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SYNTHESES OF 7α- AND 7β-PROTOILLUDANOL, AND 7(13)-PROTOILLUDENE, POSSIBLE BIOGENETIC INTERMEDIATES FOR ILLUDOID* SESQUITERPENES

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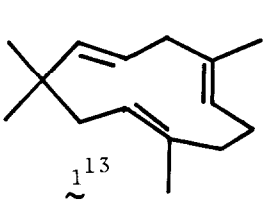
Several groups suggested[1] that the cis-anti-cis protoilludanyl cation 2 was a key intermediate in the conversion of humulene into illudoids*. Recent studies on the biosynthesis[2,3] of illudins using labeled mevalonate showed the labeling pattern was in accord with this hypothesis. However, no direct evidence for the intermediacy of 2 has yet been obtained. We now wish to describe stereocontrolled syntheses of equivalents of the cation 2, cis-anti-cis 7α-protoilludanol 4, its 7β-isomer 6 and their anhydro compound 5[4], which seem to be of interest in both biogenetic and synthetic aspects.

Photochemical cycloaddition of cis-bicyclo[3.3.0]octenone 7[5] and ethylene in n-hexane (6hr, 0°, 300W high pressure Hg lamp) gave stereoselectively the cis-anti-cis cycloadduct 8[6,7] [75%; ir(neat) 1734cm^{-1}; nmr(CCl_4) δ0.82 (1H, t, J=12Hz), 0.98, 1.05, 1.24 (each 3H, s)] and the cis-syn-cis isomer 13[6] [8%; ir (neat) 1736cm^{-1}; nmr(CCl_4) δ1.01, 1.15, 1.32 (each 3H, s)]. The cis-anti-cis cycloadduct 8 was then converted to an exomethylene compound 9[6,7] (1hr, 80°, ph_3PCH_3Br-^{t}AmONa-benzene), [92%; ir(neat) 3080, 1650, 878cm^{-1}; nmr(CCl_4) δ0.93 (1H, t, J=12Hz), 0.96, 1.04, 1.14 (each 3H, s), 3.30 (1H, broad m), 4.70 (2H, m)]. Ring enlargement of 9 was achieved by $Tl(ClO_4)_3$-^{t}BuOH-H_2O (24hr, r.t, ^{t}BuOH/H_2O = 1/3) to give rise to the desired 7-keto (13)-norprotoilludane 3[6] [57%; ir (neat) 1705cm^{-1}; nmr(CCl_4) δ0.99, 1.09, 1.24 (each 3H, s)] together with unde-

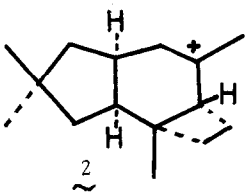
sired 8-keto (13)-norprotoilludane 14[6] [19%; ir(neat) 1709cm^{-1}; nmr(CCl_4) δ0.97, 1.07, 1.18 (each 3H, s)]. On treatment with alumina/benzene (r.t) or NaOMe/MeOH (r.t), 14 gave an equilibrium mixture of two epimers (14/15 = 67/33 by nmr), while 3 was recovered completely unchanged. The both compounds 14 and 3 incorporated three D atoms [209 (M^+)] by NaOMe/MeOD (r.t). The LIS nmr spectrum of 3 [$Eu(fod)_3$ (18mg) and the sample (11mg) in 0.4ml of CCl_4] exhibited peaks[9] at δ 1.62 (S^{10} = 2.38, 3H, s, 14- or 15-Me), 1.68 (S = 2.50, 3H, s, 14- or 15-Me), 2.64 (S = 4.25, 3H, s, 12Me), 2.66 (1H, q, $J_{10\alpha-10\beta}$= 14Hz, $J_{9-10\alpha}$= 6Hz, 10αH), 2.82 (1H, q, $J_{1\alpha-1\beta}$ =13Hz, $J_{1\alpha-2}$= 7Hz, 1αH), 3.05 (1H, q, $J_{10\alpha-10\beta}$= 14Hz, $J_{9-10\beta}$ = 4Hz, 10βH), 3.15 (1H, m, 4βH), 3.46 (1H, t, $J_{1\alpha-1\beta}$= $J_{1\beta-2}$= 13Hz, 1βH), 3.77 (1H, m, 2-H), 4.55 (2H, m, 4α and 5βH), 5.30 (1H, m, 9-H), 6.45 (S = 15.0, 1H, m, 5αH), 7.75 (S = 19.3, 1H, q, $J_{8\alpha-8\beta}$= 15Hz, $J_{8\beta-9}$= 9Hz, 8βH), 8.36 (S = 20.8, 1H, q, $J_{5\alpha-6}$= 1Hz, $J_{5\beta-6}$= 4Hz, 6-H), and 8.70 (S = 20.9, 1H, q, $J_{8\alpha-8\beta}$= 15Hz, $J_{8\alpha-9}$= 7Hz, 8αH). These nmr observations, in particular the large LIS effects on 5α and 6-protons and the large diaxial-like $J_{1\beta-2}$ value, showed 3 to be the 7-keto compound with a probable conformation 16. The compounds 3 and 14 were also obtained from hydroxyazide 12[6,11] by sequential treatment with Zn-AcOH[12] and $NaNO_2$-AcOH (3/14 = 1.5/1; yield of 3 and 14, 50%). Grignard reaction of 3 with MeMgI-dry ether (reflux 4 hr.) gave stereoselectively the desired cis-anti-cis 7α-protoilludanol 4[6] [quantitative; ir(neat) 3550cm^{-1}; nmr(CCl_4) δ0.98, 1.03. 1.035, 1.10 (each 3H, s)]. The LIS spectral data[9] at $Eu(fod)_3$/4 = 0.36 [(CCl_4) δ1.26 (S = 0.83, 3H, s, 14- or 15-Me), 1.72 (S = 1.42, 3H, s, 14- or 15-Me), 2.93 (S = 5.83, 3H, s, 12-Me), 5.42 (1H, m, 2-H), 5.66 (1H, q, $J_{8\alpha-8\beta}$= 14Hz, $J_{8\beta-9}$= 11.5Hz, 8βH), 6.28 (1H, m, 6-H), 7.76 (S = 17.8, 1H, m, 5αH), 7.77 (S = 20.9, 3H, s, 13-Me), 7.95 (S = 19.2, 1H, m, 9-H), 8.50 (S = 19.4, 1H, q, $J_{8\alpha-8\beta}$= 14Hz, $J_{8\alpha-9}$= 5Hz, 8αH)] indicate proximity of C-2- , C-5α- and OH protons and are in conformity with a 7α-axial hydroxyl structure with a conformation[13] similar to 3. Methylenation (1.5 hr, r.t, ph_3PCH_3Br-^{t}AmONa-benzene) of 3 yielded 7(13)-protoilludene 5[6] [85%; ir (neat) 3070, 1645, 886cm^{-1}; nmr(CCl_4) δ0.90, 0.99, 1.13 (each 3H, s), 4.56 (broad s, 2H)] which on oxymercuration-demercuration[14] [r.t, $Hg(OAc)_2$-THF-H_2O and $NaBH_4$] furnished the epimeric 7β-protoilludanol 6[6], [70%; ir(neat) 3500cm^{-1}; nmr δ0.89, 1.01. 1.08, 1.13 (each 3H, s)]. The LIS nmr spectral data[9] at $Eu(fod)_3$/6

= 0.264 [(CCl_4)δ1.05 (S = 0.13, 3H, s, 14- or 15-Me), 1.35 (S = 0.75, 3H, s, 14- or 15-Me), 2.10 (S = 3.61, 3H, s, 12-Me), 4.12 (1H, m, 9-H), 4.75 (S = 16.0, 3H, s, 13-Me), 5.08 (S = 15.3, 2H, broad d, 8α and 8βH), 6.00 (S = 19.3, t, $J_{5\alpha\text{-}6}$ = $J_{5\beta\text{-}6}$= 7Hz, 6-H)] are compatible with the assigned stereochemistry 6[13].

Studies on the biogenetic-like syntheses of illudoids via 4, 5 and 6 are now in progress.



1[13]



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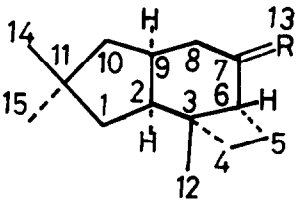

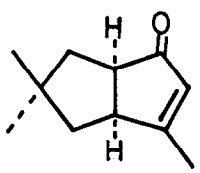

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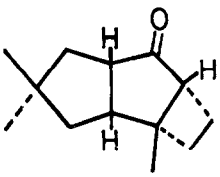

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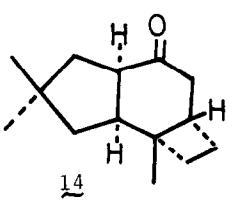
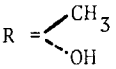


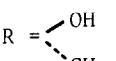
14

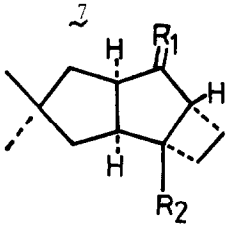
15 C-9 epimer

3 R = O

4 R = 

5 R = CH_2

6 R = 

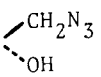


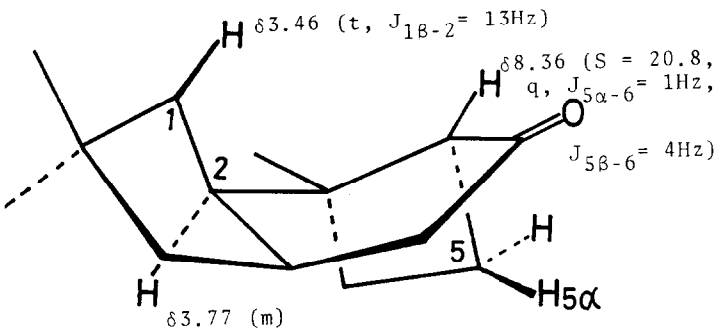
8 R_1 = O R_2 = CH_3

9 R_1 = CH_2 R_2 = CH_3

10 R_1 = O R_2 = CH_2OAc

11 R_1 =  R_2 = CH_3

12 R_1 =  R_2 = CH_3



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REFERENCES AND FOOTNOTES

* A group of sesquiterpenes biogenetically derived from humulene through 2 as an intermediate.

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2. a) M.Anchel, T.C.McMorris and M.Sigh, Phytochemistry, 9, 2339 (1970); b) J. R.Hanson and T.Marten, Chem. Commun., 171 (1973).
3. Recent studies have shown that hirsutic acid is also derived from humulene; a) T.C.Feline and G.Mallows, Chem. Commun., 63 (1974); b) M.Tanabe, K.T. Suzuki and W.C.Jankowski, Tetrahedron Lett., 2271 (1974).
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6. Obtained as an oil. Satisfactory elementary analytical data were obtained.
7. The chemical shifts and J values of Ha (Fig.I) of 8 and 9 suggest for these compounds the conformation shown in the figure, in which axial-like Ha is placed above the C=O (or C=C) bond. A similar conformation has been concluded [5] for 10 on the basis of similar grounds (Ha; δ 0.86, t, J = 12Hz).

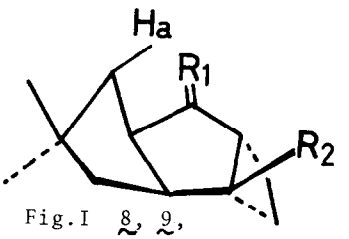

Fig.I 8, 9, 10 R_1 = O R_2 = OAc

8. D.Fărucașiu and P.v.R.Schleyer, J. Org. Chem., 38, 3455 (1973).
9. The assignments were confirmed by decoupling technique. J values were obtained by first order analysis.
10. A.F.Cockerill and D.M.Rackham, Tetrahedron Lett., 5149 (1970).
11. Compound 12 was synthesized from 9 through the following sequence of reactions, 1) OsO_4-Py (quantitatively 11 [6] was obtained.), 2) TsCl-Py, 3) DMF-NaN_3. The stereochemistry of 11 was determined as shown by LIS and decoupling tequniques. Details will be described in a full paper.
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13. Inspection of models suggests that in 16, C-6, 7, 8 and 9 are placed approximately on a plane, while in 4 (and 6) C-3, 6, 7 and 8 are nearly coplanar. A similarity can be seen between the conformation of 4 and that of humulene proposed on the basis of X-ray studies; a) A.T.McPhail and G.A.Sim, J. Chem. Soc., B, 112 (1966); b) P.D.Cradwick and G.A.Sim, Chem. Commun., 431 (1971).
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