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BIOGENETIC LIKE SYNTHESIS OF ILLUDOID SKELETON. IN VITRO CONVERSION OF HUMULENE INTO 7-PROTOILLUDYL CATION

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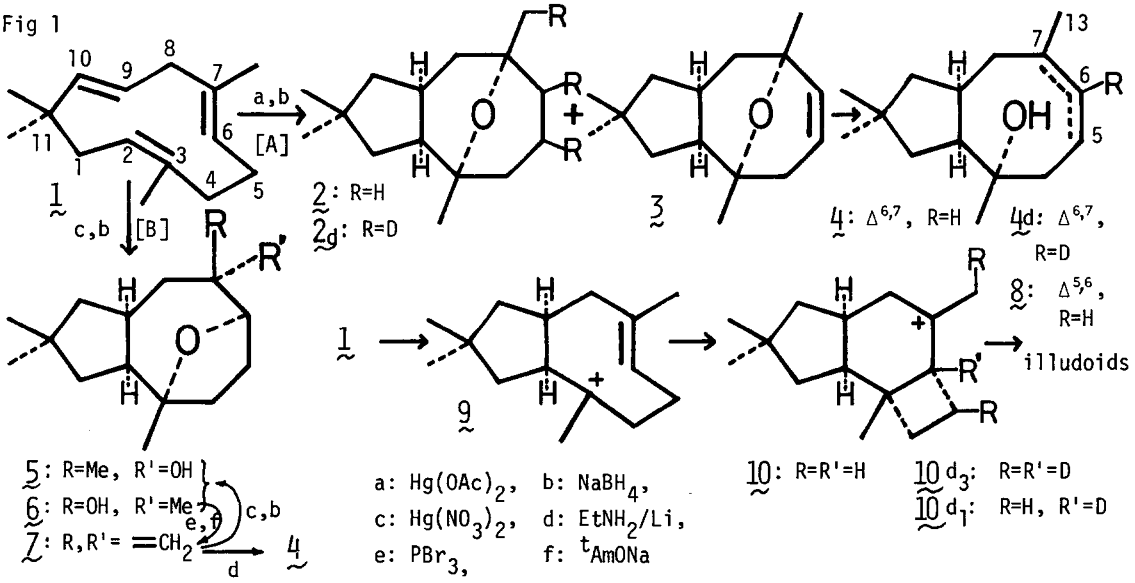
Previously we reported[1)] biogenetic like conversion of humulene (1) into a 3,6-seco-3,7-epoxyprotoilludane (2) and its 5,6-dehydro analog 3 by means of $Hg(OAc)_2$ (Fig 1, [A]). We now wish to describe here generation of 7-protoilludyl cation 10, an important biogenetic intermediate for illudoids, from 3 and newly obtained 3,6-seco-3,6-epoxyprotoilludane derivatives (6,7).

Fig 1



Humulene was treated with 3eq of $Hg(NO_3)_2$ in $AcOH/H_2O$ (2/1; 0°C, 0.5 hr) and the solvent was removed under reduced pressure by heating (60°C). The reaction mixture was then reduced with $NaBH_4$ to give three 3,6-seco-3,6-epoxyprotoilludane derivatives, 5, 6 and 7 (10%, 40%, 5%) 5: $C_{15}H_{26}O_2$[3)]; mp 95-96°C; ir 3560 cm^{-1}; nmr[4)] δ 1.00 (6H, s), 1.05, 1.17 (each 3H, s), 3.80 (1H, d, J=6). 6: $C_{15}H_{26}O_2$; mp 114-115°C; ir 3340 cm^{-1}; nmr δ 0.98, 1.05, 1.14, 1.28 (each 3H, s), 3.73 (1H, d, J=6). 7: $C_{15}H_{24}O$; ir 3080, 1645 cm^{-1}; nmr δ 0.98, 1.05, 1.18 (each 3H, s), 4.44 (1H, d, J=6), 4.58 (2H, s).

Fig 2

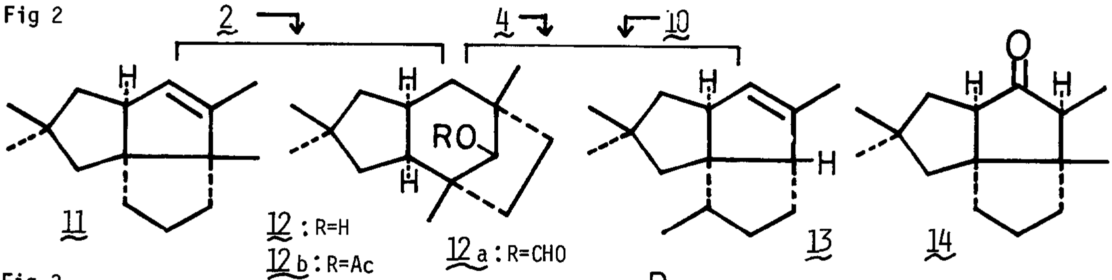


Fig 3

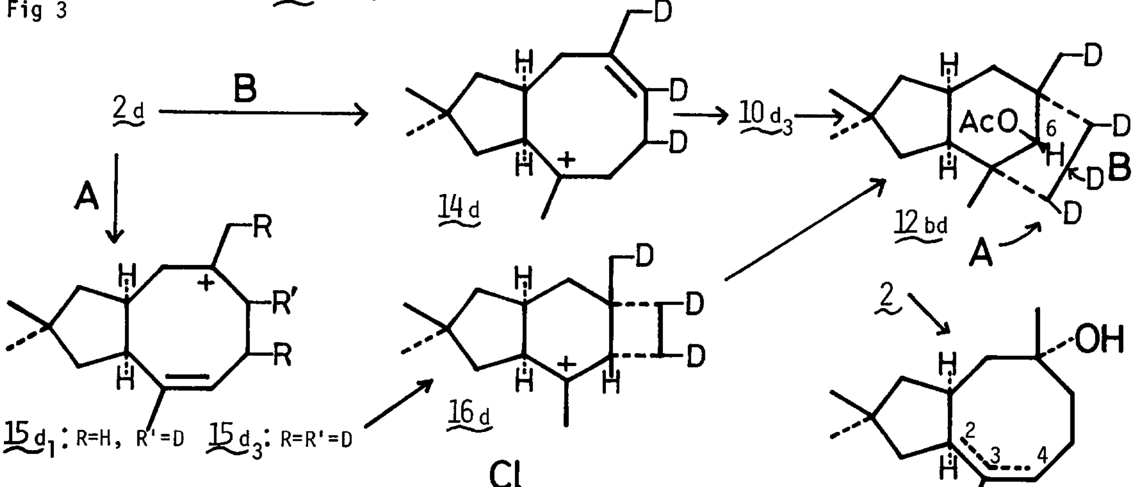
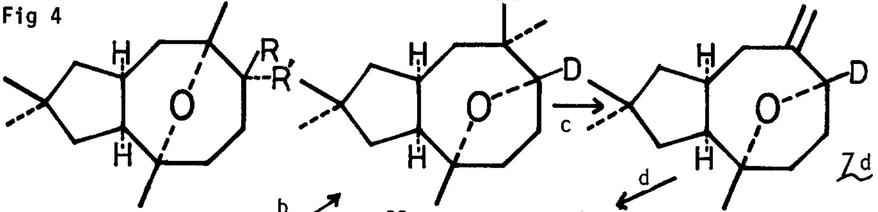


Fig 4



$\overset{a}{\lceil}$ 20 : R,R'=O

$\lfloor$ 21 : R=OH, R'=D

a : $NaBD_4$, b : MsCl, c : $^tAmONa/DMSO$,
d : $Li/EtNH_2$

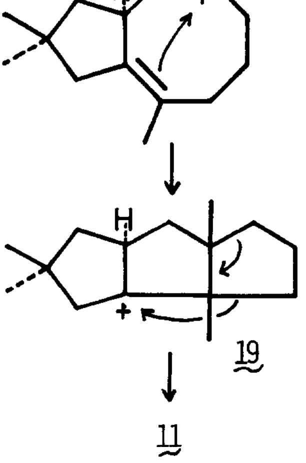
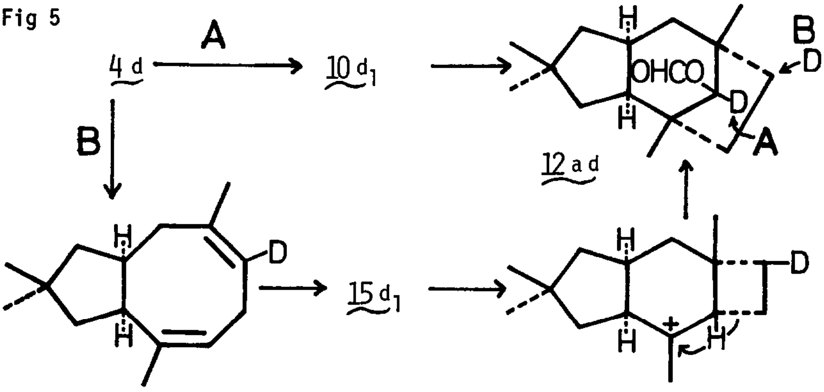
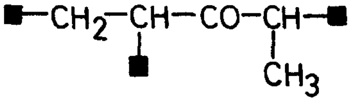


Fig 5



The structures of these ethers were deduced from the above spectral data as well as the following reactions. The unsaturated ether 7 gave alcohols 5 and 6 on further successive treatment with $Hg(NO_3)_2$ and $NaBH_4$. Configuration of the hydroxyl groups of 5 and 6 was determined by the presence of a hydrogen bond between the hydroxyl group and ether oxygen in 5 [ir; 5, 3570 cm^{-1}; 6, 3620 cm^{-1} (10^{-3} mol in CCl_4)]. The new 3,6-epoxide 7 was correlated with the known 3,7-epoxide 3[1] by conversion of both 3 and 7 into the identical cyclooctenol 4. The ether 3 was hydrogenolyzed by treatment with $EtNH_2$/Li at -20°C to give 43% of 4,[5] $C_{15}H_{26}O$ [ir 3480 cm^{-1}; nmr δ 1.03, 1.09, 1.15 (each 3H, s), 1.78 (3H, s), 5.57 (1H, t, J=8); m/e 222 (M^+)] and 32% of 8 [ir 3360 cm^{-1}; nmr δ 1.00 (3H, s), 1.02 (3H, d, J=7), 1.07, 1.12 (each 3H, s), 5.30 (1H, dd, J=9,11), 5.70 (1H, dd, J=6,11). On the other hand 7 afforded 4 in 90% yield on treatment under the similar conditions. The alcohol 6 yielded 7 (90%) on bromination (PBr_3/ether/0°C) followed by debromination (^{t}AmONa/DMSO/80°C/3 hr). Thus cyclooctenol 4, which is an equivalent to an assumed precursory cation 9[6], can be prepared in a 37% total yield from humulene through the treatment with $Hg(NO_3)_2$.[7]

On treatment with BF_3-OEt_2/Ac_2O at rt, ether 2 afforded two compounds 11 (20%) and 12b (30%). 11: nmr δ 0.98, 1.00, 1.04 (each 3H, s), 1.56 (3H, t, J=2), 2.60 (1H, tt, J=2,8), 5.10 (1H, t, J=2). 12b: nmr δ 0.84 (3H, s), 0.95 (6H, s), 1.08 (3H, s), 2.01 (3H, s), 4.50 (1H, s); ir 1750 cm^{-1}. Acetate 12b was readily identified by leading it to the previously described alcohol 12.[2] The structure of tricycloundecene 11 was clarified by examining the nmr spectrum of the corresponding ketone 14, obtained from 11 through hydroboration-oxidation. 14: nmr δ 0.94 (3H, d, J=7), 1.10 (3H, s), 1.05 (6H, s), ir: 1745 cm^{-1}; m/e 220 (M^+). In the presence of $Eu(fod)_3$ (0.43 mmol/1 mmol of 14), the spectrum [1.83, 1.92, 2.78 (each 3H, s), 4.16, 4.38 (2H, ABq, J=11), 5.07 (3H, d, J=7), 6.38 (1H, dd, J=8,13), 9.09 (1H, t, J=8), 9.37 (1H, q, J=7)] indicated the presence of the following partial structures in 14. Since the carbonyl group is contained in a five membered ring (ir), structure 14 was assigned for the ketone.



$$■\text{—}CH_2\text{—}\underset{\underset{■}{|}}{CH}\text{—}CO\text{—}\underset{\underset{CH_3}{|}}{CH}\text{—}■$$

■—CH_2—■ ■—CH_3 CH_3—■—CH_3

(The sign ■ means a quarternary carbon atom.)

There are two conceivable routes (A and B, Fig 3) for the formation of 12b from 2. The former proceeds through the protoilludyl cation 10 and the latter involves an isomeric cation 16. For the purpose of determining the reaction path, the previously described 5,6,13-trideuterio-ether 2d[1] was subjected to the same treatment. The trideuterated product 12bd (m/e 267) exhibited a singlet 1H peak due to the C-6 proton at δ 4.50. This means that initial cleavage of the C-O bond occurred at C-3 to yield deuterated 18 and the reaction proceeded successively through $15d_3$ and the cation 16d. The C-6 proton should not have been observed if the reaction had taken the path B. Similarly, tricycloundecene 11 was considered to arise through 19, by double 1,2 shift.

Formolysis of 4 (HCO_2H, Ac_2O/rt) gave seemingly similar results. The products consisted of 12a (66%) and 13[8] (26%), which have been obtained on the practically same treatment of

7-hydroxyprotoilludanes[2] corresponding to the protoilludyl cation 10.[2] Therefore both the products 12a and 13 were supposedly derived through 10 in the present formolysis also. Possible reaction paths (A and B, Fig 5) were examined here again by the use of the deuterated ether 4d, which was synthesized from 20[1] through the following 4 steps (Fig 4). 21: nmr δ 0.98, 1.10 (each 3H, s), 1.13 (6H, s); ir, 3400, 2200 cm^{-1}; m/e 239 (M$^+$). 22: nmr δ 0.98, 1.03, 1.13, 1.64 (each 3H, s); ir 2220, 1058 cm^{-1}; m/e 257 (M$^+$). 7d: nmr δ 0.98, 1.05, 1.17 (each 3H, s), 4.60 (2H, m); ir 3080, 2200, 1640, 1090, 1060 cm^{-1}; m/e 221 (M$^+$). 4d: nmr δ 1.03, 1.08, 1.15, 1.79 (each 3H, s); ir 3480, 2230 cm^{-1}; m/e 205 (M$^+$-18). As expected, the monodeuterio product 12ad exhibited no signal in the low field region below δ 3.0 in its nmr spectrum.[10] Therefore, intervention of the protoilludyl cation 10 in the formolysis of 4 was clearly demonstrated. However, at present no protoilludyl derivatives are isolated from the reaction mixture. Capture of the cation 10 by means of a suitable nucleophile is now under investigation.

References and Notes

1) S. Misumi, Y. Ohfune, A. Furusaki, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 2865 (1976).
2) Y. Ohfune, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 2869 (1976).
3) Description of molecular formula shows that satisfactory elementary analitical data were obtained.
4) All nmr spectra were taken in CCl$_4$ solution and ir spectra were measured as liquid film.
5) The cis configuration of the double bond was demonstrated by comparison of nmr spectra in the presence of Eu^{3+} of 4 and its 13-nor-compound. The spectrum of the latter exhibits J_{6-7}=11 Hz and similar J and S values to those of 4 (unpublished observation in this laboratory).
6) G. A. Cordell, Chem. Rev. 76, 425 (1976) and references cited therein.
7) Although the formation of 4 from 3 is meaningful as evidence for the structure of 7, the reaction is less suitable as a preparative method for 4.
8) This compound is possibly a biosynthetic precursor of recently isolated[9] pentalenolactone G.
9) H. Seto, T. Sasaki, H. Yonehara, J. Uzawa, Tetrahedron Lett., 923 (1978).
10) The mechanism of the formation of 13 from the cation 10 has been discussed in ref. 2.

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