

STEREOSELECTIVE SYNTHESIS OF (±)-EREMOPHIL-3,11-DIENE AND RELATED COMPOUNDS.

COMMENTS ON THE PROPOSED STRUCTURE OF EREMOPHILENE

Edward Piers and Robert J. Keziere

Department of Chemistry, University of British Columbia

Vancouver 8, B.C., Canada

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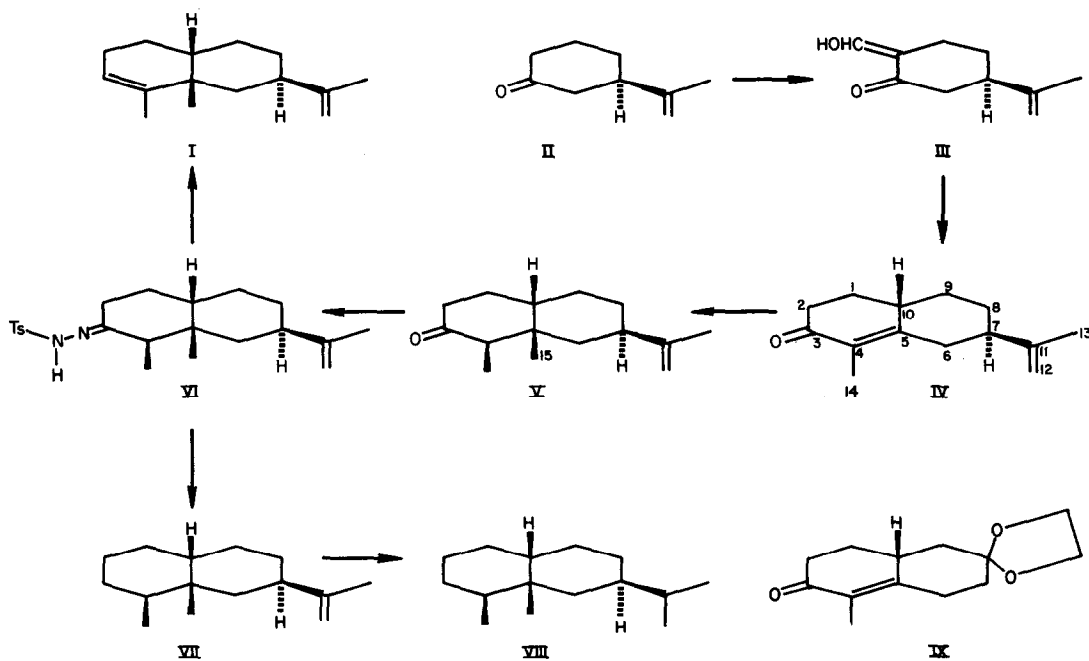
In 1964, Hochmannová and Herout (1) proposed structure I for eremophilene, a sesquiterpene hydrocarbon which had been isolated from Petasites officinalis MOENCH. (2) and from Petasites albus (L.) GAERTN. (3). This compound represents, structurally, one of the simplest members of the biogenetically interesting and steadily growing group of eremophilane-type sesquiterpenes (4). The structural assignment (1) was based upon nuclear magnetic resonance spectra, a fairly extensive chemical degradation, and upon correlation with hydroxydihydroeremophilone, a naturally occurring sesquiterpene of known absolute stereochemistry (5). We wish to report here a stereoselective total synthesis of (±)-I, and to present evidence which invalidates the structural proposal for eremophilene.

Condensation of 3-isopropenylcyclohexanone (II)*(6) with ethyl formate under standard conditions afforded, in good yield, the corresponding hydroxymethylene derivative III**, b.p. 101-102°/4 mm. The latter, upon treatment with 1-diethylamino-3-pentanone methiodide in sodium methoxide-methanol, gave, after deformylation, ring closure and appropriate work-up (7), a 64% yield of the substituted octalone IV, b.p. 127-131°/0.3 mm; UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 249 m μ ($\epsilon = 14,600$); IR (film): 6.00, 6.19, 11.25 μ ; NMR:*** τ 5.26 (unresolved multiplet, = C¹²H₂), 8.22 (poorly resolved quartet, -C¹⁴H₃, $J \approx 1.2$ and 1.8 Hz, homoallylic coupling (8)), 8.25 (triplet, -C¹³H₃, $J = 1.2$ Hz, allylic coupling (9)). The chemical shifts assigned to the vinylic methyl groups (-C¹³H₃ and -C¹⁴H₃) were confirmed

* All formulas represent racemic substances. However, for convenience, only one enantiomer is depicted in each case.

** All new substances described in this communication gave satisfactory analytical data.

*** NMR spectra were taken on either a JEOLCO C-60-H spectrometer or a Varian HA-100 spectrometer, the latter being used for decoupling experiments. Tetramethylsilane was used as the internal standard, and deuteriochloroform was the solvent in all cases.



by a frequency-swept decoupling experiment in which the olefinic protons at C-12 were strongly irradiated, whereupon the triplet at τ 8.25 collapsed to a strong, sharp singlet, while the quartet at τ 8.22 remained unaffected. The octalone IV was further characterized as its crystalline oxime derivative, m.p. 163-165°.

In order to produce the desired, characteristic eremophilane skeleton from octalone IV, it was necessary to introduce stereoselectively an angular methyl group at C-5. In connection with this, it is pertinent to point out that a number of years ago, Ireland and co-workers (10) reported an unsuccessful attempt to introduce, by cuprous bromide-catalyzed 1,4-addition of methyl magnesium bromide, an angular methyl group into octalone IX. Indeed, we have similarly found that treatment of octalone IV with methyl magnesium iodide in the presence of cupric acetate (11), gave virtually none of the desired eremophilane derivative (V). However, the crucial introduction of the angular methyl group was readily accomplished by use of the reagent lithium dimethylcopper (12), which is prepared very simply by reaction of ethereal methyllithium with cuprous iodide (molar ratio 2:1) at 0° under nitrogen. Thus, reaction of octalone IV with an excess of lithium dimethylcopper in ether at 0° and under nitrogen for 2 hours gave, after appropriate work-up, a 77% yield of (\pm)-eremophil-11-en-3-one (V). An analytical sample, isolated by preparative gas-liquid chromatography (g.l.c.), exhibited spectral properties which were in complete agreement with the proposed structure: IR

(film): 5.82, 6.10, 11.27 μ ; NMR: τ 5.33 (unresolved multiplet, $=C^{12}H_2$), 7.17 (quartet, $-C^4H$, $J_{4,14} = 6.7$ Hz), 8.29 (poorly resolved triplet, $-C^{13}H_3$), 9.11 (doublet, $-C^{14}H_3$, $J_{4,14} = 6.7$ Hz), 9.21 (singlet, $-C^{15}H_3$).

The ketone V was converted, by standard procedure, into the corresponding tosylhydrazone VI, m.p. 148-151° (decomp.). Treatment of the latter with sodium borohydride in dioxane (13) afforded, in 73% yield, (\pm)-eremophil-11-ene (VII). An analytically pure sample, obtained by preparative g.l.c., showed the following spectral properties: IR (film): 6.10, 11.28 μ ; NMR: τ 5.38 (unresolved multiplet, $=C^{12}H_2$), 8.32 (poorly resolved triplet, $-C^{13}H_3$), 9.18 (singlet, $-C^{15}H_3$), 9.28 (doublet, $-C^{14}H_3$, $J_{4,14} = 6.5$ Hz).

Hydrogenation of compound VII (ethanol, platinum oxide), gave, in 84% yield, (\pm)-7 β -eremophilane (VIII), which was shown to be identical (IR, NMR, g.l.c. retention time on three different columns) with (+)-7 β -eremophilane (2,14), obtained by literature procedures (15) from hydroxydihydroeremophilone,**** of known absolute configuration (5). This comparison was of critical importance since it showed conclusively that the 1,4-addition of lithium dimethylcopper to octalone IV had, in fact, proceeded to give the desired cis-fused decalone system (V).*****

When the tosylhydrazone VI was heated with sodium ethylene glycolate (Bamford-Stevens reaction) (16), (\pm)-eremophil-3,11-diene (I) was formed in 90% yield. An analytical sample, obtained by preparative g.l.c., was shown to contain a single component on three different g.l.c. columns, and gave the following spectral data: IR (film): 6.10, 11.28 μ ; NMR: τ 4.70 (unresolved multiplet, $-C^3H$), 5.35 (unresolved multiplet, $=C^{12}H_2$), 8.30 (triplet, $-C^{13}H_3$), 8.40 (multiplet, $-C^{14}H_3$), 8.96 (singlet, $-C^{15}H_3$). The chemical shifts assigned to vinylic methyl groups were confirmed by frequency-swept decoupling experiments. Thus, strong irradiation of the olefinic signal at τ 4.70 ($-C^3H$) caused considerable sharpening of the multiplet at τ 8.40, while similar irradiation of the C-12 protons (τ 5.35) caused the triplet at τ 8.30 to collapse to a strong, sharp singlet.

Although we were unable to secure a sample of authentic eremophilene, the infrared spectrum of (\pm)-eremophil-3,11-diene (I), obtained as described above, differed, particularly in the "finger-print" region, from the infrared spectrum of eremophilene. Further, there were significant differences in the corresponding n.m.r. spectra. Therefore, it appears that the proposed (I) structure of eremophilene is incorrect and should be revised.*****

**** We are very grateful to Dr. L. H. Zalkow for a generous sample of hydroxydihydroeremophilone and to Dr. H. Ishii for an infrared spectrum of authentic (+)-7 β -eremophilane.

***** For a possible explanation concerning the stereochemical outcome of the transformation of IV into V, see reference 11.

It should be noted that the stereoselective conversion of IV into V is of particular significance, since this reaction provides a simple and efficient entry into the vicinal dimethyl system found in eremophilane-type sesquiterpenes. We are currently studying this reaction in more detail and are also applying it to the synthesis of sesquiterpenes belonging to the eremophilane group.

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***** The infrared and n.m.r. spectra of eremophilene were kindly supplied by Dr. R. B. Bates. We have received private communications from Dr. Bates and from Dr. V. Herout, indicating that they also feel that the proposed structure of eremophilene requires revision.