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BIOMIMETIC GERMACRENE-HUMULENE REARRANGEMENT

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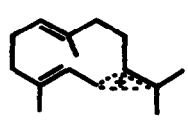
Summary: The boron trifluoride catalyzed rearrangement of 7,11-epoxygermacrone (7) provided the new diketone in high yield. This transformation represents the first biomimetic chemical conversion of a germacrane into a humulane skeleton.

The cation 1 is generally considered as the biogenetic precursor of sesquiterpenoids with germacrane and humulane carbon skeleton[1]. Recently, a non-enzymatic generation of the humulene cation 2 and its conversion into germacrene derivatives has been reported[2]. We outline here the reverse case - generation of the germacreme cation 3 and subsequent expansion of the 10-membered ring to the humulane skeleton.



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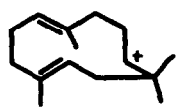

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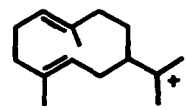
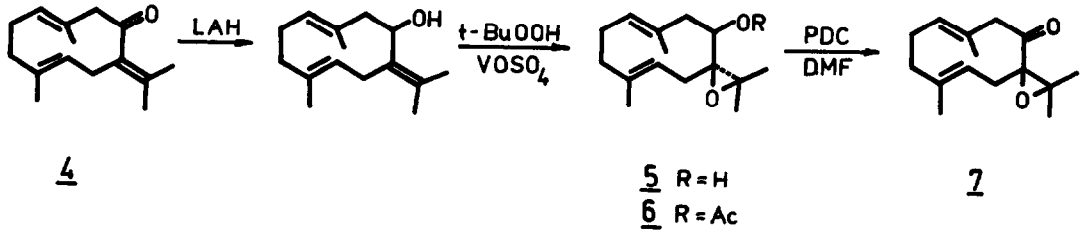


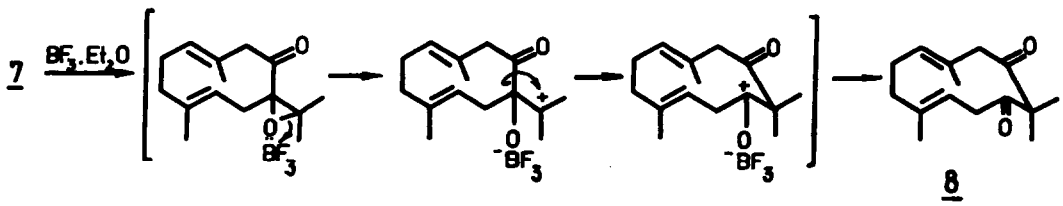
3

The most suitable functional equivalent of the cation 3 was considered to be 7,11-epoxygermacrone (7). The latter was prepared from germacrone (4) as outlined in Scheme I, as the direct epoxidation with H_2O_2 in alkali medium would lead to isomerisation of the starting material[3]. Accordingly, LAH reduction of 4[3] followed by Sharpless epoxidation[4] gave the cis-epoxyalcohol 5[5] as colourless needles (m.p. 56-57°C). Subsequent oxidation with PDC-DMF[6] afforded the desired epoxide 7 (m.p. 50-52°C) in 92% overall yield[7].



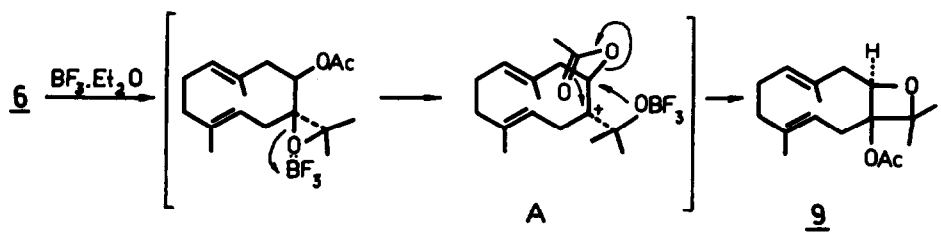
Scheme I

Treatment of 7 with equimolar amounts of $BF_3.Et_2O$ at 0^oC for 70 hours followed by chromatography on SiO_2 (petroleum ether-ether 4:1) provided the humulene diketone 8 (m.p. 80-81°C) in 75% yield[8]. The proposed pathway for the formation of 8 (Scheme II) includes a regioselective scission of the oxirane and ring expansion due to acyl migration. The latter can be regarded as a particular case of the known rearrangement of α,β -epoxyketones in which the electron-withdrawing group migrates to an electron-deficient centre[9].



Scheme II

It was interesting to note that when the carbonyl function in 7 was replaced by an acetoxy group, i.e. compound 6[10], no cation of type 3 was generated upon treatment with $BF_3.Et_2O$. In this case the germacrene derivative 9 was obtained in 78% yield[11] after chromatographic purification (SiO_2, petroleum ether-ether 5:1). The formation of 9 can be viewed as arising from C-7/O bond cleavage with the cation A as an intermediate (Scheme III).



Scheme III

Table 1. PMR (250 MHz) data of compounds 5 - 9 in $CDCl_3$, ppm, TMS (J in Hz)

Proton	5	6	7*	8	9
H-1	4.81 dbr (10)	4.86 dbr (11.5)	5.14 dbr (11)	4.94 dd (8, 1.5)	4.79 dbr (10)
H-5	4.50 dbr (11)	4.54 dbr (12)	5.00 dd (12, 2)	4.76 td (8, 1.5)	4.51 dd (12, 3)
H-6	2.63 dd (11, 15)	2.81 dd (12, 15)	3.00 dd (12, 14)	3.20 dbr (8)	3.16 dd (13, 12)
H-6'	2.2-2.3**	2.35 dbr (15)	1.94 dd (14, 2)		2.56 dd (13, 12)
H-8	3.99 dd (10, 2)	4.98 dbr (10)	-	-	4.19 d (11)
H-9	2.51 dd (10, 13)	2.66 dd (10, 13)	3.80 dbr (10)	3.11 sbr	2.9-3.0**
H-9'	2.2-2.3**	2.1-2.2**	2.3-2.4**		1.7-1.8**
H-12	1.55 s	1.39 s	1.16 sbr	1.41 s	1.26 s
H-13			1.39 sbr		1.51 s
H-14	1.59 s	1.59 s	1.60 s	1.50 sbr	1.64 s
H-15	1.46 s	1.45 s	1.40 s	1.56 sbr	1.47 s
OAc	-	2.05 s	-	-	2.22 s

*run at 50°C

**The assignment is based on decoupling experiments

Table 2. CMR (62.9 MHz) data of 8 and 9 in $CDCl_3$, ppm, TMS

Carbon	8	9	Carbon	8	9
C-1	130.40 d*	130.67 d	C-9	40.49 t	28.92 t
C-2	26.33 t	24.18 t	C-10	139.06 s	136.79 s
C-3	40.09 t	39.71 t[b]	C-11	60.65 s	86.72 s
C-4	127.28 s	129.26 s	C-12	23.07 q	25.05 q[c]
C-5	116.84 d	121.20 d	C-13	23.07 q	24.08 q[c]
C-6	47.91 t	38.95 t[b]	C-14	17.02 q	17.32 q
C-7	203.83 s[a]	89.47 s	C-15	15.72 q	15.79 q
C-8	204.68 s[a]	84.58 d	OAc	-	170.04 s
					21.47 q

*Multiplicities confirmed by DEPT measurment

[a-c]Assignment may be interchanged

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References and Notes

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5. compound 5: IR: 3500, 1660 cm^{-1}; MS: 236 (M^+); PMR: in Table 1.
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7. compound 7: IR: 1695, 1660 cm^{-1}; MS: 234 (M^+); PMR: in Table 1.
8. compound 8: IR: 1713, 1690 cm^{-1}; MS: 234 (M^+); PMR: in Table 1; CMR: in Table 2.
9. H.O. House, J.Am.Chem.Soc., 76, 1235 (1954); H.O. House and D.J. Reif, ibid., 77, 6525 (1955); H.O. House, ibid., 78, 2298 (1956); H.O. House and R,L. Wasson, ibid., 79, 1488 (1967); H. Hart and P. Lavrik, J.Org. Chem., 39, 999 (1974); J.M. Domagala, R.D. Bach and J. Wemple, J.Am.Chem. Soc., 98, 1976 (1976).
10. compound 6: m.p. 51-53°C; IR: 1750, 1670, 1250 cm^{-1}; MS: 278 (M^+); PMR: in Table 1.
11. compound 9: m.p. 81-82°C; IR: 1737, 1226, 1077, 1058, 1019 cm^{-1}; MS: 278 (M^+); PMR: in Table 1; CMR: in Table 2; the trans disposition of H-8 and the acetoxy group, as depicted in 9, is established by NOE experiments.

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