

THE SYNTHESIS OF 5 $\beta$ ,7 $\beta$ (H),10 $\alpha$ -Eudesm-4(14)en-1-one.

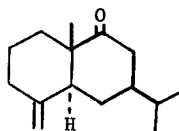
COMMENTS ON THE STRUCTURE OF CANARONE.

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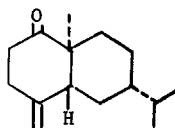
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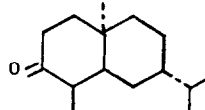
We have previously reported<sup>2</sup> the synthesis of 7 $\alpha$ (H)eudesm-4(14)en-9-one(I) and shown its non-identity with the sesquiterpenoid ketone canarone.<sup>3a</sup> We now wish to report the synthesis of 5 $\beta$ ,7 $\beta$ (H),10 $\alpha$ -eudesm-4(14)en-1-one (II), which also apparently is not enantiomeric with



I



II



III  $\Delta^4$

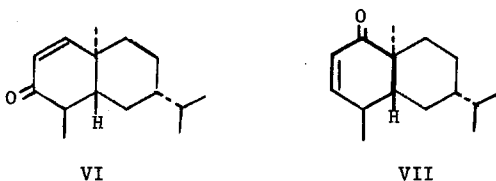
IV  $\beta$ -C-4-Me,  $\beta$ -C-5-H

V  $\alpha$ -C-4-Me,  $\beta$ -C-5-H

the natural canarone,<sup>3b</sup> thus suggesting that canarone may not, in fact, be a eudesmane sesquiterpenoid.

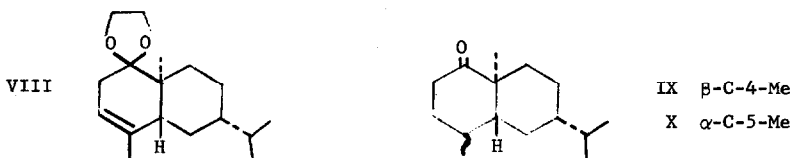
Our synthesis began with (-)  $\beta$ -cyperone prepared as previously described,<sup>4a</sup> which, very interestingly, was converted quantitatively into (-)dihydro- $\alpha$ -cyperone(III) by reduction with lithium in ammonia-ether-ethanol. This method of preparing a dihydro- $\alpha$ -cyperone appears superior to those previously reported.<sup>4b,5</sup> Further reduction of III with lithium in ammonia-ether gave tetrahydrocyperone IV contaminated with about 10% of the less stable C-4 epimer V (by glc). Preliminary studies indicated that IV could not be efficiently converted into the desired  $\alpha,\beta$ -unsaturated ketone VI directly by bromination-dehydrobromination

and hence IV was converted into the kinetically favored  $\Delta^2$  enol acetate (containing ~ 20% of the thermodynamically more stable  $\Delta^3$  enol acetate). Bromination of the latter in carbon tetrachloride in the presence of epichlorohydrin followed by dehydrobromination using  $\text{LiCl}/\text{Li}_2\text{CO}_3$  in DMF gave, after chromatography on alumina,  $\alpha,\beta$ -unsaturated ketone VI (43% from IV. In addition, 23% of the  $\Delta^4$  isomer was produced).  $\nu^{\text{film}}$  1665, 1610  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}$  0.90 (6H, d,  $J = 6$  Hz), 1.03 (3H, s), 1.12 (3H, d,  $J = 7$  Hz), 5.80 and 6.65 (2H, d of d,  $J = 10$  Hz); multiple Cotton effect curves in ORD and CD in both methanol and dioxane.<sup>6</sup>  $\alpha,\beta$ -Unsaturated ketone VI was efficiently converted into  $\alpha,\beta$ -unsaturated ketone VII as follows. Basic peroxide treatment of VI gave the epoxyketone ( $\nu^{\text{film}}$  1725  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}$  3.23 and 3.35, 2H, d of d,  $J = 4$  Hz) which when subjected to the Wharton rearrangement gave the  $\Delta^2$ -1-alcohol



( $\nu^{\text{film}}$  3350  $\text{cm}^{-1}$ ). The latter alcohol was most efficiently converted into the desired ketone VII by oxidation with Jones reagent and was isolated in pure form (gic) after chromatography on silica gel.  $\nu^{\text{film}}$  1670, 1610  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}$  0.88 (6H, d,  $J = 5$  Hz), 1.00 (3H, s), 1.10 (3H, d,  $J = 8$  Hz), 5.85 and 6.60 (2H, ABX system,  $J_{AB} = 10$  Hz,  $J_{AX} = 2.5$  Hz,  $J_{BX} = 2.0$  Hz);  $M^+$  220 (78%)  $\lambda_{\text{max}}^{\text{MeOH}}$  225 nm ( $\log \epsilon = 3.90$ ); multiple Cotton effect in ORD-CD in methanol and dioxane.<sup>6</sup>

Ketalization of VII led to the formation of the  $\Delta^3$  ketal VIII in 42% yield and the latter could be isolated in pure form after chromatography on 10%  $\text{AgNO}_3$  on silica gel.  $\nu^{\text{film}}$  1630  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}$  0.82 (3H, s), 0.83 (6H, d,  $J = 7$  Hz), 1.58 (3H, s), 3.83 (4H), 5.22 (1H, b). The  $\Delta^4$  ketal was present in the ketal mixture to an extent of about 46%. Epoxidation of VIII

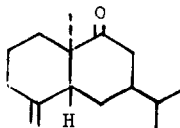


with *m*-chloroperbenzoic acid gave a mixture of epoxides in a ratio of 3.5 to 1, the major product presumably being the thermodynamically more stable  $\beta$ -epoxide (trans to C-10 methyl group). The epoxide mixture was reduced with lithium aluminum hydride and the crude alcoholic product was dehydrated with phosphorous oxychloride in pyridine. Chromatography on  $\text{AgNO}_3$ -silica gel gave the desired  $\Delta^{4(14)}$  ketal (ketal of II). The latter compound was carefully hydrolyzed under acidic conditions to give the desired  $5\beta,7\beta(\text{H}),10\alpha$ -eudesm-4(14)*en*-1-one(II), which was obtained in an analytically pure form (> 95% by glc) after chromatography on  $\text{AgNO}_3$ -silica gel. B.p.  $50^\circ/0.05$  mm (hot box);  $\nu^{\text{film}}$  3085, 1720, 1660, 1470, 1380, 1375, 1280, 1250, 890  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}_{\text{ppm}}$  0.87 (6H, d,  $J = 6$  Hz), 0.88 (3H, s), 4.68 (1H, bs,  $W_{1/2}$  5 Hz), 4.92 (1H, bs,  $W_{1/2}$  5 Hz);  $M^+_{\text{found}}$  220.1845 (38%),  $M^+_{\text{calc}}$  220.1827;  $\lambda^{\text{MeOH}}_{\text{max}}$  275 nm ( $\log \epsilon$  2.45), 254 ( $\log \epsilon$  2.38, inflection), 248 ( $\log \epsilon$  2.34, inflection); ORD ( $\text{CH}_3\text{OH}$ ):  $[\theta]_{284}$  trough,  $[\theta]_{250}$  peak; CD ( $\text{CH}_3\text{OH}$ ):  $[\theta]_{265}$  trough. A comparison with the NMR, IR and ORD curves of natural canarone<sup>7</sup> indicated that II was structurally different from canarone.

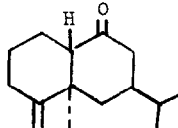
In order to further verify that canarone was not represented by structure II, the two dihydro derivatives of II, IX and X, were prepared and characterized. Thus, ketone VII was hydrogenated in the presence of 5% Pd/C to give IX<sup>6</sup> (containing < 5% isomer X, by glc).  $\nu^{\text{film}}$  1710  $\text{cm}^{-1}$ ;  $\delta^{\text{CDCl}_3}_{\text{ppm}}$  0.88 (6H, d,  $J = 5$  Hz), 0.93 (3H, s); 1.02 (3H, d,  $J = 7$  Hz);  $M^+_{222}$  (66%);  $\lambda^{\text{MeOH}}_{\text{max}}$  274-81 nm ( $\log \epsilon$  2.26); ORD ( $\text{CH}_3\text{OH}$ ):  $[\theta]_{306}$  trough,  $[\theta]_{273}$  peak; CD ( $\text{CH}_3\text{OH}$ ):  $[\theta]_{291}$  trough. Isomeric ketone X was prepared by hydrogenation of ketal VIII over 5% Pd/C followed by hydrolysis in acetone-aq. HCl. After chromatography on silica gel, pure (three glc columns) X was obtained.<sup>6</sup> B.p.  $55^\circ/0.05$  mm (hot box);  $\nu^{\text{film}}$  1710  $\text{cm}^{-1}$  (shoulder at 1735  $\text{cm}^{-1}$ );  $\delta^{\text{CDCl}_3}_{\text{ppm}}$  0.88 (6H, d,  $J = 6$  Hz), 1.00 (3H, s), 1.23 (3H, d,  $J = 7$  Hz);  $M^+_{\text{found}}$  222.2002 (70%),  $M^+_{\text{calc}}$  222.1984;  $\lambda^{\text{MeOH}}_{\text{max}}$  267 nm ( $\log \epsilon$  2.31); ORD ( $\text{CH}_3\text{OH}$ ):  $[\theta]_{303}$  trough,  $[\theta]_{263}$  peak; CD ( $\text{CH}_3\text{OH}$ )  $[\theta]_{287}$  trough. The unexpected infrared band at 1735  $\text{cm}^{-1}$  (compound X shown to be homogeneous on five glc columns) may be due to the presence of some of the twist boat conformational isomer in which the severe 1,3-diaxial interaction of the C-1 and C-4 methyls is relieved. Unfortunately, this could not be verified by ORD due to the optical impurity<sup>6</sup> of the isomers IX and X, but the negative ORD curves of IX and X verify that both are trans fused decalins. Unfortunately, only the infrared spectrum of dihydrocanarone has been reported,<sup>3b</sup> but based on this, X is not the enantiomer of dihydrocanarone.

Since dihydrocanarone was prepared by catalytic hydrogenation,<sup>6</sup> the C-4 methyl group would be expected to be cis (axial) to the bridgehead methyl group.

If indeed canarone is not a eudesmane sesquiterpenoid, as now appears to be the case, two biogenetically related sesquiterpenoids can be suggested for its structure which would account for the published chemical and spectral data,<sup>3</sup> namely XI related to intermedeol<sup>8</sup> and XII related to valencene.<sup>9</sup> We are now looking into these alternatives.



XI



XII

#### References

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6. All key compounds were fully characterized by elemental analyses, IR, UV, NMR, ORD, CD and mass spectra. Since the starting  $\beta$ -cyperone was only about 50% optically pure, intensities are not given for the ORD and CD curves.
7. We thank Dr. S. C. Bhattacharyya, Indian Institute of Technology, for these spectra. Unfortunately, an authentic sample of canarone was no longer available.
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