

SYNTHESIS OF HELMINTHOGERMACRENE AND β -ELEMENE

by

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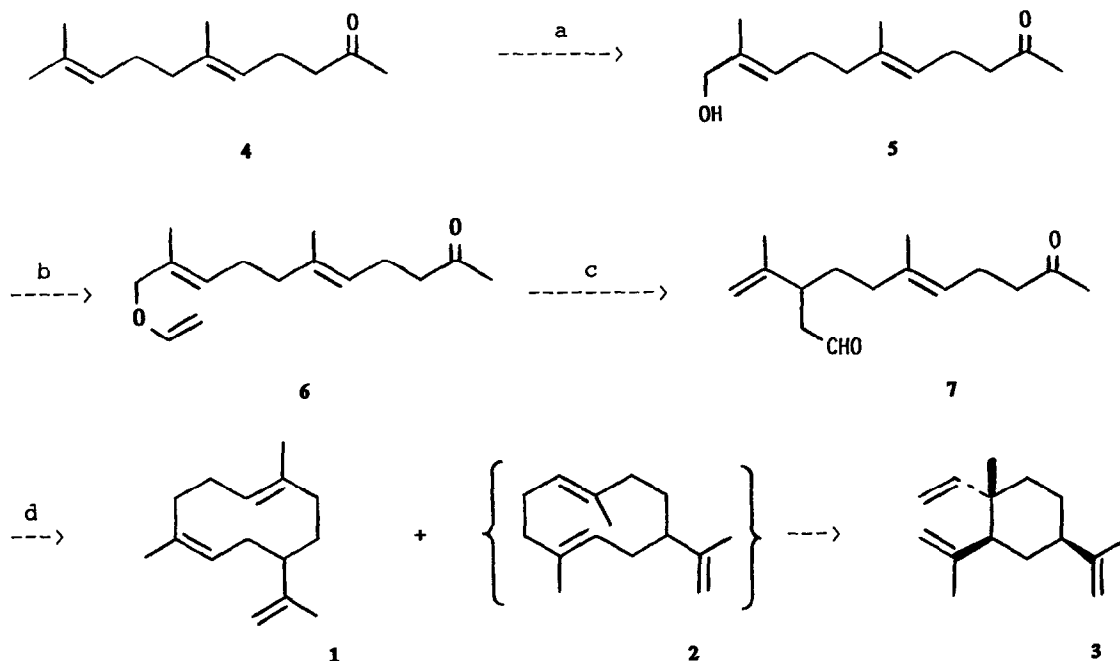
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Abstract: Helminthogermacrene (1) and β -elemene (3) have been synthesized by a short route starting from geranylacetone. Titanium-induced cyclization of 3-isopropenyl-6-methyl-10-oxo-6E-undecenal (7) was used as the key step.

In the accompanying Letter,¹ we have reviewed our progress in using the titanium-induced dicarbonyl coupling reaction² for the short and efficient synthesis of macrocarbocyclic natural products, and have detailed our recent work on synthesis of the bicyclic germacrene sesquiterpenes, bicyclogermacrene and lepidozene. We now report our efforts aimed at synthesis of the monocyclic sesquiterpenes, helminthogermacrene³ (1) and germacrene A⁴ (2).

Our work is shown in the Scheme. Palladium-catalyzed allylic oxidation of commercially available geranylacetone (4) according to our recently published method⁵ provided keto alcohol 5 in 55% yield. Formation of vinyl ether 6 by standard methods, followed by thermolysis at 200 °C then gave the necessary dicarbonyl cyclization substrate 7.

Treatment of keto aldehyde 7 with $\text{TiCl}_3/\text{Zn-Cu}$ according to previously described conditions⁶ should initially yield a mixture of germacrenes 1 and 2, since E/Z stereoselectivity at the new double bond is rarely observed in these cyclizations. It is known,⁷ however, that whereas helminthogermacrene (1) is thermally stable, germacrene A (3) undergoes Cope rearrangement at room temperature to yield β -elemene (3). We therefore expected and obtained a mixture of 1 and 3 (45:55, 60% yield) on cyclization of keto aldehyde 7. Separation of the two products was readily accomplished by column chromatography of the mixture on silica gel impregnated with 2% silver nitrate. (\pm)-Helminthogermacrene was identified by comparison of its IR, ¹H NMR, and ¹³C NMR spectra with published data;³ (\pm)- β -elemene was similarly identified by comparison with published spectra.⁸



Scheme: Synthesis of Helminthogermacrene and β -Elementene

(a) Benzoquinone, $\text{Pd}(\text{CF}_3\text{COO})_2$, *o*-methoxyacetophenone, acetic acid, then KOH, H_2O , 55%; (b) Ethyl vinyl ether, $\text{Hg}(\text{CF}_3\text{COO})_2$, room temp., 75%; (c) 200 °C, 6 hrs, 80%; (d) TiCl_3 , Zn-Cu, dimethoxyethane, reflux, 34 hr addition, 60%.

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