has been assigned to NO^{-}[9 4] is probably not correct. The frequency of an isolated NO^{-} ion should be nearer to the 1556 cm^{-1} of O_2.

(4) Griffith *et al.*, Table I, footnote *f*.

(5) Supported in part by the U. S. Atomic Energy Commission while on a Guggenheim Fellowship at the Hebrew University of Jerusalem.

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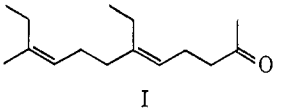
Received June 27, 1968

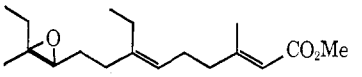
Synthetic Studies on Insect Hormones. VII.[1] An Approach to Stereospecific Synthesis of Juvenile Hormones[2]

Sir:

We wish to report a stereospecific synthesis of *trans*,-*cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one (I), a key intermediate in a synthesis[3] of juvenile hormone (II).[4]



I

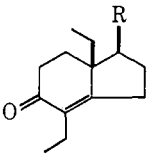


II

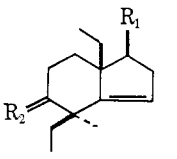
A scarcity of convenient methods for stereospecific synthesis of acyclic trisubstituted olefins led us to examine sequential fragmentation of a bicyclic precursor, VI. Control of olefin geometry is thereby transposed to control of relative stereochemistry in cyclic systems.

Consideration of the *trans* and *cis* olefin geometries in I dictates the required stereochemistry[5] at four of the asymmetric centers in the chosen precursor VI. Configuration at the fifth center, C_{3a}, does not influence the geometry of olefin formation, but markedly affects the ease of concerted internal cleavage in VIb.

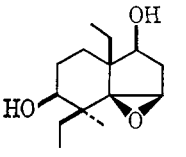
Synthesis of VI was commenced by Michael addition of 2-ethylcyclopentane-1,3-dione,[6] in refluxing methanolic potassium hydroxide solution, to propyl vinyl ketone and *p*-toluenesulfonic acid catalyzed cyclization of the adduct in boiling benzene to afford IIIa[7] [67%; bp 125–127° (0.08 mm)]. Selective reduction of the cyclopentanone carbonyl of IIIa with ethanolic sodium borohydride at 5° led stereospecifically to the required *cis*[8] relationship between hydroxyl and angular ethyl in IIIb[7] (88%; mp 61–62°).



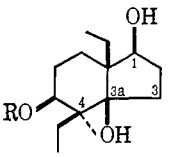
IIIa, R = carbonyl O
b, R = OH
c, R = OTHP



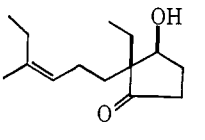
IVa, R_1 = OTHP; R_2 = O
b, R_1 = OH; R_2 = O
c, R_1 = OH; R_2 = β-OH, α-H



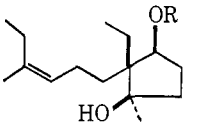
V



VIa, R = H
b, R = *p*-tosyl



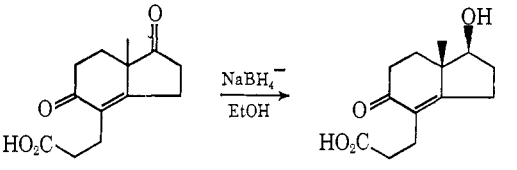
VII



VIIIa, R = H
b, R = *p*-tosyl
c, R = 3,5-dinitrobenzoyl

Protection of IIIb as a tetrahydropyran-2-yl ether (THP) allowed generation from IIIc (5 equiv of 0.37 *M* potassium *t*-butoxide in refluxing *t*-butyl alcohol) of the enolate anion which was alkylated from the less hindered α face[9] by methyl iodide at 0° to afford IVa [nmr,[10] 0.81 (t, J = 7 Hz), 1.03 (t, J = 7 Hz, ethyl CH_3), and 1.15 (s, 4α-methyl); 62% from IIIa]. Stereoselectivity of alkylation was indicated to be 95% by gas chromatographic and nmr analyses of IVa and the derived acid hydrolysis product IVb [nmr, 1.14 (s, 4α-methyl)]. Lithium tri-*t*-butoxyaluminum hydride reduction of IVb in refluxing tetrahydrofuran afforded a single crystalline diol, IVc[7] [74%; mp 153–155°; nmr, 1.09 (s, 4α-methyl), 3.33 (dd, J_{aa} = 10 Hz, 5α-H)] with the necessary *cis* orientation of the new equatorial hydroxyl[11] relative to the 4β-ethyl group.

3086 (1963), similarly obtained the alcohol ii of proven stereochemistry from diketone i which is closely similar to IIIa.

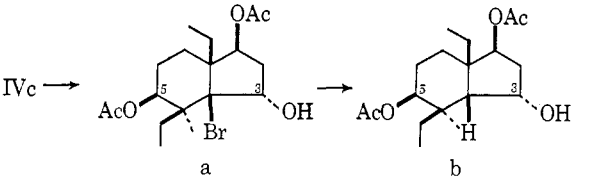


i ii

(9) α Configuration of the 4-methyl in IVa is stated here for clarity but is assigned from the later finding that fragmentation through C-4 and C-5 in VIb gave stereospecifically a *cis* olefin which fixes[5] the relative configurations at C-4 and C-5. Establishment of configuration[11] at C-5 then allowed assignment at C-4.

(10) Nmr spectra were recorded on a Varian HA-100 spectrometer using deuteriochloroform as solvent and are quoted as δ (parts per million) downfield from tetramethylsilane as internal standard. We wish to thank Miss J. Tremble and Dr. Phyllis Kaplan for these determinations.

(11) The β configuration of hydroxyl at C_5 follows from sequential conversion of IVc to a diacetate and a bromohydrin (a)[7] (mp 144–146°) and chromous acetate–thiophenol reduction of the latter to a diacetoxy secondary alcohol (b)[7] (mp 113–114°). Nmr spectra[10] of compound



a b

(1) Part VI: G. Hüppi and J. B. Siddall, *Tetrahedron Letters*, 1113 (1968).

(2) Publication No. 348 from the Syntex Institute of Steroid Chemistry.

(3) K. H. Dahm, H. Röller, and B. M. Trost, *Life Sci.*, **7**, 129 (1968); K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, **89**, 5292 (1967).

(4) H. Röller, K. H. Dahm, C. C. Sweely, and B. M. Trost, *Angew. Chem. Intern. Ed. Engl.*, **6**, 179 (1967).

(5) P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961), and ref 2 therein.

(6) We are grateful to Dr. Herchel Smith for a generous gift of this compound.

(7) Satisfactory elemental analytical data were obtained for this substance.

(8) *Cf.* Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron*, **24**, 2039 (1968), and ref 6, 8, and 9 therein; H. Smith, *et al.*, *J. Chem. Soc.*, 4472 (1964); L. Velluz, *et al.*, *C. R. Acad. Sci., Paris, Ser. C*, **257**,

Epoxidation of IVc with *m*-chloroperbenzoic acid in ether gave only α-epoxide[7] (mp 158–160°), identical with the product from methanol–sodium hydroxide treatment of the bromohydrin[11] a, whereas epoxidation in dichloromethane at 5° allowed hydroxyl-assisted formation of the β-epoxide V[7] (50%, mp 162–163°) from IVc.

Optimal geometry[12] for concerted cleavage of C_{3a}–C_4 and C_5–O bonds is attained in VIa[7] (mp 133–135°), produced in 65% yield by lithium aluminum hydride reduction of V in refluxing dioxane. Treatment of the triol VIa with *p*-toluenesulfonyl chloride (5 equiv) in pyridine at 5° led selectively to the equatorial 5β-tosylate VIb (89%; $\nu_{max}^{CCl_4}$ 1600, 1360, 1180, and 1170 cm^{-1}) which underwent quantitative[13] fragmentation on exposure to sodium hydride in dry tetrahydrofuran at 20° with formation of the *cis*-olefinic ketone VII [$\nu_{max}^{CCl_4}$ 1735 cm^{-1}; nmr 1.67 (d, J = 1.5 Hz, vinylic CH_3) and 5.04 (t, J = 7.5 Hz, vinylic H); semicarbazone[7] mp 144–145°]. Gas chromatographic and nmr analyses of VII did not reveal the presence of any *trans* isomer.

Alkylation of this ketone by ethereal methyllithium to form the diol VIIIa (57%; 3,5-dinitrobenzoate[7] VIIIc mp 91–91.5°) was facilitated by temporary protection of the hydroxyl in VII as a tetrahydropyranyl ether. Reaction of the diol VIIIa with excess *p*-toluenesulfonyl chloride–pyridine was slow but gave cleanly the tosylate VIIIb (95%) which fragmented smoothly in the presence of sodium hydride in dry tetrahydrofuran to generate the central *trans* olefinic bond in *trans,cis*-6-ethyl-10-methyldodeca-5,9-dien-2-one (I; 80% from VIIIb; $\nu_{max}^{CCl_4}$ 1715 cm^{-1}; nmr 1.66 (d, J = 1.5 Hz, vinylic CH_3), 2.12 (s, $COCH_3$), 5.04 (m, 2-vinylic H), homogeneous by gas chromatographic[14] analysis).

Assignment of *cis* geometry to the 9,10 double bond in I is based on the 1.66-ppm chemical shift of the vinylic methyl group. In this series the corresponding *trans* isomers consistently show[3] vinylic methyl signals at 1.59–1.61 ppm.

The stereospecific formation of the central 5,6 double bond in I by fragmentation enables its geometry to be related directly[5] to the configurations of angular ethyl and secondary hydroxyl in VIIIa. Since the *cis* relationship of the latter groups in VIIIa was produced from IIIa by a borohydride reduction whose stereochemical course is well established[8] in such systems, the 5,6 double bond of I can be assigned *trans* geometry.

Acknowledgment. The authors wish to thank Dr. J. H. Fried for helpful discussions.

(15) Syntex Postdoctoral Fellows: (a) 1968–1969; (b) 1967–1968.

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A Highly Stereoselective Synthesis of the Racemic Juvenile Hormone

Sir:

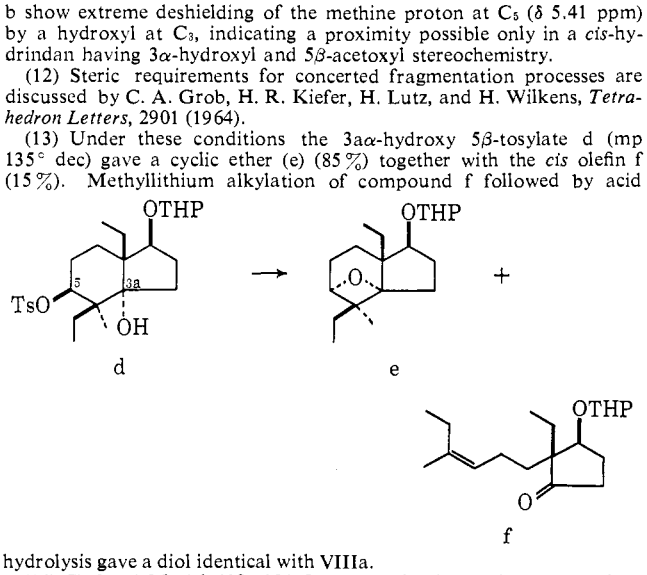
In a series of brilliant investigations Dahm, *et al.*,[1] have shown that the extremely potent substance responsible for arresting develoment at the pupa stage in *Hyalaphora cecropia* is methyl *trans,trans,cis*-10-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (**1**), called the juvenile hormone.[2] Their published work has culminated in a total synthesis of the racemic hormone which, although not stereoselective, made available many of the stereoisomers and set the stage for the next major development, namely a stereoselective synthesis. We are reporting here on the realization of this aim.[3] Our synthesis is based on an application of the highly stereoselective modification of the Julia method for producing *trans*-trisubstituted olefinic bonds[4] which involves in the key step the rearrangement of a cyclopropylcarbinyl to the homoallylic system, as illustrated here by the conversion of the carbinol **5** to the bromide **6**. By this expedient we have developed a scheme which affords the racemic juvenile hormone in 12 steps starting from methyl *trans*-γ-bromo-β,β-dimethylacrylate (**2**)[5] and 1-acetyl-1-ethylcyclopropane (**3**, R = H).[6] At the present stage of development all but two of the steps (see below) proceed in 90% yield or better; thus the hormone is now relatively easily accessible.

Ketone **3** (R = H) was treated with dimethyl carbonate and sodium hydride. The sodio derivative of the resulting β-keto ester **3** (R = CO_2CH_3) was allowed to react with the bromo ester **2** in tetrahydrofuran at

b show extreme deshielding of the methine proton at C_5 (δ 5.41 ppm) by a hydroxyl at C_3, indicating a proximity possible only in a *cis*-hydrindan having 3α-hydroxyl and 5β-acetoxyl stereochemistry.

(12) Steric requirements for concerted fragmentation processes are discussed by C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkens, *Tetrahedron Letters*, 2901 (1964).

(13) Under these conditions the 3aα-hydroxy 5β-tosylate d (mp 135° dec) gave a cyclic ether (e) (85%) together with the *cis* olefin f (15%). Methyllithium alkylation of compound f followed by acid



hydrolysis gave a diol identical with VIIIa.

(14) F & M Model 402, 4% Carbowax 20M on Diatoport S (2 m × 3 mm) at 130°.

(1) See K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, 89, 5292 (1967); *Life Sci.*, 7, 129 (1968), and references cited therein.

(2) This hormone is extremely active simply on external application to numerous species and shows promise of being a "perfect" insecticide; see, *inter alia*, C. M. Williams, *Sci. Am.*, 198, (2) 67 (1958); A. S. Meyer, H. A. Schneiderman, and L. I. Gilbert, *Nature*, 206, 272 (1965).

(3) We have learned by private communication of two recent, highly imaginative stereoselective syntheses of the juvenile hormone, one by E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, and the other by J. O. Edwards, J. Fried, and J. Siddall. We wish to express our thanks to Professor Corey and Dr. Siddall for sending us copies of their manuscripts prior to publication.

(4) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, 90, 2882 (1968).

(5) I. Ahmad, R. N. Gedye, and A. Nechvatal, *J. Chem. Soc.*, 185 (1968). We prepared the material readily by bromination of β,β-dimethylacrylic acid with N-bromosuccinimide. During the work-up the *cis* bromo acid underwent spontaneous lactonization, leaving the desired *trans* isomer as the only acidic material. The acid was easily esterified by the method of R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, 70, 3135 (1948).

(6) This ketone was prepared by the method described for producing 1-acetyl-1-methylcyclopropane (M. Julia, S. Julia, T. S. Yu, and C. Newville, *Bull. Soc. Chim. France*, 1381 (1960)) except that ethyl instead of methyl iodide was used in the alkylation step.