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Synthesis of Cecropia juvenile hormones and related compounds

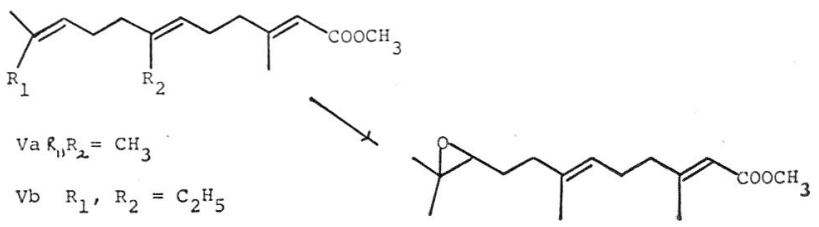
J. A. FINDLAY

Since the elucidation of structure of the first Cecropia juvenile hormone I by Dahm, Röller, Sweeley and Trost (1), a good number of laboratories have focussed attention on this remarkably potent insect hormone as a synthetic objective. This is evidenced by the recent chemical literature and by a number of the lecture titles at this Symposium.

The province of New Brunswick in Canada is very sparsely populated with respect to people but its insect population is exceedingly dense. I feel that this is ample justification for us to have ventured into the vigorously competitive area of insect hormone synthesis.

While designing a stereospecific synthesis of juvenile hormone can prove to be an exercise in chemical ingenuity and originality, we have preferred to look for a non-stereospecific route which hopefully would have the advantage of conciseness, convenience and economy.

We were encouraged in taking this non-stereospecific approach by the report (2) of the Wisconsin group that a number of synthetic isomers of the prototype juvenile hormone displayed a substantial level of biological activity in Tenebrio assays, in particular the all trans isomer II. Hence a non-stereoselective approach would not necessarily be disadvantaged by a stereoselective one especially if one's objective is to provide juvenile hormone materials in suitable quantities for further biological study.



Va $R_1, R_2 = CH_3$

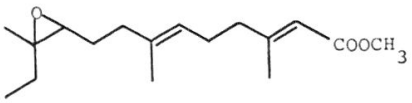
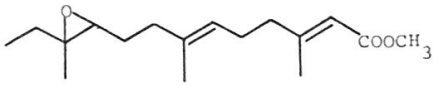
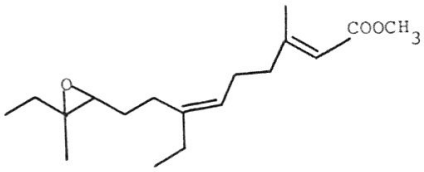
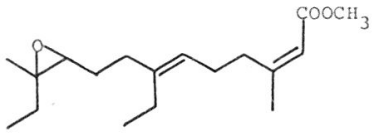
Vb $R_1, R_2 = C_2H_5$

Vc $R_1 = C_2H_5, R_2 = CH_3$

VI

TABLE 1

SPECIFIC ACTIVITY OF SYNTHETIC COMPOUNDS

			Specific Activity TU/μg
I		dl TTC	5000
II		dl TTT	2000
III		dl TCT	150
IV		dl CTC	10

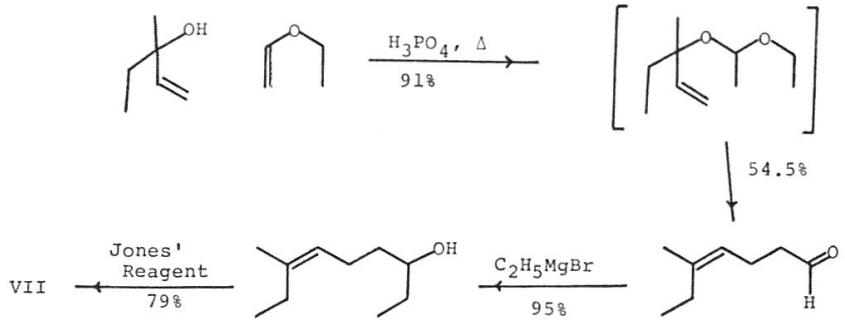
In addition we considered at the outset that it should not prove an unsurmountable task to separate geometrical isomers during the course of a synthesis by, for example, vapour phase chromatographic means.

The synthesis I am going to describe was originally executed by one first year graduate student and the route has since been successfully employed to provide juvenile hormone I and isomers in kilogram quantity.

Some years ago Professor van Tamelen described (3) a selective terminal epoxidation of methyl farnesoate Va. The structural similarity between its epoxidation product VIa and the Cecropia hormones requires no comment. It is not surprising then that most of the completed syntheses to date including our own, rely in the ultimate stage on a similar selective terminal epoxidation of an appropriately constructed triene ester Vb.

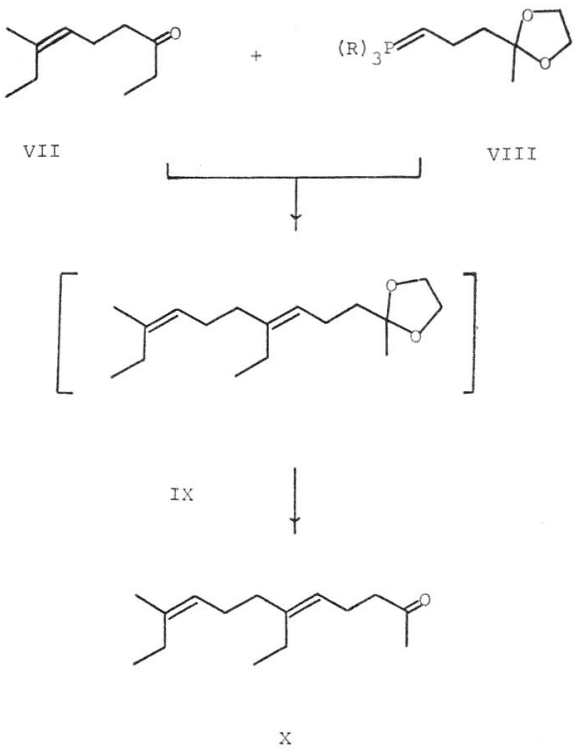
During the course of the first juvenile hormone synthesis the Wisconsin group showed (2) that the triene ester Vb is accessible via the diene ketone X. We considered then that our primary objective should be an efficient synthetic route to this diene ketone. In planning the construction of compound X we proposed to unite the 10 carbon ketone VII to a 5 carbon unit via the Wittig reaction employing the ylide VIII. The resulting ketal IX should yield the desired key intermediate X on deketalization.

The preparation of the ketone VII was accomplished in the following manner.



Synthesis of a number of similar, γ,δ-unsaturated aldehydes by this means was first reported by Saucy and Marbet (4).

It proved feasible to separate the cis/trans (38%/62%) isomeric alcohols XI by vapour phase chromatography (see Table 2). Thus it was possible to proceed with either pure cis or pure trans ketone VII or with an isomeric cis/trans mixture of known composition.



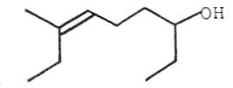
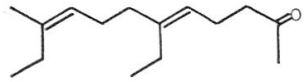
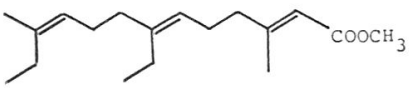
The ketal phosphonium salt VIII was prepared quantitatively from 5-iodo-2-pentanone (obtainable by NaI/acetone treatment of commercially available 5-chloro-2-pentanone) by ketalization and subsequent reaction with triphenylphosphine in boiling benzene. The stable crystalline salt VIII readily separated from this medium.

With the ketone VII and the Wittig reagent VIII thus at hand the diene ketone X was prepared as planned. Generation of the ylide VIII was accomplished with sodium hydride/dimethylsulfoxide. The intermediate ketal IX was directly deketalized with aqueous acidic tetrahydrofuran to provide the diene ketone X in 84% yield either as a mixture of two or of four isomers depending on the choice (cis or trans) of precursor ketone VII. Conversion of the key intermediate X to the triene ester Vb was accomplished in 85% yield by treatment with the anion of diethylcarbmethoxymethyl phosphonate in benzene solution.

It proved possible to separate pairs of cis/trans isomers of the diene ketone X by v.p.c. and to assign stereochemistry on the basis of the geometry of the selected precursor VII, relative retention time and n.m.r. data. Thus we were able to proceed with either pure isomers of diene ketone X or with a mixture of isomers of known composition. When a mixture of the four isomeric ketones X was converted into ester Vb the v.p.c. analysis of the latter clearly showed the presence of 8 components (see Table 2).

TABLE 2

REPRESENTATIVE V.P.C. DATA FOR SYNTHETIC ISOMERS (JH 1)

Isomer Mixture	Composition %		Retention Time (Min.)	Column Temp. °C.	He Flow Rate (ml./sec.)
 XI	C*	38	89' 30"	130	2
	T	62	92' 45"		
 X	CC	15	40' 00"	200	5
	CT	23	42' 25"		
	TC*	25	43' 30"		
	TT	37	45' 15"		
 Vb	CCC	3	38' 45"	220	2
	CCT	4	40' 10"		
	CTC	6	42' 10"		
	CTT	9	43' 30"		
	TCC	12	46' 10"		
	TCT	17	47' 50"		
	TTC*	19	50' 00"		
	TTT	30	51' 35"		

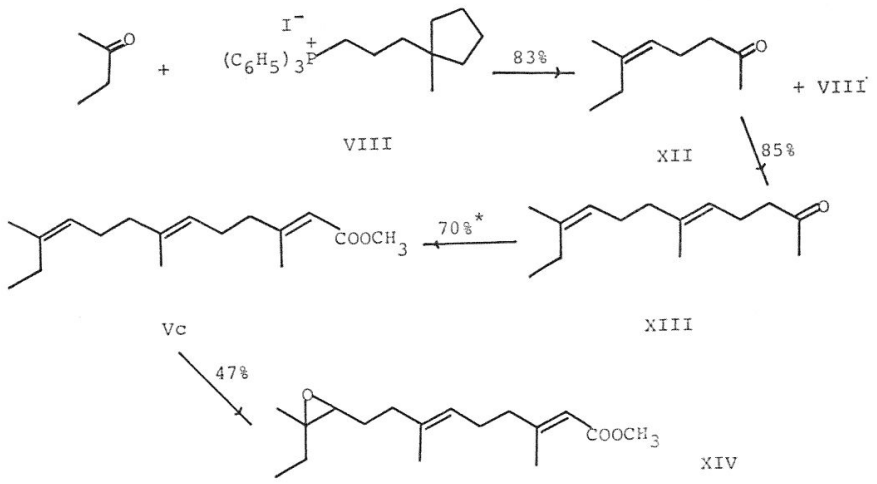
Column: 20' x 3/8" aluminum, carbowax 20M (20% on Chromosorb W)

Employing pure isomers of the ketone X it was possible to prepare simple isomer mixtures of the triene ester Vb separable by a variety

of chromatographic means. This allowed the assignment of geometry to the 8 components of the more complex mixture of isomeric triene esters Vb. Thus pure trans,trans, cis-Vb and other isomers and isomer mixtures were available for selective terminal epoxidation by known means (2, 3).

When Professor Meyer's group's fascinating detective work revealed (5) the existence of a second juvenile hormone XIV we still had a large bottle of the ketal phosphonium salt VIII in the lab. This material proved to be of double utility in the synthesis of the new Cecropia juvenile hormone.

We proceeded as follows without performing isomer separations until the penultimate stage.



* Yield based on recycling recovered precursors

A mixture of cis (60%) and trans (40%) 6-methyl-5-octene-2-one XII was obtained in 83% yield by acid catalysed deketalization of the reaction product formed from 2-butanone and the ylide of VIII. The ratio of cis to trans isomers was estimated from the n.m.r. spectrum of the mixture which displays a pair of overlapping doublets for the vinylic methyl groups at τ 8.36 ($J \simeq 1.5$ c.p.s.) and 8.40 ($J \simeq 1.5$ c.p.s.) for the cis and trans isomers, respectively (2).

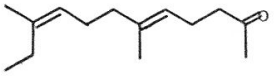
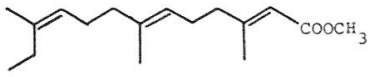
Condensation of the ketone isomers XII with the ylide of VIII afforded, after acidic work-up, the four isomers of the diene ketone XIII in 85% yield.

This mixture was shown by v.p.c. to have the approximate composition 36% cis,cis-, 24% cis,trans-, 24% trans,cis- and 16% trans,trans-XIII, the assignment being facilitated by the known ratio of isomers in the precursor XII and the finding (2) that cis isomers have shorter retention times.

Treatment of the isomeric mixture of diene ketones XIII with the sodium salt of dimethylcarbmethoxy methyl phosphonate in boiling benzene gave Vc in 43% yield with recovery of 40% of XIII readily separable by chromatography on silica gel plates. Selective terminal epoxidation of the unseparated isomers Vc was achieved by treatment with N-bromosuccinimide in ice cold aqueous dimethoxyethane to furnish the 10,11-bromohydrin of Vc which gave a yield of 47% (from Vc) of the corresponding oxide XIV when subjected to sodium in absolute methanol. Pure trans,trans,cis-oxide XIV was obtained by epoxidizing in parallel manner trans,trans,cis-triene ester XIV separated from its companion isomers by preparative v.p.c. (see Table 3). The synthetic d,l-trans,trans,cis-oxide XIV thus prepared was identical in spectroscopic properties with the data reported (5) by Professor Meyer's group for the new Cecropia juvenile hormone and it displayed the same level of activity in Tenebrio bioassays.

TABLE 3

REPRESENTATIVE V.P.C. DATA FOR SYNTHETIC INTERMEDIATES (JH 2)

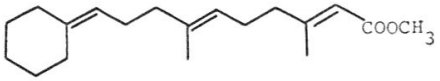
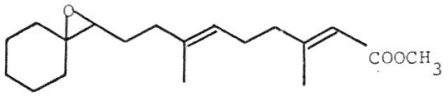
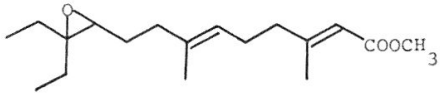
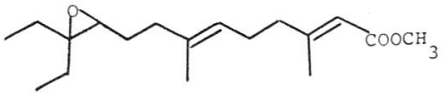
Isomer Mixture	Composition %		Retention Time (Min.)	Column Dim., Temp. °C.	He Flow Rate (ml./sec.)
	CC	36	46' 20"	20 ft. x 3/8 in. 150°C.	2
	CT	24	48' 30"		
	TC	24	51' 30"		
	TT	16	52' 45"		
	TCC	36	62' 00"	10 ft. x 3/8 in. 200°C.	1
	TCT	24	63' 30"		
	TTC	24	69' 15"		
	TTT	16	70' 45"		

Column: Aluminum, carbowax 20M (20% on Chromosorb W).

More recently, we have utilized our synthetic route to prepare the four compounds XV, XVI, XVII, XVIII as mixtures of trans,trans- (43%) and trans,cis- (57%) isomers. Overall yields were of the same order as that obtained in the last discussed synthesis.

The results of Tenebrio assay with these compounds are shown below in Table 4.

TABLE 4

		Tenebrio bioassay Dose		
		10 µg	1 µg	0.1 µg
XV		second pupa	-	-
XVI		second pupa	-	-
XVII		pupal-adult intermediates	-	-
XVIII		second pupa	pupal-adult intermediates	pupal genitalia

In conclusion, I want to acknowledge the invaluable and skilful assistance of Walter MacKay who successfully and single-handedly pioneered the syntheses of both Cecropia hormones just discussed. I am indebted also to Dr. Coll-Toledano for preparing the four compounds XV, XVI, XVII and XVIII. Thanks are also due to Dr. William S. Bowers who kindly provided us with Tenebrio bioassay and to Ayerst Research Laboratories in Montreal for subjecting our first Juvenile Hormone synthesis to the acid test of kilogram quantity preparation. Finally, I wish to express my sincere gratitude to the organizers of this Symposium for kindly inviting me to tell you about our work.

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