

Reaction of Diketene with Grignard Reagents in the Presence of Cobalt Catalyst. A Convenient Method for the Synthesis of 3-Methylenealkanoic Acids Leading to Terpenoids

Tamotsu FUJISAWA,* Toshio SATO, Yoshihiko GOTOH,
Masatoshi KAWASHIMA, and Tatsuo KAWARA

Chemistry Department of Resources, Mie University, Tsu, Mie 514

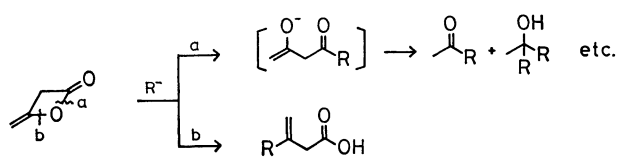
(Received March 23, 1982)

Primary alkyl Grignard reagents react regioselectively with diketene in the presence of cobalt(II) iodide to afford 3-methylenealkanoic acids in good yields. The synthetic utility of this reaction is demonstrated in the syntheses of terpenoids by two methods. Utilizing the isomerization of double bond of 3-methylenealkanoic acids, geranic acid and farnesic acid were obtained in two steps. Another method, the tandem [3,3] sigmatropic rearrangement of the corresponding allylic esters was used for the synthesis of C₁₈-Cecropia juvenile hormone.

Regioselective ring-opening reaction of β -propiolactones with diorganocuprates¹⁾ or with Grignard reagents in the presence of copper(I) salt²⁾ has been previously shown to be a useful synthetic method of β -substituted propionic acids. This three carbon homologation terminated with a carboxyl group provided a convenient procedure for the syntheses of various natural products.^{3,4)} Especially, β -methyl- β -propiolactone is a useful building block in the terpene synthesis,⁴⁾ *i.e.* geraniol was derived by the introduction of double bond into α,β -position of the ester of 3,7-dimethyl-6-octenoic acid (citronellic acid), which was obtained from β -methyl- β -propiolactone and homoprenyl Grignard reagent, followed by the reduction with LiAlH_4 .^{4a)} On the other hand, diketene (**1**) possesses not only the same carbon skeleton but also a carbon-carbon double bond. If the regioselective alkylation at the β -position of **1** is possible in a similar manner as β -methyl- β -propiolactone, it will provide a convenient method for the synthesis of 3-methylenealkanoic acids, and **1** will be employed as a C_4 unit of various terpenes involving double bond(s).

3-Methylenelcanoic acid derivatives have been reported as important precursors or intermediates for synthesis of several terpenoids.⁵⁻⁸⁾ 3-Methylenelcanoic acids have been synthesized by tedious routes *i.e.* the isomerization of the corresponding crotonic acid derivatives^{5,9)} the oxidation of homoallylic alcohol derivatives^{7a)} or the carboxylation of methallyl Grignard reagents.¹⁰⁾

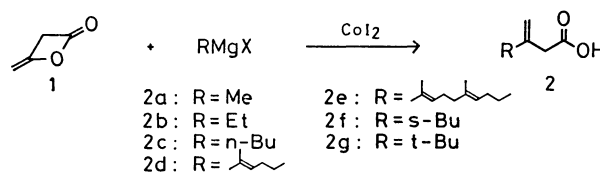
There were the enormous literatures¹¹⁾ on **1**. Nevertheless, a few reports have been published on the reaction with organometallic reagents leading to a carbon-carbon bond formation.¹²⁾ Grignard reagents react with **1** to give carbonyl carbon-oxygen bond cleavage products such as methyl ketones, 1,1-disubstituted ethanol derivatives and dehydroacetic acid in low yields.^{12a,b,13)} On the other hand, only one example of selective β -carbon-oxygen bond fission of **1** by organometallic reagent has been reported: the reaction



Scheme 1.

of trimethylsilylmethyl Grignard reagent in the presence of nickel(II) chloride as a catalyst to afford 3-trimethylsilyl-3-butenic acid.^{12c)} Thus, the catalyzed reaction of **1** with general Grignard reagents, which seems to be more useful, was explored.

The investigations were undertaken by surveying the reaction of **1** with Grignard reagents in the presence of various metal salts (10 mol%). When butylmagnesium bromide was added into a mixture of **1** and various metal halides in ether or THF at -78°C and stirred for 6 h at the same temperature, the yield of 3-methyleneheptanoic acid (**2c**), produced by β -carbon-oxygen bond fission of **1** was listed in Table 1. Cobalt(II) iodide was found to be the best catalyst.



Scheme 2.

Further, solvent effects were examined in the same conditions as shown in Table 1. 3-Methyleneheptanoic acid (**2c**) was obtained in the best yield of 66% by the use of cobalt(II) iodide in ether. Inverse addition of **1** into a mixture of butylmagnesium bromide and the catalyst decreased the yield (23%). The reaction was influenced by the halide ion of Grignard reagents, and butylmagnesium chloride, bromide, and iodide gave **2c** in 58, 66, and 39% yields, respectively. The results of the reaction of several representative Grignard reagents with **1** were shown in Table 2.

TABLE 1. REACTION OF DIKETENE WITH BUTYLMAGNESIUM BROMIDE IN THE PRESENCE OF METAL SALTS (10 mol%)
AT -78°C , 6 h

MX'	Solvent	Yield %	MX'	Solvent	Yield %
CuI	THF	1	CoBr ₂	Et ₂ O	8
NiI ₂	Et ₂ O	2	CoI ₂	Et ₂ O	66
FeI ₂	Et ₂ O	42	CoI ₂	THF	56
Fe(acac) ₃	THF	38	CoI ₂	THF-HMPA (12 : 1)	16
Co(acac) ₃	THF	54	CoI ₂	Toluene	28
CoCl ₂	Et ₂ O	1	CoI ₂	CH ₂ Cl ₂	3

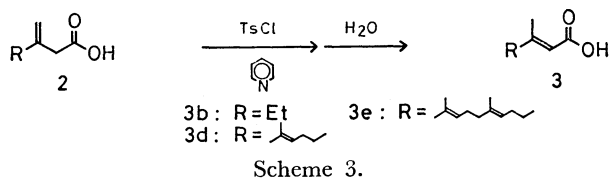
TABLE 2. REACTION OF DIKETENE WITH GRIGNARD REAGENTS^{a)}

	RMgX	Time/h	Product 2	Yield/% ^{b)}
a	MeMgBr	3		84
b	EtMgBr	6		65
c	<i>n</i> -BuMgBr	6		66
d	MgBr	6		52
e	MgBr	6		53 ^{c)}
f	<i>s</i> -BuMgCl	6		8
g	<i>t</i> -BuMgCl	6		6

a) The reaction was carried out in ether at -78°C in the presence of CoI_2 (10 mol%). b) Isolated yields by distillation. c) Isolated yield by TLC.

Primary alkyl Grignard reagents gave the corresponding acids **2** in good yields, whereas secondary and tertiary alkyl ones gave the desired acids in only a small amount. Phenyl, vinyl, and allyl Grignard reagents gave only polymeric products without the desired acids.

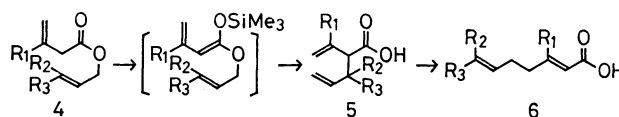
Next, the application to the synthesis of terpenoid carboxylic acids utilizing the ring-opening reaction of **1** followed by some simple transformation of 3-methylenealkanoic acid was attempted. The β,γ -unsaturated acids **2** obtained by the reaction can be isomerized successfully to α,β -unsaturated acids (**3**) by the treatment with *p*-toluenesulfonyl chloride in pyridine at 30°C for 1 h and then water (Table 3). For example,



3,7-dimethyl-2,6-octadienoic acid (geranic acid) (**3d**)^{8,14} and 3,7,11-trimethyl-2,6,10-dodecatrienoic acid (farnesic acid) (**3e**) were obtained in good yields by the reaction of **1** with homoprenyl- and homogeranyl-magnesium bromide, followed by the isomerization of the double bond of 7-methyl-3-methylene-6-octenoic

acid (isogeranic acid) (**2d**) and 7,11-dimethyl-3-methylene-6,10-dodecadienoic acid (isofarnesic acid) (**2e**).

In addition, 3-methylenealkanoic acids can be subjected to further carbon chain homologation by the tandem [3,3] sigmatropic rearrangement of the corresponding allylic ester. For example, 3-methyl-3-butenic acid (**2a**) produced by the reaction of **1** with methylmagnesium bromide can be used for a building block of a C_5 unit to form a terpene chain. The tandem [3,3] sigmatropic rearrangement of allyl 3-methylenealkanoate is performed as follows. The Claisen rearrangement of trimethylsilylketene acetal,¹⁵ which was obtained by treating the allylic esters (**4**) with lithium *N*-isopropylcyclohexylamide and trimethylsilyl chloride, produced the dienic acid (**5**), which was subsequently converted into the dienic acid (**6**) by the Cope rearrangement. For example, the Claisen



rearrangement of prenyl 3-methyl-3-butenate (**4**; $\text{R}_1, \text{R}_2, \text{R}_3 = \text{Me}$) via trimethylsilylketene acetal in THF at 67°C for 3 h gave the dienic acid (**5**; $\text{R}_1, \text{R}_2, \text{R}_3 = \text{Me}$), in sequence, geranic acid (**3d**) was obtained in a yield

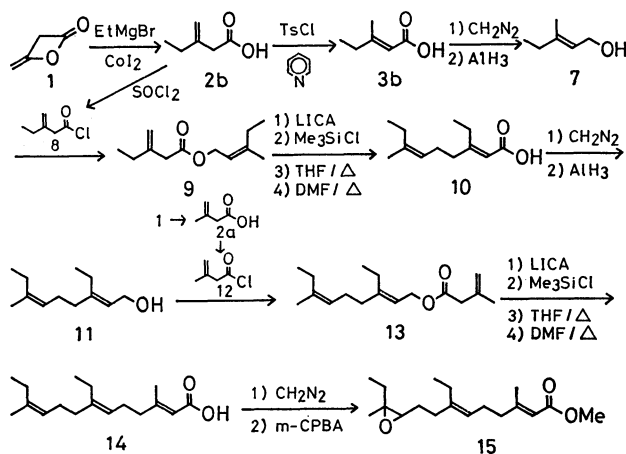
TABLE 3. ISOMERIZATION OF 3-METHYLENEALKANOIC ACID (**2**)

Acid 2	Product 3	Yield/%	
		80	$E:Z = 67:33$
		95	$E:Z = 66:34$
		86	$EE:EZ:ZE:ZZ = 47:17:27:9$

a) Homogeranyl bromide ($E:Z = 75:25$) was used as a starting material.

of 81% (*E*:*Z*=49:51) by the Cope rearrangement of **5** in DMF at 156 °C for 2 h. The tandem [3,3] sigmatropic rearrangement of geranyl 3-methyl-3-butenolate (**4e**; $R_1, R_2 = \text{Me}$, $R_3 = \text{Homoprenyl}$), afforded farnesic acid (**3e**) in 63% yield (*EE*:*EZ*:*ZE*:*ZZ*=36:13:20:31). It should be noted that the tandem [3,3] sigmatropic rearrangement of allyl 3-methylenealkanoate gave the single product, although analogous rearrangement of allyl 3-alkylcrotonate has been reported to give two isomers by the migration of double bond.¹⁶⁾

The utility of these reactions was demonstrated in the synthesis of C_{18} -Cecropia juvenile hormone from **1**. Starting material, 3-methylenepentanoic acid **2b** was prepared in 65% yield from **1** and ethylmagnesium bromide. The acid **2b** was isomerized to 3-methyl-2-pentenoic acid (**3b**) by the treatment of **2b** with *p*-toluenesulfonyl chloride in pyridine and then water, and the ratio of the *E* isomer to *Z* isomer for **3b** was 67:33. 3-Methyl-2-penten-1-ol (**7**) was obtained in 81% yield by the esterification of **3b** with diazomethane at 0 °C and the reduction with aluminum hydride at -18 °C. Alcohol **7** was treated with 3-methylenepentanoic acid (**8**), prepared in 84% yield from **2b** and thionyl chloride, to afford the allyl ester (**9**) in 87% yield. The tandem [3,3] sigmatropic rearrangement of **9** via trimethylsilylketene acetal gave 7-methyl-3-ethyl-2,6-nonadienoic acid (**10**) in 83% yield (*EE*:*EZ*:*ZE*:*ZZ*=21:13:36:30). The acid **10** was esterified with diazomethane and reduced with aluminum hydride to give 7-methyl-3-ethyl-2,6-nonadien-1-ol (**11**) in 81% yield.



Scheme 5.

Allylic ester **13** was obtained in 86% yield from **11** and 3-methyl-3-butenoyl chloride (**12**), prepared from 3-methyl-3-butenic acid (**2a**). The tandem [3,3] sigmatropic rearrangement of **13** furnished 3,11-dimethyl-7-ethyl-2,6,10-tridecatienoic acid (**14**) in 61% yield (*EEE*:*EEZ*:*EZE*:*EZZ*:*ZEE*:*ZEZ*:*ZZE*:*ZZZ*=9:7:14:11:17:13:16:13). The acid **14** was esterified with diazomethane and oxidized by the known method¹⁷⁾ with *m*-chloroperbenzoic acid at 0 °C to yield C_{18} -Cecropia juvenile hormone (**15**) in 37% yield, which consists of a mixture of eight geometrical isomers.

Thus, the cobalt-catalyzed ring-opening reaction of diketene with Grignard reagents offered a simple and convenient synthetic method for various 3-methylene-

alkanoic acids, and the reaction, which is four carbon homologation containing a terpene unit, should be useful for the synthesis of various terpenes.

Experimental

The IR spectra were recorded on a Hitachi EPI-G2 spectrometer. The NMR spectra were taken in a CCl_4 solution with a Varian A-60 spectrometer using TMS as an internal standard. The GLC analyses were performed on a Yanaco G-180 Gas Chromatograph using a ϕ 3 mm \times 2 m 20% PEG 20 M column, a ϕ 3 mm \times 2 m 15% Apieson T column, and a ϕ 0.25 mm \times 50 m FFAP column. The preparative TLC was performed on Wakogel B-5F. All boiling points are uncorrected.

Reaction of Diketene with Grignard Reagents. To a solution of cobalt(II) iodide (2.6 mmol) in ether 54 ml was added diketene (24 mmol) at -78 °C. Then ethereal solution of Grignard reagent (26.4 mmol) was slowly dropped and stirring was continued at -78 °C for the indicated period in Table 2. The reaction was quenched with 6 M (1 M = 1 mol dm^{-3}) HCl and extracted with ether. The separated organic layer was extracted with 3 M NaOH. The alkaline solution was acidified with 6 M HCl, and then extracted with ether. The ether extracts were washed with brine and dried (MgSO_4). Distillation gave 3-methylenealkanoic acid.

3-Methyl-3-butenic Acid (2a). The acid **2a** was obtained in 84% yield from diketene (**1**) and methylmagnesium bromide (0.994 M) in ether at -78 °C for 3 h; bp 88 °C/25 mmHg (1 mmHg = 133.322 Pa) (lit.¹⁰⁾ 68–70 °C/5 mmHg; IR (neat) 1710 ($\text{C}=\text{O}$) and 900 cm^{-1} ($\text{>C}=\text{CH}_2$); NMR δ = 1.81 (3H, s), 3.00 (2H, s), 4.82 (2H, s), and 11.87 (1H, s).

3-Methylenepentanoic Acid (2b). The acid **2b** was obtained in 65% yield from diketene (**1**) and ethylmagnesium bromide (1.02 M) in ether at -78 °C for 6 h; bp 95 °C/13 mmHg; IR (neat) 1700 ($\text{C}=\text{O}$) and 890 cm^{-1} ($\text{>C}=\text{CH}_2$); NMR δ = 1.08 (3H, t, J = 7 Hz), 2.10 (2H, q, J = 7 Hz), 3.20 (2H, s), 4.98 (2H, s), and 11.58 (1H, s). Found: C, 63.22; H, 9.04%. Calcd for $\text{C}_6\text{H}_{10}\text{O}_2$: C, 63.13; H, 8.83%.

3-Methyleneheptanoic Acid (2c). The acid **2c** was obtained in 66% yield from diketene (**1**) and butylmagnesium bromide (0.942 M) in ether at -78 °C for 6 h; bp 102 °C/5 mmHg; IR (neat) 1710 ($\text{C}=\text{O}$) and 900 cm^{-1} ($\text{>C}=\text{CH}_2$); NMR δ = 0.95 (3H, t, J = 7 Hz), 1.2–1.6 (4H, m), 2.0–2.3 (2H, m), 3.03 (2H, s), 4.95 (2H, s), and 11.45 (1H, s). Found: C, 67.47; H, 9.85%. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.93%.

7-Methyl-3-methylene-6-octenoic Acid (2d). The acid **2d** was obtained in 52% yield from diketene (**1**) and homoprenylmagnesium bromide (0.685 M) in ether at -78 °C for 6 h; bp 116–117 °C/1.9 mmHg; IR (neat) 1710 ($\text{C}=\text{O}$) and 900 cm^{-1} ($\text{>C}=\text{CH}_2$); NMR δ = 1.68 (3H, s), 1.74 (3H, s), 2.15–2.35 (4H, m), 2.90 (2H, s), 4.78 (2H, s), 4.75–5.15 (1H, m), and 11.85 (1H, s). IR and NMR spectra of the corresponding methyl ester were identical with reported ones.⁵⁾

7,11-Dimethyl-3-methylene-6,10-dodecadienoic Acid (2e). The acid **2e** was obtained in 53% yield from diketene (**1**) and homogeranylmagnesium bromide (0.900 M), prepared from homogeranyl bromide (*E*:*Z*=75:25),¹⁸⁾ in ether at -78 °C for 6 h; IR (neat) 1700 ($\text{C}=\text{O}$) and 890 cm^{-1} ($\text{>C}=\text{CH}_2$); NMR δ = 1.60 and 1.66 (9H, s), 1.90–2.40 (8H, m), 3.00 (2H, s), 4.88 (2H, s), 4.9–5.3 (2H, m), and 10.44 (1H, s). Found: C, 76.02; H, 10.47%. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.22; H, 10.24%.

4-Methyl-3-methylenhexanoic Acid (2f). The acid **2f** was obtained in 8% yield from diketene (**1**) and *s*-butylmagnesium chloride (0.916 M) in ether at -78°C for 6 h; bulb to bulb distillation ($200^{\circ}\text{C}/25\text{ mmHg}$); IR 1710 (C=O) and 900 cm^{-1} (>C=CH_2); NMR $\delta=0.98$ (3H, t, $J=7\text{ Hz}$), 1.05 (3H, d, $J=7\text{ Hz}$), 1.40 (2H, m), 1.8–2.3 (1H, m), 2.98 (2H, s), 4.95 (2H, s), and 10.28 (1H, s). Found: C, 67.56; H, 9.87%. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.93%.

4,4-Dimethyl-3-methylenepentanoic Acid (2g). The acid **2g** was obtained in 6% yield from diketene (**1**) and *t*-butylmagnesium chloride (0.680 M) in THF at -78°C for 6 h; bulb to bulb distillation ($200^{\circ}\text{C}/25\text{ mmHg}$); IR 1700 (C=O) and 900 cm^{-1} (>C=CH_2); NMR $\delta=1.10$ (9H, s), 2.85 (2H, s), 4.77 (2H, s), and 10.44 (1H, s). Found: C, 67.37; H, 9.98%. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.93%.

General Procedure for the Isomerization of 3-Methylenealkanoic Acid.

p-Toluenesulfonyl chloride (22 mmol) was added to a solution of 3-methylenealkanoic acid (20 mmol) in pyridine (60 ml), and stirred at 30°C for 1 h. Then, water (100 mmol) was added into the reaction solution and stirring was continued at 30°C for 30 min. The reaction mixture was poured upon cold 6 M HCl, and extracted with ether. The separated organic layer was extracted with 3 M sodium hydroxide solution. The alkaline solution was acidified with 6 M HCl, and then extracted with ether. The extracts were washed with brine and dried over anhydrous MgSO_4 . Concentration gave α,β -unsaturated acid.

3-Methyl-2-pentenoic Acid (3b).^{19a} The acid **3b** was obtained in 80% yield from 3-methylenepentanoic acid (**2b**); bp $100\text{--}104^{\circ}\text{C}/12\text{ mmHg}$; NMR $\delta=1.08$ (3H, t, $J=7.5\text{ Hz}$), 2.08 (d, $J=1\text{ Hz}$, CH_3 of **Z-3b**), 2.34 (d, $J=1\text{ Hz}$, CH_3 of **E-3b**), 2.44 (q, $J=8\text{ Hz}$, CH_2 of **E-3b**), 2.84 (q, $J=8\text{ Hz}$, CH_2 of **Z-3b**), 5.78 (1H, t, $J=1\text{ Hz}$), and 12.08 (1H, s); GLC of the methyl ester (**E:Z**=67:33), Rt. 9' 30" (**Z**), 11' 40" (**E**) (FFAP 50 m, 60°C).

3,7-Dimethyl-2,6-octadienoic Acid (3d).^{19b} The acid **3d** was obtained in 95% yield from 7-methyl-3-methylene-6-octenoic acid (**2d**); NMR $\delta=1.70$ (3H, s), 1.75 (3H, s), 2.02 (s, CH_3 of **Z-3d**), 2.20 (s, CH_3 of **E-3d**), 2.1–2.9 (4H, m), 4.92–5.34 (1H, m), 5.66 (1H, s), and 11.96 (1H, s); GLC of the methyl ester (**E:Z**=66:34), Rt. 8' 00" (**Z**), 9' 40" (**E**) (PEG 20 M, 2 m, 160°C).

3,7,11-Trimethyl-2,6,10-dodecatrienoic Acid (3e).^{19b} The acid **3e** was obtained in 86% yield from 7,11-dimethyl-3-methylene-6,10-decadienoic acid (**2e**); NMR $\delta=1.62$ and 1.68 (9H, s), 2.00–2.16 (11H, m), 4.90–5.30 (2H, m), 5.60–5.80 (1H, m), and 11.10 (1H, s); GLC of the methyl ester (**EE:EZ:ZE:ZZ**=47:17:27:9), 21' 00" (**Z,Z**), 24' 00" (**Z,E**), 26' 00" (**E,Z**), 28' 40" (**E,E**) (Apieson T 2 m, 200°C).

General Procedure for the Synthesis of 3-Methylenealkanoyl Chloride.

Thionyl chloride (3 equiv.) was added dropwise to 3-methylenealkanoic acid (1 equiv.) and the reaction mixture set aside overnight at room temperature. Distillation gave 3-methylenealkanoyl chloride.

3-Methylenepentanoyl Chloride (8). The acid chloride **8** was obtained in 84% yield from 3-methylenepentanoic acid (**2b**); bp $50^{\circ}\text{C}/100\text{ mmHg}$ (lit.²⁰ $110\text{--}117^{\circ}\text{C}$); NMR $\delta=1.04$ (3H, t, $J=7\text{ Hz}$), 2.16 (2H, q, $J=7\text{ Hz}$), 3.45 (2H, s), and 4.75–4.90 (2H, m); IR (neat) 1790 (C=O) and 900 cm^{-1} (>C=CH_2).

3-Methyl-3-butenoyl Chloride (12). The acid chloride **12** was obtained in 86% yield from 3-methyl-3-butenic acid (**2a**); bp $80^{\circ}\text{C}/100\text{ mmHg}$; NMR $\delta=1.80$ (3H, s), 3.43 (2H, s), and 4.90 (2H, m); IR (neat) 1800 (C=O) and 900 cm^{-1} (>C=CH_2).

General Procedure for the Esterification of 3-Methylenealkanoic Acid with Allylic Alcohol.

A solution of acid chloride (10.5 mmol) in ether (35 ml) was slowly added dropwise to a mixture of alcohol (10 mmol) and pyridine (11 mmol) in ether (33 ml) at -15°C for 40 min, and stirred for 1.5 h. The reaction was quenched with water and the ethereal solution was washed with water and dried (MgSO_4). The crude product was purified by column chromatography on silica gel (hexane:dichloromethane=1:1).

Prenyl 3-Methyl-3-butenate (4d). The ester **4d** was derived in 73% yield from 3-methyl-3-butenoyl chloride (**12**) and prenyl; IR (neat) 1720 (C=O) and 900 cm^{-1} (>C=CH_2); NMR $\delta=1.72$ (3H, s), 1.75 (3H, s), 1.77 (3H, s), 2.92 (2H, s), 4.48 (2H, d, $J=7.5\text{ Hz}$), 4.78 (2H, s), and 5.08–5.46 (1H, m). Found: C, 71.27; H, 9.67%. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$: C, 71.39; H, 9.59%.

Geranyl 3-Methyl-3-butenate (4e). The ester **4e** was derived in 86% yield from 3-methyl-3-butenoyl chloride (**12**) and geranyl; NMR $\delta=1.61$, 1.66, 1.70, and 1.76 (12H, s), 1.94–2.20 (4H, m), 2.86 (2H, s), 4.34 (2H, d, $J=6\text{ Hz}$), 4.70 (2H, s), and 4.90–5.40 (2H, m); IR (neat) 1720 (C=O) and 890 cm^{-1} (>C=CH_2). Found: C, 76.20; H, 10.53%. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_2$: C, 76.22; H, 10.24%.

General Procedure for the Tandem [3,3] Sigmatropic Rearrangement of Allyl 3-Methylenealkanoate.

A solution of *N*-isopropylcyclohexylamine (16.6 mmol) in THF (101 ml) was cooled to 0°C and treated with butyllithium in hexane solution (13.5 mmol, 1.5 M) over 3 min. After the mixture was stirred for an additional 10 min, the solution was cooled to -78°C and the ester (9 mmol) was added over 3 min. Within 5 min after the addition of the ester was complete, Me_3SiCl (16.3 mmol) was added to the reaction solution, and stirred at -78°C for 5 min. The reaction solution was allowed to warm to 25°C over 30 min and then refluxed for 2 h. After cooling the reaction mixture, 6 M HCl was added and extracted with ether. The ether extracts were washed with brine and dried (MgSO_4). The extracts were concentrated. DMF (30 ml) was added and refluxed for 2 h. To this solution 6 M HCl was added and extracted with ether. The ether extracts were washed with brine and dried (MgSO_4). The crude product was purified by distillation, TLC or column chromatography on silica gel.

3,7-Dimethyl-2,6-octadienoic Acid (3d).^{19b} The acid **3d** was obtained in 81% yield from prenyl 3-methyl-3-butenate (**4d**); bp $180^{\circ}\text{C}/2\text{ mmHg}$; GLC of the methyl ester (**E:Z**=49:51) Rt. 7' 30" (**Z**), 9' 10" (**E**) (20% PEG 20 M, 2 m, 160°C).

3,7,11-Trimethyl-2,6,10-dodecatrienoic Acid (3e).^{19b} The acid **3e** was obtained in 63% yield from geranyl 3-methyl-3-butenate (**4e**); TLC, R_f 0.5 (hexane:ether=2:1); GLC of the methyl ester (**EE:EZ:ZE:ZZ**=36:13:20:31) Rt. 21' 00" (6Z,2Z), 24' 00" (6E,2Z), 26' 00" (6Z,2E), and 28' 40" (6E,2E) (Apieson T 2 m, 200°C).

3-Methyl-2-penten-1-ol (7). A solution of diazomethane in ether was added to a solution of 3-methyl-2-pentanoic acid (**3b**) (10 mmol) in ether (10 ml) at 0°C . To a solution of the methyl ester in dry ether (30 ml) was slowly added an excess solution of aluminum hydride in ether (0.285 M) at -18°C , and stirred for 1 h. The reaction was quenched with saturated ammonium chloride, and then extracted with ether and dried (MgSO_4). Distillation gave **7** in 81% yield; bp $110^{\circ}\text{C}/140\text{ mmHg}$ (lit.²¹ $79\text{--}81^{\circ}\text{C}/40\text{ mmHg}$); IR 3300 cm^{-1} (O-H); NMR $\delta=1.02$ (3H, t, $J=7\text{ Hz}$), 1.62 (3H, s), 2.15 (2H, q, $J=7\text{ Hz}$), 3.40 (1H, b), 3.98 (2H, d, $J=7\text{ Hz}$), and 5.46 (1H, t, $J=7\text{ Hz}$).

3-Methyl-2-pentenyl 3-Methylenepentanoate (9). The ester **9** was derived in 87% yield from 3-methylenepentanoyl

chloride (**8**) and 3-methyl-2-penten-1-ol (**7**) according to the general procedure for the esterification as described above; NMR δ =1.04 (6H, t, J =7 Hz), 1.74 (3H, s), 1.85—2.40 (4H, m), 2.92 (2H, s), 4.44 (2H, d, J =7 Hz), 4.76 (2H, s), and 5.24 (1H, t, J =7 Hz). Found: C, 73.21; H, 10.48%. Calcd for $C_{12}H_{20}O_2$: C, 73.27; H, 10.27%.

3-Ethyl-7-methyl-2,6-nonadienoic Acid (10).^{19a)} The acid **10** was obtained in 83% yield by the tandem [3,3] sigmatropic rearrangement of 3-methyl-2-pentenyl 3-methylenepentanoate (**9**); column chromatography; TLC, R_f 0.5 (hexane:ether=2:1); GLC of the methyl ester (*EE:ZZ*:*ZE:ZZ*=21:13:36:30), Rt. 38' 50" (30%) (2*Z*,6*Z*), 44' 20" (36%) (2*Z*,6*E*), 44' 00" (13%) (2*E*,6*Z*), and 45' 50" (21%) (2*E*, 6*E*) (FFAP 50 m, 120 °C); NMR δ =0.96 (3H, t, J =7 Hz), 1.08 (3H, t, J =7 Hz), 1.60 and 1.66 (3H, s), 1.80—2.80 (8H, m), 4.90—5.20 (1H, m), 5.55 (1H, s), and 11.96 (1H, s).

3-Ethyl-7-methyl-2,6-nonadien-1-ol (11).²¹⁾ The alcohol **11** was obtained in 81% yield from 3-ethyl-7-methyl-2,6-nonadienoic acid (**10**) according to the procedure for the synthesis of **7**; bp 122—123 °C/7.5 mmHg; IR 3300 (OH) and 1660 cm^{-1} (C=C); NMR δ =1.00 (3H, t, J =7 Hz), 1.08 (3H, t, J =7 Hz), 1.46 and 1.54 (3H, s), 2.00—2.30 (8H, m), 2.16 (1H, s), 3.98 (2H, d, J =6 Hz), 4.84—5.20 (1H, m), and 5.25 (1H, t, J =6 Hz). Found: C, 78.88; H, 11.92%. Calcd for $C_{12}H_{22}O$: C, 79.02; H, 12.16%.

3-Ethyl-7-methyl-2,6-nonadienyl 3-Methyl-3-butenolate (13). The ester **13** was derived in 92% yield from 3-methyl-3-butenoyl chloride (**12**) and 3-ethyl-7-methyl-2,6-nonadien-1-ol (**11**); IR (neat) 1720 (C=O) and 900 cm^{-1} (γ -C=CH₂); NMR δ =0.82—1.23 (6H, m), 1.55 and 1.62 (3H, s), 1.82 (3H, s), 2.88 (2H, s), 4.45 (2H, d, J =7 Hz), 4.74 (2H, s), and 4.85—5.30 (2H, m). Found: C, 77.04; H, 10.52%. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%.

7-Ethyl-3,11-dimethyl-2,6,10-tridecatrienoic Acid (14).^{19a)} The acid **14** was obtained in 61% yield by the tandem [3,3] sigmatropic rearrangement of 3-ethyl-7-methyl-2,6-nonadienyl 3-methyl-3-butenolate (**13**); TLC, R_f 0.5 (hexane:ether=2:1); GLC of the methyl ester (*EEE:EEZ:EZE:EZZ:ZEE:ZEE:ZZE:ZZZ*=9:7:14:11:17:13:16:13), Rt. 23' 20" (13%) (2*Z*,6*Z*,10*Z*), 24' 40" (16%) (2*Z*,6*Z*,10*E*), 26' 20" (13%) (2*Z*,6*E*,10*Z*), 27' 40" (17%) (2*Z*,6*E*,10*E*), 30' 20" (11%) (2*E*,6*Z*,10*Z*), 32' 10" (14%) (2*E*,6*Z*,10*E*), 33' 40" (7%) (2*E*,6*E*,10*Z*), and 35' 20" (9%) (2*E*,6*E*,10*E*) (FFAP 50 m, 150 °C); NMR δ =0.98 (6H, t, J =7 Hz), 1.56 and 1.66 (3H, s), 1.80—2.35 (15H, m), 4.88—5.28 (2H, m), 5.60 (1H, s), and 11.72 (1H).

Methyl 10-Epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate (15). A solution of diazomethane in ether was added to a solution of acid **14** (1 mmol) in ether at 0 °C. The mixture was concentrated and purified by TLC (hexane:ether=2:1, R_f 0.8). A solution of *m*-chloroperbenzoic acid (318 mg, 0.96 mmol, 52% pure) in dichloromethane (2 ml) was added to a solution of methyl 7-ethyl-3,11-dimethyl-2,6,10-tridecatrienoate (242 mg, 0.87 mmol) in dichloromethane (2 ml) at 0 °C, and then stirred at 0 °C for 24 h. The reaction solution was washed with saturated sodium hydrogencarbonate solution and dried (MgSO₄).

Purification by TLC on silica gel (R_f 0.4—0.5, benzene:ethyl acetate=15:1) gave juvenile hormone (**15**) (98.2 mg, 0.33 mmol) in 37% yield from the acid **14**. IR (neat) 1710 (C=O) and 1140 cm^{-1} ; NMR δ =0.98 (6H, t, J =7 Hz), 1.16 (3H, s), 1.38—1.80 (4H, m), 1.90 and 2.16 (3H, s), 1.80—2.70 (9H, m), 3.64 (3H, s), 5.00—5.20 (1H, m),

and 5.58 (1H, s). IR and NMR spectral data were in agreement with the reported ones.^{17,19a)}

References

- 1) T. Fujisawa, T. Sato, T. Kawara, M. Kawashima, H. Shimizu, and Y. Ito, *Tetrahedron Lett.*, **21**, 2181 (1980).
- 2) T. Sato, T. Kawara, M. Kawashima, and T. Fujisawa, *Chem. Lett.*, **1980**, 571.
- 3) T. Fujisawa, T. Sato, T. Kawara, and K. Naruse, *Chem. Lett.*, **1980**, 1123; T. Sato, T. Kawara, K. Sakata, and T. Fujisawa, *Bull. Chem. Soc. Jpn.*, **54**, 505 (1981); T. Sato, T. Kawara, Y. Kokubu, and T. Fujisawa, *ibid.*, **54**, 945 (1981).
- 4) a) T. Fujisawa, T. Sato, T. Kawara, A. Noda, and T. Obinata, *Tetrahedron Lett.*, **21**, 2553 (1980); b) T. Sato, T. Kawara, A. Nishizawa, and T. Fujisawa, *ibid.*, **21**, 3377 (1980); c) T. Fujisawa, T. Sato, T. Kawara, and K. Ohashi, *ibid.*, **22**, 4823 (1981).
- 5) R. H. Bedoukian and J. Wolinsky, *J. Org. Chem.*, **40**, 2154 (1975).
- 6) D. Valentine, Jr., R. C. Sun, and K. Toth, *J. Org. Chem.*, **45**, 3703 (1980).
- 7) a) G. Cardillo, M. Contento, and S. Sandri, *Tetrahedron Lett.*, **1974**, 2215; b) G. Cainelli, G. Cardillo, M. Contento, P. Grasselli, and A. Umani-Ronchi, *Gazz. Chim. Ital.*, **103**, 117 (1973).
- 8) K. Itoh, M. Fukui, and Y. Kurachi, *J. Chem. Soc., Chem. Commun.*, **1977**, 500.
- 9) Y. Iwakura, F. Toda, R. Iwata, and Y. Torii, *Bull. Chem. Soc. Jpn.*, **42**, 841 (1969).
- 10) R. B. Wagner, *J. Am. Chem. Soc.*, **71**, 3214 (1949).
- 11) For a review, see T. Kato, *Acc. Chem. Res.*, **7**, 265 (1974); T. Kato and T. Chiba, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 733 (1981).
- 12) a) J. C. Combret, *Ann. Chim. (Paris)*, **4**, 481 (1969); b) A. Gibaud and A. Willemart, *Bull. Soc. Chim. Fr.*, **1956**, 432; c) K. Itoh, T. Yogo, and Y. Ishii, *Chem. Lett.*, **1977**, 103; d) J. R. Horder and M. F. Lappert, *J. Chem. Soc., A*, **1969**, 173.
- 13) Aldoketene dimers other than diketene have reported to react with Grignard reagents and alkyllithium in a similar manner: D. V. Nightingale and R. H. Turley, Jr., *J. Org. Chem.*, **26**, 2656 (1961); K. D. Berlin and M. H. Cooper, *ibid.*, **29**, 2057 (1964).
- 14) According to the procedure reported by Cardillo *et al.*,^{7a)} **2d** was treated with NaH at room temperature, but we could not obtain the isomerized product **3d**.
- 15) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
- 16) G. Fráter, *Helv. Chim. Acta*, **58**, 442 (1975).
- 17) K. Mori, *Tetrahedron*, **28**, 3747 (1972).
- 18) W. Biernacki and A. Gdula, *Synthesis*, **1979**, 37.
- 19) The obtained compounds were identified as methyl esters of the corresponding carboxylic acids: a) K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, **89**, 5292 (1967); b) J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *J. Chem. Soc., C*, **1966**, 2144.
- 20) J. W. Cornforth, F. P. Ross, and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 429.
- 21) S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, **1974**, 1425.