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CHEMICAL CONVERSION OF HUMULENE TO DACTYLOL. BIOMIMETIC, APPARENT 1,2-SHIFT OF A METHYL GROUP

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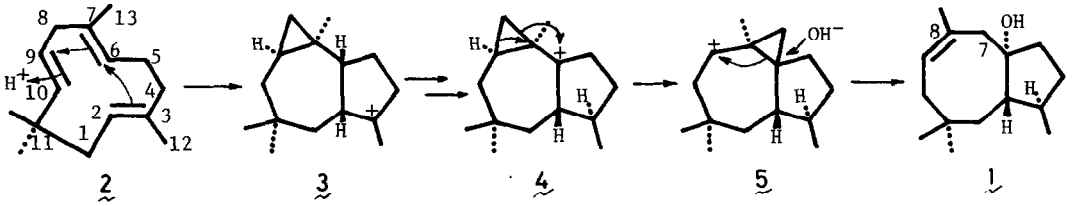
Summary: Africanol, which had been previously derived from humulene, was converted to dactylol through a formal 1,2-shift of a methyl group, which involved a cyclopropane sliding reaction and subsequent cyclopropane ring opening.

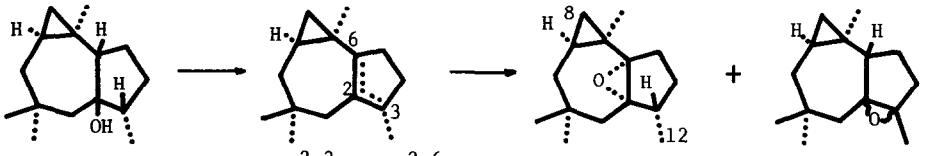
Dactylol (1) is an irregular isoprenoid alcohol isolated from a Caribbean sea hare, Aplysia dactyloma, by Schmitz et al.[1] The compound is assumed to be biosynthetically derived from humulene (2). The point of interest is its skeleton in which the C-7 olefinic methyl group is migrated to C-8. Chemical realization of the conversion of humulene to dactylol involving the methyl transposition should not only be synthetically attractive but also throw light on the possible pathway for biosynthesis of the irregular sesquiterpene. We reported previously derivation of the irregular terpene capnellene (16) from humulene through an apparent 1,2-shift of a methyl group,[2] employing "cyclopropane sliding reaction". The reaction seemed applicable to the present problem. The synthetic principle was depicted below.



2 3 4 5 1

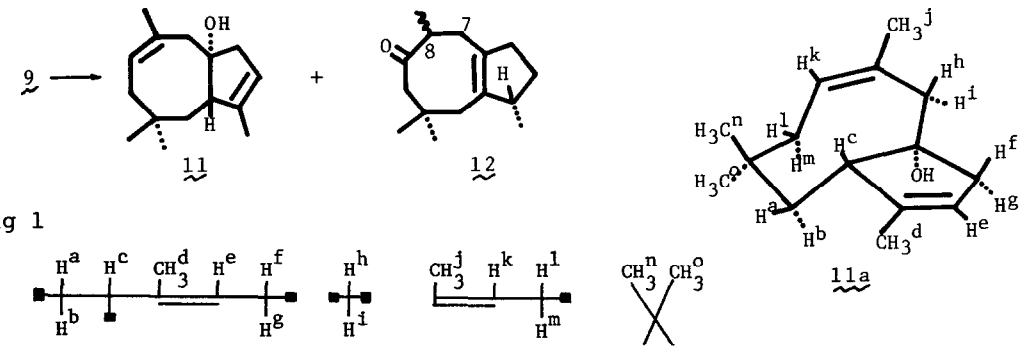
6-Africyl cation (4) seemed to be generated from africanol (6) which was already derived from humulene[3] and thus 6 was selected as the starting material. Dehydration of 6 (6, 64 mg/$POCl_3$/Py/70→90°C/1 h) gave a mixture of two tetrasubstituted olefins[4] (1:1, by NMR) which was converted to epoxides (mCPBA/CH_2Cl_2/rt/5 min). They were separated by silica-gel chromatography to give a new epoxide 9[5] (26.6 mg, 42% from 6) and a known one 10[6] (25.4 mg, 40 % from 6).

Scheme 1



6 7: $\Delta^{2,3}$, 8: $\Delta^{2,6}$ 9 10

In the NMR spectrum of 9, lanthanide induced shift values ($\delta_{Eu(fod)_3}$-δ_o/mole ratio of Eu(III) to substrate=6.97, 13-Me; 6.60 and 4.72, 1-H_2; 3.96, 9-H; 3.68, 12-Me; 3.40, 8-H; 1.98 and 1.51, 14- and 15-Me) showed clearly syn orientation of epoxide oxygen, 13-Me and 9-H. Ethereal solution of 9 (11 mg) was treated with $BF_3 \cdot OEt_2$ (5 eq) at -10 °C for 30 min to give an alcohol 11 (2 mg, 18 %, ν 3480 cm^{-1}), a ketone 12 (0.5 mg, 5 %, ν 1708 cm^{-1}) and a complex mixture of hydrocarbons. Using smaller amount of $BF_3 \cdot OEt_2$ (2 eq) at 0 °C, 8 % of 11 and 25 % of 12 were obtained. The alcohol 11 (M^+: 220.1835: $C_{15}H_{24}O$,) was shown to have partial structures drawn in Fig 1 by the NMR spectrum ($CDCl_3$, 400 MHz). From these data a molecule as depicted in formula 11a could be assembled, which was well coincided with observed NMR coupling constants.



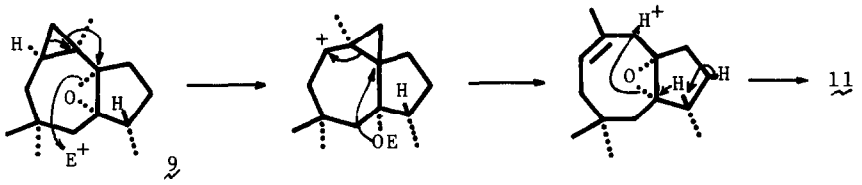
11 12 11a

Fig 1

$\delta(CDCl_3)$ a=1.12, b=1.59, c=2.40, d=1.66, e=5.37, f=2.40, g=2.26, h=2.57, i=2.23, j=1.85, k=5.50, l=2.04, m=1.61, n & o=0.94 & 0.96. J_{ab}=14, J_{ac}=~0, J_{bc}=7, J_{cd}=~1.5, J_{ce}=~1.5, J_{de}=~1.5, J_{df}=~1.5, J_{dg}=~1.5, J_{ef}=~1.5, J_{eg}=~1.5, J_{fg}=14, J_{hi}=14, J_{jk}=~1, J_{kl}=7, J_{km}=11, J_{ml}=13 Hz. In pyridine-chloroform (1 : 1) solution, H^b exhibited the largest shift ($\delta_{CDCl_3} - \delta_{pyr}$ = -0.36 ppm) which showed 1,3-diaxial deshielding.[9] The shifts of other protons falled in a range of -0.09 ~ +0.07 ppm.

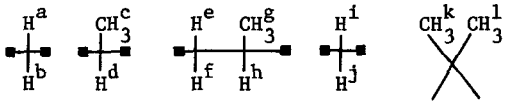
The trans-fused skeleton was inferred from the pyridine-induced shift (Fig 1). An apparent methyl migration, interpreted as shown in Scheme 2, was thus accomplished through the cyclopropane sliding reaction. Hydrogenation of 11 (3 mg, H_2/PtO_2/EtOH/9 h) took place selectively at the double bond on the five membered ring to afford a hydroxy mono-olefin (2.7 mg, 90 %), whose spectral data were identical with those of natural dactylol.

Scheme 2



The NMR spectrum revealed that the ketone 12 (M^+: 220.1829: $C_{15}H_{24}O$) was assembled by partial structures shown in Fig 2 and its structure was expressed by formula 12 except for the position of 13-Me group. The position of the methyl group was clarified by NMR analysis (500 MHz, $CDCl_3$) of reduction products ($LiAlH_4$, Et_2O) 13 and 14, which contained partial structures 13a and 14a (Fig 3) respectively. Thus the apparent methyl migration was observed also in product 12. A possible reaction course was described in Scheme 3. The configuration at C-8 of 12 is not clear at present.

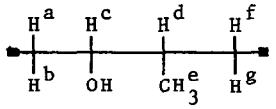
Fig 2



δ(J) a=1.92(12), b=2.60(12), c=0.94(7), e=2.01(13, 4), f=2.46(13, 13), g=1.10(7), h=2.60(13, 7, 4), i=1.87(14), j=2.15(14), k & l=0.94 & 1.08

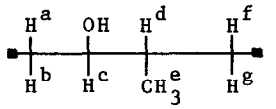
Fig 3

13a



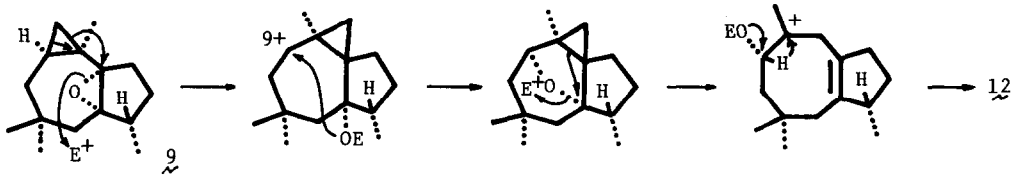
δ(J) a=1.24(14, 0), b=1.80(14, 7), c=3.30(8, 7), d=1.53(m), e=1.04(7), f=2.0(5), g=2.01(9)

14a

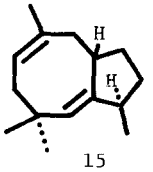


a=1.97(14, 7), b=1.05(14, 0), c=3.90 (7, 4), d=2.09(m), e=0.93(7), f & g=2.1 & 1.97

Scheme 3



Dactylol (1) has the same skeleton as precapnelladiene (15)[7], which has been assumed to intervene in the biosynthesis of capnellene (16).[8] The present conversion of humulene to dactylol suggests strongly that cyclopropane sliding reaction plays a roll in the biosynthesis of precapnellanoids and capnellanoids.



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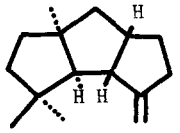

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Acknowledgment: We thank Prof. F. J. Schmitz for spectra of dactylol.

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2) T. Fujita, T. Ohtsuka, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 23, 4091 (1982).

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4) These results were a little different from the similar experiments described in the following report. B. Tursch, J. C. Braekman, D. Daloze, P. Fritz, A. Kelecom, R. Karlson, D. Losman, ibid, 747 (1974).

5) Spectral data of 9 were as follows. M^+220.1831 $C_{15}H_{24}O$, IR 1260, 920, 813 cm^{-1}, NMR: δ 0.93(3H, s), 0.98(3H, d, J=7), 1.01(3H, s), 1.12(3H, s), 0.26(1H, t, J=4.5), 0.59(1H, dd, J=8, 4.5), 0.67(1H, m), 1.58 & 1.83(2H. ABq, J=15 Hz).

6) A mixture of α and β epoxides (1:1). See ref. 3.

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