Tetrahedron Letters No. 33, pp 2865 - 2868, 1976. Pergamon Press. Printed in Great Britain.

A NEW MODE OF *in vitro* CYCLIZATION OF HUMULENE, FORMATION OF 3,6-SECOPROTOILLUDANE SKELETON

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(Received in Japan 5 June 1976; received in UK for publication 29 June 1976)

In the hypothesis of illudoids[1] biosynthesis[2], formation of the key intermediate protoilludyl cation 2 has been reasonably explained by the cationic cyclization of humulene, initiated at the $\Delta^{9,10}$ double bond (Scheme I). However, to date, all attempts[3] of chemical cyclization afforded products resulting from the initial electrophilic attack at $\Delta^{6,7}$ bond. We now report a new mode of humulene cyclization of the former type, which leads to the 3,6-secoprotoilludane skeleton[4].

Oximercuration[5] of humulene with an excess of $Hg(OAc)_2$ in a mixture of THF and H_2O (1/1) (rt, 6hr) and subsequent demercuration with $NaBH_4$ (rt, 2hr) gave a mixture of two tricyclic ethers 3 and 4 in 60% yield (3/4 = 3/1; determined by vpc and nmr). Separation of the ethers was performed by means of column chromatography on $AgNO_3$-silicagel[6] to give pure samples. 3[7]: oil; nmr(CCl_4) δ0.97 (3H, s) 1.09 (6H, s), 1.13 (3H, s); ir(neat) 1050cm^{-1}; mass 222 (M^+=$C_{15}H_{26}O^+$), 109 (base peak). 4[7]: oil; nmr(CCl_4) δ0.95, 1.02 (each 3H, s), 1.12 (6H, s), 5.54 (2H, s); ir(neat) 3030, 1100, 1075, 1040cm^{-1}; mass 220 (M^+=$C_{15}H_{24}O^+$), 109 (base peak). The olefinic ether 4 was readily hydrogenated (H_2, PtO_2, EtOH) to give the saturated ether 3 quantitatively. The nmr spectrum of 5[7], mp 108°~111°, derived from 4 (OsO_4,Pyr, rt, 1hr; $NaHSO_3$, 95%) exhibited peaks at δ(CCl_4) 1.30 (6H, s,

$CH_3-\overset{|}{\underset{|}{C}}-O\times2$), 1.85 (1H, q, H_A, J_{AB}=14Hz, J_{AX}=6Hz), 3.28 (1H, d, H_Y, J_{XY}=4Hz (1H, d×q, H_X, J_{XY}=4Hz, J_{AX}=6Hz, J_{BX}=12Hz) and indicated the presence of t tial structure A. Since the nmr spectra of 3, 4 and 5 exhibited no signal the methine group bearing ethereal oxygen atom, the ether moiety $CH_3-\blacksquare-O-$ was obtained as a partial structure for these compounds. The partial stru coupled with mechanistic considerations[8] suggested a formula like 4 for t olefinic ether. Treatment of 4 with MCPBA (CH_2Cl_2, rt, 100%) gave an epox mp 39°~40.5°, [nmr(CCl_4) δ2.48 (1H, d, J=4.5Hz), 3.07 (1H, t, J=4.5Hz)] was converted to an alcohol 7[7] (80%), mp 75.5°~76.5°, nmr(CCl_4) δ3.09 (1 J=3.5Hz). The Jones oxidation of 7 afforded a ketone 8[7] (90%), mp 56.5°~ nmr(CCl_4) δ0.99, 1.09, 1.27, 1.31 (each 3H, s); ir(nujol) 1735cm^{-1}; mass ($M^+=C_{15}H_{24}O_2^+$).

Elucidation of the structures 3 and 4 was achieved by X-ray crystal lographic analysis of the keto-ether 8: $P2_1/c$, a=9.558(5), b=6.195(3), c= (10)Å, β=109.48(5)°, Z=4. The structure was solved by the direct method a fined by the block-diagonal-matrix least-squares method using 2109 indepe reflections (Cu Kα, $\theta \leq 70°$). The final R value including hydrogen atoms was The perspective view of 8 thus obtained is shown in Fig.2 and the final a coordinates are given in Table 1.

The ethers 3 and 4 here obtained correspond to ether analogs of the thetical biosynthetic intermediate 1 and its dehydro compound respectivel Therefore it is hoped that these ethers could be transformed to illudoids in vitro processes. Studies along this line are now in progress.

Table I. The final atomic coordinates

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
O(1)	−0.1445	−0.0311	0.10061	C(8)	−0.0265	0.4022	0.08159
O(2)	0.0676	0.3923	0.18856	C(9)	0.1317	0.3769	0.08029
C(1)	0.3929	0.2976	0.13255	C(10)	0.1709	0.1667	0.05583
C(2)	0.2545	0.4032	0.14078	C(11)	0.3417	0.1746	0.07261
C(3)	0.2128	0.3117	0.19302	C(12)	0.3150	0.4087	0.25041
C(4)	0.2134	0.0611	0.19801	C(13)	−0.1934	0.4008	0.14295
C(5)	0.0601	−0.0293	0.19134	C(14)	0.3838	0.3041	0.02623
C(6)	−0.0530	0.0702	0.13893	C(15)	0.4096	−0.0497	0.07773
C(7)	−0.0485	0.3160	0.13738				

Scheme I

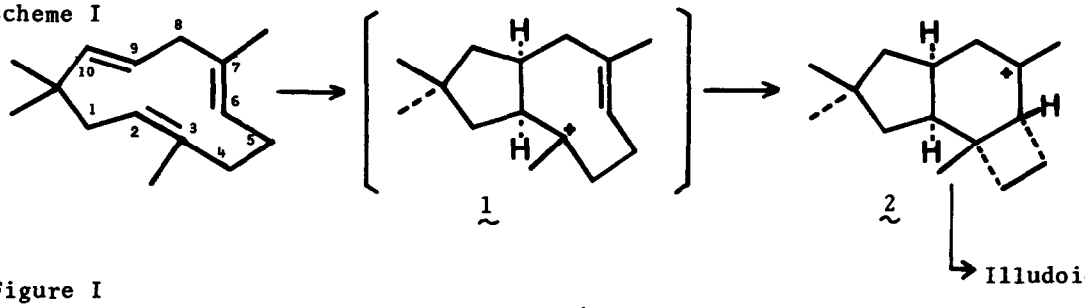
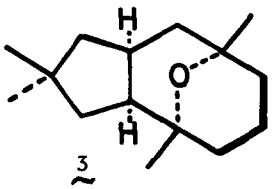
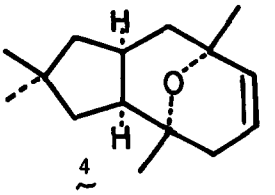


Figure I


3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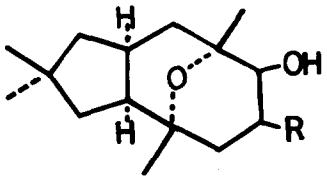
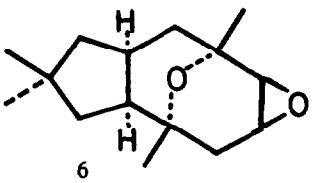


5 R = OH
7 R = H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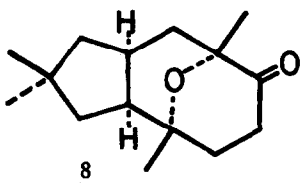
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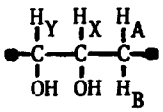
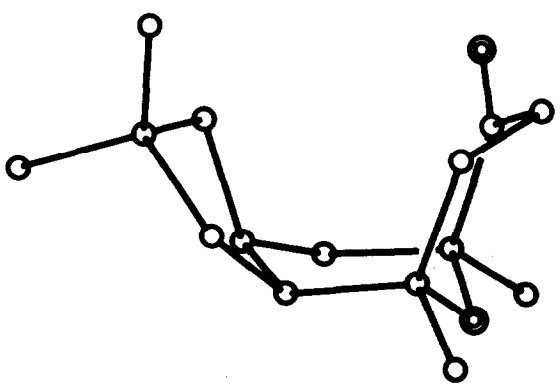


A

■ = a quarternary carbon atom

Figure II



References and notes

1. Naming: Y.Ohfune, H.Shirahama and T.Matsumoto, Tetrahedron Lett., 4377 (1975).

2. For review: W.Parker, J.S.Roberts and R.Ramage, Quart.Rev., 21, 331 (1967)

3. a) Y.Naya and Y.Hirose, Chem.Lett., 133, 727 (1973), b) D.Baines, J.Forrester and W.Parker, J.Chem.Soc., Perkin I, 1958 (1974), c) W.G.Dauben and N.D.Vietmeyer, J.Org.Chem., 40, 479 (1975), and references cited therein. d) G.Mehta and B.J.Singh, Tetrahedron Lett., 3961 (1975), e) An effective preparation of 9,10-epoxy humulene was very recently developed; A.Satter, J.Forrester, M.Moir, J.S.Roberts and W.Parker, Tetrahedron Lett., 1403 (1976).

4. Biogenetic-like synthesis of hirsutene: Y.Ohfune, H.Shirahama and T.Matsumoto, Tetrahedron Lett., in press.

5. H.C.Brown and P.Geoghegan,Jr., J.Amer.Chem.Soc., 89, 1523 (1967).

6. A.C.Gupta and Sukh Dev, J.Chromatography, 12, 189 (1963).

7. Satisfactory elementary analytical data were obtained.

8. Although the detailed mechanism for their formation is not clear, the following process may be suggested.