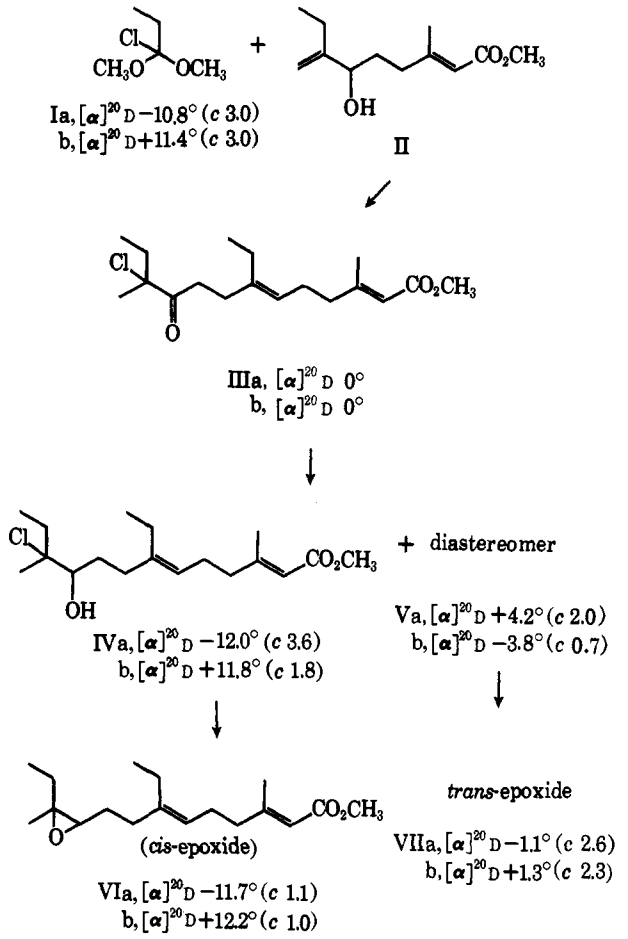
Communications to the Editor

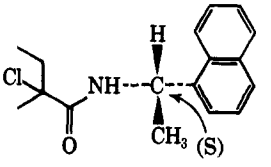
The Synthesis of the Optically Active Form of the C-18 *Cecropia* Juvenile Hormone

Sir:

Of the numerous syntheses of juvenile hormone, none has yet led to the optically active product. Meyer and Hanzmann[1] recently demonstrated that material isolated from the *Cecropia* moth, consisting of a 9:1 mixture of the C-18 and C-17 hormones, is optically active ($[\alpha]_D \sim +7°$); hence the production of the synthetic enantiomeric forms of the hormones gains importance, particularly with respect to making both isomers available for biological tests. In the present communication we describe the synthesis of both enantiomeric forms (VIa and VIb) of the natural (trans,trans,cis) C-18 hormone as well as of the trans,-trans,trans isomer (VIIa and VIIb).



The synthesis was carried out according to a scheme recently described for producing racemic juvenile hormone.[2] Thus the chloro ketal I was prepared, as described below, in both enantiomeric forms a and b, and allowed to interact with the dienol ester II to give, *via* a Claisen rearrangement, the two enantiomeric chloro ketones IIIa and IIIb:[3a,b] CD (IIIa in 95% ethanol, *c* 0.8) (340–250 mμ), $[\theta]_{296}$ +637; (IIIb in 95% ethanol, *c* 1.24) (340–250 mμ), $[\theta]_{297}$ −700. The reaction conditions were modified (1 mmol of I, 2 mmol of II, 0.37 ml of toluene, and 0.025 mmol of 2,4-dinitrophenol) so as to use the chloro ketals efficiently (40% yield with respect to I). Each of these chloro ketones, on reduction with sodium borohydride, gave a pair of diastereoisomeric chlorohydrins, IVa and Va (from IIIa) and IVb and Vb (from IIIb) which were separated by preparative thin-layer chromatography on silica gel.[2] Isomers IVa and IVb were enantiomeric[3a] as were Va and Vb.[3a] Each of these four chlorohydrins, on treatment with methanolic potassium carbonate, was converted into the epoxy compound. Thus IVb gave juvenile hormone VIb (dextrorotatory) and IVa gave the levorotatory enantiomer VIa.[3a-c] Similarly Va gave the levorotatory form of the trans epoxy isomer VIIa, and Vb afforded the dextrorotatory enantiomer VIIb.[3a-c] These four isomers are being subjected to biological tests.[3d]



(1) A. S. Meyer and E. Hanzmann, *Biochem. Biophys. Res. Commun.*, 41, 891 (1970).

(2) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci.*, 67, 1462, 1824 (1970).

(3) The two enantiomers and the racemic material (ref 2) all had identical properties with respect to (a) tlc behavior, (b) vpc behavior, and (c) nmr spectral characteristics. Unless indicated otherwise, chloroform solutions were used for obtaining rotation measurements.

(3d) Note Added in Proof. Biological tests (private communication from J. B. Siddall and G. B. Staal, Zoecon Corporation) for morphogenetic activity in fresh (0–24 hr) pupae of the wax moth *Galleria mellonella*, by topical application to the ventral side of the pupae, showed that both enantiomers VIa and VIb were active, but the latter (+) isomer was approximately nine times more active than VIa. The slopes were also approximately parallel and the 50% activity dose for isomer VIb was 0.025 μg/pupa. Tests in *Tenebrio* (private communication from H. A. Röller and D. Meyer, Texas A & M University) showed that our (+)-isomer VIb had activity equal to that of natural juvenile hormone (JH) and was 6–8 times more active than the enantiomer VIa; moreover, the *trans*-epoxide VIIa was 3–4 times more active than the enantiomer VIIb.

In connection with these biological results, the question of the enantiomeric purity of our products becomes especially important. We have made the reasonable assumption that no racemization occurred at any of the steps of the synthesis; however, the matter remains to be proved. Indeed in preliminary experiments, performed by B. E. Ratcliffe, involving esterification of the chlorohydrins with excess optically active α-methoxy-α-trifluoromethylphenylacetyl chloride in pyridine (which required 3 days at room temperature—a treatment which in itself could possibly have caused some racemization) and observing the fluorine nmr signals at 100 MHz (thanks to the help of L. J. Durham) of the resulting esters (the method of J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969); we thank Professor Mosher for a generous supply of the acid chloride), we have obtained evidence that the ester of IVa is contaminated with 5–10% of its enantiomer. Also K. Nakanishi and D. A. Schooley have kindly conducted high-pressure liquid chromatography experiments on our esters, and reached a similar conclusion, namely that the enantiomeric impurity amounted to approximately 8%. Therefore, our specimen of (−)-JH (VIa) *may* contain up to 10% of the (+) isomer, which could account for most or even all of the observed biological activity; hence further work must be done on the difficult problem of ensuring unequivocally that we have in hand 100% optically pure (−)-JH, before quantitative conclusions can be reached regarding its biological activity.

The two enantiomeric forms (Ia and Ib) of the chloro ketal were prepared as follows. α-Methylbutyraldehyde was converted, by the action of cupric chloride in dimethylformide,[4] into α-chloro-α-methylbutyraldehyde, n^{23}D 1.4214 (*Anal.* Found: C, 49.7; H, 7.5; Cl, 29.3), which was oxidized with potassium permanganate in ~4 *N* sulfuric acid[5] to α-chloro-α-methylbutyric acid, n^{23}D 1.4402 (*Anal.* Found: C, 43.8; H, 6.6; Cl, 25.8). This chloro acid was converted by treatment with thionyl chloride into the acid chloride which without purification was allowed to interact with (−)-α-(1-naphthyl)ethylamine in dioxane containing triethylamine,[6] giving a mixture of diastereomeric amides VIIIa and VIIIb, mp 60–63°, which was separated by preparative tlc on silica gel (hexane–EtOAc, 9:1). Thus a total of 1.3 g of VIIIa, mp 72–73° (*Anal.* Found: C, 70.6; H, 7.0; Cl, 12.1; N, 4.8) and 1.26 g of VIIIb, mp 73–74° (*Anal.* Found: C, 70.6; H, 6.9; Cl, 12.1; N, 4.8) were obtained. The nmr spectrum at 100 MHz ($CDCl_3$, TMS internal standard) included, in particular, a singlet at δ 1.70 (3 H) for the methyl group on the carbon holding the chlorine atom, while in the spectrum of VIIIb this band appeared at δ 1.79 ppm. The amides were hydrolyzed by heating with a 1:1 mixture of dioxane and ~25 *N* sulfuric acid at 95° for 4 hr to give in 95–100% yield the enantiomeric forms of the aforementioned chloro acid, $[\alpha]^{20}$D (for isomer a, derived from VIIIa) +7.9° (*c* 1.6, 95% ethanol); $[\alpha]^{20}$D (for isomer b, derived from VIIIb) −7.8° (*c* 1.7, 95% ethanol). These acids were each converted into the chloro ketals by the following especially refined procedure, without purification of intermediates. The acid (2 mmol) was heated with 6 mmol of thionyl chloride at 70° for 3.5 hr; then 5.3 mmol of formic acid was added to destroy the excess thionyl chloride (70°, 15 min). The mixture was diluted with ether and added at 0° to 9 mmol of diazomethane in ether. After 1 hr at 23°, the solvent was evaporated and the residue was dissolved in 2 ml of methylene chloride and treated with 1.5 ml of 47% hydriodic acid at 23° for 10 min.[7] The crude chloro ketone (containing about 7% of methyl ester by vpc) was ketalized[2] with 2 ml of methanol, 9.5 mmol of methyl orthoformate, and 20 mg of *p*-toluenesulfonic acid. The crude product was finally treated with excess sodium borohydride in methanol in order to remove a trace of unidentified iodine-containing impurities; then it was filtered through Florisil with pentane. The overall yields of the chloro ketals Ia and Ib[3a-c] were 51 and 56%, respectively, from the resolved chloro acids.

Since the (−)-naphthylethylamine is known to have the *S* configuration,[8] we expect to be able to determine, by X-ray diffraction analysis, the absolute configuration of the chloroacyl moiety and in turn of juvenile hormone.[9]

(4) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).
(5) *Cf.* J. R. Ruhoff, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 315.
(6) *Cf.* G. Haas and V. Prelog, *Helv. Chim. Acta*, **52**, 1202 (1969).
(7) *Cf.* M. L. Wolfrom and R. L. Brown, *J. Amer. Chem. Soc.*, **65**, 1516 (1943).
(8) H. Wolf, E. Bunnenberg, and C. Djerassi, *Chem.Ber.*, **97**, 533 (1964).
(9) NOTE ADDED IN PROOF. Juvenile hormone has now been shown to have the 10*R*,11*S* configuration by the synthetic work of D. J. Faulkner and M. R. Petersen, *J. Amer. Chem. Soc.*, **93**, 3767 (1971). In addition, K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon have established the 10*R*,11*S* and 10*S*,11*R* configuration for our samples of (+)-JH and (−)-JH, their results being based on clarification of the mode of hydrolysis of the epoxide function and determination of the chirality of the resultant α-glycols by a CD method employing Pr(DPM)$_3$ (*Chem. Commun.*, in press).

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Synthesis of C-18 *Cecropia* Juvenile Hormone to Obtain Optically Active Forms of Known Absolute Configuration

Sir:

During the past 3 years there have been several stereoselective syntheses of racemic juvenile hormone,[1] yet the optically active forms have not previously been prepared. Meyer and Hanzmann[2] recently isolated an optically active ($[\alpha]$D ≃+7°) mixture of C-18 and C-17 juvenile hormones from the *Cecropia* moth, but were unable to determine the absolute configuration of the natural product. We wish to report the synthesis of both enantiomeric forms of juvenile hormone from starting materials of known absolute configuration.

Our synthetic sequence required the preparation of both enantiomeric forms of 2,2-dimethoxy-3-methylpentan-3-ol (**1**). 3-Methylpent-1-yn-3-ol was converted, by the action of phthalic anhydride in pyridine, into its phthalate half-ester, which was resolved by fractional crystallization of the brucine salt.[3] The (−)-hydrogen phthalate was hydrolyzed with 10 *N* potassium hydroxide solution and (−)-3-methylpent-1-yn-3-ol, $[\alpha]^{23}$D −1.81° (neat), was isolated by steam distillation. Addition of methanol to (−)-3-methylpent-1-yn-3-ol using a mercuric oxide–boron trifluoride etherate–trifluoroacetic acid catalyst[4] gave (−)-2,2-dimethoxy-3-methylpentan-3-ol,[5] $[\alpha]^{23}$D −0.3° (*c* 3.34).[6] (+)-3-Methylpent-1-yn-3-ol, $[\alpha]^{23}$D +1.54° (neat), and (+)-2,2-dimethoxy-3-methylpentan-3-ol, $[\alpha]^{23}$D +0.3° (*c* 2.74), were obtained using the same synthetic sequence. Since the literature[3,7] gave conflicting values for the optical rotation of (−)-3-methylpent-1-yn-3-ol, we converted the (−)-hydroxy ketal **1a** into the corresponding ketol, by the action of dilute acid, then oxidized the methyl ketone, using sodium hypobromite solution, to (−)-2-hydroxy-2-methylbutyric acid, $[\alpha]^{23}$D −7.1° (*c* 2.66) [lit. $[\alpha]^{22}$D −8.5° (*c* 3.0)] of known absolute configuration.[8] Thus the (−)-

(1) P. Loew, J. B. Siddall, V. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci.*, **67**, 1462 (1970), and ref 1 and 2 cited therein.
(2) A. S. Meyer and E. Hanzmann, *Biochem. Biophys. Res. Commun.*, **41**, 891 (1970).
(3) J. R. Hickman and J. Kenyon, *J. Chem. Soc.*, 2051 (1955).
(4) I. A. Favoroskaya and N. A. Kotylov-Shakhmatov, *Zh. Obshch. Khim.*, **27**, 2406 (1957).
(5) All new compounds gave satisfactory analytical and spectral data. The enantiomeric and racemic materials exhibited identical tlc and vpc behavior.
(6) Unless otherwise indicated, all rotation measurements were recorded using solutions in chloroform.
(7) M.-L. Capmau, W. Chodkiewicz, and P. Cadiot, *Tetrahedron Lett.*, 1835 (1964).
(8) B. W. Christensen and A. Kjaer, *Acta Chem. Scand.*, **16**, 2466 (1962).