

NEW STEREO- AND REGIOSPECIFIC SYNTHESIS OF HUMULENE BY MEANS OF THE
PALLADIUM-CATALYZED CYCLIZATION OF HALOALKENYLBORANES

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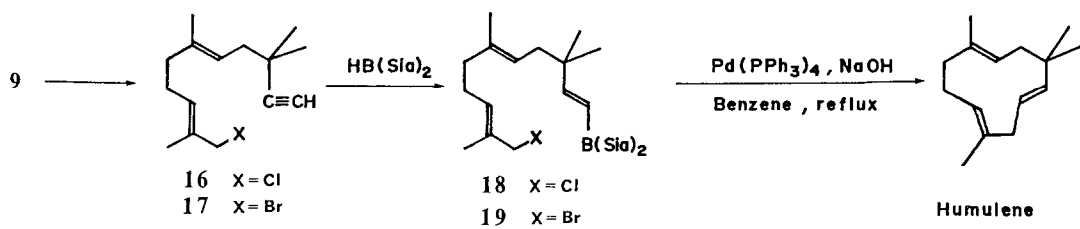
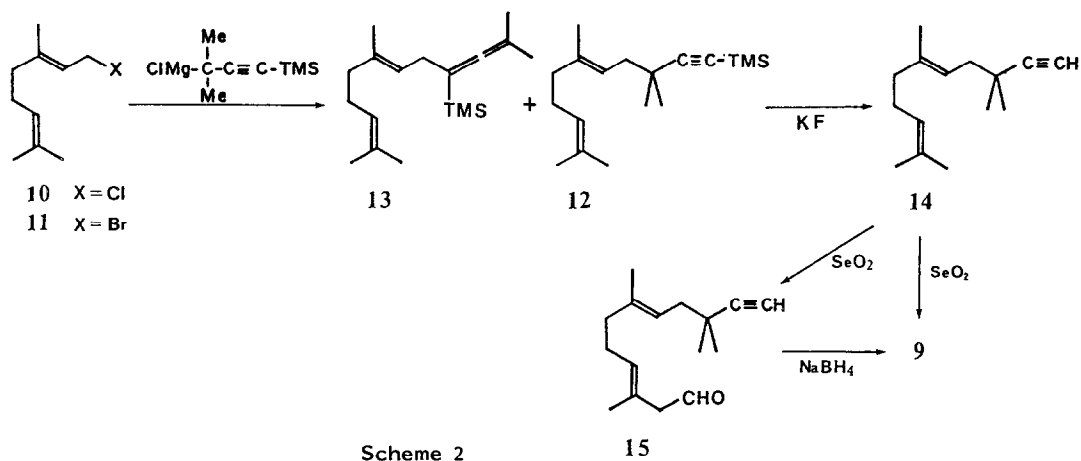
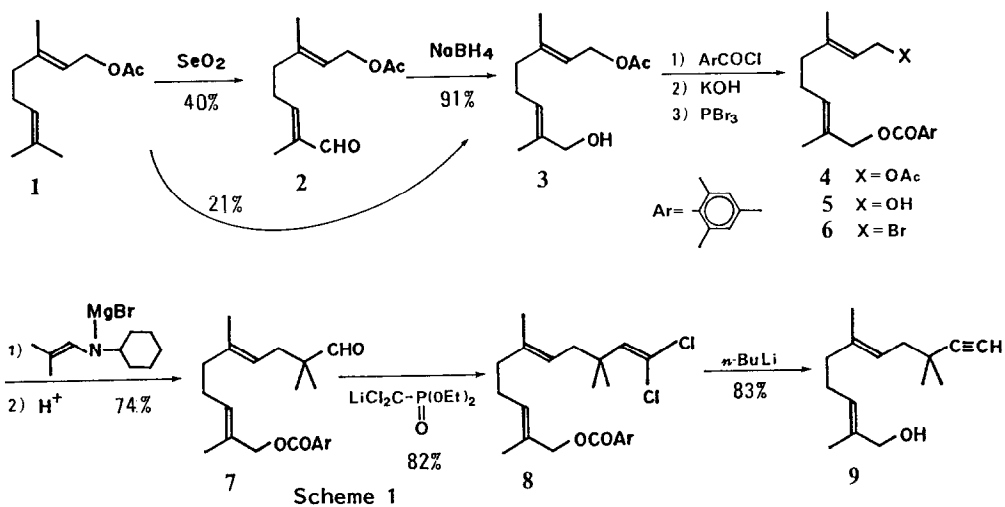
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Abstract: We describe a new stereo- and regiospecific synthesis of humulene, the major sesquiterpene of hops, by means of the palladium-catalyzed cyclization of haloalkenylboranes derived from geranyl halides via 4 principal steps.

In our recent papers,¹⁾ we reported a new stereospecific synthesis of pheromone, bombykol, and its three geometrical isomers by the palladium-catalyzed cross-coupling reaction between an appropriate alkenylborane and an alkenyl halide in the presence of a base.

In this paper we wish to report a new stereo- and regiospecific synthesis of humulene,²⁾ the major sesquiterpene constituent of oil of hops, by means of the palladium-catalyzed intramolecular coupling of haloalkenyldisiamylboranes (18) or (19) as the key step, prepared from geranyl halides via 4 principal steps. (Scheme 1-3). Since the first total synthesis by Corey and Hamanaka,³⁾ this sesquiterpene hydrocarbon has been the target for the elaborate synthesis by the several groups of investigators⁴⁾ because of its unique triply-unsaturated eleven-membered cyclic structure. The method reported herein, however, perhaps represents the simplest process yet devised for the synthesis of this sesquiterpene with the best overall yield from readily accessible material.

In our first attempt, we obtained (2E, 6E)-2,6,9,9-tetramethylundeca-2,6-dien-10-yn-1-ol (9), the key acetylenic precursor for this palladium-catalyzed cyclization, as shown in Scheme 1. Oxidation of geranyl acetate (1) with an equivalent of SeO₂ in a refluxing 95% ethanol for 1 h gave a mixture of (2E, 6E)-2,6-dimethylocta-2,6-diene-1,8-diol 8-acetate (3) (21%) and an aldehyde (2) (40%) by means of a modified procedure of the reported method.⁵⁾ Reduction of the latter with NaBH₄ gave alcohol (3) in a 91% yield. The hydroxyl group of alcohol (3) was protected by converting it into an oily mesitoate (4) with mesitoyl chloride and pyridine in a refluxing benzene for 6 h in a 91% yield. The acetoxy group of the mesitoate (4) was then hydrolyzed with potassium



hydroxide in ethanol at room temperature for 30 min to give an oily hydroxy-mesitoate (5) in a 91% yield. The hydroxyl group of (5) was replaced by bromine by treating it with PBr_3 at 0°C for 4 h to give bromide (6) in a quantitative yield. Following the procedure devised by stork,⁶⁾ we then added this bromide (6) to a refluxing THF solution containing N-(2-methylpropylidene)cyclohexylimine and ethylmagnesium bromide and the solution was heated under reflux for 16 h to give oily (4E,8E)-10-mesityloxy-2,2,5,9-tetramethyldeca-4,8-dienal (7) in a 74% isolated yield.

This dienal was then transformed into the terminal acetylenic alcohol (9) according to the method devised by Normant.⁷⁾ Thus, the reaction of (7) with trichloromethane phosphonate⁸⁾ in a mixture of THF and diethyl ether containing butyllithium by the reported procedure gave a dichloroalkene (8) in an 82% yield. The treatment of (8) with butyllithium in THF at -78°C then afforded (9) in an 83% yield.

Subsequently, we found that the acetylenic alcohol (9) can be obtained more simply with an improved overall yield from geranyl halides, as shown in Scheme 2. Thus, a Grignard reagent prepared from 1-trimethylsilyl-3-chloro-3-methyl-1-butyne⁹⁾ and magnesium in THF reacted regioselectively with geranyl bromide (11)¹⁰⁾ in a mixture of THF and HMPA at 0°C to give (5E,9E)-1-trimethylsilyl-3,3,6,10-tetramethylundeca-5,9-dien-1-yne (12) with a small amount of an accompanying allene derivative (13). The combined yield of (12) and (13) determined by GLC was 98% and the ratio of (12) and (13) was 99:1. The use of geranyl chloride (10) instead of the bromide in this Grignard reaction was found to give an acetylene derivative (12) with a far smaller selectivity and the ratio of (12) and (13) was 58:42. The mixture in DMF obtained from the bromide, was treated with an aqueous KF ¹¹⁾ for 8 h at $70\sim 80^\circ\text{C}$ and distillation of the crude product (94% yield by GLC) with Kugelrohr gave a pure (5E,9E)-3,3,6,10-tetramethylundeca-5,9-dien-1-yne (14) in an 88% isolated yield. The treatment of this acetylene derivative (14) in a 95% ethanol containing pyridine with SeO_2 under reflux in an atmosphere of nitrogen gave an orange coloured oil of a 7:3 mixture of (2E,6E)-2,6,9,9-tetramethylundeca-2,6-dien-10-yn-1-ol (9) and an aldehyde (15) (GLC and $^1\text{HNMR}$). This mixture without further purification was subjected to reduction with NaBH_4 in a 95% ethanol at 0°C for 1 h to give a crude alcohol (9) (61% yield by GLC). Purification of this crude alcohol by column chromatography gave a pure acetylenic alcohol (9) in a 45% isolated yield.

The alcohol (9) in DMF containing s-collidine and LiCl was treated with mesyl chloride¹²⁾ at 0°C for 2 h to give (5E,9E)-11-chloro-3,3,5,9-tetramethylundeca-5,9-dien-1-yne (16) which was purified by distillation with Kugelrohr (75% isolated yield). The corresponding bromo-derivative (17) was obtained by the reaction of alcohol (9) with PBr_3 in diethyl ether at 0°C for 4 h in an 81% isolated yield.¹³⁾ These haloacetylenes in THF were subjected to hydroboration with disiamylborane¹⁴⁾ at -10°C by the standard procedure to give haloalkenylborane (18) or (19). Either borane (18) or (19) was

immediately dissolved in benzene and was slowly added to a boiling solution containing $\text{Pd}(\text{PPh}_3)_4$ ¹⁵ (20 mol%) and 4N-aqueous NaOH .¹⁶⁾ After the solution was heated under reflux for another 30 min in an atmosphere of nitrogen, an excess of borane was removed by oxidation with 30% H_2O_2 and 4N- NaOH as usual. After a normal work-up, a crude product containing humulene (a 32% yield by GLC) was obtained. Purification of the crude product by column chromatography (silica gel-hexane) followed by preparative GLC gave a pure humulene. Direct comparison with natural humulene¹⁷⁾ has shown that both humulene are identical.

The present synthesis demonstrates that the palladium-catalyzed cross-coupling of alkenylboranes with organic halides developed by us¹⁸⁾ can be applied even to the synthesis of cyclic compounds in an intramolecular manner. Full details of the present results will be reported in due course.

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