

SYNTHESIS OF *dl*-TETRAHYDROEREMOPHILONE

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We wish to report the synthesis of *dl*-tetrahydroeremophilone 1 (1), a reduction product of eremophilone 2 (1, 2). The key step involves the acid catalyzed cyclization of triene 6, which immediately introduces two of the three asymmetric centers in the correct relative orientation.

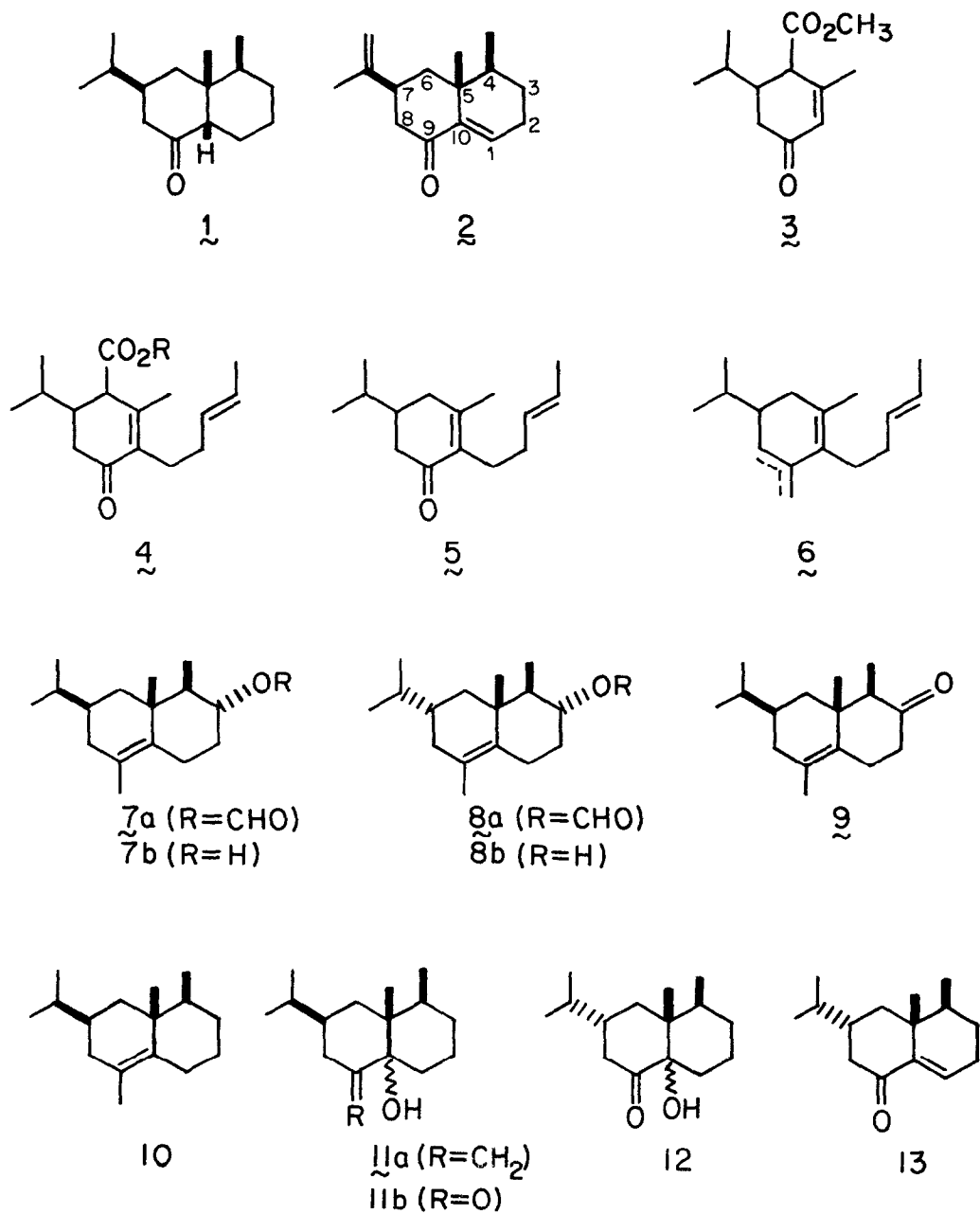
The starting material for the synthesis was the keto ester 3, which was prepared by an adaptation of the procedure of Horning *et al.*, who had previously prepared the corresponding ethyl ester. Alkylation of keto ester 3 with trans 1-bromopentene-3 (4) afforded keto ester 4, which was hydrolyzed and decarboxylated to the unsaturated ketone 5. Addition of methyl lithium to ketone 5, followed by phosphorous oxychloride and pyridine dehydration gave a mixture of trienes 6 (22% overall yield from 3).

The triene mixture 6 was cyclized by treatment with anhydrous formic acid at room temperature for 20 minutes (5), to yield a mixture of products which were separated by chromatography on Florisil. In this manner a mixture of two formates 7a and 8a, was obtained in 67% yield. The formates were reductively cleaved with lithium aluminum hydride to yield a mixture of alcohols 7b and 8b epimeric at C₇ in a ratio of 2:3 (6). The mixture was partially separated on alumina to afford two crystalline alcohols 7b, m. p. 47-54° and 8b, m. p. 91-93°. The assignment of stereochemistry rests upon conversion of 7b to tetrahydroeremophilone which is known to possess the all cis configuration.

Oxidation of alcohol 7b with Jones reagent (7) gave ketone 9, b. p. 115-120°/1.0 mm, which underwent Wolff-Kishner reduction (8) to afford the olefin 10, b. p. 90-95°/0.8 mm (71% yield). Photo-oxygenation (9) of 10, followed immediately by lithium aluminum hydride reduction gave a mixture of allylic alcohols 11a, which were added to one equivalent of

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ozone-saturated methylene chloride at -70° . Immediate reduction of the ozonide with zinc dust and acetic acid afforded the ketol 11b, m. p. $70-71^{\circ}$ (45% yield). Acetylation of the ketol 11b with acetic anhydride and phosphoric acid (10) followed by calcium and ammonia reduction (1) gave *dl*-cis-tetrahydroeremophilone 1 identical in all respects to the natural



material prepared by the procedure of Djerassi *et al.* (1).

All attempts to dehydrate the ketol 11b to the corresponding unsaturated ketone and thus achieve a total synthesis of dihydroeremophilone have been unsuccessful to this date, due to rearrangements and other complications.

When the epimeric alcohol 8b was submitted to the same series of reactions, ketol 12 was produced which was different from 11b. Interestingly enough, ketol 12 undergoes facile dehydration to the corresponding unsaturated ketone 13.

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