conditions[4]. Molecular modelling and NMR studies on caryophyllene (**2**)[2,8] suggest that the preferred conformation is that described as βα, where the exocyclic double bond projects upwards (β) while the olefinic methyl group points downwards (α). A further conformation, ββ, with both groups pointing upwards is probably the other major contributor in solution. Epoxidation with *m*-chloroperoxybenzoic acid gives the β-epoxide[2], consistent with dominant attack on the βα-form. In epoxides, such as (**3**), the conformation is more restricted as the epoxidic oxygen cannot easily project towards the centre of the 9-membered ring. Intramolecular opening of the epoxide ring in this favoured βα-orientation (Figure 2) leads naturally to (**6**) with the

stereochemistry shown (Figure 1). Enolate attack on the epoxide ring of epoxy ketone (**3**) to form a *cis* fused cyclopropane as in (**5**), requires a disfavoured αα-conformation.

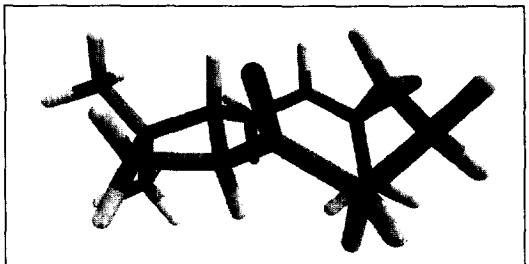
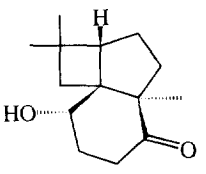


Figure 2. βα-Conformation of kobusone (**3**)

Warnhoff and Srinivasan noted that treatment of epoxy ketone (**3**) with sodium methoxide in boiling methanol for 6 hours gave predominantly (**4**), along with smaller quantities (~5% each) of (**6**) and a further compound (**7**) which they suggested resulted from intramolecular hydride transfer. With a *tert*-butyl alcohol/water/KOH system the proportion of (**7**) rose to 27%, although the reaction period in this case was 64 hours[4]. Our study, in an ethanol/KOH system, was conducted over a period of 4 hours, after which time 15% of epoxy ketone (**3**) remained. Both (**4**) and (**6**) were isolated, but no (**7**) was detected. When the reaction time was extended to 72 hours, complete conversion of (**3**) was achieved, both (**4**) and (**7**) were obtained, but (**6**) was not present at significant levels. Instead, a new diol (**8**) was isolated.



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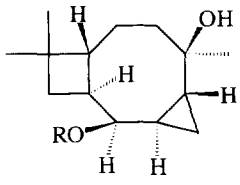


(**8**) R = H
(**9**) R = Ac

Diol (**8**) gave microanalytical data consistent with $C_{14}H_{24}O_2$, and this formulation was supported by mass spectrometry with peaks at 209 and 206 Dalton corresponding to $[M^+]$-CH_3 and $[M^+]$-H_2O. The IR spectrum showed a strong hydroxyl stretch at 3375 cm^{-1}, as well as signals consistent with secondary (1291, 1092 cm^{-1}) and tertiary (1374, 1152 cm^{-1}) alcohol groups. No carbonyl bands were observed. As ^1H and ^{13}C NMR spectra (Table 1) indicated that there were no multiple bonds, the compound must be tricyclic. In the COSY spectrum, the C-1 methine proton signal (δ 2.15) showed coupling to a broad singlet at δ 3.90, consistent with the presence of a secondary alcohol function at C-2. LRHETCOR correlation experiments supported this hypothesis, suggesting that the compound was a diol derived from hydroxy ketone (**6**) by a reductive process.

Table 1. ^{1}H and ^{13}C NMR data for tricyclic diol (8).

	Chemical Shift[a]		Correlations	
C	δ_C	δ_H[b]	LRHETCOR[c]	COSY[d]
1	48.2	2.15 (*dddd*, 3,8.5,10,10)		3.90, 1.52, 1.45, 1.78
2	64.8	3.90 (*brs*, $W_{h/2}$ 5)		2.15, 1.78, 1.45
3	21.2	0.59 (*m*, $W_{h/2}$ 23)	64.8	3.90
4	2.1	0.50 (*m*, $W_{h/2}$ 16)		1.15
5	19.4	1.15 (*m*)	64.8	0.50, 0.59
6	73.2	-		
7	46.9	1.62 (*m*)	20.3	0.83, 1.88
		1.88 (*m*, $W_{h/2}$ 22)	27.3	
8	27.3	1.11 (*m*)	20.3	1.64, 1.78
		1.64 (*m*)	46.9	1.88, 1.11
9	44.9	1.78 (*dd*, 10,10)	35.5, 64.8	2.15
10	35.5	-		
11	33.5	1.45 (*dd*, 10,10)	21.5	2.15
		1.52 (*dd*, 10,10)	21.5, 29.5, 35.5, 48.2, 64.8	2.15
12	29.5	0.97 (*s*)	21.5, 35.5	
13	21.5	0.99 (*s*)	29.5, 33.5, 35.5	
14	20.3	0.83 (*s*)	19.4, 46.9, 73.2	1.62

[a]Recorded in $CDCl_3$ relative to TMS and reported in ppm.

[b]Coupling constants in Hz.

[c]Correlation from ^{1}H signal to ^{13}C signals listed.

[d]Correlation from ^{1}H signal to ^{1}H signals listed.

The stereochemistry of (**8**) was determined by NOE experiments, results of which are summarised in Figure 3[7]. Again there were enhancements which supported the α-orientation of H-1 and H-3, and the β orientation of H-5. This provides further support for the *trans*-fusion of the cyclobutane and cyclopropane rings. Additionally, irradiation of H-1 gave enhancement of the H-2 resonance. Unlike β-caryophyllene, the larger ring is relatively constrained. Molecular models show that H-1 and H-2 cannot approach closely unless H-2 lies towards the α face. Furthermore, the ^{1}H NMR H-1/H-2 coupling constants predicted for the energy minimised structures of (**8**) and its C-2 epimer are considerably different (2.2 and 10.4 Hz respectively). H-2 resonates as a broad singlet, again supporting the α-orientation of H-2 as in (**8**). In addition, the α-face of the carbonyl group of (**6**) is much less crowded than the β-face, thereby facilitating introduction of an α-hydrogen. The structure of (**8**) was verified by its synthesis as the sole product of lithium aluminium hydride reduction of (**6**).

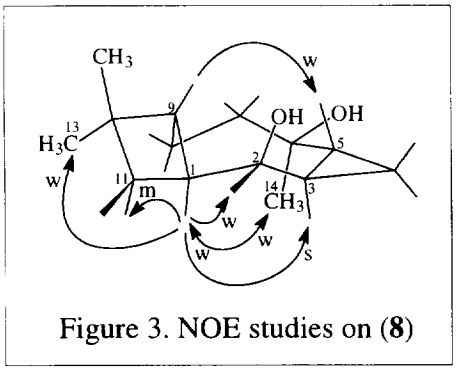
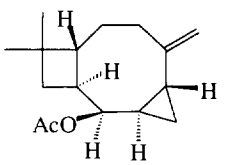


Figure 3. NOE studies on (**8**)

Diol (**8**) was further characterised by acetylation. Reaction with acetic anhydride and pyridine yielded monoacetate (**9**) in good yield. Changes in the ^{13}C NMR chemical shifts on acetylation were consistent with introduction of an acetate group at C-2. Also, in the ^{1}H NMR spectrum, the H-2 resonance appeared at δ 5.15 ppm for the acetate, compared to δ 3.90 for the alcohol.

Formation of diol (**8**), by KOH/ethanol treatment of epoxy ketone (**3**), appears somewhat bizarre in that an overall reduction has taken place. The authenticity of this conversion was verified by repetition of the reaction, and also by treating a pure sample of hydroxy ketone (**6**) under similar conditions, which led to the isolation of diol (**8**) in 45% yield, along with unchanged (**6**). The reduction persisted when ethanol which had been treated to remove all aldehyde impurities was employed, but did not take place when [1,1-$^{2}H_2$]-ethanol was used. Presumably the rate decrease resulting from a primary isotope effect suppresses the reaction to the extent that it is no longer observed. With a 1:1 mixture of deuterated and undeuterated ethanol some reduction did take place but NMR showed no significant deuteration at C-2 in the resulting diol. The reduction would thus appear to involve an intermolecular hydride transfer from ethanol, but such a process is not normal in the absence of a cation with at least a moderate degree of Lewis acidity. The conventional Meerwein-Pondorf-Verley reduction is regularly conducted in the presence of aluminium salts and it is proposed that both the carbonyl compound and the hydride donor bind to the same cation, with the result that the hydride is delivered through a cyclic intermediate. Despite the unfavourable nature of the cation for such a process in the reduction of (**6**) with KOH/ethanol, there is some precedent for similar reductions with alkoxides of weakly coordinating metals[9]. However, the reason for the strong propensity for reduction of the carbonyl grouping in (**6**) remains unsolved.

Attempted diacetate formation, by treating hydroxy acetate (**9**) with isopropenyl acetate and *p*-toluenesulfonic acid was unsuccessful, but induced loss of the tertiary alcohol group with the formation of acetoxy alkene (**10**). Formation of (**10**) was evidenced by a microanalysis consistent with $C_{16}H_{24}O_2$ and the appearance of signals in the NMR spectra as expected for an exocyclic methylene group {δ_H 4.41 (*brs*), 4.50 (*s*); δ_C 102.8 (*t*), 152.3 (*s*)}. Signals attributed to the cyclobutyl ring, cyclopropyl ring and acetate group were at similar chemical shifts to those of acetate (**9**).



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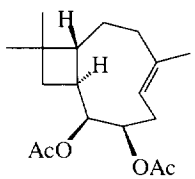

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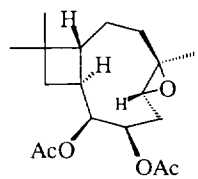


(12)

When diol (**8**) was treated directly with isopropenyl acetate and *p*-toluenesulfonic acid, a more extensive change eventuated. Microanalysis supported the molecular formula $C_{18}H_{28}O_4$, while NMR spectra indicated that the cyclopropyl group had been removed, a new trisubstituted double bond had been formed {δ_H 5.46 (1H, *dd*, *J* 7,8 Hz; δ_C 117.2 (*d*), 139.6 (*s*)}, and two acetate groups were present {δ_H 2.01 (3H, *s*), 2.22 (3H, *s*); δ_C 170.88 (s), 170.93 (s)}. Data were consistent with structure (**11**). The *trans*-nature of the trisubstituted double bond was established from the chemical shift of the olefinic methyl signals {δ_H 1.72 (3H, *s*); δ_C 16.2}. In these caryophyllene derivatives, a *cis*-double bond generally leads to a methyl carbon signal at ~25 ppm and the corresponding signal in the proton spectrum is typically ~δ 1.65. The stereochemistry of the acetate groupings was determined by detailed NMR analysis of the epoxide (**12**).

As for β-caryophyllene, prolonged storage of (**11**) in contact with air resulted in the formation of an epoxide. Detailed analysis of the COSY and HMBC spectra of this compound (**12**) established the overall structure and NMR data are summarised in Table 2.

Table 2. ^{1}H and ^{13}C NMR data for bicyclic diacetate (12).

	Chemical Shift[a]		Correlations	
C	δ_C	δ_H[b]	HMBC[c]	COSY[d]
1	45.2	1.83 (*dd*, 9.5,10)	29.9, 33.5, 39.8, 42.8, 77.3	-
2	27.6	1.47 (*m*)	-	2.16
		1.63 (*m*)	56.8, 74.2, 77.3	-
3	39.8	0.98 (*m*)	-	2.16
		2.16 (*ddd*, 3.5,3.5,13)	45.2, 56.8	0.98, 1.47, 1.66
4	59.2	-	-	-
5	56.8	3.07 (*dd*, 6,9)	39.8	1.66, 2.30
6	30.3	1.66 (*m*)	-	1.46, 3.07, 4.87
		2.30 (*m*)	56.8, 59.2, 74.2	3.07, 4.87
7	74.2	4.87 (*dd*, 6.5,9)	77.3, 170.4	1.66, 2.30
8	77.3	5.13 (*s*)	37.5, 42.8, 45.2, 74.2, 170.6	-
9	42.8	2.38 (*ddd*, 9,9,9)	27.6, 37.5, 45.2, 74.2, 77.3	1.32
10	37.5	1.32 (*m*)	22.3, 29.9, 33.5, 42.8	2.38
		1.75 (*dd*, 9,10.5)	45.2	-
11	33.5	-	-	-
				-
12	22.3	0.97 (*s*)	37.5, 33.5	-
13	29.9	0.92 (*s*)	33.5	-
14	16.3	1.35 (*s*)	39.8, 56.8, 59.2	-

[a] Recorded in $CDCl_3$ relative to TMS and reported in ppm. Acetate signals δ_H 2.03, 2.24; δ_C 170.5, 170.7.

[b] Coupling constants in Hz.

[c] Correlation from ^{1}H signal to ^{13}C signals listed.

[d] Correlation from ^{1}H signal to ^{1}H signals listed.

Irradiation of the epoxidic methine proton, H-5, produced enhancements of the H-1 and one of the H-3 signals. This established the *trans*-geometry and the orientation of the β-epoxide unit as shown (Figure 4[7]). Interactions between the epoxidic methyl and H-7, and between H-7 and H-9 revealed the β-orientation of the C-7 acetate grouping and the *trans*-orientation of the ring junction. Like other *trans*-fused caryophyllene derivatives, no NOE effects connecting H-1 and H-9 were observed. Establishment of the

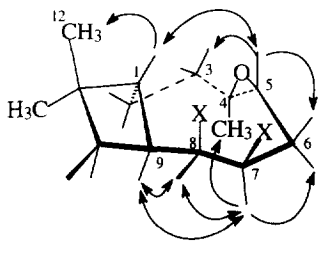
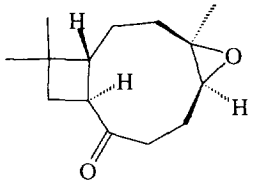


Figure 4. NOE studies on (**12**)

orientation of the acetate grouping at C-8 required the assistance of molecular modelling. Conformational searching of all possible diacetate isomers showed that only in the 7β,8β-diacetate do H-6, H-7, H-8 and H-9 attain a suitable geometry to lead to the set of enhancements shown in Figure 4. Furthermore, the predicted ^{1}H NMR coupling constants provide further support for this isomer. If any one of the H-7, H-8 or H-9 stereochemistries differ from that shown, at least one large coupling constant is predicted for the lowest energy conformation. It was observed that all the relevant coupling constants were small and the H-8 resonated as a broadened singlet.

CONCLUSION

Correction of the structure of (**6**) allows for some further rationalisation of the earlier findings of Warnhoff and Srinivasan[4]. These workers examined the reactions of three isomeric epoxy ketones (**3**), (**13**) and (**14**) with KOH/water/*tert*-butyl alcohol. As mentioned previously, ketone (**3**) produced ketol (**4**), the isomer (**7**) resulting from internal hydride shift, and the cyclopropane derivative which we now have shown to be (**6**) rather the originally proposed (**5**). Reaction of (**13**) gave a tricyclic ketol (**15**) analogous to (**7**), along with a cyclopropane derivative (**16**) containing a cyclic hemiacetal unit. Compound (**14**) produced a similar cyclic hemiacetal (**17**) which was proposed to have a *cis*-fused cyclobutane ring. This was found to be in equilibrium with ketol (**18**). Cyclic hemiacetal formation is only possible if the cyclopropane is *cis* fused. Compound (**6**) with *trans* fusion is unable to achieve hemiacetal formation as a compound which has a tetrahydrofuran ring *trans*-fused to a cyclopropane ring would be a very minor equilibrium contributor.



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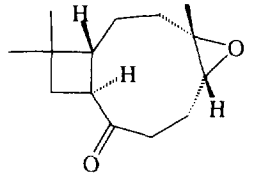

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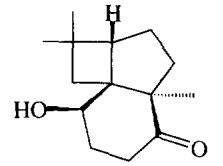

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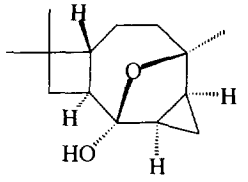

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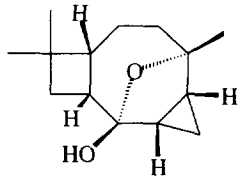

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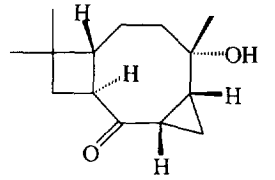

(**18**)

EXPERIMENTAL

General. Preparative layer chromatography (PLC) was performed on 1.25 mm layers of Merck (Art 7747) silica PF_{254} coated on glass plates. Column chromatography used silica gel 60 Merck (Art 9385). Basic Al_2O_3 implies Merck 60 (Art 1067) or Fluka type 507 C alumina. IR spectra were obtained as KBr disks, as neat films or as Nujol mulls on NaCl disks and frequencies (ν_{max}) are reported as cm^{-1}. Spectra were recorded on Perkin Elmer 1600 series Fourier transform machines. MS were recorded on a Kratos MS80RFA instrument. ^{1}H NMR spectra were recorded on a Varian VXR-300 machine operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Samples were

run at 25° in $CDCl_3$ and are reported in shift (δ ppm) relative to tetramethylsilane (δ 0.00) as internal standard. Carbon types were determined by the DEPT pulse sequence. HETCOR and HMQC pulse sequences were used to ascertain C-H connectivity with J_{CH}=130-140 Hz. LRHETCOR and HMBC spectra were optimised for long range coupling of 6-10 Hz. Kobusone was prepared according to published methods[2,3].

Ethanol/KOH Treatment of Kobusone (3). A solution of kobusone (**3**) (0.438 g, 1.97 mmol) in 10% w/v KOH/ethanol (50 cm^3) was heated under reflux for 4 h. The mixture was cooled, diluted with H_2O (100 cm^3), extracted with Et_2O (3 x 30 cm^3) and dried ($MgSO_4$). Evaporation gave partially crystalline crude material (0.438 g). Column chromatography on basic Al_2O_3, eluting with Et_2O gave: (a) unchanged (**3**) (0.069 g, 0.31 mmol); (b) ketol (**4**) *[CAS 24173-77-1]* (0.241 g, 1.08 mmol). Recrystallised from Et_2O (2x). MP 148° (Lit[4] 147-148.5); spectral data, see reference 2. Anal. Found: C, 75.6; H, 10.30. Calc. for $C_{14}H_{22}O_2$: C, 75.60, H, 10.0%. (c) *[1α,3α,5β,6β,9β]-6-hydroxy-6,10,10-trimethyltricyclo[7.2.0.0^{3,5}]undecan-2-one* (**6**) (0.089 g, 0.40 mmol). Recrystallised from Et_2O (2x). MP 145-146° (lit[4] 145-146°); IR (nujol): 3419 (OH), 1699 (C=O), 1374, 1137 (CO); ^{1}H NMR: 0.83 (1H, *ddd*, *J* 6,6,8 Hz, H-4), 0.98 (6H, *s*, H-12 & 13), 1.00 (1H, *m*, H-5), 1.04 (3H, *s*, H-14), 1.37 (1H, *ddd*, *J* 5,7,8 Hz, H-4), 1.47 (1H, *dd*, *J* 7.5,11 Hz, H-11), 1.52 (1H, *m*, H-8), 1.66 (1H, *m*, H-7β), 1.74 (1H, *ddd*, *J* 6,7,8 Hz, H-3), 1.82 (1H, *ddd*, *J* 2,8,8 Hz, H-9), 1.84 (1H, *m*, H-8), 1.91 (1H, *dd*, *J* 10,11 Hz, H-11α), 2.00 (1H, *ddd*, *J* 1,7,14 Hz, H-7), 3.15 (1H, *ddd*, *J* 7.5,10.5,10.5 Hz, H-1); ^{13}C NMR: 5.0 (CH_2, C-4), 19.3 (CH_3, C-13), 20.2 (CH_3, C-14), 24.5 (CH, C-3), 25.7 (CH_2, C-8), 28.3 (CH_3, C-12), 31.2 (CH_2, C-11), 33.0 (CH, C-5), 35.5 (C, C-10), 46.1 (CH_2, C-7), 51.5 (CH, C-1), 57.4 (CH, C-9), 72.8 (C, C-6), 208.7 (C, C-2). Anal. Found: C, 75.6; H, 10.0. Calc. for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0%.

When a solution of kobusone (**3**) (1.8 g) in 10% w/v KOH/ethanol (150 cm^3) was heated under reflux for 72 h and the reaction mixture worked up as described above, column chromatography gave: (a) a mixture of ketol (**4**) and its isomer (**7**) (0.773 g); (b) ketol (**4**) (0.259 g); (c) *[1α,2β,3α,5β,6β,9β]-6,10,10-trimethyltricyclo[7.2.0.0^{3,5}]undecane-2,6-diol* (**8**) (0.142 g). Distilled 102-105°(block)/0.07 mm. MP 152-155°; IR (KBr): 3056 (OH), 1291, 1092, 1374, 1152 (C-O); ^{1}H NMR and ^{13}C NMR, see Table 1. EIMS: *m/z* 209 [M^+-CH_3], 206 [M^+-H_2O]. Anal. Found: C,74.8; H, 10.8. Calc. for $C_{14}H_{24}O_2$: C, 75.0; H, 10.8%.

Ethanol/KOH Treatment of Ketol (6). (a) A solution of ketol (**6**) (0.017 g, 0.077 mmol) in 10% w/v KOH/ethanol (50 cm^3) was heated under reflux for 48 h. The mixture was cooled, diluted with H_2O (70 cm^3), extracted with Et_2O (3 x 25 cm^3) and dried ($MgSO_4$). Column chromatography on neutral Al_2O_3, eluting with ether, gave diol (**8**) (0.008 g).

(b) Aldehyde free ethanol was prepared by heating freshly distilled ethanol (100 ml) with zinc dust (1 g) and KOH (1 g) under reflux in an atmosphere of nitrogen for 3h. The ethanol was distilled under nitrogen and stored over activated 3A sieves under a nitrogen atmosphere. A solution of ketol (**6**) (0.005 g, 0.022 mmol) in 10% w/v KOH/ethanol (15 cm^3) was heated under reflux for 27 h. Work up as above gave a 3:2 mixture of ketol (**6**) and diol (**8**) (0.008 g) (analysis by ^{1}H NMR and GC).

(c) A solution of acetyl chloride (1.68 g, 21.4 mmol) in THF (1.5 ml) was added slowly to a stirred suspension of $LiAlD_4$ (0.494g, 11.77 mmol) in THF (20 ml) at 0° under an atmosphere of argon. The mixture was stirred for 5 min then heated under reflux for 2h. After cooling, THF was removed under vacuum and the pale green complex quenched with water (3ml) with stirring. The deuterated ethanol was distilled under vacuum into a cold trap (liquid N_2) before being dried with anhydrous $MgSO_4$ (3g). The product was distilled once more and dried over activated 4A sieves. A solution of ketol (**6**) (0.0074 g, 0.033 mmol) and KOH (0.043 g) in [1,1-$^2H_2$]-

ethanol (0.45 ml) was heated to 115° for 20 h in a sealed tube. The tube was cooled then opened and the solvent was removed under vacuum. The residue was rinsed with CH_2Cl_2 and the CH_2Cl_2 extracts were washed with water, dried and evaporated. NMR revealed the product to be solely ketol (**6**). Under identical conditions with undeuterated ethanol as solvent, complete conversion into diol (**8**) was observed. With a 1:1 mixture of ethanol and [1,1-$^2H_2$]-ethanol, both (**6**) and (**8**) were obtained in a 5:1 ratio over the same reaction time.

*$LiAlH_4$ Reduction of Ketol (**6**).* A stirred solution of ketol (**6**) (0.010 g, 0.046 mmol) in dry ether (10 cm^3) was treated with $LiAlH_4$ (0.005 g, 0.14 mmol) under a N_2 atmosphere at room temperature for 5 h. The reaction was quenched cautiously with H_2O (10 cm^3) and extracted with Et_2O (2 x 10 cm^3). The combined organic fractions were dried ($MgSO_4$) and evaporated to give diol (**8**) (0.007 g).

*Monoacetylation of Diol (**8**).* A solution of diol (**8**) (0.080 g, 0.36 mmol) in dry pyridine (3 cm^3) and acetic anhydride (2 cm^3) was stirred at room temperature for 14 h. The reaction mixture was diluted with H_2O (20 cm^3) and extracted with Et_2O (3 x 10 cm^3). The combined organic fractions were washed with dil. HCl (1M, 10 cm^3), H_2O (10 cm^3), aqueous $NaHCO_3$ (0.5M, 2 x 15 cm^3), and H_2O (15 cm^3). Drying ($MgSO_4$) followed by evaporation, gave an oil (0.097 g) which was purified by PLC (40% EtOAc/Et_2O) to give *[1α,2β,3α,5β,6β,9β]-2-acetoxy-6,10,10-trimethyltricyclo[7.2.0.0^{3,5}]undecan-6-ol* (**9**) as an oil (0.080 g). Distilled 100-105°(block)/0.1 mm. IR (film): 3444 (OH), 1741, 1232 (acetate); ^{1}H NMR: 0.29 (1H, *ddd*, *J* 5,5,8.5 Hz, H-4), 0.52 (1H, *m*, $W_{h/2}$ 21 Hz, H-4), 0.65 (1H, *m*, $W_{h/2}$ 16 Hz, H-3), 0.83 (3H, *s*, H-14), 0.96 (3H, *s*, H-12), 0.97 (3H, *s*, H-13), 1.15 (1H, *m*, $W_{h/2}$ 22 Hz, H-5), 1.20 (1H, *m*, H-8), 1.26 (1H, *dd*, *J* 10,10.5 Hz, H-11), 1.49 (1H, *dd*, *J* 8,10 Hz, H-11), 1.67 (1H, *m*, H-8), 1.70 (1H, *m*, H-7), 1.86 (1H, *m*, H-9), 1.88 (1H, *m*, H-7), 2.05 (3H, *s*, $OCOCH_3$), 2.21 (1H, *dddd*, *J* 3,8,10.5,10.5 Hz, H-1), 5.15 (1H, *brs*, $W_{h/2}$ 5 Hz, H-2); ^{13}C NMR: 2.8 (CH_2, C-4), 19.1 (CH, C-3), 20.4 (CH_3, C-14), 20.5 (CH, C-5), 20.9 (CH_3, $OCOCH_3$), 21.2 (CH_3, C-13), 27.1 (CH_2, C-8), 29.6 (CH_3, C-12), 34.5 (CH_2, C-11), 35.7 (C, C-10), 46.4 (CH, C-9), 46.4 (CH, C-1), 46.8 (CH_2, C-7), 67.9 (CH, C-2), 72.9 (C, C-6), 170.6 (C, OCOCH3). Anal. Found: C, 72.0; H, 9.5. Calc. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.8%.

*Reaction of Monoacetate (**9**) with Isopropenyl Acetate.* A solution of monoacetate (**9**) (0.042 g, 0.16 mmol) and *p*-toluenesulfonic acid (0.005 g, 0.026 mmol) in isopropenyl actetate (3 cm^3) was stirred at room temperature for 48 h. The reaction mixture was diluted with Et_2O (10 cm^3), washed with dil. NaOH (1M, 10 cm^3) then H_2O (10 cm^3), dried ($MgSO_4$) and evaporated. PLC (35% Et_2O/hexanes) gave as an oil, *[1α,2β,3α,5β,9β]-2-acetoxy-6-methylene-10,10-trimethyltricyclo[7.2.0.0^{3,5}]undecane* (**10**). Distilled 105° (block)/0.1 mm. IR (film): 3070, 1640 (C=CH_2), 1741, 1368 (acetate); ^{1}H NMR: 0.47 (2H, *m*, $W_{h/2}$ 18 Hz, H-4, H-3), 0.92 (1H, *m*, $W_{h/2}$ 10 Hz, H-4), 0.98 (6H, *s*, H-12, H-13), 1.26 (1H, *m*, H-8), 1.28 (1H, *m*, H-11), 1.35 (1H, *m*, H-5), 1.51 (1H, *dd*, *J* 9,10 Hz, H-11), 1.80 (1H, *ddd*, *J* 4,4,15 Hz, H-8), 2.00 (1H, *brdd*, *J* 9,10 Hz, H-9), 2.07 (3H, *s*, $OCOCH_3$), 2.18 (1H, *brdd*, *J* 13,13 Hz, H-7), 2.29 (1H, *dddd*, *J* 1,8,10,10 Hz, H-1), 2.46 (1H, *ddd*, *J* 2,5,14 Hz, H-7), 4.41 (1H, *brs*, H-14), 4.50 (1H, *brs*, H-14), 5.18 (1H, *brd*, *J* 2.5 Hz, H-2); ^{13}C NMR: 4.8 (CH_2, C-4), 16.1 (CH, C-5), 21.0 (CH_3, $OCOCH_3$), 21.2 (CH_3, C-13), 26.9 (CH, C-3), 29.7 (CH_3, C-12), 31.4 (CH_2, C-8), 34.6 (CH_2, C-11), 35.8 (C, C-10), 40.4 (CH_2, C-7), 46.1 (CH, C-9), 46.7 (CH, C-1), 68.5 (CH, C-2), 102.8 (CH_2, C-14), 152.3 (C, C-6), 170.6 (C, $OCOCH_3$). Anal. Found: C, 77.2; H, 9.6. Calc. for $C_{16}H_{24}O_2$: C, 77.4; H, 9.6%;

Reaction of Diol (8) with Isopropenyl Acetate. A solution of diol (**8**) (0.100 g, 0.45 mmol) and *p*-toluenesulfonic acid (0.010 g, 0.026 mmol) in isopropenyl actetate (4 cm^3) was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O (15 cm^3), washed with dil. NaOH (1M, 2 x 10 cm^3) then H_2O (10 cm^3), dried ($MgSO_4$) and evaporated. PLC (50% Et_2O/hexanes) gave as an oil, *[1α,2β,3β,9β]-2,3-diacetoxy-6,10,10-trimethylbicyclo[7.2.0]undec-5-ene* (**11**) (0.060 g). Distilled 100° (block)/0.09 mm. IR (film): 1738, 1241 (acetate); ^{1}H NMR: 0.91 (3H, *s*, H-12), 0.93 (3H, *s*, H-13), 1.30 (1H, *dd*, *J* 10,10 Hz, H-10), 1.42 (2H, *m*, both H-2), 1.68 (1H, *m*, H-10), 1.72 (1H, *brs*, H-14), 1.93 (1H, *brddd*, *J* 7,8,12 Hz, H-1), 2.00 (1H, *m*, H-6), 2.01 (3H, *s*, $OCOCH_3$), 2.05 (2H, *m*, both H-3), 2.17 (1H, *m*, H-9), 2.22 (3H, *s*, $OCOCH_3$), 2.59 (1H, *brddd*, *J* 7,10,12 Hz, H-6), 4.86 (1H, *dd*, *J* 7,10 Hz, H-7), 4.96 (1H, *brs*, H-8), 5.46 (1H, *dd*, *J* 7,8 Hz, H-5); ^{13}C NMR: 16.2 (CH_3, C-14), 21.1 (CH_3, $OCOCH_3$), 21.3 (CH_3, $OCOCH_3$), 22.9 (CH_3, C-13), 27.7 (CH_2, C-6), 29.7 (CH_2, C-2), 30.0 (CH_3, C-12), 32.9 (C, C-11), 38.5 (CH_2, C-10), 39.6 (CH_2, C-3), 43.3 (CH, C-9), 45.8 (CH, C-1), 75.7 (CH, C-7), 77.9 (CH, C-8), 117.2 (CH, C-5), 139.6 (C, C-4), 170.88 (C, $OCOCH_3$), 170.93 (C, $OCOCH_3$). Anal. Found: C, 70.3; H, 9.1. Calc. for $C_{18}H_{28}O_4$: C, 70.1; H, 9.2%.

Epoxide (12). Prolonged storage of (**11**) in contact with air at ambient temp. resulted in the formation of *[1α,2β,3β,5α,6β,9β]-2,3-diacetoxy-5,6-epoxy-6,10,10-trimethylbicyclo[7.2.0]undecane* (**12**). IR (film): 1737, 1248 (acetate); 1027, 807 (epoxide); ^{1}H NMR and ^{13}C NMR see Table 2; $[\alpha]_D^{20}$ -1.37 (c 1.41, $CHCl_3$). HRMS: *m/z* 264.17254 [M^+-AcOH]. Required for $C_{16}H_{24}O_3$ [M^+-AcOH] 264.17198.

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