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

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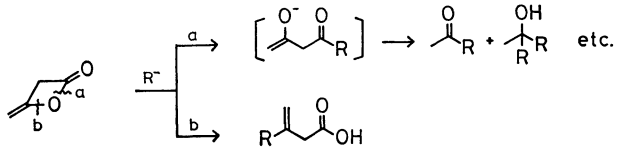
Primary alkyl Grignard reagents react regioselectively with diketene in the presence of cobalt(II) iodide to afford 3-methylenealkanoic acids in good yields. The synthetic utility of this reaction is demonstrated in the syntheses of terpenoids by two methods. Utilizing the isomerization of double bond 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 C_{18}-Cecropia juvenile hormone.

Regioselective ring-opening reaction of β-propiolactones with diorganocuprates[1] or with Grignard reagents in the presence of copper(I) salt[2] 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-Methylenealkanoic acid derivatives have been reported as important precursors or intermediates for synthesis of several terpenoids.[5-8] 3-Methylenealkanoic 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]

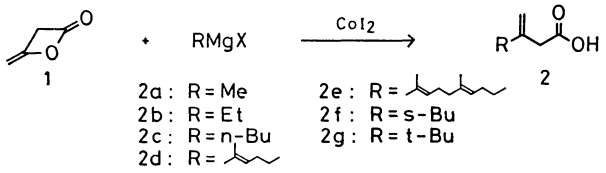
There were the enormous literatures[11] on **1**. Nevertheless, a few reports have been published on the reaction with organometallic reagents leading to a carbon-carbon bond formation.[12] Grignard reagents react with **1** to give carbonyl carbon-oxygen bond cleavage products such as methyl ketones, 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-butenoic 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.



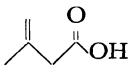
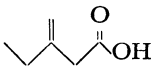
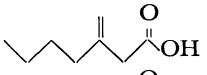
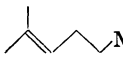
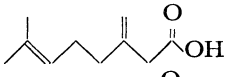
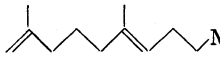
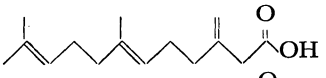
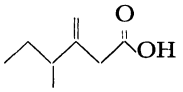
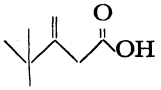
Scheme 2.

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_2O	8
NiI_2	Et_2O	2	CoI_2	Et_2O	66
FeI_2	Et_2O	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_2O	1	CoI_2	CH_2Cl_2	3

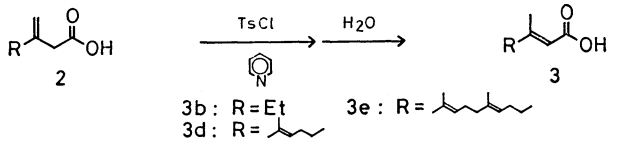
TABLE 2. REACTION OF DIKETENE WITH GRIGNARD REAGENTS[a)]

	RMgX	Time/h	Product **2**	Yield/%[b)]
a	MeMgBr	3		84
b	EtMgBr	6		65
c	*n*-BuMgBr	6		66
d		6		52
e		6		53[c)]
f	*s*-BuMgCl	6		8
g	*t*-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.

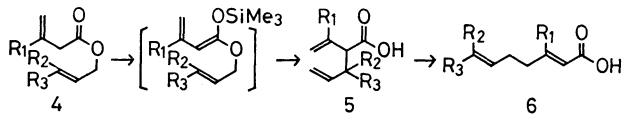
Next, the application to the synthesis of terpenoic carboxylic acids utilizing the ring-opening reaction of **1** followed by some simple transformation of 3-methylenealkanoic acid was attempted. The β,γ-unsaturated acids **2** obtained by the reaction can be isomerized successfully to α,β-unsaturated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



Scheme 3.

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 homogeranylmagnesium 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**).

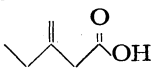
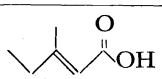
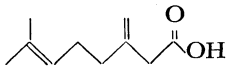
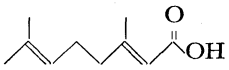
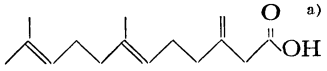
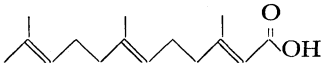
In addition, 3-methylenealkanoic acids can be subjected to further carbon chain homologation by the tandem [3,3] sigmatropic rearrangement of the corresponding allylic ester. For example, 3-methyl-3-butenoic acid (**2a**) produced by the reaction of **1** with methylmagnesium bromide can be used for 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 dienoic acid (**5**), which was subsequently converted into the dienoic acid (**6**) by the Cope rearrangement. For example, the Claisen



Scheme 4.

rearrangement of prenyl 3-methyl-3-butenoate (**4**; R_1, R_2,R_3=Me) *via* trimethylsilylketene acetal in THF at 67 °C for 3 h gave the dienoic acid (**5**; R_1,R_2,R_3=Me), in sequence, geranic acid (**3d**) was obtained in a yield

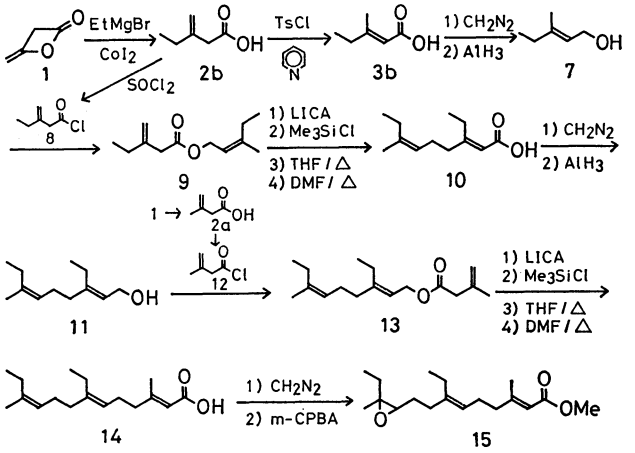
TABLE 3. ISOMERIZATION OF 3-METHYLENEALKANOIC ACID (**2**)

Acid **2**	Product **3**	Yield/%	
	 (**3b**)	80	*E*:*Z*=67:33
	 (**3d**)	95	*E*:*Z*=66:34
 a)	 (**3e**)	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-butenoate (**4e**; R_1,R_2=Me, R_3=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-methylenepentanoyl chloride (**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-butenoic acid (**2a**). The tandem [3,3] sigmatropic rearrangement of **13** furnished 3,11-dimethyl-7-ethyl-2,6,10-tridecatrienoic 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 method[17] 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-methylenealkanoic 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×2 m 20% PEG 20 M column, a ϕ 3 mm×2 m 15% Apieson T column, and a ϕ 0.25 mm×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-butenoic 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 (C=O) and 900 cm^{-1} (>C=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 (C=O) and 890 cm^{-1} (>C=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 $C_6H_{10}O_2$: 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 (C=O) and 900 cm^{-1} (>C=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 $C_8H_{14}O_2$: 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 (C=O) and 900 cm^{-1} (>C=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 (C=O) and 890 cm^{-1} (>C=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 $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

4-Methyl-3-methylenehexanoic 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 °C/25 mmHg); IR 1710 (C=O) and 900 cm^{-1} (>C=CH_2); NMR δ=0.98 (3H, t, J=7 Hz), 1.05 (3H, d, J=7 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 $C_8H_{14}O_2$: 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 °C/25 mmHg); IR 1700 (C=O) and 900 cm^{-1} (>C=CH_2); NMR δ=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 $C_8H_{14}O_2$: 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—104 °C/12 mmHg; NMR δ=1.08 (3H, t, J=7.5 Hz), 2.08 (d, J=1 Hz, CH_3 of *Z*-**3b**), 2.34 (d, J=1 Hz, CH_3 of *E*-**3b**), 2.44 (q, J=8 Hz, CH_2 of *E*-**3b**), 2.84 (q, J=8 Hz, CH_2 of *Z*-**3b**), 5.78 (1H, t, J=1 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 δ=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 δ=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 °C/100 mmHg (lit,[20] 110—117 °C); NMR δ=1.04 (3H, t, J=7 Hz), 2.16 (2H, q, J=7 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-butenoic acid (**2a**); bp 80 °C/100 mmHg; NMR δ=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-butenoate (4d). The ester **4d** was derived in 73% yield from 3-methyl-3-butenoyl chloride (**12**) and prenol; IR (neat) 1720 (C=O) and 900 cm^{-1} (>C=CH_2); NMR δ=1.72 (3H, s), 1.75 (3H, s), 1.77 (3H, s), 2.92 (2H, s), 4.48 (2H, d, J=7.5 Hz), 4.78 (2H, s), and 5.08—5.46 (1H, m). Found: C, 71.27; H, 9.67%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

Geranyl 3-Methyl-3-butenoate (4e). The ester **4e** was derived in 86% yield from 3-methyl-3-butenoyl chloride (**12**) and geraniol; NMR δ=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 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 $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

General Procedure of 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-butenoate (**4d**); bp 180 °C/2 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-butenoate (**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″ (6*Z*,2*Z*), 24′ 00″ (6*E*,2*Z*), 26′ 00″ (6*Z*,2*E*), and 28′ 40″ (6*E*,2*E*) (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 °C/140 mmHg (lit,[21] 79—81 °C/40 mmHg); IR 3300 cm^{-1} (O–H); NMR δ=1.02 (3H, t, J=7 Hz), 1.62 (3H, s), 2.15 (2H, q, J=7 Hz), 3.40 (1H, b), 3.98 (2H, d, J=7 Hz), and 5.46 (1H, t, J=7 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*:*EZ*:*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-butenoate (**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} (>C=CH$_2$); 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-butenoate (**13**); TLC, R_f 0.5 (hexane:ether=2:1), GLC of the methyl ester (*EEE*:*EEZ*:*EZE*:*EZZ*:*ZEE*:*ZEZ*:*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 ($MgSO_4$).

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]

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