CHEMISTRY LETTERS, pp. 387-390, 1975. Published by the Chemical Society of Japan

THE SYNTHESIS OF HYPACRONE, A NOVEL SECO-ILLUDOID SESQUITERPENE FROM HYPOLEPIS PUNCTATA METT.

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The short step synthesis of hypacrone [1] was completed by the condensation of cyclopentenone [4] (C_8 unit) with 1,1-diacetylcyclopropane [6] (C_7 unit), confirming the unique seco-illudane structure of this compound.

Hypacrone is a novel seco-illudoid sesquiterpene isolated from a fern, Hypolepis punctata Mett., as its characteristic acrid principle.1) The structure has been proposed as [1] by the spectral analyses and the facile chemical transformation into pterosins,2)3) the illudoid constituents of the fern. This paper reports the synthesis of hypacrone [1] via the general scheme including the condensation of 3,5,5-trimethylcyclopentenone [4] (C_8 unit) with 1,1-diacetylcyclopropane [6] (C_7 unit).

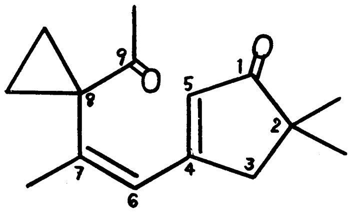
α-Lithio compound, derived from sodium isobutyrate and lithium diisopropylamide in THF,4) was alkylated with β-methallyl chloride to give 2,2,4-trimethyl-4-pentenoic acid [3] in 76 % yield; ν_{max}^{neat} 3300-2600, 1700, 1650 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 1.20 (6H,s), 1.70 (3H,br s), 2.30 (2H,s), 4.63 (1H,m), 4.73 (1H,m), 12.15 (1H,br). The acid [3] was transformed to a cyclopentenone derivative by the treatment of its acid chloride [$(COCl)_2$ in benzene] with aluminum chloride (1.3 mol eq.) in carbon disulfide at 47°C for 6 hrs. Single distillation (bp. 98-100°/40 mmHg) of the crude product gave pure 3,5,5-trimethylcyclopent-2-enone [4] as a colorless liquid in 60 % yield; ν_{max}^{neat} 3080, 1700, 1620 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 1.04 (6H,s), 2.08 (3H, br s), 2.36 (2H,br s), 5.72 (1H,br s). The successful result in the condensation of [4] with 1,1-diacetylcyclopropane [6], prepared from acetylacetone and $Hg(OAc)_2$ adduct of ethylene,5) was obtained, after several fruitless attempts, by an analogous procedure to that reported by Mukaiyama et al.6) The enone [4] was converted into a dienol trimethylsilyl ether [5] [$LiN(i\text{-}Pr)_2$ in hexane at -78°C, then $(CH_3)_3SiCl$], which was used for the following reaction without isolation.7) To the cooled reaction mixture prepared above, were successively added a methylene chloride solution of 1,1-diacetylcyclopropane [6] (1 mol eq.) and that of excess titanium tetrachloride (2 mol eq.). After 3 hrs at this temperature, the mixture was decomposed with water and extracted with ether. The desired diketo carbinol [7] was separated by SiO_2 column chromatography in 30 % yield as a colorless syrup; $\nu_{max}^{CCl_4}$

3400, 3040, 1700, 1685, 1615 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 1.00 (6H,s), 1.00-1.20 (4H,complex), 1.18 (3H, s), 1.77 (3H, s), 2.48 (2H, s), 2.68, 2.84 (each 1H, d,J=14), 3.65 (1H, br; disappeared by D_2O addition), 5.68 (1H,s), m/e 240 (M^+), 232 (M^+-H_2O), λ_{max}^{EtOH} 235 nm. Dehydration of [7] was performed by vapor phase pyrolysis at 190°C (by passing through a vpc column) to give in 60 % yield a dienone [8]; $\nu_{max}^{CCl_4}$ 1700, 1630, 1590 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 0.92 (2H,m), 1.08 (6H,s), 1.32 (2H,m), 2.06 (6H,s), 2.56 (2H,s), 5.82 (1H,br s), 6.12 (1H,br s), m/e 232 (M^+), 217 (M^+-CH_3), 204 ($M^+-C_2H_4$), 189 (M^+-CH_3CO), λ_{max}^{EtOH} 284 nm (log ε = 4.18). All of the nmr signals of [8] were corresponding to those of natural hypacrone [1] except for some deviation in their chemical shift values.[8] Since the "cis" configuration has been assigned to the C_6-C_7 double bond of natural hypacrone [1] from its capability of conversion into pterosin-Z [2] by acid treatment,[2] the compound [8] should be in the "trans" orientation. In fact, the latter was unaffected under the same conditions as those used for the conversion of hypacrone [1] (2N-H_2SO_4, 90°C, 3 hrs).

The isomerization (trans to cis) of the double bond in trans-hypacrone [8] was achieved by irradiation in methanol in the presence of 2-acetonaphthone as sensitizer (0°C, 450-W Ushio high pressure mercury lamp, pyrex filter). After irradiation for one hour, the nmr spectrum of [8] became overlapped with that of natural hypacrone [1].[9] The photo-equilibration between both compounds was completed without any side reaction after 3 hrs, when the ratio of [8] to [1] was approximately 1 : 1. This ratio was also obtained from equilibration of natural hypacrone [1] under the same irradiation conditions.

trans-Hypacrone [8] was reduced with lithium aluminum hydride in ether to give dienediol [9] in quantitative yield, ν_{max}^{neat} 3340, 3040 cm^{-1}, $\delta_{ppm}^{CD_3OD}$ 0.4-0.65 (4H, m), 1.00 (3H,s), 1.02 (3H,s), 1.10 (3H,d,J=6), 1.91 (3H, s), 2.24 (1H,br), 2.34 (1H,br), 3.40 (1H,q,J=6), 4.10 (1H,br), 5.44 (1H,br), 5.82 (1H,br), λ_{max}^{EtOH} 249 nm. Irradiation of [9] in methanol (the same condition as described above) also caused trans-cis isomerization of the corresponding double bond. However, the subsequent internal cyclization immediately follows in this case, to give a tricyclic spiro ether [10]. This transformation was rapid (finished within 15 min., monitored by nmr) and almost quantitative (single spot on tlc). The nmr spectra (in CCl_4 and benzene-d_6) showed that the photo-product [10] was a mixture of two diastereoisomers in the approximately 1:1 ratio, $\nu_{max}^{CCl_4}$ 3080, 1100 cm^{-1}, m/e 218 (M^+). The nmr spectra of both components, [10a] and [10b], were given as follows; [10a] $\delta_{ppm}^{C_6D_6}$ 0.86 (3H,d,J=6), 1.05 (3H,s), 1.16 (3H,s), 1.32 (3H,d,J=1.5), 1.72, 1.90 (each 1H,d,J=14), 3.92 (1H,q,J=6), 5.33 (1H,br s), 5.41, 5.59 (each 1H,d,J=5.5), [10b] $\delta_{ppm}^{C_6D_6}$ 0.88 (3H,d,J=6), 1.05 (3H,s), 1.16 (3H,s), 1.32 (3H,d,J=1.5) 1.80, 1.99 (each 1H,d,J=14), 3.92 (1H,q,J=6), 5.33 (1H,br s), 5.52, 5.66 (each 1H, d,J=5.5).

The isolation of the synthetic hypacrone and the stereochemical studies of the isomeric tricyclic ethers, [10a] and [10b], are in progress.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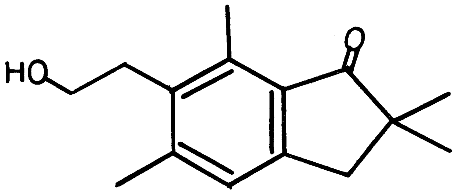
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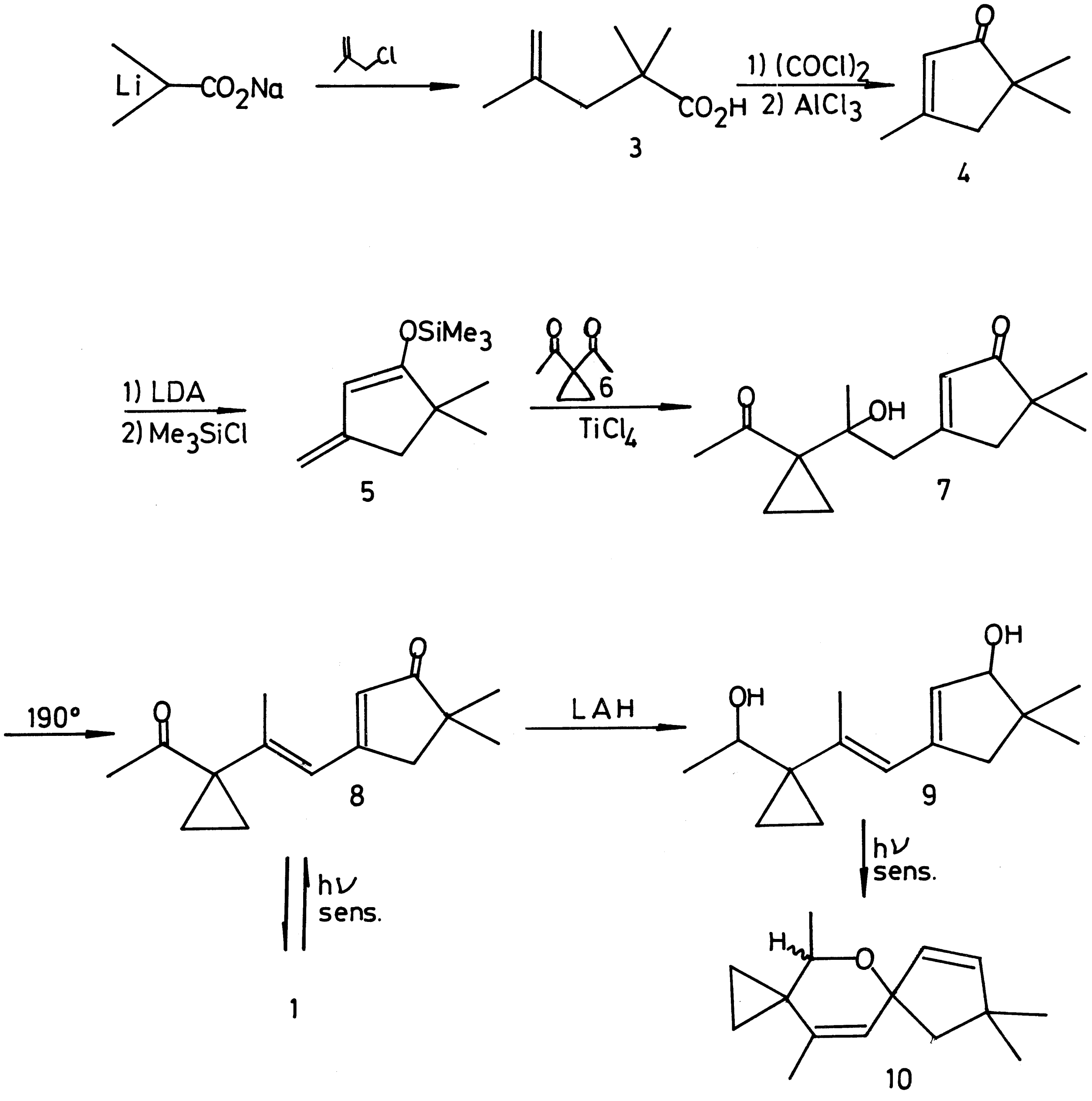
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TiCl₄
OH
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190°
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LAH
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7. The dienol silyl ether [5] could be isolated by the usual treatment of the reaction mixture, and was characterized by the following spectral data; ν_{max}^{neat} 3080, 1630, 1605 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 0.23 (9H,s), 1.03 (6H,s), 4.10 (1H,m), 4.22 (1H,m), 4.94 (1H,br s). However, its susceptibility to hydrolysis during the working up, even under neutral condition, lowered markedly the isolation yield (only 15 %).
8. The spectral data of natural hypacrone [1] were as follows$^{1)}$; ν_{max}^{neat} 1695, 1625, 1590 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 0.94 (2H,m), 1.04 (6H,s), 1.50 (2H,m), 2.06 (3H ,d,J=1.3), 2.11 (3H,s), 2.49 (2H,d,J=1.5), 5.82 (1H,br s), 6.22 (1H,br s), m/e 232 (M^+), 217 (M^+-CH_3), 204 ($M^+-C_2H_4$), 189 (M^+-CH_3CO), λ_{max}^{EtOH} 285 nm (log ε = 4.26).
9. The nmr spectra were determined in three different solvents : methanol-d_4, carbon tetrachloride and benzene-d_6. The signals of both isomers were identified separately by comparison with the spectra of pure components in all solvents.

(Received February 17, 1975)