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# BIOGENETIC-LIKE CONVERSION OF $\Delta^{7(8)}$-PROTOILLUDENE TO HIRSUTENE

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Hirsutene[1] A is one of the illudoid[2] sesquiterpenes and is supposed[1] to be a biogenetic precursor of the antitumoric substance coriolin[3]. Previously, we reported[4] a synthesis of hirsutene along the line of the assumed biosynthetic route (Fig. I), through a rearrangement of a chemically synthesized alcohol corresponding to B. We now wish to describe transformation of $\Delta^{7(13)}$-protoilludene 1[2] into hirsutene through a process which involves the hitherto unknown biogenetic type triple skeletal rearrangement (Fig. I) as the key step.

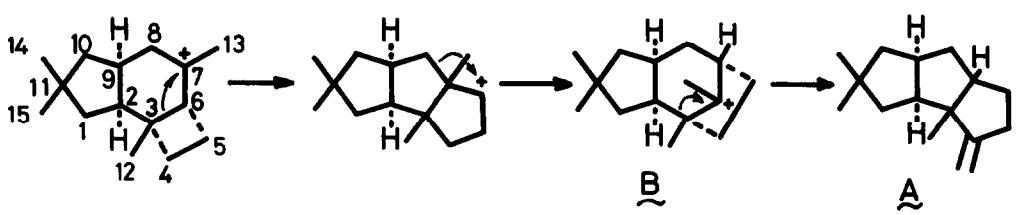
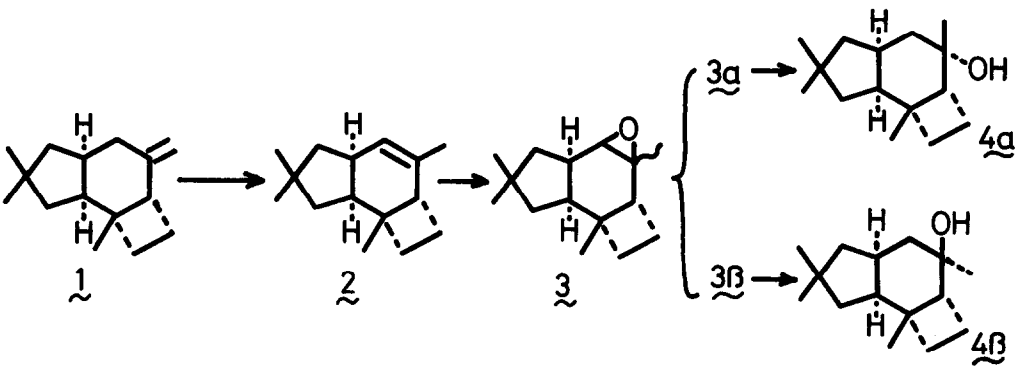



Fig. I

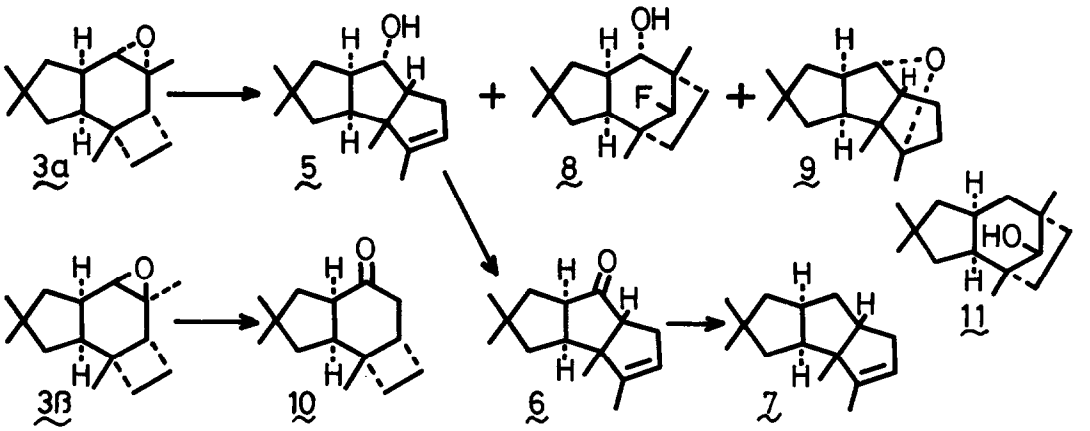
Treatment of $\Delta^{7(13)}$-protoilludene 1 with 0.1 eq. $I_2$ in refluxing toluene (6hr) gave $\Delta^{7(8)}$-protoilludene 2[5] in 93% yield [$\delta(CCl_4)$ 0.98 (6H,s), 1.17 (3H, s), 1.58 (3H, broad s), 5.08 (1H,m), m/e 204 ($M^+$)]. Epoxidation of 2 with m-CPBA in $CH_2Cl_2$, at 0° (1.5hr) afforded a mixture ($\alpha/\beta$=1/1) of 7,8-protoilludene oxides 3[5] (98%), which was separated by preparative tlc (Hex-$CHCl_3$, 1:4) to 3α[5] [$\delta(CCl_4)$ 0.97 (3H,s), 1.09 (6H,s), 1.19 (3H,s), 2.75 (1H,d,J=1.5Hz), m/e 220 ($M^+$) and 3β[5] [$\delta(CCl_4)$ 1.02 (6H,s), 1.13 (3H,s), 1.22 (3H,s), 2.56 (1H,s), m/e 220

($M^+$)]. Stereochemistry of 3α and 3β was determined by reduction of the each isomer with LAH in THF (16hr, 0°) to the known 7α- and 7β-protoilludanols (4α and 4β)[2] in ca. 80% yield, respectively.




The rearrangement of 3 (isomeric mixture) was accomplished by treatment with a catalytic amount of $BF_3$-etherate in dry hexane (0°, 20min) to give compounds 5[5] (7.1%), 8[5] (11.3%), 9[5] (31.4%), and 10[5] (30.2%). On the other hand, treatment of 3β under the similar conditions afforded only 10 as a single isolable product (30%).

endo-Hirsuten-8α-ol (5) : m.p. 36°~37°; δ($CCl_4$) 0.96, 1.02, 1.10 (each 3H, s), 1.75 (3H, broad s), 3.77 (1H,d-d,J=7.5Hz), 5.3 (1H,m) ; m/e 220 ($M^+$). The 8α configuration was assigned because 5 was produced from 3, but not from 3β. Oxidation of 5 with Jones reagent afforded a cyclopentanone 6[5] (84.7%) [δ($CCl_4$) 0.98, 1.05, 1.22 (each 3H,s), 1.72 (3H, broad s), 5.22 (1H,m), ν(neat) 1740 $cm^{-1}$]. Treatment of the tosylhydrazone derived from 6 with $NaBH_3CN$ and a catalytic



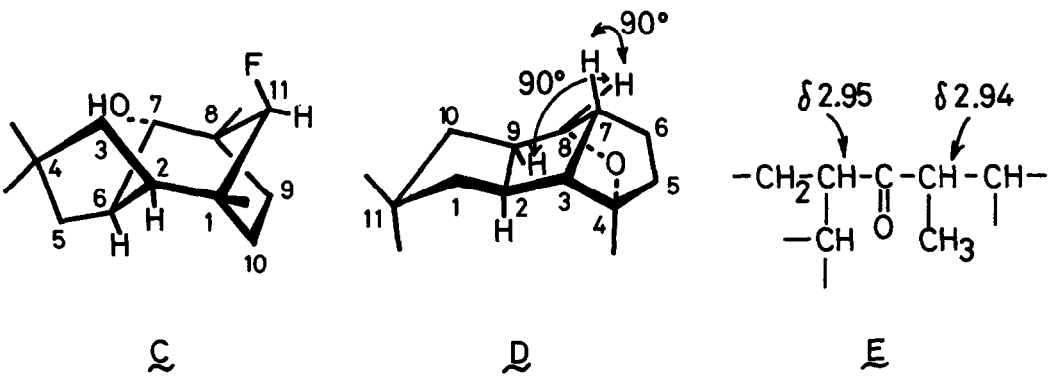
amount of p-TsOH in DMF/sulfolane (1/1) at 110° (4hr)[6] afforded endo-hirsutene 7, identical in all respects with the authentic sample[4]. Since endo-hirsutene has been already converted to the natural hirsutene[2], the present experiment means the first in vitro conversion of protoilludene to hirsutene.

cis-anti-cis-11β-Fluoro-1,4,4,8-tetramethyltricyclo[6.2.1.$0^{2,6}$]-undecan-7α-ol (8) : m.p. 105°~107°; δ($CDCl_3$) 0.98 (3H,s), 1.10 (6H,s), 1.12 (3H,s), 3.56 (1H,d,J=10.5Hz), 4.16 (1H,d,J=53Hz). The nmr spectrum in the presence of $Eu^{3+}$ [$Eu(fod)_3$/8=0.30, $CDCl_3$] exhibited peaks at the following positions : δ1.41 (3H, s,4β-$CH_3$), 1.86 (3H,s,4α-$CH_3$), 2.70 (3H,s,1-$CH_3$), 3.00 (1H,d-d,$J_{3\alpha-3\beta}$=6Hz, $J_{2\alpha-3\beta}$=11.5Hz, 3β-H), 3.68 (1H,m,10β-H), 4.40 (1H,d-d,$J_{2\alpha-3\alpha}$=11.5Hz, $J_{3\alpha-3\beta}$=6Hz, 3α-H), 4.41 (1H,m,10α-H), 4.73 (1H,m,9β-H), 5.00 (1H,d-t,$J_{2\alpha-6\alpha}$=7Hz, $J_{2\alpha-3\alpha,\beta}$=11.5 Hz, 2α-H), 5.26 (1H,d-d,$J_{5\beta-6\alpha}$=6.5Hz, $J_{5\alpha-5\beta}$=13.5Hz, 5β-H), 6.76 (1H,d,$J_{11\alpha-F}$= 53Hz, 11α-H), 7.92 (S[7]=20.8, 1H,d-d,$J_{5\alpha-5\beta}$=13.5Hz, $J_{5\alpha-6\alpha}$=3.5Hz, 5α-H), 8.33 (S =22.8, 1H,m, 9α-H), 10.83 (S=29.9, 1H,d-d-d-d,$J_{2\alpha-6\alpha}$=7Hz, $J_{6\alpha-7\beta}$=9.5Hz, $J_{5\alpha-6\alpha}$= 3.5Hz, $J_{5\beta-6\alpha}$=6.5Hz, 6α-H), 17.18 (1H,d,$J_{6\alpha-7\beta}$=9.5Hz, 7β-H). These data are in conformity with stereostructure C (Fig. II).

4α-8α-Epoxyhirsutane (9) : δ($CCl_4$) 0.94, 1.07, 1.18 (each 3H,s), 2.71 (3H, m), 3.40 (1H,s) ; m/e 220 ($M^+$). No hydroxyl band in the ir spectrum. The stereostructure and conformation of 9 were revealed by nmr studies. Relatively large lanthanide induced shifts of signals due to 2α-H (S=7.38), 9α-H (S=7.38), 5α-H (S=8.87), 6α-H (S=10.1) and upfield induced shift[8] of the 11α-$CH_3$ peak (S=-0.8) as well as the singlet nature of the 8β-H signal indicated conformation D (Fig. II).

8-Ketoprotoilludane (10) : The double resonance nmr and ir spectra of 10 [δ($CCl_4$) 0.82 (3H,d,J=7Hz), 0.98, 1.09, 1.20 (each 3H,s), 2.94 (1H,quint,J=7Hz), 2.95 (1H,d-t,J=7.5, 8Hz), ν(neat) 1710 $cm^{-1}$] showed the presence of partial structure E (Fig. II) and accordingly structure 10 for this compound. Comparison of the nmr spectrum in the presence of $Eu(fod)_3$ with that of 8-keto-13-norprotoilludene[2] indicates that the two compounds have an almost identical conformation and the $J_{6\beta-7\alpha}$ value (7Hz) of the both compounds shows the 7-$CH_3$ group of 10 to have the β configuration[9].

It should be noted that attempted direct in vitro conversion of unsubstituted protoilludyl cation equivalents (7-protoilludanols) to hirsutene has been hitherto unsuccesfull[10], giving rise to alcohol 11. However, it became clear through the present investigation that the conversion is possible, if a suitably modified, substituted substrate is used.




C D E

Fig. II

References and Footnotes

1) S. Nozoe, J. Furukawa, U. Sankawa and S. Shibata, Tetrahedron Lett., 195 (1976).

2) Y. Ohfune, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 4377 (1975).

3) H. Nakamura, T. Takita and H. Umezawa, J. Antibiotics, 27, 301 (1974).

4) Y. Ohfune, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 2795 (1976).

5) Satisfactory analytical and spectral data were obtained for this compound.

6) R. O. Hutchins, B. E. Maryanoff and C. A. Milewski, J. Amer. Chem. Soc., 93, 1793 (1971); ibid., 95, 3662 (1973).

7) A. F. Cockerill and D. M. Rackham, Tetrahedron Lett., 5149 (1970).

8) B. L. Shapiro, J. R. Hlubucek and G. R. Sullivan, J. Amer. Chem. Soc., 93, 3281 (1971).

9) 8-Keto-13-norprotoilludane exhibits $J_{6\beta-7\alpha}$=7Hz and $J_{6\beta-7\beta}$=2Hz.

10) Y. Ohfune, H. Shirahama and T. Matsumoto, Tetrahedron Lett., 2869 (1976).