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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Peter Loew, William S. Johnson*
Department of Chemistry, Stanford University
Stanford, California 94305
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Synthesis of C-18 *Cecropia* Juvenile Hormone to Obtain Optically Active Forms of Known Absolute Configuration

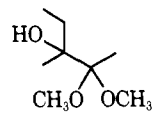
Sir:

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.

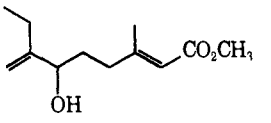
Our synthetic sequence required the preparation of both enantiomeric forms of 2,2-dimethoxy-3-methylpentan-3-ol (**1**). 3-Methylpent-1-yn-3-ol was converted, by the action of phthalic anhydride in pyridine, into its phthalate half-ester, which was resolved by fractional crystallization of the brucine 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. $[\alpha]^{25}$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).

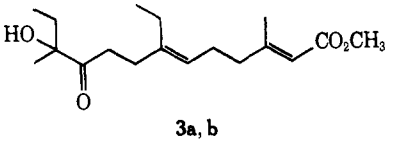
hydroxy ketal **1a** possessed the *R* configuration and had an optical purity of 92%. Using the observed rotations for the enantiomeric forms of 3-methylpent-1-yn-3-ol, the (*S*)-(+)-hydroxy ketal **1b** was calculated to have an optical purity of 85%.



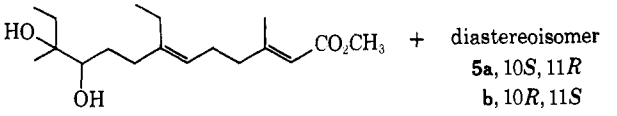
1a, $[\alpha]^{23}D$ −0.3° (*c* 3.3)
b, $[\alpha]^{23}D$ +0.3° (*c* 2.7)



2

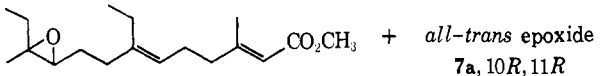


3a, b



4a, 10*R*, 11*R*
b, 10*S*, 11*S*

+ diastereoisomer
5a, 10*S*, 11*R*
b, 10*R*, 11*S*



6a, 10*S*, 11*R*
b, 10*R*, 11*S*

+ *all-trans* epoxide
7a, 10*R*, 11*R*
b, 10*S*, 11*S*

Table I. Observed Optical Rotations

Composition[a]	$[\alpha]^{23}D$, deg	Concn, g/100 ml
75% **4a**, 25% **5a**	+2.8	2.5
75% **4b**, 25% **5b**	−1.6	3.0
80% **5a**, 20% **4a**	−0.8	3.2
90% **5b**, 10% **4b**	+0.3	3.1
75% **6a**, 25% **7a**	−7.3	0.5
75% **6b**, 25% **7b**	+4.8	1.0
80% **7a**, 20% **6a**	−2.2	1.0
90% **7b**, 10% **6b**	+0.7	1.0

[a] The ratio of signals at 1.17 (trans) and 1.19 ppm (cis) in the 220-MHz nmr spectra of the epoxides in $CDCl_3$ solution.

Both enantiomeric hydroxy ketals **1a** and **1b** were allowed to react at 110° with 1.2 equiv of the hydroxy ester **2** in a solution of xylene containing 2,4-dinitrophenol. The resulting ketols **3a** and **3b**, formed *via* a Claisen rearrangement,[9] were immediately reduced using sodium borohydride in methanol solution at 0° to obtain diastereoisomeric pairs of diols **4a** and **5a** (from **1a**) and **4b** and **5b** (from **1b**), which were partially separated with great difficulty by preparative thin-layer chromatography on silica gel. The diols were allowed to react with *p*-toluenesulfonyl chloride in pyridine to form the corresponding monotosylates, which were treated with sodium methoxide in anhydrous methanol to obtain the epoxides. Thus the *threo*-diols **4a** and **4b** gave rise to the required *trans,trans,cis*-epoxides **6a** and **6b**, while the *erythro*-diols gave the *all-trans*-epoxides **7a** and **7b**. Examination of the 220-MHz nmr spectra of the product epoxides revealed that each epoxide was contaminated with its diastereoisomer. The observed optical rotations (Table I) must therefore be related to the approximate composition of the diastereoisomeric mixtures. There was no doubt, however, that dextrorotatory C-18 *Cecropia* juvenile hormone had been synthesized from (*S*)-(+)-2,2-dimethoxy-3-methylpentan-3-ol. Thus the natural hormone of Meyer and Hanzmann must have the 10*R*,11*S* configuration.

(9) D. J. Faulkner and M. R. Petersen, *Tetrahedron Lett.*, 3243 (1969).

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D. John Faulkner,* Michael R. Petersen
Scripps Institution of Oceanography
La Jolla, California 92037
Received April 13, 1971

The Structure of Lipoxamycin, a Novel Antifungal Antibiotic

Sir:

The production, isolation, characterization, and testing of lipoxamycin have been reported.[1] In this communication[2] we describe reactions (Scheme I) and data to support structure **1** for this new antifungal agent produced by a new strain of *Streptomyces virginiae*.

Potentiometric titration[3] of lipoxamycin sulfate ($C_{19}H_{36}N_2O_5 \cdot {}^1/_2H_2SO_4$, mp 155°) showed the presence of a basic group ($pK_a = 6.8$) and a weakly acidic group ($pK_a = 9.8$). Lipoxamycin ($C_{19}H_{36}N_2O_5$, mp 68–70°) (**1**) was obtained after the first equivalent of alkali. A positive (red) ferric chloride test is ascribed to the weakly acidic center which is in accord with an inferred hydroxamic acid group.

1 shows absorptions in the ir including NH/OH ν_{max}^{Nujol} 3150–3350 cm^{-1} and C=O at 1700 and 1640 cm^{-1}, with Nujol masking strong $-CH_2-$ and $-CH_3$ absorptions found in a melt spectrum. The pmr spectrum of **1** contains a doublet at δ 0.9 (J = 5.9 Hz) assigned to the methyls of an isopropyl grouping, aliphatic methylene multiplet at 1.3–1.8, a methylene (adjacent to carbonyl) triplet at 2.38 (J = 7.0 Hz), and unresolved resonances at 2.7, 3.8, and 4.75.

The antibiotic is very sensitive to oxidation; thus, periodic acid converts **1** to bis-1-nitrosolipoxane[4] (**2**), formulated as the *C*-nitroso dimer ($C_{32}H_{58}N_2O_6$, mp 94–96°) expected[5] from an N-substituted hydroxamic acid. **2** shows absorptions in uv and ir spectra at λ_{max}^{EtOH} 283 mμ (ε 10,360) and ν_{max}^{Nujol} 1705, 1330, 1230, 1210,

(1) H. A. Whaley, O. K. Sebek, and C. Lewis, Abstracts of Tenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct 19, 1970.

(2) Satisfactory elemental analyses were obtained for all compounds. The pmr spectra were obtained from samples in $CDCl_3$ solution using a Varian A-60, HR-60, or T-60 instrument and chemical shifts are reported in parts per million downfield from an internal tetramethylsilane. Mass spectra were obtained by electron impact in a CEC 21-110 spectrometer using the peak matching method for high-resolution ion measurement. All melting points were determined by the capillary tube method and are corrected.

(3) Because of the poor aqueous solubility of lipoxamycin sulfate, the best titration data were obtained in 60% ethanol and excess NaOH with immediate backtitration with acid: equiv wt, 209 with a break at 437; pK_a, 6.8 and 9.8.

(4) Convenient trivial names for this series of degradation products from lipoxamycin are obtained by renaming 14-methyl-3,9-dioxopentadecane "lipoxane"; then the $C_{16}H_{29}O_2$ radical derived from that can be called lipoxyl.

(5) T. Emery and J. B. Neilands, *J. Amer. Chem. Soc.*, **82**, 4903 (1960).