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Stereospecific chemical synthesis of juvenile hormones

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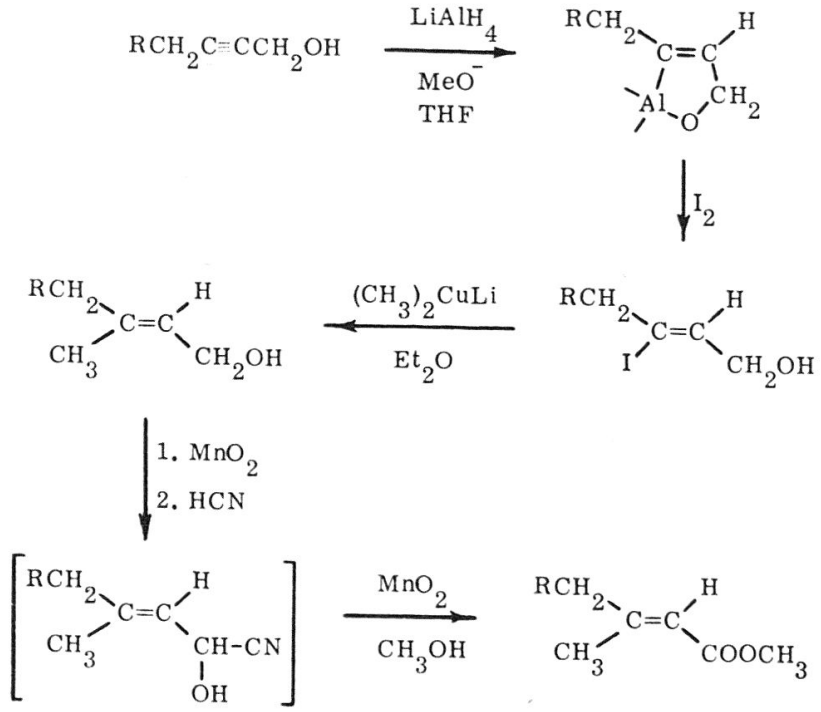
The major objectives of our research on the synthesis of juvenile hormones have been twofold : first, the development of stereospecific synthetic routes which would yield the pure hormones uncontaminated by isomeric structures, and secondly, the discovery of new methods for the stereospecific formation of the trisubstituted olefinic units which represent the major obstacle to the successful synthesis of the juvenile hormones and other acyclic isoprenoids. Such synthetic methods would fill a void which has been conspicuously displayed in those synthetic studies in the isoprenoid area which have relied on conventional processes of olefin formation. This lecture will be concerned, therefore, both with new synthetic reactions applicable to the stereospecific synthesis of acyclic isoprenoids and with the application of these methods to juvenile hormone synthesis in particular. Whatever success we have achieved in this enterprise is largely to the credit of the very able collaborators with whom I have been associated. In particular, the outstanding contributions of Hisashi Yamamoto, John Katzenellenbogen, Norman Gilman, and Steven Roman must be mentioned.

Attention will first be centered on several new processes for the stereospecific synthesis of trisubstituted olefins which have been developed at Harvard since 1966. These methods allow access to the four different arrangements which are possible about a carbon-carbon double bond with two different alkyl (or functionalized alkyl) groups, a methyl group and a hydrogen atom as substituents.

Figure 1 shows a route which depends on the stereospecific generation of a vinyl aluminum intermediate by the action of lithium aluminum hydride on a propargylic alcohol. The underlying rationale for the investigation of this method arose from a number of previous findings including (1) the well-known unique lability of $C \equiv C$ to reduction by $LiAlH_4$ in propargylic alcohols, (2) the stereospecific formation of *trans* allylic alcohols of type $RCH = CHCH_2OH$ from propargylic alcohols and $LiAlH_4$, and (3) the demonstration by Hochstein and Brown of an organo aluminum intermediate in the reduction of cinnamyl alcohol by $LiAlH_4$ (1). It was found by experimentation that

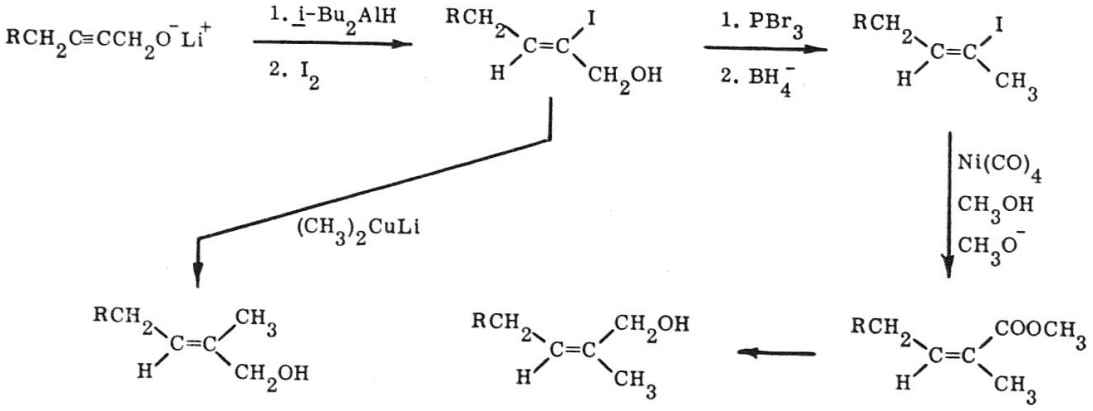
NEW METHODOLOGY APPLICABLE TO
STEREOSPECIFIC SYNTHESIS OF ACYCLIC ISOPRENOIDS



e.g., R = geranyl, n-hexyl

Fig. 1

NEW METHODOLOGY APPLICABLE TO
STEREOSPECIFIC SYNTHESIS OF ISOPRENOIDS



e.g., R = n-hexyl, π-tricyclyl

Fig. 1a

the reaction of propargylic alcohols with $LiAlH_4$ in tetrahydrofuran (THF) followed by iodination afforded a mixture of 3- and 2-iodinated alcohols in proportion which varied with the history and nature of the hydride reagent. It was further ascertained that the addition of sodium methoxide to the reagent led to exclusive formation of 3-iodo alcohol, whereas the addition of small amounts of aluminum chloride greatly favored formation of the 2-iodo alcohol (2). In connection with a program of research on carbon-carbon bond formation between unlike groups using organo-transition metal reagents (3), an excellent new process was at hand for the stereospecific replacement of iodo by methyl (or other alkyl) leading to the overall route to trisubstituted olefins shown in Figure 1. A method was also developed (4) for the oxidative one-flask conversion of primary allylic alcohols to methyl esters by the scheme shown in Figure 1 which proceeds via aldehyde, cyanohydrin, and acyl cyanide intermediates with manganese dioxide serving as the effective oxidizing agent. This method is efficient and stereospecific and obviously well suited to the synthesis of juvenile hormones.

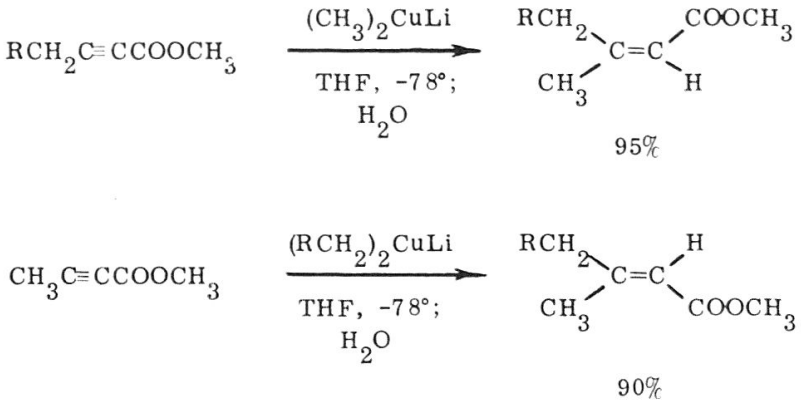
Figure 1a demonstrates a highly efficient method for the conversion of a propargylic alcohol into a 2-iodo-*trans*-allylic alcohol using the reaction of diisobutylaluminum hydride on the lithium alkoxide (5). This alternative to the $LiAlH_4$–$AlCl_3$ reagent leads to both stereospecific and position specific reduction and contrasts to the *cis* course of reduction observed for the reaction of dialkylaluminum hydrides with acetylenic hydrocarbons. As shown in Figure 1a, this approach coupled with the use of either organocopper (3) or organonickel (5, 6) reagents allows the stereospecific synthesis of 2-methyl *cis-* or *trans-*allylic alcohols.

Figure 2 shows still another new approach to trisubstituted olefins which has been developed at Harvard (7). This method, mentioned earlier in Dr. Siddall's lecture, was also studied by him at Syntex Corp. Figure 3 shows the synthesis of a 4,5-dehydrojuvenile hormone which rests partly on the methodology just discussed. The final product has been found to possess high juvenile hormone activity in studies by Prof. Carroll Williams. Interestingly, he observed even higher activity than that of C_{18}-cecropia hormone in certain bugs. The reduction of this dehydro compound to the C_{18}-cecropia juvenile hormone did not proceed cleanly even with the most favorable reagent studied (HN = = NH), and so this sequence, though completely stereospecific, does not provide an efficient route to the natural hormone.

Figure 4 shows how the intermediate C_{12}-dienol, a synthesis of which appears in Figure 3, was converted to the C_{18}-cecropia hormone in the first stereospecific synthetic route to this substance (8). The approach demonstrates the applicability of the methods outlined earlier in the lecture.

Figures 5 (9) and 6 (10, 11) outline two additional syntheses of the C_{12}-dienol intermediate which involve novel chemistry.

NEW METHODOLOGY APPLICABLE TO
STEREOSPECIFIC SYNTHESIS OF ISOPRENOIDS



R = geranyl, n-hexyl

Fig. 2

A DEHYDRO CECROPIA HORMONE

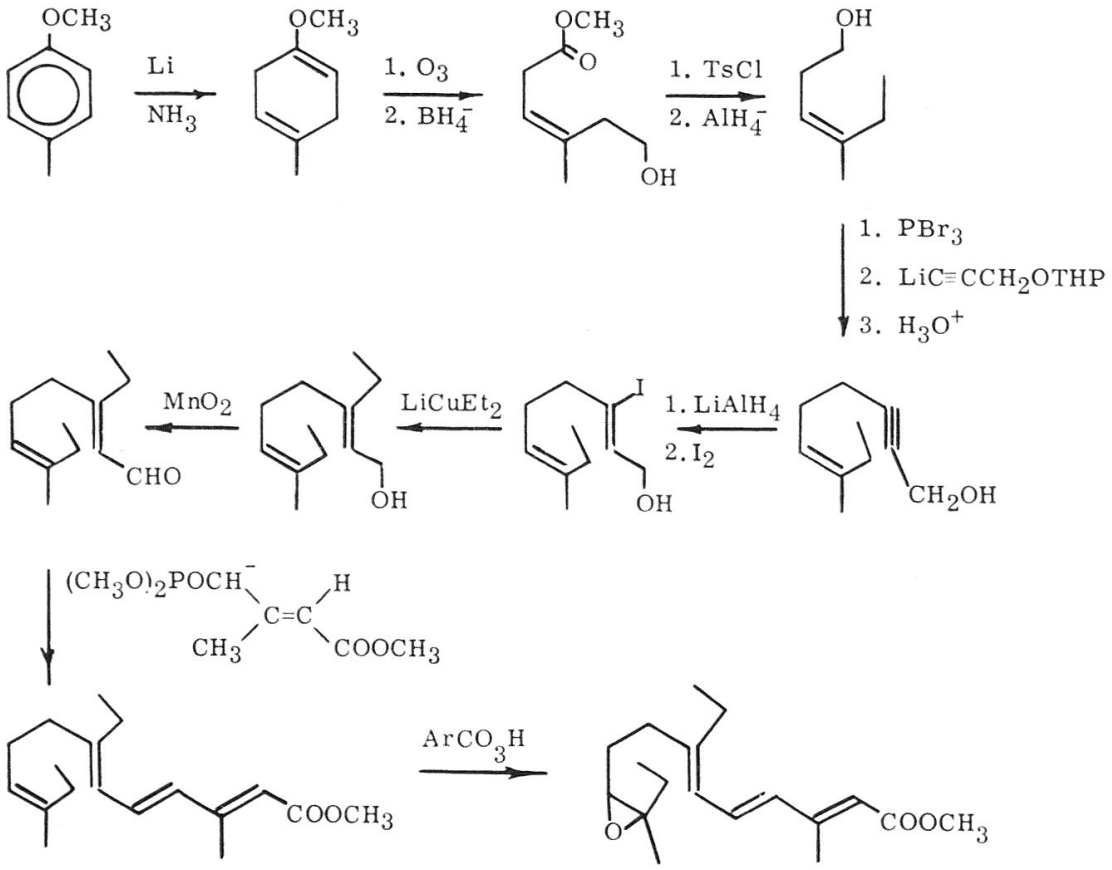
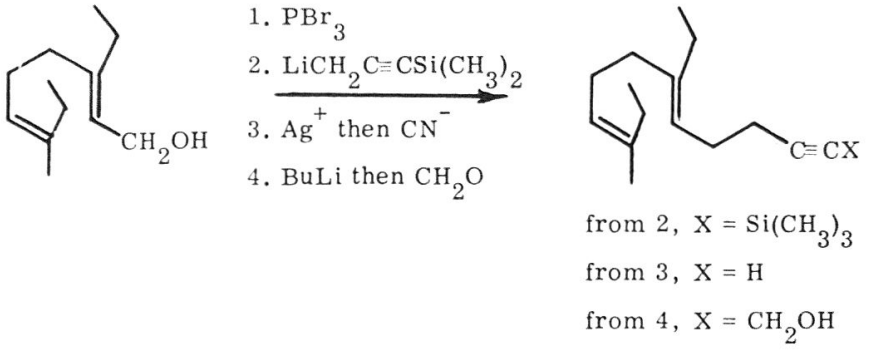


Fig. 3

FIRST SYNTHESIS OF C_{18}-CECROPIA HORMONE



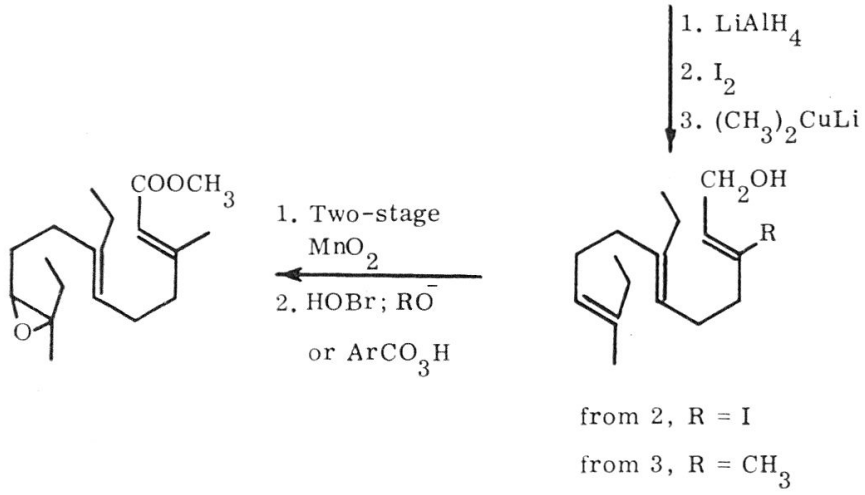
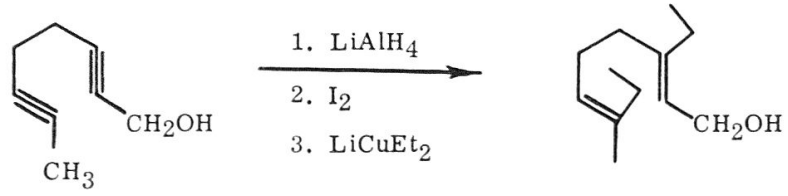


Fig. 4

ALTERNATE SYNTHESIS OF C_{12} DIENOL



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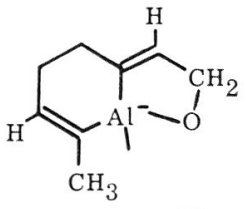

Fig. 5

ANOTHER SYNTHESIS OF C_{12}-DIENOL

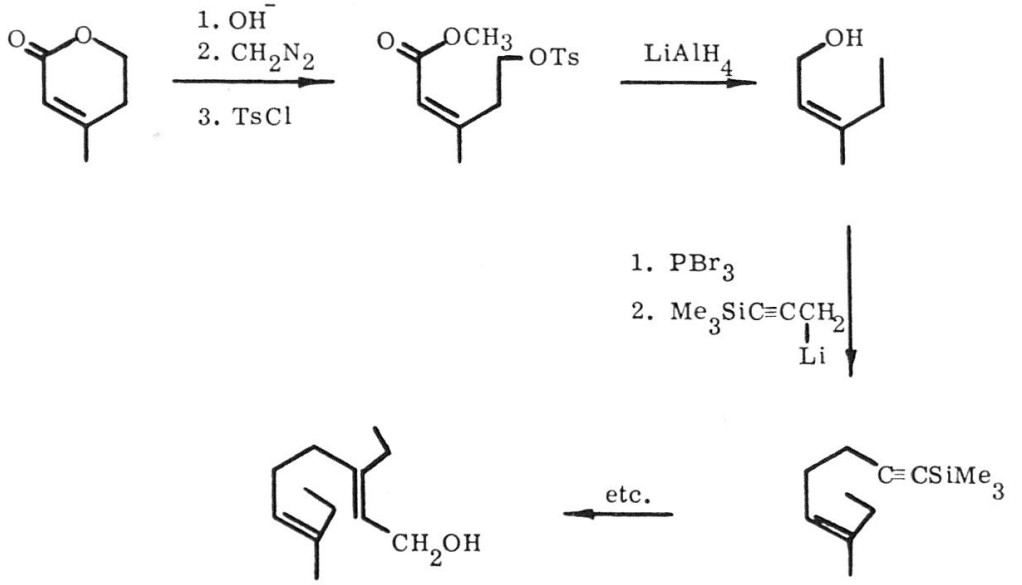

Fig. 6

The latest synthesis of juvenile hormones to be completed at Harvard is stereospecific, simple, and direct. It depends heavily on the application of β-oxido phosphonium ylides to olefin synthesis as recently developed by us (12). Figure 7 outlines the new method in general form. It is apparent that the method allows the joining of *three* structural units in one synthetic step. The reaction is remarkable in that an

STEREOSPECIFIC SYNTHESIS OF TRISUBSTITUTED OLEFINS FROM β-OXIDO PHOSPHONIUM YLIDES AND ALDEHYDES

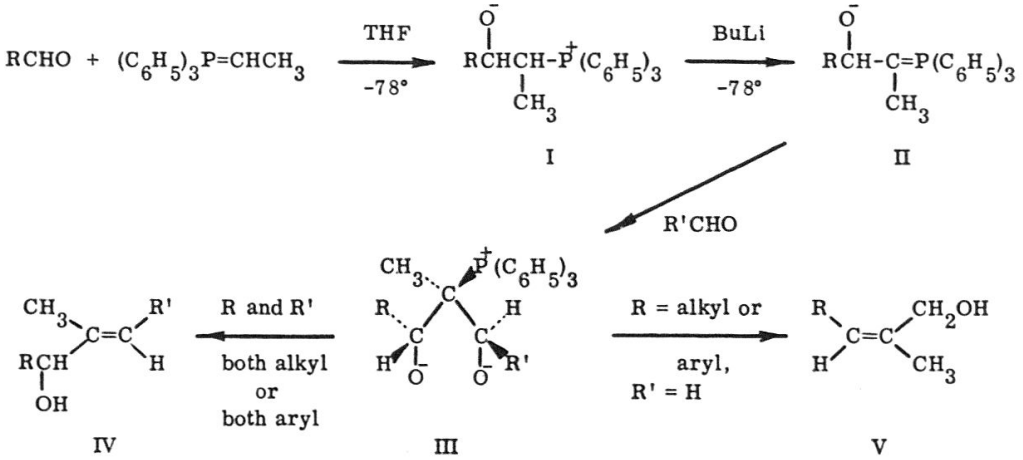

Fig. 7

intermediate containing *three* new stereocenters is generated stereospecifically and, further, a directional specificity operates in the final olefin-forming elimination.

Figure 8 shows the application of the oxido ylide method to the stereospecific synthesis of 5-methyl-*cis*-4-hepten-1-ol, a valuable intermediate for juvenile hormone synthesis (13). Figure 9 shows still another stereospecific route to the same alcohol (after borohydride reduction)

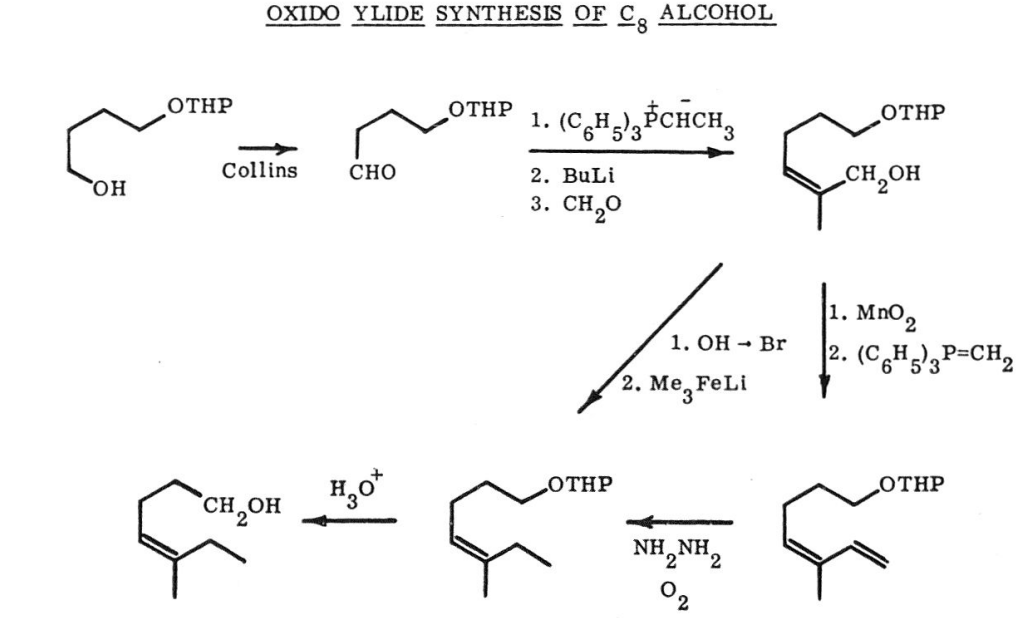

Fig. 8

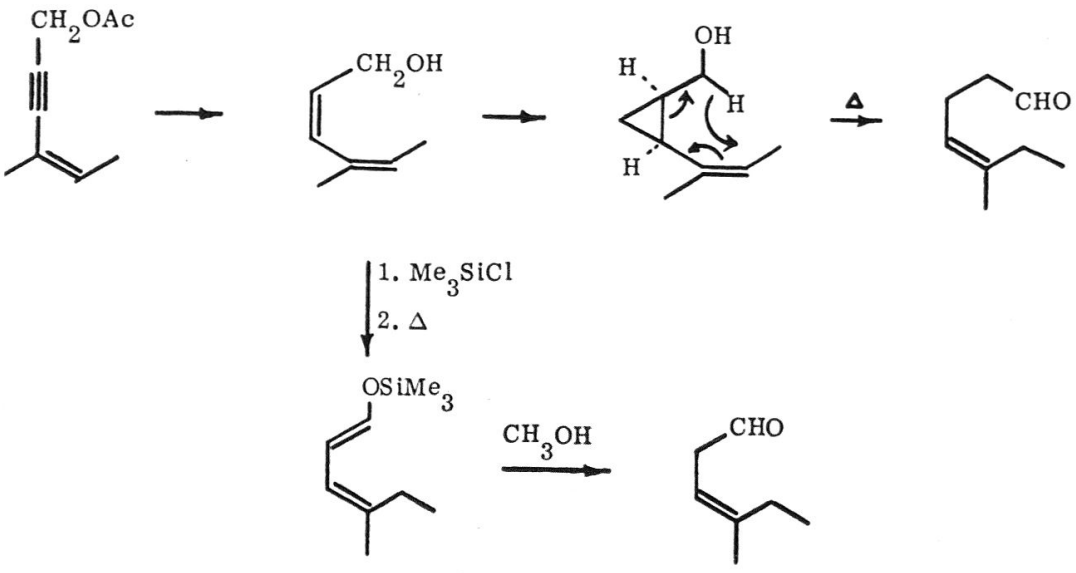

Fig. 9

involving a 1,5-hydrogen shift of a *cis*-vinylcyclopropylcarbinol (13). This process is based on earlier findings of several groups (14–17) on the thermal decomposition of simple *cis*-2-alkylvinylcyclopropanes. The use of one of the intermediates for the efficient synthesis of 4-methyl-*cis*-3-hexenal (or -ol) is also outlined in Figure 9 (18).

Next, an application of the 3-component oxido ylide method to the stereospecific synthesis of juvenile hormones is outlined in Figure 10 (19). A single intermediate, generated in one step as shown, leads by a simple and short route to both C_{17}- and C_{18}-cecropia hormones. This is certainly the simplest synthesis of these substances now known which is stereospecific and leads directly to the pure substances. The method has also been used to generate the methyl-ethyl transposed position isomer of the C_{17}-hormone and the interesting chloro isostere of the C_{18}-hormone which are shown in Figure 10.

β-OXIDO YLIDE SYNTHESIS OF CECROPIA HORMONES

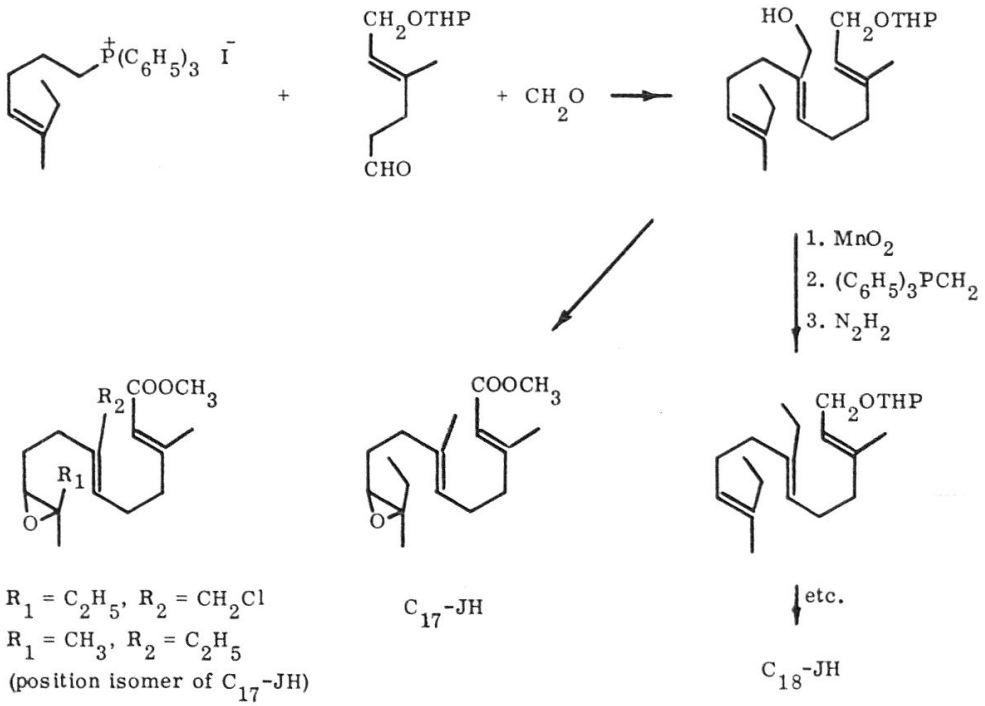

Fig. 10

Finally, it seems appropriate to amplify the results reported during an earlier discussion at this meeting with regard to the biological properties of certain imino analogs of the juvenile hormones, for example, structure I in which R may be CH_3 or C_2H_5. These substances *per se* have only very low juvenile hormone type activity. However, Mr. Alfred Ajami, working with Prof. Riddiford at Harvard, has shown that the injection into cecropia pupae of a mixture of C_{18}-cecropia hormone

in small amount and an imino analog (typically 0.01 μg hormone and 1 μg imino compound) results in a level of hormonal activity which would correspond to that expected from much larger doses of the hormone. Enhancements of up to 10-fold have been observed. This result is understandable on the basis that the imino compound inhibits an enzyme which catalyzes the destruction of the juvenile hormone by a proton-catalyzed heterolytic cleavage of the oxido function. Such an enzymatic reaction of the juvenile hormones could lead to a 1,2-glycol by hydration or to cyclization involving the proximate double bond. Enzymic processes of both types are known (20, 21), and inhibition by imino analogs has been demonstrated (21). The rapid metabolism of the juvenile hormones reported by Dr. Siddall substantiates this supposition. It is clear that the epoxide cleavage reaction could be an important part of the natural process which regulates juvenile hormone levels in the insect (22).

The high activities of mixtures in juvenile hormone assays, e.g., the Williams-Law mixture, might be due to the presence of two types of active substances — one which has juvenile hormone activity and another which inhibits breakdown of the hormonally active substances. Further investigation of the inhibition of hormone metabolism is clearly desirable, and such studies are now being continued at Harvard (22).

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