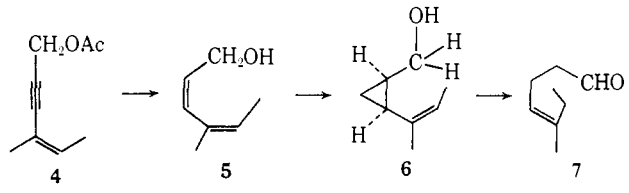


Figure 1.

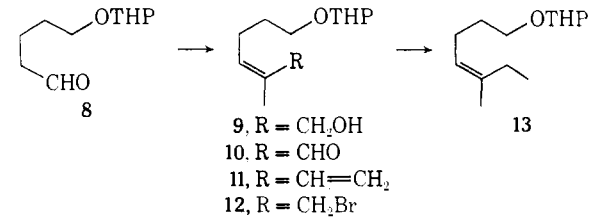


Figure 2.

complex.[15] Reaction of **8** with 1 equiv of ethylidinetriphenylphosphorane in tetrahydrofuran (from the phosphonium bromide and *n*-butyllithium at 0°) at −78°[10] produced the Wittig betaine which after *ca.* 5 min was treated dropwise over 20 min with 1 equiv of *n*-butyllithium. The resulting deep red solution of β-oxido phosphonium ylide[16] was allowed to warm to 0° and then treated with 2 equiv of dry paraformaldehyde. After 0.5 hr at 0° and 1 hr at 25°, the product was isolated by addition of water, extraction, and column chromatography on neutral alumina to give the pure alcohol **9**[11,16] in 60% yield. Oxidation of **9** with activated manganese dioxide in hexane afforded the aldehyde **10**[11] which was transformed into the conjugated diene **11**[11] (80% from **9**) by treatment[10] with methylenetriphenylphosphorane in tetrahydrofuran. Reduction of **11** with excess diimide (from 9 equiv of hydrazine and 7 equiv of 30% hydrogen peroxide in ethanol containing a trace of copper sulfate)[17] at 0° proceeded selectively to give after hydrolysis with 5 m*M* *p*-toluenesulfonic acid in methanol (30 min at 25°) 66% yield of the desired alcohol **1**, free of stereoisomeric impurities as determined by vapor-phase chromatographic analysis and identical in all respects with samples of **1** obtained by the process involving intermediates **4**–**7**.

The alcohol **9** could also be converted to **1** by an alternative route *via* the bromide **12**[11a] which was prepared in 98% yield by treating a solution of **9** and excess lithium bromide in dry ether at −78° successively with *n*-butyllithium (1 equiv) and methanesulfonyl chloride (1.05 equiv), allowing the resulting suspension to warm to −10° over 30 min, and then maintaining the reactants at −10° for 30 min and 25° for 6 hr.[18] Reaction of **12** with trimethylironlithium[19] (6 equiv) in tetrahydrofuran–ether (4:1)[10] at −78° for 20 hr followed by isolation of **13** and cleavage of the tetrahydropyranyl group in acidic methanol afforded after distillation the alcohol **1** in 77% yield and *ca.* 95% purity by vapor-phase chromatographic analysis.[20]

The unsaturated alcohol **1**, which is now easily available by the above-described synthetic routes, has been used successfully in the synthesis of the C_{17} and C_{18} Cecropia juvenile hormones, as is reported in the following communication.[1] These syntheses provide an independent confirmation, if needed, of the stereochemistry of **1**.[21]

(15) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(16) See E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226, 3523 (1970).

(17) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961).

(18) (a) G. Stork, P. A. Grieco, and M. Gregson, *ibid.*, 1393 (1969); (b) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, in press.

(19) E. J. Corey and G. H. Posner, *Tetrahedron Lett.*, 315 (1970).

(20) The iron reagent[19] is superior to dimethylcopperlithium [E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967)] in this case, since the latter reagent affords approximately a 1:1 mixture of **1** and the isomeric product resulting from allylic transposition in the cross-coupling reaction [see R. J. Anderson, C. A. Henrick, and J. B. Siddall, *ibid.*, **92**, 735 (1970)]. The utility of the iron reagent in such cases is also borne out in other experiments performed in these laboratories by H. Yamamoto.

(21) This work was assisted financially by a grant from the Hoffmann-La Roche Co. and a National Institutes of Health Fellowship to D. K. H.

* Address correspondence to this author.

E. J. Corey,* Hisashi Yamamoto, David K. Herron, Kazuo Achiwa

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received August 5, 1970

Simple, Stereospecific Syntheses of C_{17}- and C_{18}-Cecropia Juvenile Hormones (Racemic) from a Common Intermediate

Sir:

The extraordinary level of current chemical interest in insect juvenile hormones (JH) and the possibility of their application to the control of insect populations are reflected in the development of a wide range of synthetic approaches to the presently known JH of Cecropia. Perhaps of greatest interest are those routes which are stereospecific or highly stereoselective.[1-5] This communication records an unusually simple and efficient route which utilizes a *single* synthetic intermediate for the two known Cecropia juvenile hormones (C_{17} and C_{18} JH) and which is also *stereospecific*. This approach depends crucially on the recently developed method for stereospecific synthesis of trisubstituted olefins from β-oxido phosphonium ylides.[6,7]

Reaction of the phosphonium iodide **1**[8,9] (mp 178–179°) in dry tetrahydrofuran (THF) with 1 equiv of *n*-butyllithium at 0° for 30 min[10] afforded a solution of

(1) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, **90**, 5618 (1968).

(2) W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *ibid.*, 90, 6225 (1968).

(3) R. Zurflüh, E. N. Wall, J. B. Siddall, and J. Edwards, *ibid.*, **90**, 6224 (1968).

(4) W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and J. Faulkner, *ibid.*, **92**, 4463 (1970).

(5) For references to other syntheses, see E. E. van Tamelen and J. P. McCormick, *ibid.*, **92**, 737 (1970). For more general reviews, see (a) C. E. Berkoff, *Quart. Rev., Chem. Soc.*, **23**, 372 (1969); (b) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970).

(6) E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226, 3523 (1970).

(7) E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).

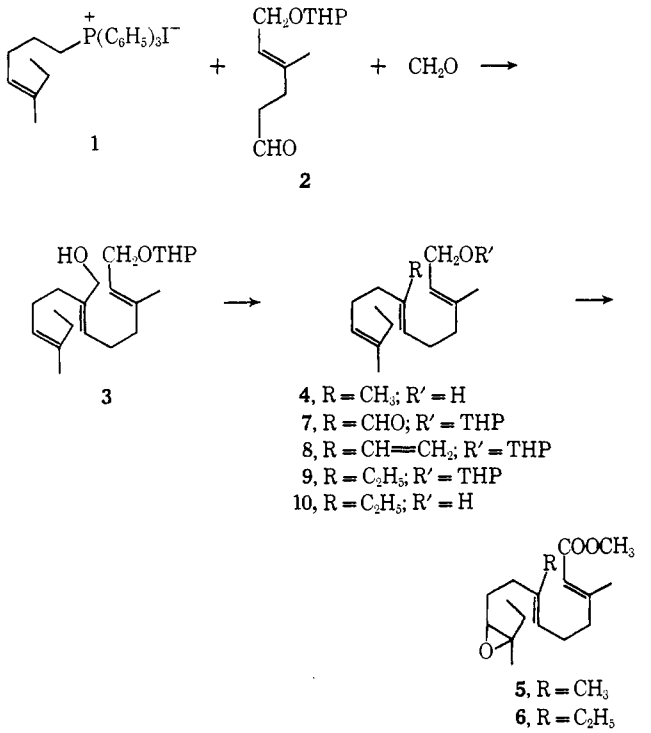
(8) Prepared from the corresponding unsaturated alcohol [E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Amer. Chem. Soc.*, **92**, 6635 (1970)] in 75% yield by the sequence ROH → ROTs (tosyl chloride–pyridine at −20° for 24 hr) → RI (sodium iodide in dry acetone at 25° for 18 hr) → $RP^+(C_6H_5)_3I^-$ (triphenylphosphine in benzene).

(9) Satisfactory (a) spectroscopic and (b) analytical data were obtained for this intermediate. Unless indicated otherwise, all intermediates were colorless oils.

the corresponding ylide. This was cooled to −78° and allowed to react with the aldehyde **2**[9,11] at −78° for 5 min. The resulting solution of the carbonyl adduct (Wittig betaine) was warmed to −25° and then treated with 2 equiv of *sec*-butyllithium (1.26 *M* in pentane)[6,7,12] over a 5-min period to give a deep red solution of β-oxido ylide. The solution of β-oxido ylide was then brought to 0°, and after the addition of 3 equiv of dry paraformaldehyde in one portion, the resulting mixture was stirred at 25° for 30 min. Addition of water, extraction, and chromatographic separation to remove triphenylphosphine oxide yielded the unsaturated alcohol derivative **3**[9] (50%) uncontaminated by stereoisomeric or other impurities. Thus in a single step the basic JH chain was assembled from three components specifically in the correct stereochemical form.[13]

The synthesis of the *dl*-C_{17} JH **5**[9] was then accomplished from **3** by the sequence: A, $CH_2OH \rightarrow CH_3$ and $CH_2OTHP \rightarrow CH_2OH$ to give **4**[9] (pyridine–sulfur trioxide complex in THF at 0° for 9 hr followed by lithium aluminum hydride at 0° for 12 hr,[14] with removal of tetrahydropyranyl group using 5 m*M* methanolic *p*-toluenesulfonic acid at 25° for 1 hr); B, CH_2OH of **4** → $COOCH_3$[9] (manganese dioxide oxidation first in hexane then in methanol containing sodium cyanide and hydrogen cyanide,[15] 60%); and finally C, terminal epoxidation as previously described[1] (60% yield).[16,17] The homogeneity of the various synthetic intermediates was established by careful vapor-phase chromatographic (vpc) analysis.

The conversion of the intermediate **3** to the *dl*-C_{18} JH **6** was also accomplished by a sequence of straightforward steps. Oxidation of **3** with excess activated manganese dioxide in hexane at 25° for 1 hr gave the aldehyde **7**[9] which was converted to the vinyl derivative **8**[9] (93% from **3**) using methylenetriphenylphosphorane in THF. Diimide reduction of **8** using ethanolic hydrogen peroxide–hydrazine in the presence of copper ion catalyst[18] was completely selective and afforded the desired triene **9**[9] in 70% yield. Removal of the tetrahydropyranyl group in **9** gave the corresponding alcohol **10**[9] homogeneous by vpc analysis and identical with the trienol previously synthesized and converted into C_{18} JH **6**.[15,19]



Using the reactions outlined above, both the C_{17} and the C_{18} JH can now be prepared in substantial amount using ordinary laboratory equipment, since all yields are good and since no complex separations are required. The advantages of the route are also considerable for the synthesis of analogs and labeled forms of these hormones.[20]

(20) This work was assisted financially by a grant from the Hoffmann-La Roche Co.

* Address correspondence to this author.

E. J. Corey,* Hisashi Yamamoto
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received August 5, 1970

(10) This and other reactions involving strongly basic reagents were performed under an atmosphere of dry nitrogen or argon.

(11) Prepared in a manner analogous to the corresponding acetoxy aldehyde; see E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 4318 (1969); G. Stork, M. Gregson, and P. A. Grieco, *Tetrahedron Lett.*, 1391 (1969).

(12) *sec*-Butyllithium in tetrahydrofuran has been found in several instances in these laboratories to be the reagent of choice for generation of β-oxido phosphonium ylides from Wittig betaines.

(13) The stereochemical course of this synthetic sequence was predicted from previous work.[6,7]

(14) E. J. Corey and K. Achiwa, *J. Org. Chem.*, **34**, 3667 (1969).

(15) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, **90**, 5616 (1968).

(16) The introduction of the epoxide function can in all probability be accomplished with greater efficiency at several of the earlier stages of the synthesis. This point is under investigation.

(17) The synthesis of the *dl*-C_{17} JH has previously been accomplished by W. S. Johnson, S. F. Campbell, A. Krishnakumaran, and A. S. Meyer, *Proc. Nat. Acad. Sci. U. S.*, **62**, 1005 (1969).

(18) E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Lett.*, 347 (1961); E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, **87**, 5736 (1965).

(19) The epoxide function can also be introduced selectively at the desired location by reaction of the vinyl derivative **8** with 1 equiv of *m*-chloroperbenzoic acid in methylene chloride containing sodium bicarbonate.

New Stereospecific Synthetic Routes to Farnesol and Its Derivatives, Including a Biologically Active Position Isomer of C_{17} Cecropia Juvenile Hormone

Sir:

This communication reports the application of the stereospecific synthesis of olefins from β-oxido phosphonium ylides and carbonyl compounds which has recently been described[1,2] to the synthesis of farnesol and certain of its derivatives. The approaches parallel those described in the foregoing communication for the synthesis of the Cecropia juvenile hormones.[3]

Farnesol itself (**4**) has been synthesized in *two steps* stereospecifically from the phosphonium salt **1**, the aldehyde **2**, and paraformaldehyde, as follows. The phosphonium iodide **1**,[4,5] mp 134–135°, was converted

(1) E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226, 3523 (1970).

(2) E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).

(3) E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 6636 (1970).

(4) Prepared from 5-methyl-4-hexen-1-ol by the sequence ROH → ROTs → RI → $RP^+(C_6H_5)_3I^-$ using the conditions described in the foregoing communication[3] for the homologous series. The starting