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BIOGENETIC-LIKE SYNTHESIS OF d,l-HIRSUTENE

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Hirsutene is a tricyclic sesquiterpene hydrocarbon isolated from Coriolus consors and its structure was determined as shown in formula 10[1]. The biosynthetic pathway[2] to hirsutene* has been suggested to involve a sequence of rearrangements depicted in Scheme I. We now wish to describe a chemical synthesis of hirsutene along the proposed biosynthetic route, starting from the previously described 7-keto-13-norprotoilludane 1[3].

The keto compound 1 was stereoselectively reduced to 7β-alcohol 2[4] with $NaBH_4$ in EtOH (0°, 2hr, 100%). 2[5,6]; nmr(CCl_4) δ0.99, 1.06, 1.16 (each 3H, s), 3.72 (1H, d.d.d., J=4, 7, 11Hz). On treatment with 1 eq. p-TsOH in benzene (80°, 2hr), 2 afforded a mixture of endo-alcohol 3 and its tosylate 4 (40% and 30% respectively). 3[5,6]; nmr(CCl_4) δ0.91, 1.01, 1.08 (each 3H, s), 3.52 (1H, d, J=5Hz). 4[6]; (m.p 140°~ 142°). The tosylate 4 was reduced to 3 with $LiAlH_4$ in THF (97%, r.t, 15hr). The endo configuration of the hydroxy group of 3 was assigned by the fact that the corresponding ketone 5, obtained by the Jones oxidation of 3 (95%), was reduced quantitatively to the original alcohol 3 with $NaBH_4$ in EtOH (0°, 2hr)[7]. 5[5,6]; nmr(CCl_4) δ0.90, 0.98, 1.10 (each 3H, s); ir(neat) 1750cm^{-1}. Methylenation (r.t, 2hr, ph_3PCH_3Br-^tAmONa-benzene) of 5 yielded exomethylene compound 6 (92%), a protohirsutyl cation equivalent. 6[5,6]; nmr(CCl_4) δ0.96 (6H, s), 1.06 (3H, s), 4.38, 4.72 (each 1H, broad s). Acid-catalyzed rearrangement of 6 to the hirsutane skeleton was accomplished by treatment with a catalytic amount of p-TsOH in benzene (80°, 20min); an endo isomer 7[5,6] of hirsutene was produced in 95% yield. 7; nmr(CCl_4) δ0.96, 0.97, 1.08 (each 3H, s), 1.60 (3H, broad s), 5.01 (1H, broad t, J=2.5Hz); mass 204 (M^+), 94 (base peak). Epoxydation of 7 (r.t, 30min, m-CPBA-CH_2Cl_2, 98%) afforded endo-epoxide 8[5,6], nmr(CCl_4) δ0.95, 0.98, 1.07, 1.26 (each 3H, s), 3.11 (2H, broad s), which was reduced to tertiary alcohol 9 with $LiAlH_4$ in THF.

9[5,6]; m.p 49° 50°; nmr(CCl_4) δ0.90, 0.94, 1.05, 1.13 (each 3H, s). Dehydration of 9 (MsCl-Py, 35°, 16hr) gave rise to an isomeric mixture consisting of the starting compound 7 and the desired d,l-hirsutene 10, in the ratio of 7 to 1, in 70% yield. The mixture was carefully separated by 10% $AgNO_3$-silica gel chromatography (n-hexane) to give pure 10; the hydrocarbon 10 showed completely *identical vpc, mass and nmr data with those of natural hirsutene.* 10; *nmr*(CCl_4) δ0.92 (6H, s), 1.05 (3H, s), 4.72 (2H, m); ir(neat) 1655, 878 cm^{-1}; mass 204 (M^+), 94 (base peak). Since the cis-anti-cis stereochemistry of 1 has been established[3], the present synthesis confirms the proposed cis-anti-cis skeleton of hirsutene.

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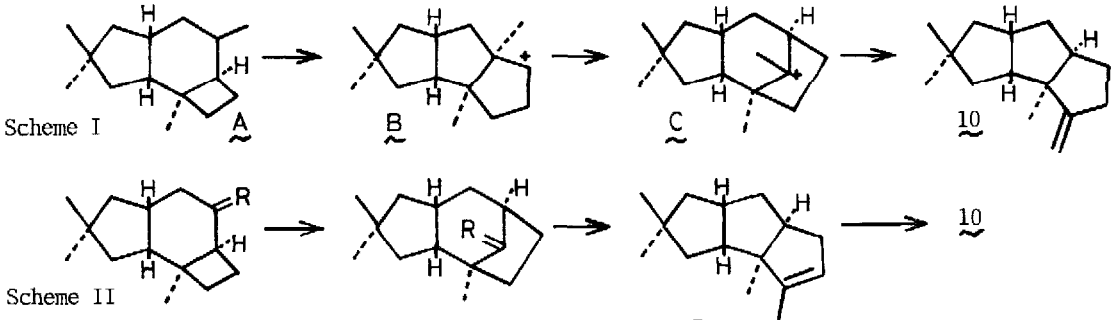

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