Stereoselective Addition of Organocopper Reagents to Acetylenic Esters and Amides. Synthesis of Juvenile Hormone Analogs[1]

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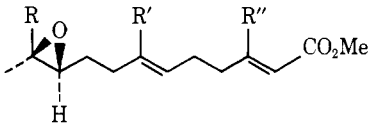
Abstract: The stereoselective conjugate addition of some organocopper(I) reagents to α,β-acetylenic esters to give substituted α,β-unsaturated esters is discussed, as applied to the synthesis of trisubstituted double bonds, and in particular the preparation of the juvenile hormone analog methyl (2*E*,6*E*)-3,7-diethyl-*cis*-10,11-epoxy-11-methyl-2,6-tridecadienoate (JH 0, **1d**) and the 2*E*,6*E*,*trans*-10 isomer **18c**. The effects of the reaction conditions and of the type of organocopper(I) reagent used on the stereochemistry of the product are outlined. Both alkyl groups of a lithium di-*n*-alkylcuprate can be transferred to the acetylenic ester. Polymeric copper reagents prepared from alkyllithiums give the best overall results. The lithium methyl(*tert*-butyl)cuprate complex selectively transfers the *tert*-butyl group to methyl 2-butynoate. Some examples are also given for the stereoselective conjugate addition of organocopper(I) reagents to α,β-acetylenic amides. The biological activities of **1d** and **18c** on three insect species are given and compared with those found for the known natural juvenile hormones.

Considerable attention has been focused in the last few years on the stereoselective synthesis of trisubstituted double bonds.[4] More than anything else, the structure elucidation of the C-18 *cecropia* juvenile hormone **1c** (JH I) by Röller, *et al.*,[5] prompted the development of many of these stereoselective olefin syntheses.[6] The observation, that the 2*Z* and 6*Z* isomers of **1c** and related compounds showed much lower biological activities than the 2*E*,6*E* isomers, demonstrated that the geometry of the natural juvenile hormone was important for high biological activity.[7] Thus, investigations began in our own and in other laboratories to develop stereoselective methods for the synthesis of **1c** and related analogs.

In 1968, a new approach to the stereoselective formation of α,β-unsaturated esters was developed in these laboratories[8] and independently by a group at Harvard,[9] involving the conjugate addition of organocopper(I) reagents to α,β-acetylenic esters at low temperatures. In this reaction,[10a] a number of *n*-alkyl-,[8-11] *sec*-alkyl-,[10b] *tert*-alkyl-,[10b] aryl-,[11a] vinyl-,[12] allyl-,[10b,12b] and homoallyl[6,8,10,13] copper(I) reagents have been used, and the α,β-acetylenic carbonyl substrate has included substituted[6,8-13] and unsubstituted (alkyl propynoates) acetylenic esters,[10b,11a,12] acetylenic acids,[10b,11a,b,d,g] acetylenic amides,[10b,11b] and acetylenic ketones.[10a] We would like to describe in detail here some of our previously unpublished[10b] work on this useful method, as applied to the synthesis of trisubstituted double bonds, and, in particular, the preparation of the juvenile hormone analog JH 0 (**1d**).[14]



1a, R = Me; R′ = Me; R″ = Me (JH III)
b, R = Et; R′ = Me; R″ = Me (JH II)
c, R = Et; R′ = Et; R″ = Me (JH I)
d, R = Et; R′ = Et; R″ = Et (JH 0)

Results and Discussion

The conjugate addition of organocopper(I) reagents to α,β-acetylenic esters **3** at low temperatures gives, after protonation, the α,β-olefinic esters **5** in high yield. However, the stereoselectivity of the reaction was found to be a function of the reaction temperature and time, and also of the nature of the reagent, solvent, and ligands present.[8,9] The presumed vinylcopper intermediate can undergo equilibration in diethyl ether (after <1 hour) at −78°,[8] whereas in tetrahydrofuran[9,10b] or in diethyl ether containing a suitable ligand, very little loss of stereochemistry occurs, and the stereoselectivity of the reaction can be >99%.

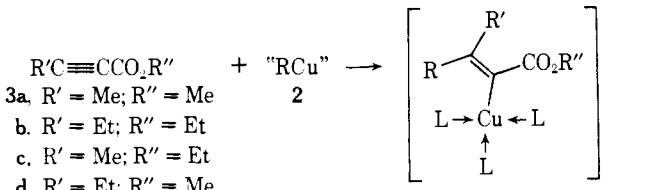
The conjugate addition of various *n*-butylcopper(I) reagents to methyl 2-butynoate (**3a**) to give the β-substituted-α,β-unsaturated ester **5a** has been studied in some detail (Table I), as a representative example (of *n*-alkyl reagents). The acetylenic ester reacts essentially completely with 1 equiv of lithium di-*n*-butylcuprate, and stereoselectivity is high when the reaction is run at −78° in tetrahydrofuran (THF) or in diethyl ether containing *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a ligand (entries 2 and 3, Table I). Of special synthetic significance, however, is our finding that *both* alkyl groups of an organocuprate complex may be transferred to an acetylenic ester. Thus, 1 equiv of **3a** reacts completely with 0.6 equiv of lithium di-*n*-butylcuprate to give a high yield of pure **5a** (*cf.* entries 2 and 3 with 5 and 6). Apparently, a mixed "ate" complex such as **7** can still add effectively in a conjugate manner to another molecule of acetylenic ester to give essentially *complete utilization of the n-butyl groups.*[15]

Polymeric copper complexes ("RCu") also readily add to acetylenic esters.[16] The use of polymeric copper complexes derived *from lithium alkyls*, in fact, gives reproducibly the highest stereoselectivity in this conjugate addition reaction. Several aspects of this reaction deserve comment. Tetrahydrofuran *and* ether are suitable solvents for the addition of this polymeric *n*-butylcopper reagent to **3a** (entries 7 and 8, Table I). The high stereoselectivity of olefin formation obtained in pure ether with this complex is particularly interesting since the reaction with 1 equiv of the lithium di-*n*-butylcuprate complex in ether (without an additional ligand) gives much lower stereoselectivity (entry 1, Table I; see also ref 8 and 9). However, reaction with 0.50 equiv of the "ate" complex does give a stereoselective reaction (entry 4, Table I). Apparently, at −78° the stereochemical integrity of the polymeric vinylcopper species **4** (or of a divinyl "ate" complex in the case of entry 4) is maintained in ether, whereas that of the mixed vinyl-alkyl "ate" complex **7** in the absence of an additional ligand is not maintained (even at −78°). If a ligand (*e.g.*, TMEDA) is added to this

Table I. Conjugate Addition of *n*-Butylcopper(I) Complexes to Methyl 2-Butynoate (**3a**)

Entry	Organocopper reagent (equiv)	Solvent and/or additional ligand (equiv)	Temp, °C: Formation of reagent	Temp, °C: Addition reaction	Time, min: Formation of reagent	Time, min: Addition reaction	Product[a]: 5a	6a	3a	Distilled yield
1	$(n\text{-Bu})_2$CuLi (1.02)	Et_2O	−40	−78	30	30	74	26		
2	$(n\text{-Bu})_2$CuLi (1.1)	THF	−40	−78	45	50	97	3		86
3	$(n\text{-Bu})_2$CuLi (1.1)	Et_2O–TMEDA (1.5)	−40	−78	40	50	97	3		82
4	$(n\text{-Bu})_2$CuLi (0.50)	Et_2O	−40	−78	30	30	94	3	3	92
5	$(n\text{-Bu})_2$CuLi (0.62)	THF	−45	−78	30	30	99	1		84
6	$(n\text{-Bu})_2$CuLi (0.62)	Et_2O–TMEDA (1.5)	−40	−78	30	50	96	4		79
7	*n*-BuLi·CuI (1.06)	THF	−40	−78	30	90	>99	<1		96
8	*n*-BuLi·CuI (1.05)	Et_2O	−40	−78	15	45	98	2		91
9	*n*-BuLi·CuI (1.2)	Et_2O–TMEDA (1.8)	−40	−78	30	210	94		6	
10	*n*-BuLi·CuI (1.06)	Et_2O–TMEDA (1.3)	−40	−45	30	20	99	1		92
11	*n*-BuMgBr·CuI (1.1)	THF	−40	−78	60	210	85	15		97
12	*n*-BuMgBr·CuI (1.1)	THF–TMEDA (3.0)	−40	−78	30	90	97	3		97
13	*n*-BuMgBr·CuI (1.1)	Et_2O–TMEDA (3.0)	−40	−78	60	180	92	3	5	83
14	*n*-BuMgBr·CuI (1.1)	Et_2O–TMEDA (3.0)	−40	−40	60	30	84	16		89

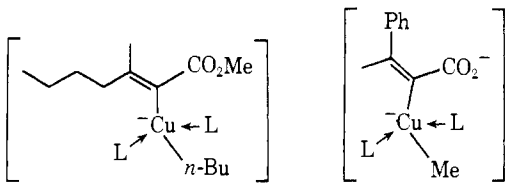
[a] Ratio of products determined before distillation by glc analysis at 120° on a 1 m × 2 mm glass column packed with 20% UCON 75-H-90,000 on Chromosorb W (acid washed).



4, R = *n*-Bu; R' = Me; R'' = Me

5a, R = *n*-Bu; R' = Me; R'' = Me
b, R = *t*-Bu; R' = Me; R'' = Me
c, R = Et; R' = Me; R'' = Me
d, R = Me; R' = Me; R'' = Me

6a, R = *n*-Bu; R' = Me; R'' = Me
b, R = *t*-Bu; R' = Me; R'' = Me
c, R = Et; R' = Me; R'' = Me



7 8

polymeric *n*-butylcopper (*n*-BuLi·CuI) reaction in ether at −78°, the addition occurs in a very highly stereoselective manner, but a small amount of starting ester **3a** is always recovered, even when a 20% excess of the organometallic reagent is used (entry 9, Table I). Incomplete reaction may be avoided by conducting the reaction at higher temperatures (*e.g.*, −45°; entry 10, Table I), and under these conditions the ratio of *Z*:*E* isomers in the product (1:99, respectively) still shows a highly selective cis addition to the alkyne. The presumed intermediate vinylcopper complex **4** must be stereochemically stable even at −45° for at least the reaction time (*ca.* 20 min). Thus although these polymeric copper reagents give satisfactory product stereochemistry in pure ether at −78°, the use of a ligand gives even higher stereoselectivity.

The differences noted above in the stereochemical purity of the reaction product are presumably due to the relative stabilities of the mixed "ate" complex **7** and the polymeric complex **4**. In this context, it has been reported by Klein and Turkel[11a] that addition of polymeric methylcopper to phenylpropiolic *acid*, followed by protonation, gave mainly (*Z*)-β-methylcinnamic acid, the product from cis addition to the alkyne, whereas lithium dimethylcuprate on reaction with phenylpropiolic acid gave mainly the *E* isomer. Moreover, when methyllithium was added to the intermediate "enolate" in the polymeric methylcopper reaction, isomerization occurred, and (*E*)-β-methylcinnamic acid was isolated. Their results indicate that a mixed "ate" complex such as **8** (or alternatively the "lithium enolate") does not maintain stereochemical integrity under their conditions (*ca.* 1 hr at −60° followed by 24 hr at room temperature). However, we found that reaction of 2-pentynoic *acid* with 3 equiv of lithium dimethylcuprate in ether at −10° for 30 min gave a mixture of the (*Z*)- and (*E*)-3-methyl-2-pentenoic acids in the ratio 92:8, respectively.[10b]

Polymeric copper(I) complexes derived from Grignard reagents also add to acetylenic esters in a conjugate manner.[8,10b] This addition, however, differs markedly from the analogous reaction in which the polymeric copper complex is prepared from the corresponding lithium reagent. Thus, while the latter reaction is highly stereoselective in tetrahydrofuran, the former yields a mixture of isomers (*cf.* entries 7 and 11, Table I). Only when the reaction of polymeric copper complexes derived from Grignard reagents is carried out in the presence of suitable ligands, *e.g.*, TMEDA, is the product obtained with high stereoselectivity (entries 12 and 13, Table I). Some recovered starting material is again observed when the conjugate addition is carried out in ether–TMEDA at −78° (*cf.* entries 9 and 13, Table I). From our work it is apparent that when either a lithium organocuprate or a polymeric copper complex derived from a Grignard reagent is allowed to react with an acetylenic ester, the stereochemistry of the product is sensitive to the reaction conditions. In order to obtain high stereochemical purity in the olefin product, it is important that conditions be carefully chosen, and that the reaction temperature is maintained near −78° during the addition of the acetylenic ester to the reagent *and* during the protonation of the vinylcopper intermediate.

The successful addition of a *tert*-butyl group to an acetylenic ester requires a modification of the reaction conditions. The reaction of methyl 2-butynoate (**3a**) with polymeric *tert*-butylcopper (prepared from the lithium reagent) in ether at −78° for 4 hr gives only partial reaction (with 65% recovered **3a**) and a poor *Z*:*E* ratio (17:83, respectively) in the product; addition of 1.2 equiv of TMEDA to the reaction medium (2.5 hr at −78°) is also unsatisfactory (29% recovered acetylenic ester; *Z*:*E* ratio of **6b**:**5b** is 23:77). Use of 1 equiv of pyrrolidine as the ligand under similar conditions gives higher stereoselectivity (30% recovered

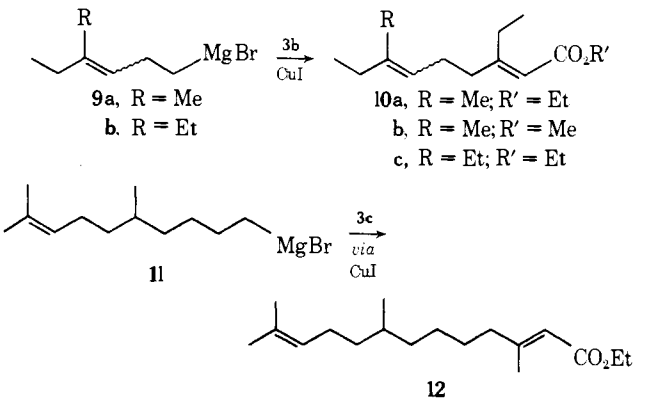
Table II. Reaction of 4-Methyl-3-hexenylmagnesium Bromide·*n*CuI·*n'* Ligand with Ethyl 2-Pentynoate (**3b**)[a]

CuI, equiv	Ligand (equiv)	Time, min, for formation of copper complex	Time, min, for reaction with **3b**	% yield of **10a**	*Z*:*E* ratio
1	TMEDA (2)	120	30	90	*ca.* 1:99
2	Pyrrolidine (3)	120	30	92	*ca.* 1:99
1	$(n\text{-Bu})_3P$ (2)	140	100	0	
4	$(n\text{-Bu})_3P$ (5)	180	40	90	43:57[b]
1	$(MeO)_3P$ (4)	135 (−78 to 0°)	100 (at 0°)	0	
1	HMPA[c] (50% in ether)	20 (−35°) 100 (−78°)	90	20	22:78

[a] All reactions were performed at −78° in diethyl ether, unless otherwise stated, and were quenched at that temperature by dropwise addition of ethanol. [b] *Cf.* ref 8 in which a *Z*:*E* ratio of 4:96, respectively, was obtained at a reaction temperature of −90°. [c] Hexamethylphosphoramide.

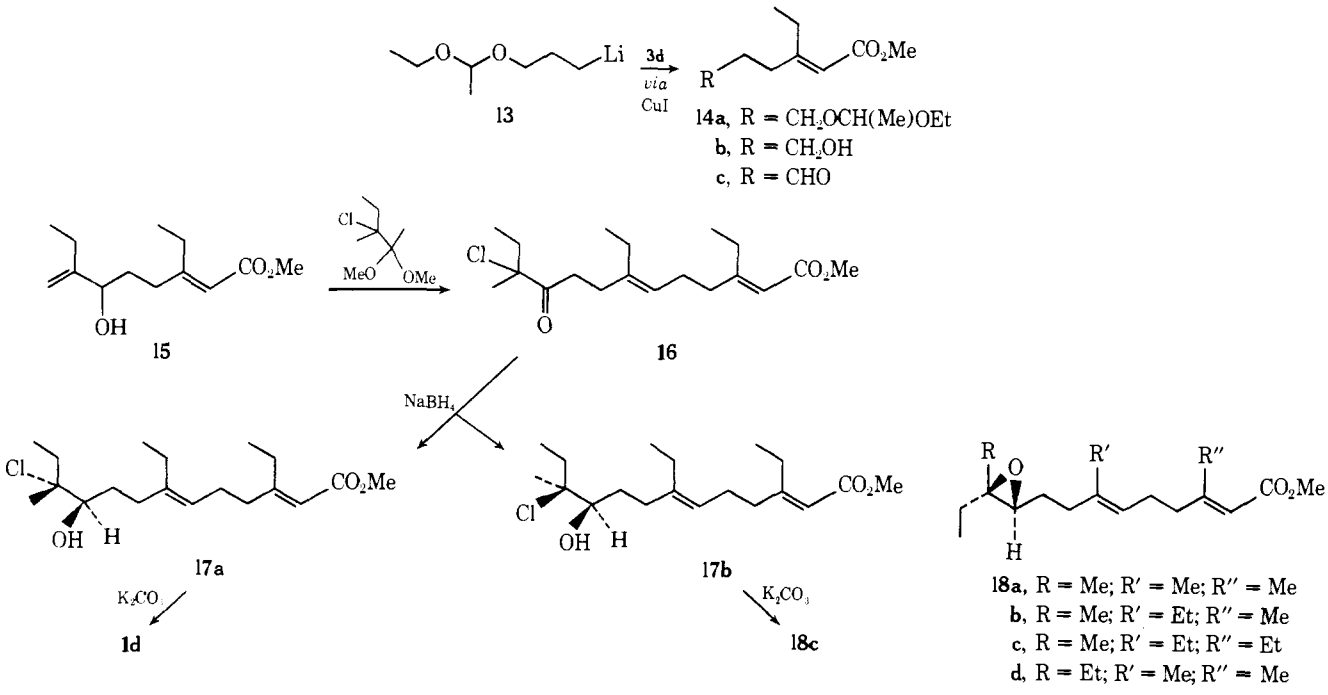
3a; *Z*:*E* ratio is 2:98, respectively). The copper complex derived from *tert*-butyllithium and tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] in ether gives (0.5 hr at −78°) essentially complete reaction with **3a**, but the ratio of olefinic product isomers is still poor (**6b**:**5b**, 14:86) (*cf.* ref 10b). Thus, we examined an alternate method to solubilize polymeric copper reagents. Several years ago[10b] we found that lithium methyl(*tert*-butyl)cuprate selectively transfers the *tert*-butyl group to α,β-acetylenic esters. A suspension of polymeric methylcopper (prepared from methyllithium and cuprous iodide) in ether at −40° is treated with 1 equiv of *tert*-butyllithium (no additional ligand is added). Addition of **3a** to the resulting black solution (at −78°), followed by quenching, results in stereoselective cis alkylation of the acetylenic ester. Almost all of the alkylation is attributable to *tert*-butyl transfer, and only 3% results from methyl transfer. The product consists of a mixture of **5b**, **6b**, and **5d** in the ratio 94:3:3, respectively. The yield of desired alkylation products in this reaction is >90%, indicating that little disproportionation of the reagent occurs in the time taken to prepare and use the reagent. Recently several reports of selective transfer using mixed cuprate reagents have appeared in the literature.[17]

One of the useful applications of the addition reaction is the preparation of 1,5-dienes *via* the conjugate addition of homoalkylcopper reagents to α,β-acetylenic esters.[6,8,10,13] We have investigated this reaction in some detail, in particular with copper complexes prepared from homoallylic Grignard reagents. The major synthetic problem encountered in such an addition is the preparation of the homoallylic Grignard reagent itself. However, by slow addition of the homoallylic bromide to magnesium in ether, yields of 70% can be consistently achieved. A variety of ligands and Grignard reagents have been examined for this conjugate addition reaction (*e.g.*, Table II; see also Experimental Section). We have found that TMEDA and pyrrolidine are the most suitable ligands, of those examined, for complexation with the homoallylcopper reagents. These copper complexes, in diethyl ether, react stereoselectively and in high yield with α,β-acetylenic esters. In the case of TMEDA, a ratio of at least 1 equiv of cuprous iodide and 2 equiv of ligand per equiv of Grignard reagent is preferable, especially when the Grignard reagent is difficult to prepare. Even though pyrrolidine possesses a potentially active hydrogen, it can also be used effectively to coordinate the alkylcopper at low temperatures (−30 to −78°). Optimal conversions with pyrrolidine as the ligand are obtained when >1 equiv of cuprous iodide and 2–3 equiv of ligand are used for every equivalent of Grignard reagent. Of the phosphorus-containing ligands used, only tri-*n*-butylphosphine was found to effectively complex the alkylcopper polymer for conjugate addition. However, yields of α,β-olefinic esters were variable with tri-*n*-butylphosphine as the ligand. Moreover, the stereochemical outcome of the conjugate addition using the last ligand was difficult to reproduce. Results similar to those in Table II have been obtained from a variety of alkyl and alkenyl Grignard reagents, for example, the preparation of **12** from **3c** and the Grignard reagent **11.**

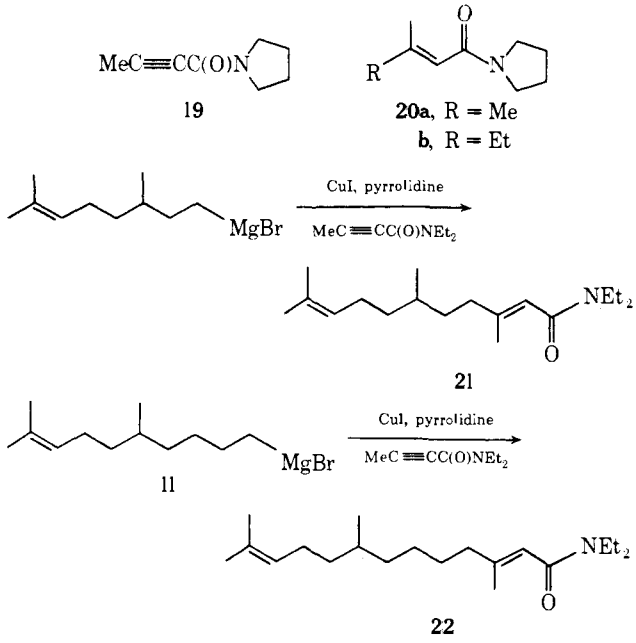


The general utility of polymeric copper complexes derived from alkyllithium reagents in conjugate addition to acetylenic esters is exemplified by the synthesis of methyl (*E*)-3-ethyl-6-hydroxy-2-hexenoate (**14b**), an intermediate in the synthesis of the juvenile hormone analog **1d** (JH 0).[14] Addition of a functionalized three-carbon organometallic to methyl 2-pentynoate (**3d**) was carried out by the use of the lithioacetal **13**.[18] The polymeric copper complex, prepared with 1.2 equiv of CuI and 1.2 equiv of TMEDA, added stereoselectively to **3d** to give the acetal ester **14a** (99.5% *E* isomer) in 85% yield. Acid hydrolysis of **14a** gave the pure hydroxy ester **14b** in 91% yield. Oxidation to the aldehyde **14c** and reaction of the latter with 1-butenyl-2-magnesium bromide gave the allylic alcohol **15.** From this intermediate, samples of the juvenile hormone homolog **1d** and of its isomer **18c** were prepared in a manner similar to a route (*via* the chloro ketone **16**) previously used to prepare **1c**.[19]

Our investigations of the conjugate addition of organocopper complexes to α,β-acetylenic carbonyl substrates have also included acetylenic amides.[8,10b] In contrast to a report that methylcopper fails to react with phenylpropiolic amides,[11b] we found that lithium dimethylcuprate adds to 1-(2-butynoyl)pyrrolidine (**19**) in ether to give the α,β-ethylenic amide **20a** in reasonable yield. More importantly, addition of lithium diethylcuprate to **19** in ether at −78°, with no additional ligand added, gives **20b** (glc analysis showed 99% *E* stereoisomer). Polymeric alkylcopper reagents, when complexed with suitable ligands, also add in a conjugate fashion to α,β-acetylenic amides. Thus, both citronellylmagnesium bromide and 5,9-dimethyl-8-decenylmagnesium bromide in the presence of excess CuI and 3 equiv of pyrrolidine react at −78° in ether with *N*,*N*-diethyl-2-butynamide to give *N*,*N*-diethyl-3,6,10-trimethyl-2,9-unde-



cadienamide (**21**) and *N,N*-diethyl-3,8,12-trimethyl-2,11-tridecadienamide (**22**), respectively. Both **21** and **22** were shown by glc analysis to contain >99% of the *E* stereoisomer.



Bioassay data for **1d, 18c,** and some related compounds on the yellow fever mosquito (*Aedes aegypti*), the greater wax moth (*Galleria mellonella*), and the yellow mealworm (*Tenebrio molitor*) are given in Table III. The *cis*-10,11-epoxides (**1b, 1c,** and **1d**) have higher biological activity than the corresponding *trans*-10,11-epoxides (**18a, 18b,** and **18c**) although these differences are small compared with those obtained when the natural *E* stereochemistry at C-2 and C-6 is changed to the *Z* configuration.[7,14] The analog **18d**[21] with two ethyl groups at C-11 shows high biological activity [*cf.* **1b** (JH II) and **18a**].

Experimental Section

Preparative thin-layer chromatography was carried out on 1 m × 20 cm plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. Nmr spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200 G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at 20 or 70 eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. All solvents were dried over activated molecular sieves, and all reactions were carried out under an inert atmosphere.

Methyl 3-Methyl-2-heptenoate. A. An authentic comparison sample of a mixture of the *Z* and *E* isomers of methyl 3-methyl-2-heptenoate was prepared by reaction of 2-hexanone with trimethylphosphonoacetate. Thus, 1.05 g (10.5 mmol) of 2-hexanone and 1.82 g (10 mmol) of trimethylphosphonoacetate were dissolved in 15 ml of dry DMF and cooled to 0° under a N_2 atmosphere. Finely powdered NaOH (0.44 g, 11 mmol) was added, and the reaction mixture was allowed to reach room temperature. After 24 hr, the reaction mixture was poured in saturated brine and worked up with pentane in the usual manner to give 0.70 g (4.5 mmol) of methyl 3-methyl-2-heptenoate: bp (bath, short path) 55° (10 mm); glc analysis showed a *Z:E* ratio of 42:58, respectively; nmr ($CDCl_3$) δ 1.88 (d, J = 1.5 Hz, C-3 CH_3 from *Z* isomer) and 2.17 ppm (d, J = 1.5 Hz, C-3 CH_3 from *E* isomer).

B. Lithium Di-*n*-butylcuprate in THF (entry 5, Table I). To 1.09 g (5.7 mmol) of cuprous iodide suspended in 15 ml of dry tetrahydrofuran at −45° under a nitrogen atmosphere was added 7.05 ml (11.3 mmol) of 1.60 *M* *n*-butyllithium in hexane. After 30 min, the temperature was lowered to −78°, and 0.89 g (9.1 mmol) of methyl 2-butynoate (**3a**) in 1 ml of THF was added over 10 min. After 0.5 hr, 1 ml of methanol was added dropwise followed by 5 ml of saturated aqueous NH_4Cl. The reaction mixture was then warmed to room temperature, and the solid was filtered off and washed with excess ether, and the organic fraction was then washed with saturated brine and dried ($CaSO_4$). The solvent was removed at atmospheric pressure by distillation through a Vigreux column. Short-path distillation of the residue [bp (bath) 55° (10 mm)] gave 1.18 g (7.6 mmol, 84% yield) of **5a** (1% *Z* isomer, 99% *E* isomer from glc analysis): ir (CCl_4) 1720 (C=O) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.17 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.70 (s, 3, CO_2CH_3), and 5.68 ppm (m, 1, H-2).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.10; H, 10.28.

C. From Lithium Di-*n*-butylcuprate in Ether–TMEDA (entry 6, Table I). To a suspension of 1.21 g (6.35 mmol) of cuprous iodide in 30 ml of dry diethyl ether at −40° under N_2 was added 7.73 ml (12.4 mmol) of 1.6 *M* *n*-butyllithium in hexane followed immediately by 1.10 g (9.5 mmol) of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). After 30 min (negative Gilman I color test),[22] the mixture was cooled to −78°, and 0.98 g (10 mmol) of **3a** in 3

Table III. Inhibition Dose (ID_{50}) Values on Sensitive Synchronized Insect Instars[a]

Compd	*Aedes aegypti*, ppm	*Galleria mellonella*, μg/pupa	*Tenebrio molitor*, μg/pupa
1a (JH III)[b]	0.35	12.0	4.5
1b (JH II)[b]	0.26	0.13	4.3
18a[b]	0.53	3.0	10.0
1c (JH I)[c]	0.15	0.060	0.70
18b[c]	0.33	0.70	2.3
1d (JH 0)	1.0	1.0	0.15
18c	15	18	1.5
18d[b]	0.28	0.52	0.24

[a] Bioassays were carried out as previously described (ref 14 and 20). [b] Prepared in ref 21. [c] Prepared in ref 6 and 19.

ml of ether was added dropwise. The suspension was maintained at −78° for 50 min and was then quenched by the slow addition of 2 ml of methanol followed by 2 ml of saturated aqueous $(NH_4)_2SO_4$. After the mixture had warmed to room temperature, it was filtered, and the collected solid was washed with an additional 75 ml of ether. The combined organic layers were washed with saturated $(NH_4)_2SO_4$, 5% aqueous HCl, saturated $NaHCO_3$, and then with saturated brine and dried ($CaSO_4$). Solvent was removed by distillation, and the residue was distilled, bp (bath, short path) 55° (10 mm). A 79% yield of **5a** (1.23 g, 7.9 mmol) was obtained (4% *Z* isomer, 96% *E* isomer by glc analysis).

D. From Polymeric *n*-BuCu·LiI in THF (entry 7, Table I). To 2.09 g (11.0 mmol) of cuprous iodide suspended in 30 ml of dry THF at −40° under a N_2 atmosphere was added 6.60 ml (10.6 mmol) of 1.60 *M* *n*-butyllithium in hexane. After 30 min, the suspension was cooled to −78°, and 0.98 g (10 mmol) of **3a** in 1 ml of THF was added dropwise. After 1.5 hr, the reaction mixture was quenched by the dropwise addition of 2 ml of methanol. The suspension was warmed to *ca.* −20°, and 2 ml of saturated aqueous $(NH_4)_2SO_4$ was added with stirring. When the gray suspension had warmed to room temperature, the solid was filtered off and was washed with *ca.* 100 ml of ether, and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated aqueous sodium chloride and then dried ($CaSO_4$). The solvent was removed by distillation through a Vigreux column, and the residue was then distilled, bp (bath, short path) 75° (20 mm). From this reaction, 1.50 g (9.6 mmol, 96% yield) of **5a** was isolated (>99% *E* isomer).

E. From Polymeric *n*-BuCu·LiI in Ether–TMEDA (entry 10, Table I). To 2.09 g (11.0 mmol) of cuprous iodide in 30 ml of dry diethyl ether at −40° under N_2 atmosphere was added 6.60 ml (10.6 mmol) of 1.60 *M* *n*-butyllithium in hexane followed immediately by 1.51 g (13.0 mmol) of TMEDA. After the mixture had been stirred for 30 min (negative Gilman I color test),[22] the brown suspension was cooled to about −50°, and 0.98 g (10 mmol) of **3a** in 1 ml of ether was added dropwise *via* syringe. The temperature was maintained in the range −45 to −50° for 20 min, and then 2 ml of methanol was added dropwise to quench the reaction. The cooling bath was removed, and 1 ml of saturated aqueous $(NH_4)_2SO_4$ was added. When the suspension had warmed to room temperature, the solid was filtered off and washed with *ca.* 100 ml of ether. The combined organic layers were washed with saturated aqueous $(NH_4)_2SO_4$, 5% aqueous HCl, saturated $NaHCO_3$, and saturated brine and then were dried ($CaSO_4$). Distillative removal of solvent through a Vigreux column followed by microdistillation of the residue [bp (bath, short path) 70° (20 mm)] gave 1.43 g (9.2 mmol, 92% yield) of **5a** (1% *Z* isomer, 99% *E* isomer from glc analysis).

F. From Polymeric *n*-BuCu·MgBrI in THF–TMEDA (entry 12, Table I). Cuprous iodide (2.28 g, 12 mmol) was suspended in 30 ml of dry THF at −40° under N_2, and 4.5 ml (11 mmol) of 2.45 *M* *n*-butylmagnesium bromide in ether was added along with 3.5 g (30 mmol) of TMEDA. After 30 min (negative Gilman I test),[22] the suspension was cooled to −78°, and 0.98 g (10 mmol) of **3a** in 1 ml of THF was added dropwise. After 1.5 hr, the reaction mixture was quenched by the very slow addition of 2 ml of methanol at −78°. Then 1 ml of saturated aqueous NH_4Cl was added to the mixture as it warmed to room temperature. The solid was filtered off and washed with about 100 ml of ether, and the filtrate was then worked up as in E to give 1.52 g (9.7 mmol, 97% yield) of **5a**, bp (bath, short path) 70° (20 mm) (2.5% *Z* isomer, 97.5% *E* isomer by glc analysis).

G. From Polymeric *n*-BuCu·MgBrI in Ether–TMEDA (entry 13, Table I). Reaction conditions were essentially identical with those of the preceding experiment with the exception that diethyl ether was used as solvent. The polymeric copper complex was formed during 1 hr at −40°, and the addition to **3a** was allowed to run for 3 hr at −78°. Short-path distillation of the product, after work-up, gave 1.30 g (8.3 mmol, 83% yield) of product. Glc analysis showed that the reaction mixture consisted of 5% methyl 2-butynoate (**3a**), 3% methyl (*Z*)-3-methyl-2-heptenoate (**6a**), and 92% methyl (*E*)-3-methyl-2-heptenoate (**5a**).

Methyl 3-Methyl-2-pentenoate (5c and 6c). A. From Lithium Diethylcuprate. To 7.07 g (0.037 mol) of CuI suspended in 125 ml of THF under argon at −55° was added 58 ml (0.070 mol) of 1.2 *M* ethyllithium in benzene. After the black mixture had stirred at −50° for 2 hr (negative Gilman I test),[22] the mixture was cooled to −78°, and 3.34 g (0.034 mol) of **3a** was added. After 2.25 hr at −78°, methanol (15 ml) was added dropwise (at −78°) followed by ether (60 ml), and the mixture was allowed to come to room temperature. Addition of saturated aqueous NH_4Cl and work-up by ether extraction in the normal manner gave 3.91 g (90% yield) of product. Analysis by glc showed the presence of 97% of the *E* isomer **5c** and 3% of the *Z* isomer **6c** (with no **3a** present).

B. From Methylcopper. To 4.27 g (0.0224 mol) of CuI in 35 ml of ether under argon was added 4 ml (0.027 mol) of TMEDA with stirring, and the mixture was cooled to −45°, and 14 ml (0.0227 mol) of 1.62 *M* methyllithium in ether was added. After 1.5 hr at −45° (negative Gilman I test),[22] the mixture was cooled to −78°, and 2.47 g (0.022 mol) of **3d** was added. After the mixture had been stirred for 1.5 hr at −78°, methanol (5 ml) was added dropwise (at −78°) followed by ether (20 ml), and the mixture was allowed to come to room temperature. Working up in the usual manner gave 2.55 g of product. Analysis by glc showed the presence of 86% of the *Z* isomer **6c**, 0.5% of the *E* isomer **5c**, and 13.5% of starting ester **3d**.

Methyl (*E*)-3,4,4-Trimethyl-2-pentenoate (5b) from Mixed Cuprate. To 1.0 g (5.25 mmol) of cuprous iodide in 30 ml of dry ether at 0° under a N_2 atmosphere was added 3.1 ml (5.2 mmol) of 1.67 *M* methyllithium in ether. After 30 min, the yellow suspension was cooled to −78°, and 4.0 ml (5.0 mmol) of 1.24 *M* *tert*-butyllithium in pentane was added. The yellow-green suspension was slowly warmed to −40°, at which temperature most of the solid had dissolved to give a black solution. The solution was again cooled to −78°, and 0.48 g (4.89 mmol) of methyl 2-butynoate (**3a**) in 4 ml of ether was added dropwise. After 45 min at −78°, the reaction mixture was quenched by the dropwise addition of water. The mixture was then poured into additional ether and saturated aqueous NH_4Cl. The phases were separated, and the organic layer was washed with brine and then dried ($MgSO_4$). The ether was removed, and the residue was distilled to give 0.74 g of product (*ca.* 97% yield). Glc analysis showed it to contain 3.2% methyl 3-methyl-2-butenoate (**5d**), 2.8% methyl (*Z*)-3,4,4-trimethyl-2-pentenoate (**6b**), and 94% **methyl (*E*)-3,4,4-trimethyl-2-pentenoate (5b)**. The latter was characterized: bp 89° (21 mm); ir (CCl_4) 1725 (C=O) and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.10 [s, 9, $(CH_3)_3C$], 2.16 (d, 3, *J* = 1.5 Hz, C-3 CH_3), 3.68 (s, 3, CO_2CH_3), and 5.77 ppm (m, 1, H-2).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.44; H, 10.43.

Methyl (*Z*)-3,4,4-trimethyl-2-pentenoate (**6b**) was characterized by glc-mass spectrum and by characteristic signals in the nmr spectrum of the product at ($CDCl_3$) δ 1.20 [s, $(CH_3)_3C$] and 1.85 ppm (d, *J* = 1.5 Hz, C-3 CH_3).

4-Methyl-3-hexenylmagnesium Bromide (9a). Magnesium turnings (9.75 g, 0.40 mol) were placed in a 2-l. three-necked flask fitted with a reflux condensor, an argon inlet, and a 1-l. addition funnel containing 63.7 g (0.36 mol) of 1-bromo-4-methyl-3-hexene[23] (76% 3*E* isomer, 24% 3*Z* isomer from glc analysis) dissolved in 900 ml of dry diethyl ether. Ether (100 ml) and a small portion of the ethereal bromide solution were then added to the magnesium. After the reaction had been initiated by the addition of a crystal of iodine, the remaining bromide solution was added dropwise over 9.5 hr, and the solution was then stirred overnight. Hydrolysis of

an aliquot with aqueous NH_4Cl and glc analysis of the product indicated complete reaction of the bromide. The Grignard solution was stored in a refrigerator at 4°.

Determination of the Grignard reagent concentration by uv spectral analysis with benzophenone gave a concentration of 0.25 *M* (69% yield from the bromide).[24]

Ethyl 3-Ethyl-7-methyl-2,6-nonadienoate (10a). Cuprous iodide (2.29 g, 12 mmol) was placed in a 100-ml flask equipped with a serum cap, an argon inlet, and a magnetic stirrer, and 30 ml of dry diethyl ether and 1.28 g (18 mmol) of pyrrolidine were added *via* syringe. The green suspension was cooled to −78°, and 18 ml (4.5 mmol) of 0.25 *M* 4-methyl-3-hexenylmagnesium bromide was added. After the yellow suspension had been stirred at −78° for 2 hr, 0.84 g (6.7 mmol) of ethyl 2-pentynoate (**3b**) in 5 ml of ether was added dropwise over 10 min. The mixture was quenched after 30 min by the dropwise addition of 0.75 ml of ethanol and was then warmed to room temperature and was poured into saturated aqueous NH_4Cl. The organic phase was washed with brine and then dried ($MgSO_4$). The residue, after solvent removal, was column chromatographed in hexane on 15 g of silica gel to yield 0.81 g (3.6 mmol, 80% yield based on Grignard reagent) of ethyl 3-ethyl-7-methyl-2,6-nonadienoate (**10a**) (99% 2*E* isomer, 1% 2*Z* isomer from glc analysis): nmr ($CDCl_3$) δ 0.97 (t, J = 7 Hz, H-9), 1.07 (t, 3, J = 7.5 Hz, C-3 CH_2CH_3), 1.27 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.60 (C-7 CH_3 of 6*E* isomer), 1.65 (C-7 CH_3 of 6*Z* isomer), 2.63 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 4.15 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.10 (m, 1, H-6), and 5.63 ppm (br s, 1, H-2).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.75.

Addition of ethyl 2-pentynoate to an organometallic complex prepared from 1 equiv of cuprous iodide, 1 equiv of 4-methyl-3-hexenylmagnesium bromide, and 4 equiv of trimethyl phosphite in ether gave no detectable quantities of ethyl 3-ethyl-7-methyl-2,6-nonadienoate but yielded mainly starting material. In another variation of the same addition, ethyl 2-pentynoate was added to a complex prepared from 1 equiv of 4-methyl-3-hexenylmagnesium bromide, 4 equiv of cuprous iodide-tri-*n*-butylphosphine, and 1 equiv of tri-*n*-butylphosphine in ether at −78°. The product, ethyl 3-ethyl-7-methyl-2,6-nonadienoate, was a mixture of the 2*E* and 2*Z* isomers (57:43, respectively) (*cf.* ref 8). Finally, when ethyl 2-pentynoate was added to a mixture of 1 equiv of cuprous iodide and 1 equiv of 4-methyl-3-hexenylmagnesium bromide in ether–hexamethylphosphoramide (1:1) at −78°, only a small amount (~20%) of coupling occurred with poor stereoselectivity (see Table II).

Methyl 3-Ethyl-7-methyl-2,6-nonadienoate (10b). To 57.0 g (0.30 mol) of cuprous iodide in a 2-l. three-necked flask equipped with a mechanical stirrer, argon inlet, and a 1-l. dropping funnel containing 640 ml (0.16 mol) of 0.25 *M* 4-methyl-3-hexenylmagnesium bromide in ether were added 600 ml of dry ether and 65.3 ml (51.3 g, 0.44 mol) of *N,N,N′,N′*-tetramethylethylenediamine. The suspension was cooled to −78°, and the Grignard solution was added dropwise over 1 hr. After the mixture had been stirred, an additional 2 hr at −78°, 16.8 g (0.15 mol) of methyl 2-pentynoate (**3d**) was added dropwise to the orange suspension over a 35-min period. The mixture was stirred 1.5 hr at −78° and then was quenched by dropwise addition of 15 ml of methanol over 15 min. The suspension was warmed to room temperature and poured into 600 ml of saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was reextracted with ether. The combined organic layers were washed with brine and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and distillation of the residue gave 27.7 g (0.13 mol, 87% yield based on **3d**) of **methyl 3-ethyl-7-methyl-2,6-nonadienoate (10b)** (98% 2*E* isomer, 2% 2*Z* isomer from glc analysis): bp 78–80° (0.3 mm); nmr ($CDCl_3$) δ 2.64 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 5.11 (m, 1, H-6), and 5.65 ppm (br s, 1, H-2).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.42; H, 10.51.

4-Ethyl-3-hexenylmagnesium Bromide (9b). Ethyl cyclopropyl ketone (87.70 g, 0.89 mol) was added over 1 hr with cooling to ethyllithium (1.3 mol) in benzene–ether, and the reaction mixture was stirred overnight at room temperature. Excess reagent was destroyed with 10% aqueous NH_4Cl, and the mixture was poured into 10% NH_4Cl and extracted with ether. The organic layer was then washed with 10% NH_4Cl, water, and brine and dried (Na_2SO_4), and the solvent was removed and the product fractionally distilled to give 82.80 g (73% yield) of 3-cyclopropyl-3-pentanol (99% purity by glc).

Cold HBr (48%, 265 ml) was added to the cyclopropyl alcohol (82.80 g, 0.65 mol) at 5° over 10 min with stirring. The reaction mixture was then stirred at 10° for 30 min and poured into 100 ml of cold water, and the organic layer was decanted. The aqueous phase was extracted with pentane, and the combined organic layers were washed with water, brine, saturated $NaHCO_3$, and water until neutral and dried (Na_2SO_4). The product was fractionally distilled giving 98.37 g (79% yield) of 1-bromo-4-ethyl-3-hexene (purity by glc was >98%): nmr ($CDCl_3$) δ 0.98 (t, 3, J = 7 Hz, CH_2CH_3), 1.00 (t, 3, J = 7 Hz, CH_2CH_3), 2.06 (q, 2, J = 7 Hz, CH_2CH_3), 2.57 (q, 2, J = 7 Hz, CH_2CH_3), 3.33 (t, 2, J = 7 Hz, H-1), and 5.08 ppm (t, 1, J = 7 Hz, H-3).

The Grignard was prepared by adding the bromide (77.3 g, 0.404 mol) in 750 ml of ether slowly to magnesium turnings (14.5 g, 0.60 mol) over 17 hr. The final concentration of Grignard was found to be 0.34 *M*.[24]

Ethyl (*E*)-3,7-Diethyl-2,6-nonadienoate (10c). TMEDA (50.7 g, 0.436 mol, 2.4 equiv) was added at room temperature to a mechanically stirred suspension of 41.5 g (0.218 mol, 1.2 equiv) of cuprous iodide in 1 l. of dry diethyl ether under argon. The suspension was cooled to −78°, and the 0.34 *M* Grignard solution **9b** (540 ml, 0.184 mol) was then added. The reaction mixture was stirred at −78° until the Gilman I test was negative (2 hr).[22] Ethyl 2-pentynoate (**3b**) (23.2 g, 0.184 mol) was then added, and after 1.5 hr at −78°, the reaction mixture was quenched by slow addition of 20 ml of ethanol (carefully maintaining the temperature at −78°) and then poured into 1 l. of saturated aqueous NH_4Cl. The mixture was extracted with ether, and the organic layer was washed with saturated NH_4Cl until the aqueous phase was colorless, 10% aqueous HCl, water, and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue distilled to give 31 g (0.13 mol) of **10c** (70.7% yield; the *Z*:*E* ratio of 95:5 by glc analysis; 3.5 g (0.028 mol) of **3b** was also recovered): bp 82–86° (0.15 mm); nmr ($CDCl_3$) δ 2.63 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 4.14 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.05 (m, 1, H-6), and 5.62 ppm (br s, 1, H-2).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.69; H, 10.95.

Ethyl (*E*)-3,8,12-Trimethyl-2,11-tridecadienoate (12). Pyrrolidine (12.8 g, 0.180 mol, 2.95 equiv) was added at room temperature to a mechanically stirred suspension of 23.2 g (0.122 mol, 2 equiv) of cuprous iodide in 250 ml of dry ether under argon. The suspension was cooled to −78°, and 86 ml (61 mmol) of 0.71 *M* 5,9-dimethyl-8-decenylmagnesium bromide[25] in ether was then added. The reaction mixture was stirred at −78° until the Gilman I test[22] was negative (1.5 hr). Ethyl 2-butynoate (**3c**) (6.85 g, 61 mmol) was then added, and after 30 min at −78°, 60 ml of water was added dropwise to quench the reaction mixture. The mixture was then poured into 500 ml of water and was extracted with ether. The organic layer was washed with 10% HCl, saturated $NaHCO_3$ and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue fractionally distilled to give 8.2 g (0.029 mol, 48% yield) of **12** (containing 2.5% of the *Z* isomer by glc analysis): bp 108–109° (0.03 mm); nmr ($CDCl_3$) δ 0.88 (d, 3, J = 5 Hz, C-8 CH_3), 1.27 (t, 3, J = 7 Hz, $CO_2CH_2CH_3$), 1.62 (br s, 3, C-12 CH_3), 1.70 (br s, 3, H-13), 2.15 (d, 3, J = 1.3 Hz, C-3 CH_3), 4.17 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 5.13 (m, 1, H-11), and 5.69 ppm (br s, 2, H-2).

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 77.42; H, 11.98.

Methyl (*E*)-6-[(1-Ethoxy)ethoxy]-3-ethyl-2-hexenoate (14a). To a mechanically stirred suspension of 1.33 g (7 mmol) of cuprous iodide in 6 ml of dry diethyl ether at −30° under a N_2 atmosphere was added 13.5 ml (5.8 mmol) of 0.43 *M* 3-[(1-ethoxy)ethoxy]propyllithium[18] followed immediately by 0.81 g (7 mmol) of TMEDA. After 30 min, the yellow suspension was cooled to −78°, and 0.73 g (6.5 mmol) of methyl 2-pentynoate (**3d**) in 5 ml of dry ether was added dropwise over 0.5 hr. The red-orange suspension was maintained at −78° for 2 hr and then was quenched by the dropwise addition of 2 ml of methanol. The cooling bath was removed, and the reaction mixture was poured into saturated aqueous NH_4Cl. An additional 100 ml of ether was added, and the layers were separated. After a reextraction of the aqueous phase with ether, the combined organic extracts were washed with brine

and dried ($CaSO_4$), and the solvent was removed *in vacuo* to give 1.4 g of crude product which was purified by chromatography on two 1 m × 20 cm preparative silica plates (1.5 mm thick; developed with ethyl acetate–hexane, 1:9) to give 1.2 g (4.91 mmol, 85% yield) of **14a** (99.5% *E* isomer, 0.5% *Z* isomer from glc analysis): bp (bath, short path) 65° (0.05 mm); ir (CCl_4) 1720 (C=O) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.65 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 4.69 [q, 1, J = 5.5 Hz, $OCH(CH_3)O$], and 5.67 ppm (br s, 1, H-2).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.87; H, 9.74.

Methyl (*E*)-3-Ethyl-6-hydroxy-2-hexenoate (14b). The acetal ester **14a** (1.15 g, 4.71 mmol) was dissolved in 30 ml of THF and 15 ml of water, and 150 mg of trichloroacetic acid was added. The solution was heated under reflux for 1.5 hr and then stirred at room temperature overnight. The reaction solution was poured into a mixture of 75 ml of ether and 50 ml of 2 *M* aqueous Na_2CO_3. The organic phase was washed once with brine and dried ($CaSO_4$). Removal of solvent *in vacuo* gave 0.74 g (4.30 mmol, 91% yield) of the alcohol ester **14b**: bp (bath, short path) 70° (0.05 mm); nmr ($CDCl_3$) δ 1.10 (t, 3, J = 7.5 Hz, C-3 CH_2CH_3), 2.65 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 3.67 (t, 2, J = 6 Hz, H-6), 3.72 (s, 3, CO_2CH_3), and 5.67 ppm (br s, 1, H-2).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.24.

Methyl (*E*)-3-Ethyl-6-oxo-2-hexenoate (14c). To a mechanically stirred suspension of 19.2 g (0.19 mol) of chromium trioxide in 500 ml of dichloromethane at 0° under a N_2 atmosphere was added 30.3 g (0.38 mol) of pyridine. After 30 min, 5.5 g (0.032 mol) of **14b** in 10 ml of dichloromethane was added to the complex. The reaction mixture was stirred for 15 min and then was filtered through a short column of neutral alumina (Woelm activity IV, 40 g). The eluate was diluted with ether, then washed with 5% hydrochloric acid and saturated brine, and dried ($CaSO_4$), and the solvent was removed *in vacuo* to give 4.97 g (0.029 mol, 91% yield) of **14c**: bp (bath, short path) 50° (0.05 mm); ir (film) 1720 (C=O) and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.10 (t, 3, J = 7.5 Hz, C-3 CH_2CH_3), 2.65 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 3.72 (s, 3, CO_2CH_3), 5.63 (br s, 1, H-2), and 9.90 ppm (br s, 1, CHO); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 170 (2), 81 (100).

Methyl (*E*)-3-Ethyl-6-hydroxy-7-methylene-2-nonenoate (15). A solution of 1-butenyl-2-magnesium bromide prepared from magnesium and 6.75 g (50 mmol) of 2-bromo-1-butene in 75 ml of THF was slowly added to 4.97 g (29.2 mmol) of **14c** in 110 ml of ether at −70° under a N_2 atmosphere. After 1 hr, the cooling bath was warmed to −40° for an additional 0.5 hr, and then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The reaction mixture was poured into ether, and the organic layer was washed with saturated brine and dried ($CaSO_4$), and the solvent was removed *in vacuo* to give 6.60 g of crude allylic alcohol (80% pure by glc analysis).

A small sample of **15** was purified by preparative tlc on silica gel plates (developed in 25% ethyl acetate in hexane): ir (CCl_4) 3590 (OH), 1720 (C=O), and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.63 (q, 2, J = 7 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 4.87 and 5.03 (two br s, 2, $C=CH_2$), and 5.65 ppm (br s, 1, H-2); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 226 (2), 111 (100).

Methyl (2*E*,6*E*)-11-Chloro-3,7-diethyl-11-methyl-10-oxo-2,6-tridecadienoate (16). A solution of 2.26 g of the crude allylic alcohol **15** above (*ca.* 8.3 mmol), 9.02 g (50 mmol) of 3-chloro-2,2-dimethoxy-3-methylpentane, and 0.2 g of propanoic acid in 30 ml of toluene was heated to 90° with a N_2 stream passing over the surface of the mixture to remove the methanol as it was formed. After 5 hr, the reaction mixture was concentrated *in vacuo*, then poured into 2 *N* aqueous NaOH, and extracted with ether. The combined organic layers were washed with saturated brine and dried ($CaSO_4$), and the solvent was removed *in vacuo* (to 0.01 mm). The residue was purified by chromatography on silica gel preparative thin-layer plates (1.5 mm, developed with 7% ethyl acetate in hexane) to give 2.09 g (6.1 mmol, 74% yield) of the chloro ketone **16**: ir (film) 1725, 1715 (C=O), 1650, and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.62 (s, 3, C-11 CH_3), 2.63 (q, 2, J = 7 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 5.12 (m, 1, H-6), and 5.65 ppm (br s, 1, H-2); mass spectrum (20 eV) *m/e* (rel intensity) 310 (4), 274 (6), 95 (100).

Methyl (2*E*,6*E*)-11-Chloro-3,7-diethyl-10-hydroxy-11-methyl-2,6-tridecadienoate (17). A solution of 2.17 g (6.34 mmol) of the chloro ketone **16** in 150 ml of methanol was cooled to 0°, and 1.40 g (37 mmol) of $NaBH_4$ was added portionwise. After the solution had been stirred for 45 min, it was poured into ice water and extracted with ether. The combined organic layers were washed with saturated brine and dried ($CaSO_4$), and the solvent was removed *in vacuo* to give 2.03 g of the chlorohydrins **17a** and **17b**. The diastereomers were separated by chromatography on silica gel preparative thin-layer plates (1 m × 20 cm; thickness, 1.5 mm) with six developments with 7% ethyl acetate in hexane. In this manner, 580 mg (1.68 mmol) of the threo chlorohydrin **17a** (upper band) and 440 mg (1.28 mol) of the erythro chlorohydrin **17b** (lower band) were obtained, each in *ca.* 96% purity (purity determined by hplc analysis: μ-Porasil, 30 × 0.4 cm, 15% ether in pentane).

The threo diastereomer **17a** was characterized as follows: ir (CCl_4) 3595 (OH), 1715 (C=O), and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.50 (s, 3, C-11 CH_3), 2.63 (q, 2, J = 7.5 Hz, C-3 CH_2CH_3), 3.53 (m, 1, H-10), 3.72 (s, 3, CO_2Me), 5.13 (m, 1, H-6), and 5.65 ppm (br s, 1, H-2).

The erythro diastereomer **17b** was characterized as follows: ir (CCl_4) 3595 (OH), 1715 (C=O) and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.53 (s, 3, C-11 CH_3), 2.64 (q, 2, J = 7 Hz, C-3 CH_2CH_3), 3.48 (m, 1, H-10), 3.71 (s, 3, CO_2CH_3), 5.15 (m, 1, H-6), and 5.67 ppm (br s, 1, H-2).

Anal. Calcd for $C_{19}H_{33}O_3Cl$: C, 66.17; H, 9.65; Cl, 10.29. Found: C, 66.14; H, 9.64; Cl, 10.27.

Methyl (2*E*,6*E*)-3,7-Diethyl-10,11-epoxy-11-methyl-2,6-tridecadienoate (1d and 18c). Erythro **17b** and threo **17a** chlorohydrins were converted to the trans (**18c**) and cis (**1d**) epoxides, respectively, as follows. Thus, 695 mg (5.03 mmol) of anhydrous K_2CO_3 was added to a solution of 720 mg (2.09 mmol) of the threo chlorohydrin **17a** in 18 ml of methanol. After the mixture had been stirred for 2.5 hr, it was poured into brine solution and extracted with ether. The organic phase was washed with brine until neutral and then dried ($CaSO_4$). After solvent removal *in vacuo*, the residue was distilled with a microstill to give 543 mg (1.76 mmol, 84% yield) of the cis epoxide **1d**: bp (bath, short path) 85° (0.002 mm); ir (CCl_4) 1725 (C=O) and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.97 (t, 3, J = 7 Hz, CH_2CH_3), 1.00 (t, 3, J = 7 Hz, CH_2CH_3), 1.07 (t, 3, J = 7 Hz, C-3 CH_2CH_3), 1.28 (s, 3, C-11 CH_3), 2.64 (q, 2, J = 7 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 5.13 (m, 1, H-6), and 5.65 ppm (br s, 1, H-2); mass spectrum (20 eV) *m/e* (rel intensity) 95 (100).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.81; H, 10.43.

The trans epoxide **18c** (348 mg, 1.13 mmol, 71% yield) was prepared from 540 mg (1.57 mmol) of erythro chlorohydrin **17b** in a similar manner: bp (bath, short path) 90° (0.005 mm); nmr ($CDCl_3$) δ 0.95 (t, 3, J = 7 Hz, CH_2CH_3), 0.98 (t, 3, J = 7 Hz, CH_2CH_3), 1.08 (t, 3, J = 7 Hz, C-3 CH_2CH_3), 1.25 (s, 3, C-11 CH_3), 2.64 (q, 2, J = 7 Hz, C-3 CH_2CH_3), 3.70 (s, 3, CO_2CH_3), 5.13 (m, 1, H-6), and 5.65 ppm (br s, 1, H-2).

1-(3-Methyl-2-butenoyl)pyrrolidine (20a). Lithium dimethylcuprate was prepared by adding 3.0 ml (4.8 mmol) of 1.6 *M* methyllithium in diethyl ether to 0.5 g (2.6 mmol) of cuprous iodide suspended in 30 ml of dry ether at 0° under an argon atmosphere. After 30 min, the homogeneous solution was cooled to −78°, and 0.35 g (2.55 mmol) of 1-(2-butynoyl)pyrrolidine (**19**) in 3 ml of ether was added. The suspension was stirred for 30 min at −78° and was then quenched by addition of water. The flask was warmed to room temperature, the organic and aqueous phases were separated, and the aqueous phase was extracted twice with ether. The combined organic fractions were then washed with brine and were dried ($MgSO_4$). The residue, after solvent removal *in vacuo*, was distilled (short path) to give 0.20 g (1.31 mmol, 51% yield) of **20a**: bp (bath) 85° (0.15 mm); ir (CCl_4) 1650 (C=O) and 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.83 (d, 3, J = 1.5 Hz, H-4), 2.05 (d, 3, J = 1.5 Hz, C-3 CH_3), and 5.80 ppm (m, 1, H-2).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.40; H, 10.01; N, 9.04.

(*E*)-1-(3-Methyl-2-pentenoyl)pyrrolidine (20b). To 5.0 g (26.3 mmol) of cuprous iodide suspended in 300 ml of dry diethyl ether at −15° under an argon atmosphere was added 40 ml (48 mmol) of 1.2 *M* ethyllithium in benzene *via* syringe. After 30 min, the mixture was cooled to −78°, and 3.0 g (21.9 mmol) of **19** in 15 ml of ether was added over 5 min. The mixture was stirred at −78°

for 45 min and then quenched by the slow addition of 40 ml of water. When the reaction mixture reached room temperature, the phases were separated, and the aqueous fraction was extracted again with ether. The combined organic layers were washed with brine and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was distilled to give 2.7 g (16.1 mmol, 74% yield) of **20b** (99% *E* isomer from glc analysis): bp 81–84° (0.25 mm); ir (CCl_4), 1660 (C=O) and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.05 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.03 (d, 3, J = 1.5 Hz, C-3 CH_3), and 5.78 ppm (m, 1, H-2).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25. Found: C, 71.84; H, 10.35.

(*E*)-*N,N*-Diethyl-3,6,10-trimethyl-2,9-undecadienamide (21). To 11.5 g (60.4 mmol) of cuprous iodide in a 500-ml three-necked flask fitted with a dropping funnel, an argon inlet, and a mechanical stirrer were added 100 ml of dry diethyl ether and 6.35 g (89 mmol) of pyrrolidine. The flask was cooled to −78°, and 96 ml (30.2 mmol) of 0.315 *M* citronellylmagnesium bromide was added. After 1.5 hr, 4.22 g (30.3 mmol) of *N,N*-diethyl-2-butynamide in 10 ml of ether was added over 5 min. After 30 min at −78°, the reaction mixture was quenched by the addition of water and was then warmed to room temperature. The reaction mixture was poured into additional water, and the phases were separated. After further ether extraction of the aqueous layer, the organic extracts were combined and washed with brine and then dried (Na_2SO_4). The solvent was removed *in vacuo*, and the crude product was distilled to yield 3.09 g (11.1 mmol, 37% yield) of **21** (>99% *E* isomer from glc analysis): bp 118° (0.03 mm); ir (film) 1650 (C=O) and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (d, 3, J = 5.5, C-6 CH_3), 1.12 (t, 6, J = 7 Hz, NCH_2CH_3), 1.59 (br s, 3, C-10 CH_3), 1.67 (br s, 3, H-11), 1.88 (d, 3, J = 1.3 Hz, C-3 CH_3), 3.36 (m, 4, NCH_2CH_3), 5.09 (m, 1, H-9), and 5.79 ppm (m, 1, H-2).

Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.35; H, 12.12; N, 4.85.

(*E*)-*N,N*-Diethyl-3,8,12-trimethyl-2,11-tridecadienamide (22). A 500-ml three-necked flask equipped with a dropping funnel, an argon inlet, and a mechanical stirrer was charged with 20.3 g (0.107 mol) of cuprous iodide, 160 ml of dry diethyl ether, and 11.4 g (0.16 mol) of pyrrolidine. The stirred suspension was cooled to −78°, and 76 ml (0.053 mol) of 0.70 *M* 5,9-dimethyl-8-decenylmagnesium bromide[25] in ether was added. After 1.5 hr, 7.38 g (0.053 mol) of *N,N*-diethyl-2-butynamide in 20 ml of ether was added dropwise. After 0.5 hr at −78°, the reaction mixture was quenched by the slow addition of 50 ml of water and was allowed to warm to room temperature. The reaction mixture was diluted with an additional 100 ml of water, the phases were separated, and the water layer was extracted again with ether. The combined organic layers were washed with saturated brine and were dried (Na_2SO_4). After solvent had been removed *in vacuo*, the product was distilled to give 11.0 g (0.036 mol, 68% yield) of **22** (>99% *E* isomer from glc analysis): bp 130° (0.06 mm); ir (film) 1650 (C=O) and 1625 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (d, 3, J = 5.5 Hz, C-8 CH_3), 1.13 (t, 6, J = 6.5 Hz, NCH_2CH_3), 1.62 (br s, 3, C-12 CH_3), 1.70 (br s, 3, H-13), 1.92 (d, 3, J = 1.2 Hz, C-3 CH_3), 3.42 (m, 4, NCH_2CH_3), 5.15 (m, 1, H-11), and 5.83 ppm (br s, 1, H-2).

Anal. Calcd for $C_{20}H_{37}NO$: C, 78.12; H, 12.13; N, 4.55. Found: C, 78.15; H, 12.25; N, 4.68.

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References and Notes

(1) Contribution No. 31 from the Research Laboratory of Zoecon Corporation.
(2) Zoecon Postdoctoral Fellow, 1968–1969.
(3) Zoecon Postdoctoral Fellow, 1969–1970.
(4) J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, 135 (1971); D. J. Faulkner, *Synthesis*, 175 (1971).
(5) H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967).
(6) C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Amer. Chem. Soc.*, **94**, 5374 (1972), and references cited therein.
(7) (a) K. H. Dahm, B. M. Trost, and H. Röller, *J. Amer. Chem. Soc.*, **89**, 5292 (1967); (b) K. H. Dahm, H. Röller, and B. M. Trost, *Life Sci.*, **7**, 129 (1968); (c) V. B. Wigglesworth, *J. Insect Physiol.*, **15**, 73 (1969); B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970); B. Schwieter-Peyer, *Insect Biochem.*, **3**, 275 (1973).
(8) J. B. Siddall, M. Biskup, and J. H. Fried, *J. Amer. Chem. Soc.*, **91**, 1853 (1969).
(9) E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969).
(10) (a) G. H. Posner, *Org. React.*, **19**, 1 (1972); (b) C. A. Henrick and J. B. Siddall, unpublished results discussed in ref 10a; (c) *cf.* C. Bretting, J. Munch-Petersen, P. M. Jorgensen, and S. Refn, *Acta Chem. Scand.*, **14**, 151 (1960); G. Boularand and R. Vessière, *Bull. Soc. Chim. Fr.*, 1706 (1967).
(11) (a) J. Klein and R. M. Turkel, *J. Amer. Chem. Soc.*, **91**, 6186 (1969); (b) J. Klein and N. Aminadav, *J. Chem. Soc. C*, 1380 (1970); (c) S. Rämsby, *Acta Chem. Scand.*, **25**, 1471 (1971); (d) J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2583 (1971); (e) S. B. Bowlus and J. A. Katzenellenbogen, *Ibid.*, 1277 (1973); (f) S. B. Bowlus and J. A. Katzenellenbogen, *J. Org. Chem.*, **38**, 2733 (1973); (g) see also R. Levene, J. Y. Becker, and J. Klein, *J. Organometal. Chem.*, **67**, 467 (1974).
(12) (a) F. Näf and P. Degen, *Helv. Chim Acta*, **54**, 1939 (1971); (b) E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *J. Amer. Chem. Soc.*, **94**, 4395 (1972); (c) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).
(13) R. J. Liedtke and C. Djerassi, *J. Org. Chem.*, **37**, 2111 (1972).
(14) C. A. Henrick, W. E. Willy, B. A. Garcia, and G. B. Staal, *J. Agr. Food Chem.*, in press; see also D. A. Schooley, K. J. Judy, B. J. Bergot, M. S. Hall, and J. B. Siddall, *Proc. Nat. Acad. Sci. U.S.*, **70**, 2921 (1973).
(15) Essentially complete utilization of both the alkyl groups of the organocuprate complex has also been reported for the reaction with *S*-alkyl thioesters to give ketones: R. J. Anderson, C. A. Henrick, and L. D. Rosenblum, *J. Amer. Chem. Soc.*, **96**, 3654 (1974).
(16) For comparison, attempts to alkylate allylic acetates with polymeric copper reagents other than "ate" complexes were not successful: R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970).
(17) (a) For example, E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972); J-P. Gorlier, L. Hamon, J. Levisalles, and J. Wagnon, *J. Chem. Soc., Chem. Commun.*, 88 (1973); G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 7788 (1973); H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973). (b) Mixed "ate" complexes of the type, lithium *n*- or *sec*-alkyl(*tert*-butyl)cuprate, tri-*n*-butylphosphine have been shown to *selectively transfer the n- or sec-alkyl group* in conjugate addition to mesityl oxide and to methyl vinyl ketone: G. M. Whitesides and P. E. Kendall, *J. Org. Chem.*, **37**, 3718 (1972); W. H. Mandeville and G. M. Whitesides, *Ibid.*, **39**, 400 (1974). (c) Lithium methyl(vinyl)cuprate has been reported to selectively transfer the vinyl group to 2-cyclopentenone: G. H. Posner, C. E. Whitten, J. J. Sterling, and D. J. Brunelle, *Tetrahedron Lett.*, 2591 (1974).
(18) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972).
(19) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. U.S.*, **67**, 1462, 1824 (1970).
(20) C. A. Henrick, G. B. Staal, and J. B. Siddall, *J. Agr. Food Chem.*, **21**, 354 (1973).
(21) R. J. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurflüh, *J. Amer. Chem. Soc.*, **94**, 5379 (1972).
(22) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).
(23) B. H. Braun, M. Jacobson, M. Schwarz, P. E. Sonnet, N. Wakabayashi, and R. M. Waters, *J. Econ. Entomol.*, **61**, 866 (1968); see also ref 7b.
(24) R. D'Hollander and M. Anteunis, *Bull. Soc. Chim. Belg.*, **72**, 77 (1963).
(25) 1-Bromo-5,9-dimethyl-8-decene has been described by L. Ruzicka and R. Steiger, *Helv. Chim. Acta*, **10**, 680 (1927).