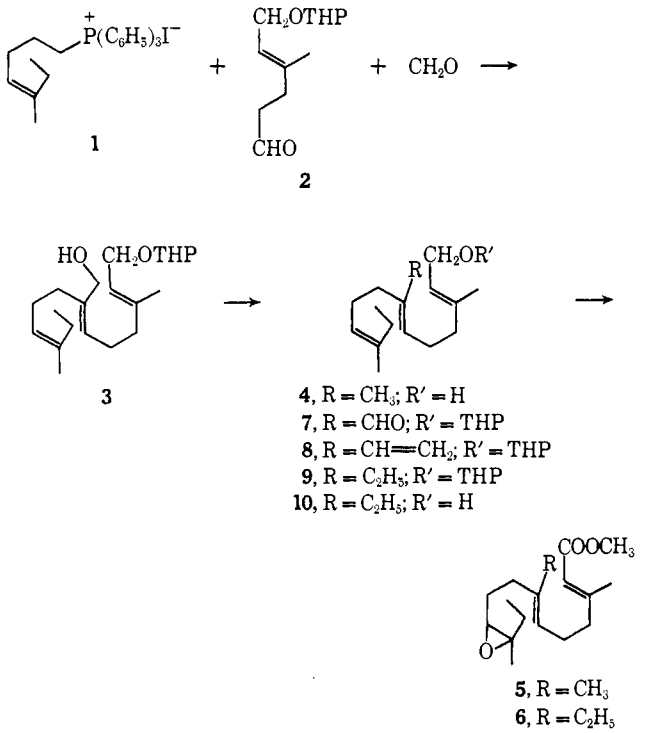
the corresponding ylide. This was cooled to −78° and allowed to react with the aldehyde **2**[9,11] at −78° for 5 min. The resulting solution of the carbonyl adduct (Wittig betaine) was warmed to −25° and then treated with 2 equiv of *sec*-butyllithium (1.26 *M* in pentane)[6,7,12] over a 5-min period 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]




**1** **2** **3**

**4**, R = $CH_3$; R′ = H
**7**, R = CHO; R′ = THP
**8**, R = CH=$CH_2$; R′ = THP
**9**, R = $C_2H_5$; R′ = THP
**10**, R = $C_2H_5$; R′ = H

**5**, R = $CH_3$
**6**, R = $C_2H_5$

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]

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(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

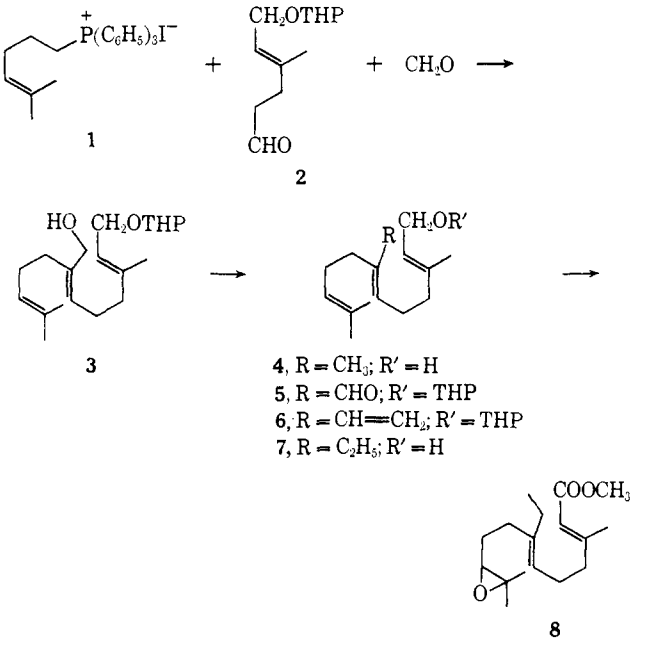
to the corresponding ylide with 1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at 0°;[6] then the mixture was cooled to −78° and the aldehyde **2**[3] was added. After decolorization of the ylide (*ca.* 5 min), the reaction mixture was brought to −25°, treated with 2 equiv of *sec*-butyllithium, brought to 0°, and then treated with 3 equiv of dry paraformaldehyde. The mixture was stirred at 25° for 30 min, and the product was isolated by addition of water, extraction, and chromatographic removal (silica gel) of triphenylphosphine oxide and other much more polar by-products. The hydroxy farnesol derivative **3**[5] was thus obtained in 46% yield. Deoxygenation of the allylic alcohol unit in **3** using the bisulfate ester–hydride method[3,7] with THF as solvent, followed by acid-catalyzed removal of the tetrahydropyranyl group, produced *trans,trans*-farnesol (**4**)[5] free of isomeric impurities as determined by vapor-phase chromatography (vpc) (using a 4 ft × 0.125 in. 3% OV-1 column at 150°) and thin layer chromatography in 75% yield from **3**.[8]

The stereochemical control and the flexibility inherent in this approach to the construction of the farnesol system suggest the application of the method to the synthesis of numerous biologically and biogenetically interesting structures of the acyclic triisoprenoid type. Studies in this area will be reported in future publications. One obvious objective, the synthesis of the position isomer **8** of the $C_{17}$ Cecropia juvenile hormone,[9] has already been attained in the following way using procedures which parallel those described in the accompanying communication[3] for the synthesis of the two known insect juvenile hormones.

The hydroxylated farnesol derivative **3** was oxidized using excess manganese dioxide in hexane at 25° for 1 hr to the aldehyde **5**[5] which was then treated[6] with methylenetriphenylphosphorane (1.2 equiv in THF) to give the tetraene **6**[5] in 93% overall yield from **3**. Exposure of **6** to a moderate excess of diimide at 0° in ethanol (generated from 8.5 equiv of hydrazine and *ca.* 0.05 equiv of copper sulfate in ethanol by slow addition of 7 equiv of 30% aqueous hydrogen peroxide),[10] followed by cleavage of the tetrahydropyranyl ether in methanol containing *p*-toluenesulfonic acid (5 m*M*) at 25° for 1 hr, led to highly selective formation of the homofarnesol **7**[5] (71% yield after isolation). The hydroxymethylene group of **7** was converted to carbomethoxy by oxidation with manganese dioxide, first in hexane then in methanol containing sodium cyanide–hydrogen cyanide,[11,12] and the resulting ester was epoxidized at the terminal olefinic group as previously described for the $C_{18}$ Cecropia juvenile hormone case[12,13] to give the epoxy homofarnesoic acid methyl ester **8**[5] (*ca.* 35% from **7**).

Detailed studies on the biological activity of the synthetic epoxy ester **8** are being conducted by Professor Lynn M. Riddiford and Mr. Alfred M. Ajami[14] and will be reported elsewhere. Their investigation has shown that **8** possesses high biological activity, the level of which varies considerably from one species of insect to another. In some instances, however, the activity shown by **8** is higher than that of the $C_{18}$ Cecropia juvenile hormone. In addition, with certain species of insects the application of **8** results in a striking degree of localization of hormonal effects.

Further studies in this area will be reported in due course.[15]




alcohol is readily available from the reaction of lithium aluminum hydride in tetrahydrofuran with 5-methyl-4-hexenoic acid: G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).

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

(6) Reaction mixture maintained under an inert atmosphere.

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

(8) For another recent stereospecific synthesis of farnesol, see E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967).

(9) A. S. Meyer, H. A. Schneiderman, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968).

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

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

(12) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968).

(13) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(14) Biological Laboratories, Harvard University.

(15) This work was assisted financially by the Hoffmann-La Roche Co.

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## Structures of Rubratoxins A and B

*Sir:*

*Pencillium rubrum* has been identified as one of several organisms responsible for fatal poisoning of livestock and poultry fed infected cereals.[1] Attempts to isolate chemical agents associated with the hepatotoxic activity of *P. rubrum*[2] have resulted in characterization of two substances, named rubratoxins A and B.[3] Spectral

(1) J. E. Burnside, W. L. Sippet, J. Forgacs, W. T. Carll, M. B. Atwood, and E. R. Coll, *Amer. J. Vet. Res.*, **18**, 817 (1957); J. Forgacs, H. Koch, W. T. Carll, and R. H. White-Stevens, *ibid.*, **19**, 744 (1958); A. W. Hayes and B. J. Wilson, *Appl. Microbiol.*, **16**, 1163 (1968); G. N. Wogan and R. I. Mateles, *Progr. Ind. Microbiol.*, 7, 149 (1968).

(2) (a) B. J. Wilson and C. H. Wilson, *J. Bacteriol.*, **83**, 693 (1962); B. J. Wilson and C. H. Wilson, *ibid.*, **84**, 283 (1962); (b) J. D. White, Ph.D. Thesis, Massachusetts Institute of Technology, 1965.