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THE TOTAL SYNTHESIS OF (±)-HIBAENE[1]

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The tetracyclic diterpenoid hydrocarbon hibaene (10) has recently been isolated in both enantiomeric forms.[3] The complete structure of the hydrocarbon was first elucidated by Kitahara and Yoshikoshi[3a], who worked with (-)-hibaene; shortly afterwards, Kapadi and Dev reported[3b] the isolation of the (+)-enantiomer. The chemical transformation of (+)-hibaene into (-)-kaurene very recently reported by Kapadi and Dev[4], lends satisfying support to the biogenetic scheme suggested[5] for the origin of these hydrocarbons. Another facet of the chemistry of hibaene is the synthesis[6] of the molecule, and we report here, a stereoselective scheme that has accomplished this goal.

Our interest in the hydrocarbon hibaene (10) stems from the possibility of gaining entrance into this system via the acid catalysed rearrangement of the bridgehead hydroxy olefin (8). The synthesis of this intriguing, synthetic intermediate was of particular interest, as the C/D ring system is also found in both steviol and the gibberellins. Thus, our approach to the synthesis of (±)-hibaene (10) has embodied in it a possible solution to a portion of the structural complexities of these latter molecules.

For this synthesis, our point of departure from earlier work[8] was the keto acetal (1). Condensation of this material with ethylenetriphenylphosphorane afforded the olefin (2) [m.p. 86-88.5°; C, 79.71 and H, 1105°] in 98% yield. Hydroboration of the olefin (2) followed by oxidation and equilibration under mildly basic conditions proceeded smoothly to complete the introduction of the 13 β-acetyl group and afford the new keto acetal (3) [m.p. 84-87°; C, 76.24 and H, 10.66] in 80% overall yield. Aldol-type cyclisation of this keto acetal was effected during hydrolysis of the acetal in dilute aqueous hydrochloric-acetone solution, and after acetylation there was obtained an 87% yield of the keto acetate (4) [m.p. 183-185°; C, 76.60 and H, 9.95].

The bridged ring system having thus been constructed, we proposed to introduce the bridgehead hydroxyl function through Baeyer-Villiger oxidation of the ketoacetate (4). However, only a very low yield of diacetate (6) could be realised by this method, despite the application of a wide variety of reagents and conditions. In order to circumvent this unsatisfactory process, we turned our attention to the Beckmann rearrangement of the derived oxime. By this method it was possible to obtain a 94% overall yield of the amidoacetate (5) [m.p. 212-213°; C, 73.65 and H, 9.94] by heating the oximinotosylate in dioxane-water solution. Subsequent treatment of this amidoacetate (5) with nitrogen dioxide in acetic acid-sodium acetate buffer[9] afforded a 96% yield of the desired diacetate (6) [m.p. 164-166°; C, 73.20 and H, 9.53]. By this four-stage sequence we were therefore able to effect the replacement of

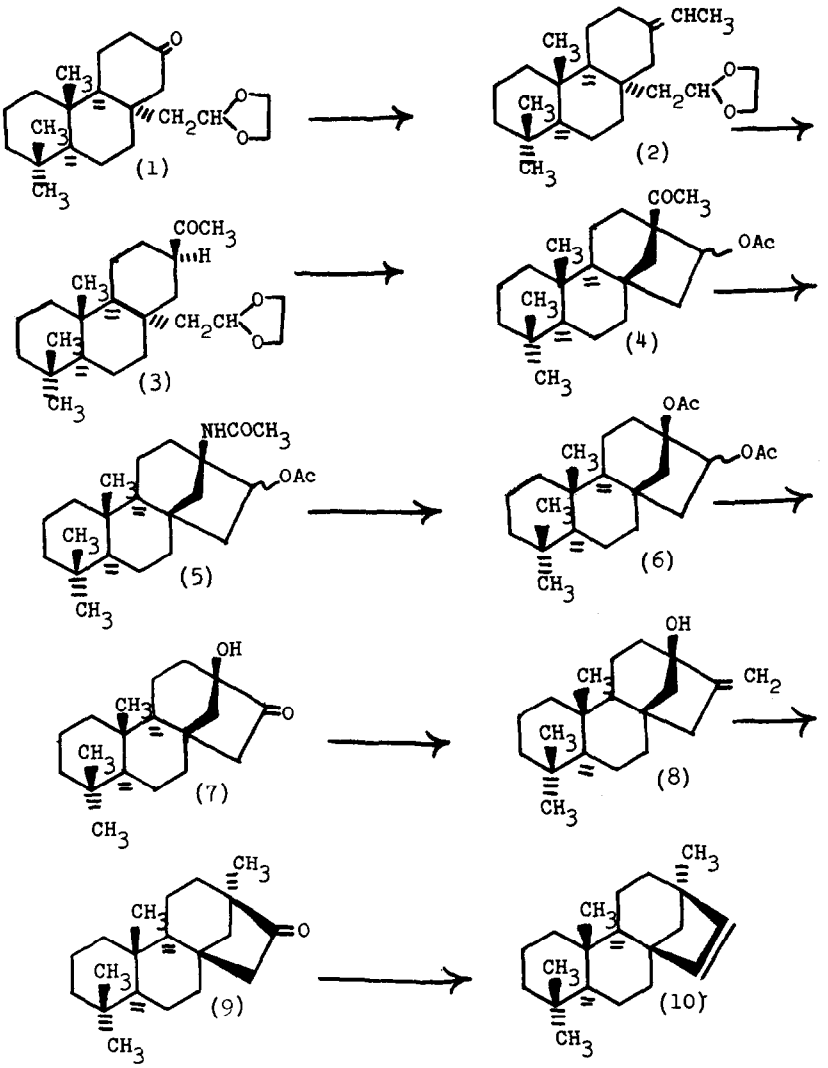

CHART A: The Synthesis of (±)-Hibaene (10) from the Keto-acetal (1)[13]

the bridgehead acetyl group with acetoxyl in 90% overall yield, whereas the direct peracid oxidation of the ketoacetate (4) accomplished the same change in 10% yield at best.

Further transformations toward the hibaene structure were undertaken by hydrolysis of the diacetate (6) and oxidation of the derived diol with Jones reagent[10] at -24° for 3 minutes. The acyloin (7) [m.p. 174-176°; C, 78.55 and H, 10.46] was isolated in 90% yield. These conditions were found to prevent oxidative cleavage and gave an optimum yield of the acyloin (7). On treatment of the acyloin (7) with methylenetriphenylphosphorane in T.H.F.-t-butyl alcohol solution, there was obtained an 82% yield of the desired bridgehead hydroxyolefin (8) [m.p. 151-153°; C, 83.24 and H, 11.03]. This intermediate was available in 46% overall yield from the initial ketoacetal (1), and the route traversed provides an attractive alternative to that developed by Stork and co-workers[11] with the same objective in mind.

Rearrangement of the hydroxyolefin (8) in 3N hydrochloric acid-methanol afforded the ketone (9) [m.p. 117-119°; C, 83.03 and H, 11.17] in 60% yield and thereby provided entry into the hibaene system. The total synthesis of (±)-hibaene (10) was then realised when the ketone (9) was reduced with sodium borohydride and the Δ^{15} olefinic bond introduced through elimination of the derived tosylate in refluxing collidine. This sample of (±)-hibaene (10), obtained in 30% overall yield from the ketone (9), was a colorless, mobile oil [evap. dist. at 120° (0.01 mm); C, 87.92; H, 11.74%], the infrared and proton magnetic resonance spectra of which were indistinguishable from those

of (+)-hibaene, obtained by Wolff-Kishner reduction of (+)-stachenone[12].

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13. While only one enantiomeric form is represented, all compounds employed for this synthesis were racemic unless otherwise designated.