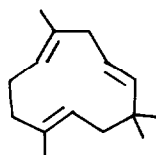


STEREOSPECIFIC SYNTHESIS OF HUMULENE BY
TITANIUM-INDUCED DICARBONYL COUPLING

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Abstract: An efficient stereospecific synthesis of humulene was accomplished using titanium-induced cyclization of 3,3,7-trimethyl-11-oxoundeca-4E,7E-dienal as the key step.

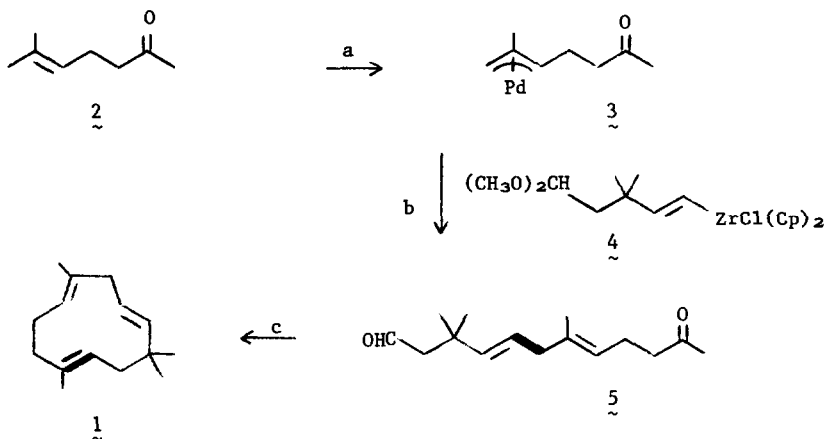
The general problem of devising stereoselective syntheses of macrocarbocycles is a difficult matter, but one which we feel has been simplified by our development of the titanium-induced cyclization of dicarbonyl compounds.¹ Having recently completed an efficient and remarkably short synthesis of the 15-membered ring diterpene flexibilene,² we now report the application of our synthetic methodology to a synthesis of humulene.



Humulene, 1

Humulene, 1, an unusual 11-membered ring sesquiterpene isolated from oil of hops, has been the target of three successful synthetic attempts to date. Of the three, all require at least 10 steps. Two^{3,4} use the non-stereoselective nickel-catalyzed cyclization of a bis-allylic dibromide as the key step, while the third⁵ uses palladium-catalyzed intramolecular alkylation of an allylic acetate by a β -keto ester anion. In neither of the nickel-based syntheses were the yields of the key cyclizations reported, while the palladium-catalyzed ring closure took place in 45% yield. In light of this history, we would like to suggest that humulene can be considered a chemical benchmark against which progress in macrocarbocyclic synthesis can be gauged.

Examination of humulene indicates that there are three potential dicarbonyl precursors whose cyclization could lead to the desired product. We chose keto aldehyde 5 as the most likely choice, and our successful route is shown in the Scheme. Treatment⁶ of commercially available 6-methyl-5-hepten-2-one (2) with palladium chloride gave crystalline π -allyl palladium chloride complex 3, and hydrozirconation⁷ of 5,5-dimethoxy-3,3-dimethyl-1-pentyne² gave vinyl zirconium reagent 4. Reaction of 3 with 4 in methylene chloride solution at -78° in the presence of maleic anhydride according to the method of Schwartz⁸ then provided keto-aldehyde 5, and slow addition of 5 to a previously prepared slurry of $\text{TiCl}_3/\text{Zn-Cu}$, followed by reflux for 18 hours, gave pure humulene as the only isolable product (60%). No traces of double bond isomers were detected by ¹³C or ¹H high field NMR. The product was purified by distillation (Kugelrohr) and was identical with the natural material by spectroscopic comparison.



Scheme. Synthesis of Humulene.

a) PdCl₂, acetone, 57%, b) 3 + 4, maleic anhydride, CH₂Cl₂, -78°, 84%; c) 6.0 equiv. TiCl₃, Zn-Cu, DME, reflux, 18 hr, 60%.

The stereospecific synthesis of humulene reported herein requires fewer than half the number of steps used in other reported syntheses, and the critical cyclization occurs in an isolated yield of 60%. If one looks at humulene syntheses as a benchmark of progress in macrocarbobicyclization reactions, we believe that the titanium-induced dicarbonyl coupling reaction reaches a very high level.

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