A New Approach to the Stereospecific Total Synthesis of Racemic *Cecropia* Juvenile Hormone†

By KIYOSI KONDO,* AKIRA NEGISHI, KIYOHIDE MATSUI, and DAIEI TUNEMOTO
(*Sagami Chemical Research Center*, 3100 *Onuma, Sagamihara-shi* 229, *Japan*)
and SATORU MASAMUNE
(*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada*)

Summary 4-Methyl-5,6-dihydro-2*H*-thiopyran and its dimer (**4**) are used as structural units for the synthesis of C_{18}-juvenile hormone.

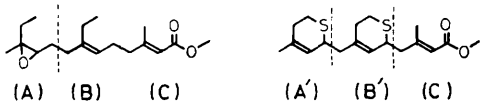
WE describe herein a new and economically feasible method for the stereospecific synthesis[1] of a racemic *Cecropia* juvenile hormone (C_{18}-J.H.), based on condensation of dihydrothiopyrans. The structure of C_{18}-J.H. can be divided into three structural units (A)—(C). The configuration of two ethyl groups in units (A) and (B) might be retained if they were blocked with two sulphur atoms [see (A′) and (B′)]. These blocking atoms could easily be removed by reductive desulphurization.

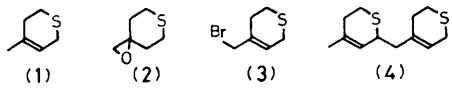
A key intermediate, the thiopyran (**4**), was synthesised by two methods. Condensation of tetrahydrothiopyran-4-one[2] with dimethyloxosulphonium methylide afforded the epoxide (**2**)‡ (65%), m.p. 52°. The carbanion prepared from the thiopyran (**1**)[3] and Bu^{n}Li in the presence of 2,3-diazabicyclo[2,2,2]octane (DABCO) was treated with the epoxide (**2**) in THF at −20° and the resulting adduct was further dehydrated with $SOCl_2$–pyridine to give the desired dimeric dihydrothiopyran (**4**) [73% based on (**2**)],

† Presented at the 26th Annual Meeting of Japan Chemical Society, April 1st, 1972, Hiratsuka, Japan.

‡ All new compounds gave satisfactory elemental analyses and i.r. and n.m.r. spectra consistent with the assigned structures.

b.p. 85° at 0·2 mmHg. The other method was based on the condensation of (**1**) with (**3**), which was prepared from tetrahydrothiopyran-4-one by treatment with HCN, followed by solvolysis with EtOH, dehydration, reduction, and bromination with PBr_3.

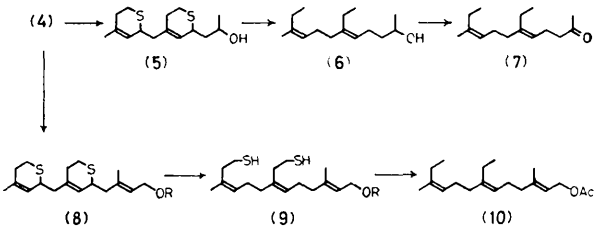




Attachment of the final unit (C) and the removal of the blocking sulphur atoms were carried out by the following routes.

Route A: The dimer (**4**) was converted into a carbanion by treatment with Bu^nLi–DABCO and was then treated with propylene oxide to afford the alcohol (**5**) (84%). Reductive desulphurization of (**5**) by treatment with metallic Li in ethylamine[4] at −20° produced the dodecadienol (**6**) (60%), b.p. 97—98° at 0·45 mmHg. Oxidation of the alcohol (**6**) with Jones reagent yielded the ketone (**7**) (85%), b.p. 98—99° at 1·5 mmHg, which was further transformed into deoxy C_{18}-J.H. by condensation with diethyl methoxycarbonylmethylphosphonate.[5] Epoxidation[6] of the ester gave racemic J.H., which was identical spectroscopically with natural J.H.[7]

Route B: The carbanion of dimer (**4**) was condensed with *trans*-4-chloro-3-methylbut-2-enyl tetrahydropyranyl ether, prepared from isoprene,[8] to yield the triene (**8**; R = THP) (60%). The trienol (**8**; R = H) was treated with Li in ethylamine at −70° and the resulting dithio-alcohol (**9**; R = H) was converted into the corresponding acetate (**9**; R = Ac) (80%). Final desulphurization of (**9**; R = Ac) was achieved by treatment with excess of deactivated Raney nickel (W-2/acetone) to give the acetate (**10**) as a colourless oil (55%), b.p. 115° at 0·15 mmHg. Deoxy-C_{18}-J.H. obtained from (**10**) by the method of Corey *et al.*[9] was identical spectroscopically with that prepared from the ketone (**7**).



C_{18}-J.H. can thus be obtained with 100% stereospecificity at C-6 and C-10 and 95% or more at C-2[10] by route A, and with complete stereospecificity by route B.

This investigation was supported by Kawakami Memorial Foundation. S.M. thanks the Defence Research Board of Canada and Hoffmann-La Roche, Inc. for financial support.

(*Received*, 30*th August* 1972; *Com.* 1514.)

[1] E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, 19668, **90**, 5618; R. Zurflüh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *ibid.*, 6224; W. S. Johnson, T. Li, D. J. Faulkner, and S. F. Campbell, *ibid.*, p. 6225; E. J. Corey and H. Yamamoto, *ibid.*, 1970, **92**, 6636; E. E. van Tamelen, P. McCurry, and U. Huber, *Proc. Nat. Acad. Sci. U.S.A.*, 1971, **68**, 1294.
[2] E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, 1948, **70**, 1813.
[3] R. F. Naylor, *J. Chem. Soc.*, 1949, 2749.
[4] A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1957, 1969.
[5] K. H. Dahm, B. M. Trost, and H. Röller, *J. Amer. Chem. Soc.*, 1967, **89**, 5292.
[6] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.
[7] B. M. Trost, *Accounts Chem. Res.*, 1970, **3**, 120.
[8] W. Oroshnik and R. A. Mallory, *J. Amer. Chem. Soc.*, 1950, **72**, 4608.
[9] E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, 1968, **90**, 5616.
[10] Y. Butsugan, M. Murai, and T. Matsuura, *Nippon Kagaku Zasshi*, 1969, **89**, 431.