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THE TOTAL SYNTHESIS OF (+)-EREMOPHILENE AND (+)-EREMOLIGENOL

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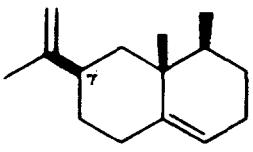
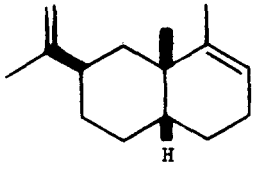
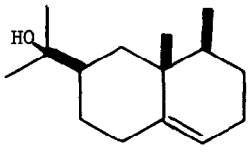
The structure of the sesquiterpene hydrocarbon eremophilene (1) has recently been revised to I (2) from the original proposal Ia (3) and is therefore related by hydration to the alcohol eremoligenol II (4). This modification, stimulated by the recent synthesis (5) of Ia, is consonant with the emerging structural patterns within this rapidly expanding group of sesquiterpenoids. We now report the total synthesis of (+)-eremophilene and (+)-eremoligenol by a stereoselective route which fully confirms the structure and stereochemistry of these two natural products, the biogenetic parents of the sesquiterpene family related to eremophilone III.



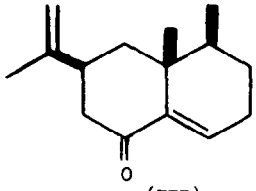
(I)



(Ia)



(II)



(III)

The synthetic scheme** originates from the dimethyl octalone IV prepared in a previous study (6) and known to have the proper cis relationship between the adjacent methyl groups (7). The key step in the reaction sequence is the double reduction of the β-keto ester enol acetate VI which serves to remove both the conjugated double bond and the extraneous oxygen function and to generate the required axial configuration in the product ester VII.

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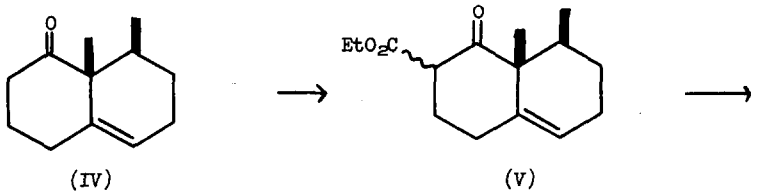
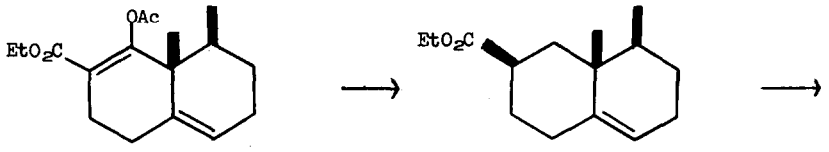
**All new, numbered compounds have been characterized by appropriate microanalytical and spectral data.

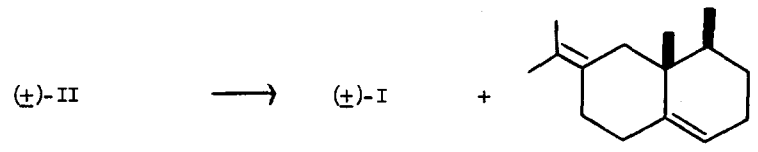
The ester enol acetate VI [ν_{max} 1770, 1715, and 1629 cm^{-1}; τ 7.89 (3H, s); 8.88 (3H, s) and 8.89 (3H, d, J~6Hz)] is obtained from the reaction of the sodium salt of V (6) with acetyl chloride in dimethoxyethane (30 min. at 25°). Reduction of unpurified VI with lithium in liquid ammonia followed by quenching with ammonium chloride affords the desired ester VII [$n_D^{25°}$ 1.4905; ν_{max} 1729 cm^{-1}; τ 9.12 (3H, d, J~6Hz) and 9.18 (3H, s)] in 34% yield from V after purification by column chromatography.



(IV) (V)



(VI) (VII)



(VIII)

The axial configuration of the carbethoxy grouping in VII follows from the upfield shift of nmr signal (τ 9.18) due to the angular methyl group (8) and is confirmed by equilibration to a more stable isomer in which the quaternary methyl resonance is found at τ 9.05. The production of the less stable, axial isomer is presumably the result of a kinetically-controlled protonation of the intermediate ester enolate anion from the less hindered, equatorial direction.

The reaction of VII with excess methyl lithium in ether (2.5 hr. at 25°) affords (±)-eremoligenol (II) in 81% yield after column chromatography. The infrared (film) and nmr ($CDCl_3$ or pyridine) spectra of racemic II are superimposable upon the corresponding spectra (supplied by Dr. H. Ishii) of natural eremoligenol (4). Dehydration of (±)-II (4) with thionyl chloride

in pyridine (0° for 15 min.) furnishes (±)-eremophilene (I) and its double bond isomer (±)-VIII (28 and 14% resp., after prep. glc on 20% SE-30). The synthetic eremophilene was identified by comparison of its infrared (~ 20% soln.) and 100 MHz nmr spectra with those of an authentic sample (provided by Professor V. Herout) (2). These nmr spectral data are distinguishable from the corresponding data reported for its stereoisomer, valencene, the C-7 epimer of enantio-I (2,9). The nmr chemical shift parameters from synthetic (±)-VIII accord with literature values reported for enantio-VIII derived from valeraniol (9).

The simple overall conversion IV → VII in three steps represents a new and potentially useful synthetic method which we plan to investigate further. At this point no effort has been made to optimize the yield in the reduction stage VI → VII. This reaction is presumed to proceed through the α,β-unsaturated ester which then undergoes a second reduction to the enolate anion of VII. Spencer and co-workers have recently demonstrated that enol ether derivatives of β-diketones are similarly reduced to saturated ketones (10). Although it has not been possible to prepare the methyl enol ether of V, the methyl enol ether of trans-V (6) undergoes smooth reduction (67%) to the corresponding axial ester.

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