Synthesis of Hypacrone

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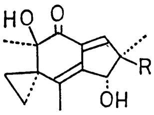
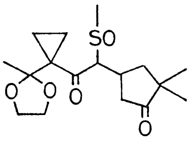
Synopsis. Hypacrone, an illudoid sesquiterpene, was synthesized from 2,2-dimethyl-4-(3,3-ethano-4,4-ethylenedioxy-1-methylsulfinyl-2-oxopentyl)-1-cyclopentanone which is a key intermediate also in the synthesis of illudins.

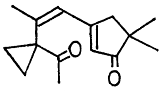
Reports were given on the total synthesis of illudins (**1**)[1)] employing a sulfoxide **2**[2)] as the key intermediate. In this report, we wish to describe the synthesis of another illudoid[3)] sesquiterpene, hypacrone (**3**),[4)] with use of **2**.



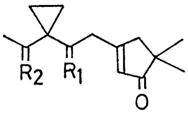
(1) illudin M R=CH_3
illudin S R=CH_2OH



(2)



(3)



(4) R_1= O, R_2= $<^{O}_{O}]$

(5) R_1= $<^{OH}_{CH_3}$, R_2= $<^{O}_{O}]$

(6) R_1= $<^{OH}_{CH_3}$, R_2= O

Elimination of sulfenic acid was carried out by boiling sulfoxide **2** in toluene for 5 h, diketone **4** being obtained in quantitative yield. Methylation of easily enolizable diketone **4**[5)] by means of methyllithium gave **5** which upon deacetalization with a catalytic amount of *p*-toluenesulfonic acid in acetone gave diketone **6**. The spectral data of **6** (IR and NMR) are identical with those of an authentic sample.[4b)] The total synthesis of hypacrone (**3**) through **6** was already reported by Nishizawa *et al.*[4b)]

Experimental

IR spectra were recorded with a Hitachi EPI-G3 spectrometer. NMR spectra were obtained at 100 MHz on a JEOL JNM-4H-100 instrument using TMS as an internal standard, mass spectra on a JEOL JMS-01SG-2 mass spectrometer.

*Diketone **4**.* Sulfoxide **2**(200 mg) was boiled in toluene for 5 h. The resulting reaction mixture was washed with $NaHCO_3$ and then with a NaCl solution, and dried over Na_2SO_4. Removal of the solvent gave a practically pure product **4**(160 mg) which on chromatography on silica gel gave pure **4**(140 mg, 86%) as a slightly yellow oil: IR (neat) 3070, 1700, 1615 and 1045 cm^{-1}; NMR $\delta(CDCl_3)$ 1.10 (6H s and 4H, m), 1.15 (3H, s), 2.50 (2H, bs), 3.73 (2H, bs), 3.95 (4H, m), and 5.95 (1H, bs); MS (*m/e*) 278 (M^+); Anal. Found: C, 69.35; H, 7.82, Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.94%.

*Enone **5**.* To a solution of **4**(180 mg) in dry ether (10 ml) was added a 0.8 M ether solution of MeLi (1.2 ml)[6)] at −40 to −30 °C under nitrogen atmosphere. After stirring for 2 h the reaction was quenched with a NH_4Cl solution, extraction being carried out with $CHCl_3$. The extracts were washed with a NaCl solution, dried, and evaporated. The crude material was purified by chromatography on silica gel (AcOEt–benzene) affording unchanged **4** (120 mg, 70%) and methylated product **5** (20 mg, 10%) as a colorless oil: IR(neat) 3450, 1695, 1610, and 1045 cm^{-1}; NMR $\delta(CDCl_3)$ 1.07 (4H, m), 1.10 (6H, s), 1.25 (3H, s), 1.47 (3H, s), 2.52 (2H, bs), 2.75 (2H, bs), 3.95 (4H, bs), and 5.96 (1H, bs); MS(*m/e*) 276 (M^+-H_2O); Anal. Found: C, 69.25; H, 8.72, Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

*Diketone **6**.* A solution of acetal **5** (15 mg) and *p*-TsOH (1 mg) in acetone (2 ml) was refluxed for 2 h and quenched with solid $NaHCO_3$. After filtration, the solution was evaporated. Purification of the crude material was carried out by preparative TLC (silica gel, $CHCl_3$–ether) to give the known diketone **6** as a colorless oil: MS(*m/e*) 250 (M^+).[4b)]

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References

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5) This vinylogous 1,3-diketone was soluble in aqueous alkaline solution, giving methane on treatment with MeMgI.

6) Using a larger amount of MeLi did not improve the yield.