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Regio- and Stereoselective Ring Opening of ω-Alkenyllactones Using Organocopper Reagents[1)]

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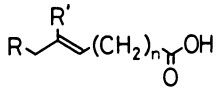
New synthetic methods are described for the preparation of (*E*)-3-, (*E*)-4-, and (*E*)-5-alkenoic acids by the regio- and stereoselective ring opening of β, γ, and δ-lactones with unsaturated substituents at the ω-position using organocopper reagents such as halomagnesium diorganocuprates or Grignard reagents in the presence of copper(I) iodide. Both the organocopper reagents with primary, secondary, tertiary alkyl, and phenyl groups gave the corresponding carbon homologated alkenoic acids in good yields. Alkadienoic acids were also obtained in good yields by the reactions of ω-alkenyllactones with divinyl- and diallylcuprates. Utilizing the ring opening of β-isopropenyl-β-propiolactone, homoterpenoid carboxylic acids were easily obtained in good yields. The ring opening of β-(1-chlorovinyl)-β-propiolactone afforded 4-chloro-3-alkenoic acids which were easily transformed to 4-oxoalkanoic acids and 4-oxo-2-alkenoic acids.

Nucleophilic displacement reactions of allylic compounds have received considerable attention[2)] because of their synthetic and mechanistic importance on the regio- and stereochemistry. Recently their attentions have been poured into the applications of organometallic reagents to selective carbon homologation with newly formed carbon–carbon double bond. Among organometallic reagents, organocopper reagents have been most widely used for the substitution reactions and applied to the synthesis of various kinds of alkenes. The regio- and stereoselective synthesis of alkenes is very important but not so easy since the selectivity is affected by many factors such as the structure of substrate, the nature of organocopper reagent, solvent, temperature and so on.[3,4)] On the other hand, there were many reports on the synthetic methods of alkenoic acids which are useful building blocks for the synthesis of natural products. The representative methods such as Ramberg-Bäcklund rearrangement of ω-halo-ω-(alkylsulfonyl)alkanoic acids,[5)] Knoevenagel condensation of malonic acid with aldehyde,[6)] and the reduction of the alkynoic acid[7)] are capable for disubstituted alkenes, but not for trisubstituted alkenes such as terpenoid carboxylic acid. Moreover, there is no sufficient method, to our knowledge, in all of aspects of stereoselectivity of carbon–carbon double bond, the product yield, the applicability, and the convenience of the synthetic procedure.



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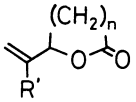

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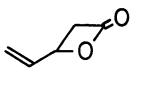
Previously the synthetic methods of 3-substituted propanoic acids by the reactions of β-propiolactones with organocopper reagents were reported.[8)] The high regioselectivity of the ring opening of the lactone was achieved by the attack of organocopper reagents, considered as "soft base", to the "soft" β-carbon atom of the lactone rather than the attack to the "hard" carbonyl carbon atom.[9)] Therefore, if β-propiolactone possesses a vinyl group at β-carbon, it is expected that the "softer" organocopper reagent attacks the "softer" terminal vinyl carbon of the lactone in the S_N2' manner to afford 4-substituted 3-alkenoic acid. Moreover, this concept seems to be capable for the new synthetic method of alkenoic acid **1** by the ring opening of ω-alkenyllactones **2** using organocopper reagents. Actually ring opening of γ- and δ-lactones possessing ω-unsaturated substituent with organocopper reagents have been reported.[10)] The present paper shows the detail on the regio- and stereoselective ring opening of ω-alkenyllactones such as β-vinyl-β-propiolactone, β-isopropenyl-β-propiolactone, β-(1-chlorovinyl)-β-propiolactone, γ-vinyl-γ-butyrolactone, and δ-vinyl-δ-valerolactone with organocopper reagents to afford various kinds of alkenoic acids.



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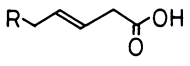

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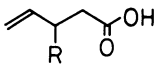

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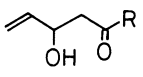

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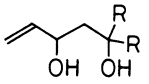

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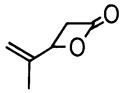
When β-vinyl-β-propiolactone (**3**), prepared by the cycloaddition of acrylaldehyde with ketene,[11)] was treated with butylmagnesium bromide in the presence of copper(I) iodide (2 mol%) in THF at −30 °C, two kinds of carboxylic acids, 3-nonenoic acid (**4b**) and 3-butyl-4-pentenoic acid (**5b**), formed by both S_N2' and S_N2 reactions respectively, were obtained in 91% yield

Table 1. Reactions of β-Vinyl-β-propiolactone with Butylmetallic Compounds

BuM	Solvent	Temp/°C	Time/min	Yield[a]/%	Product ratio[b]				
					4	((E)-:(Z)-)	5	6	7
BuMgBr	THF	−30	15	36	28	(81:19)	3	47	22
BuCu·PBu$_3$	Et$_2$O	−30	15	79	48	(56:44)	52	0	0
BuCu·BF$_3$	THF	−30	15	66	95	(85:15)	5	0	0
BuCu·SMe$_2$	THF-Me$_2$S[c]	−30	15	85	96	(84:16)	4	0	0
Bu$_2$CuLi	THF	−30	15	82	95	(83:17)	5	0	0
BuMgBr, 2 mol% CuI	THF-Me$_2$S[c]	0	15	94	87	(74:26)	13	0	0
BuMgBr, 2 mol% CuI	THF-Me$_2$S[c]	−30	15	96	98	(84:16)	2	0	0
BuMgBr, 2 mol% CuI	THF	−30	15	91	98	(83:17)	2	0	0
BuMgBr, 2 mol% CuI	Et$_2$O	−30	15	68	80	(83:17)	20	0	0
BuMgBr, 2 mol% CuI	THF-Me$_2$S[c]	−78	15	96	99	(87:13)	1	0	0
BuMgBr, 2 mol% CuI	THF-Me$_2$S[c]	−100	15	94	>99	(90:10)	<1	0	0

a) Isolated yield. b) Determined by GLC analysis. c) For the case of butylcopper–dimethyl sulfide and copper-catalyzed butyl Grignard reagent, the ratio of THF to Me$_2$S was 5:1 and 20:1, respectively.

without accompanying the products **6** and **7** by the attack to the carbonyl carbon. GLC analysis of the acids showed the ratio of **4b** to **5b** as 98:2, indicating that the reaction regioselectively proceeds through S_N2' pathway. Butyl Grignard reagent and other butylcopper reagents were used in this ring opening of the lactone **3**. It should be noted that the reaction of the lactone **3** with butylmagnesium bromide in the absence of copper catalyst in THF at −30 °C gave only 11% of **4b** along with **6** and **7**. Although three kinds of monoorganocopper complexes with tributylphosphine, trifluoroborane,[12] and dimethyl sulfide gave only carboxylic acids **4** and **5** in high yields, the ratio of the S_N2' product to the S_N2 product was somewhat inferior to that of the reaction of Grignard reagents in the presence of copper(I) iodide. Even lithium diorganocuprate which is commonly used in the allylic substitutions did not reveal the selectivity as high as copper-catalyzed Grignard reagent. Therefore optimum conditions were examined in the reaction of the lactone **3** with Grignard reagent in the presence of copper(I) iodide. The solvent and temperature effects on both the regioselectivity and the stereochemistry of the newly formed double bond of **4b** were examined. When homogeneous reaction was carried out by adding dimethyl sulfide as a co-solvent of THF to dissolve the copper catalyst, the yield of the acids increased from 91% to 96% with the same ratio of **4b** to **5b** (98:2). Ether, instead of THF, was employed as a solvent to result in decreasing both the yield (68%) and regioselectivity (**4b**:**5b**=80:20). High regio- and stereoselectivity by the S_N2' reaction was exhibited at a lower temperature. When the reaction was carried out at −100 °C, **4b** was obtained in a high yield of 94% along with only a trace amount of **5b** and the ratio of the *E*- to *Z*-isomer of **4b** was 90:10. These results are shown in Table 1. Since it was reported that the active species in copper-catalyzed Grignard reaction were halomagnesium cuprates,[3,13] the reaction of the lactone **3** with dibutylcuprate, prepared from one equivalent of copper(I) iodide and two equivalents of butylmagnesium bromide, was examined. Expectedly the reaction proceeded regio- and stereoselectively to afford the acid **4b** in a yield of 92% (E:Z=89:11) along with a small amount of **5b**. The reactions of several representative Grignard reagents in the presence of copper catalyst and diorganocuprates with the lactone **3** were examined. Both of the reactions of diorganocuprates and of Grignard reagents in the presence of a catalytic amount of copper(I) iodide proceeded with similar selectivity to afford the corresponding 3-alkenoic acids **4a—g** in similar good yields, when the organic groups of organocopper reagents are primary, secondary, and tertiary alkyl ones. In contrast to the poor result of the copper-catalyzed reaction of allylmagnesium bromide, the reaction using diallylcuprate proceeded with higher regio- and stereoselectivity to give the corresponding dienoic acid. The result was not improved in the case of divinylcuprate. These results are summarized in Table 2.



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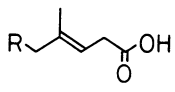
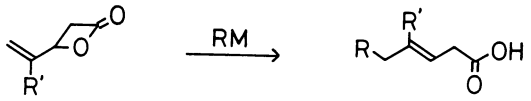


9

Synthesis of 4-methyl-5-substituted 3-pentenoic acids **9** was performed by using regio- and stereoselective ring opening of β-isopropenyl-β-propiolactone (**8**) prepared by the cycloaddition of methacrylaldehyde with ketene.[11b] Grignard reagents with primary, secondary, and tertiary alkyl groups, and with phenyl group furnished the acids **9a—e** in good yields, respectively. Although copper-catalyzed Grignard reagents with vinyl and allyl groups gave the acids **9f** and **9g** in poor yields, the use of divinyl- and diallylcuprate increased the yield of **9f** and **9g** in similar to the case of the lactone **3**. On the stereochemistry of the products, the ratio of *E*-isomer to *Z*-isomer was ranging from 82:18 to 66:34.

Table 2. Reactions of β-Alkenyl-β-propiolactone with Organocopper Reagents[a]



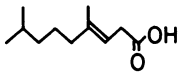
RM	R'=H **3**				
	Temp/°C	Time/min	Yield/%	(**4**:**5**)	(*E*)-:(*Z*)-**4**
MeMgBr, cat. CuI[b]	−100	15	**4a**, **5a** 70	(97: 3)	92: 8
Me_2CuMgX[c]	−78	60	**4a**, **5a** 70	(98: 2)	91: 9
BuMgBr, cat. CuI[b]	−100	15	**4b**, **5b** 94	(>99:<1)	90:10
Bu_2CuMgX[c]	−78	60	**4b**, **5b** 92	(99: 1)	89:11
s-BuMgCl, cat. CuI[b]	−100	15	**4c**, **5c** 96	(>99:<1)	88:12
s-Bu_2CuMgX[c]	−78	60	**4c**, **5c** 72	(>99:<1)	79:21
t-BuMgCl, cat. CuI[b]	−78	50	**4d** 84	—	86:14
t-Bu_2CuMgX[c]	−78	60	**4d**, **5d** 79	(>99:<1)	78:22
PhMgBr, cat. CuI[b]	−100	15	**4e**, **5e** 91	(91: 9)	83:17
Ph_2CuMgX[c]	−78	60	**4e**, **5e** 72	(89: 11)	91: 9
CH_2=CHMgBr, cat. CuI[b]	−78	30	**4f**, **5f** 61	(92: 8)	78:22
$(CH_2=CH)_2CuMgX$[c]	−50	60	**4f**, **5f** 64	(87: 13)	82:18
$CH_2=CHCH_2MgBr$, cat. CuI[b]	−50	120	**4g**, **5g** 25	(87: 13)	77:23
$(CH_2=CHCH_2)_2CuMgX$[c]	−50	60	**4g**, **5g** 88	(98: 2)	89:11

RM	R'=Me **8**			
	Temp/°C	Time/min	Yield/%	(*E*):(*Z*)
MeMgBr, cat. CuI[b]	−78	60	**9a** 80	66:34
Me_2CuMgX[c]	−78	60	**9a** 89	73:27
BuMgBr, cat. CuI[b]	−78	60	**9b** 92	73:27
Bu_2CuMgX[c]	−78	60	**9b** 83	82:18
s-BuMgCl, cat. CuI[b]	−78	60	**9c** 91	76:24
s-Bu_2CuMgX[c]	−78	60	**9c** 93	71:29
t-BuMgCl, cat. CuI[b]	−78	60	**9d** 88	72:28
t-Bu_2CuMgX[c]	−78	60	**9d** 98	66:34
PhMgBr, cat. CuI[b]	−78	60	**9e** 84	72:28
Ph_2CuMgX[c]	−78	60	**9e** 96	72:28
CH_2=CHMgBr, cat. CuI[b]	−78	60	**9f** 48	74:26
$(CH_2=CH)_2CuMgX$[c]	−78	60	**9f** 88	69:31
$CH_2=CHCH_2MgBr$, cat. CuI[b]	−78	60	**9g** 20	68:32
$(CH_2=CHCH_2)_2CuMgX$[c]	−78	60	**9g** 77	76:24

RM	R'=Cl **10**			
	Temp/°C	Time/min	Yield/%	(*Z*):(*E*)
MeMgBr, cat. CuI[b]	−78	50	**11a** 80	93: 7
Me_2CuMgX[c]	−50	50	**11a** 80	90:10
BuMgBr, cat. CuI[b]	−78	50	**11b** 81	89:11
Bu_2CuMgX[c]	−50	50	**11b** 85	89:11
s-BuMgCl, cat. CuI[b]	−78	50	**11c** 89	85:15
s-Bu_2CuMgX[c]	−50	50	**11c** 91	86:14
t-BuMgCl, cat. CuI[b]	−78	50	**11d** 91	80:20
t-Bu_2CuMgX[c]	−50	50	**11d** 80	86:14
PhMgBr, cat. CuI[b]	−78	50	**11e** 76	83:17
Ph_2CuMgX[c]	−50	50	**11e** 92	84:16
CH_2=CHMgBr, cat. CuI[b]	−78	50	**11f** 51	95: 5
$(CH_2=CH)_2CuMgX$[c]	−50	50	**11f** 71	91: 9
$CH_2=CHCH_2MgBr$, cat. CuI[b]	−78	50	**11g** 25	92: 8
$(CH_2=CHCH_2)_2CuMgX$[c]	−50	50	**11g** 77	91: 9

a) All products were isolated and the isomer ratios were determined by GLC analysis. b) Reactions were performed in THF-Me_2S (20:1). In the ring opening of **3** and **8**, 2 mol% of CuI was used. In the ring opening of **10**, 4 mol% of CuI was used. c) Reactions were performed in THF-Me_2S (10:1).

Compared with the ring opening of the vinyllactone **3**, the reaction of the isopropenyllactone **8** was found to give exclusively regioselective products by S_N2' reaction without any products through S_N2 pathway, but the stereoselectivity of newly formed carbon–carbon double bond somewhat decreased. These results are also summarized in Table 2.



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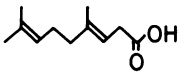
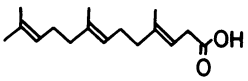
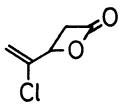


9i



9j

Ring opening of the lactone **8** was applied to the synthesis of homoterpenoid carboxylic acids which were useful for the synthesis of terpenoid natural products.[14] 4,8-Dimethyl-3-nonenoic acid (**9h**) was obtained in 85% yield by the reaction of the lactone **8** with isopentylmagnesium bromide in the presence of copper(I) iodide (2 mol%). Homogeranic acid (**9i**) and homofarnesylic acid (**9j**) were obtained by the reaction of the lactone **8** with halomagnesium diprenylcuprate and digeranylcuprate in 89% and 68% yields, respectively. The isomer ratios of (*E*) to (*Z*) of newly formed carbon–carbon double bond of these acids **9h—j** were ca. 75:25.



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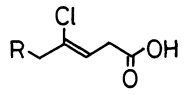
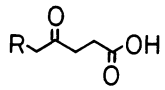


11

The synthesis of 4-chloro-3-alkenoic acid **11** was tried by the ring opening of β-(1-chlorovinyl)-β-propiolactone (**10**) prepared by the cycloaddition of α-chloroacrylaldehyde with ketene.[11b] When the lactone **10** was treated with various kinds of Grignard reagents in the presence of 4 mol% of copper(I) iodide, in THF–Me_2S at −78 °C, only S_N2' products, **11a—g** were formed in high yields. As the substituents of Grignard reagents, not only primary, secondary, and tertiary alkyl groups, but also phenyl and vinyl groups could be used to give good results. Diphenyl-, divinyl-, and diallylcuprates gave the corresponding acids **11e—g** in much higher yields than the corresponding Grignard reagents in the presence of copper(I) iodide. Stereochemistry of the newly formed carbon–carbon double bond of **11a—g** was determined to be predominant *Z* configuration in all cases, by comparing the NMR spectra with those of *E*- and *Z*-isomers of ethyl 4-chloro-3-pentenoate[15] and by capillary GLC analysis. Although the major isomer of obtained acid is named as *Z*-isomer in nomenclature, the relative configuration of the carbon–carbon double bond is same as that of (*E*)-3-alkenoic acid obtained by the ring opening reaction of the lactone **3**. These results are summarized also in Table 2.



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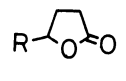

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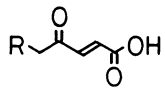

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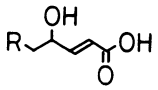


15

The utility of the acids **11** was demonstrated by the transformation to 4-oxoalkanoic acids **12** which are well-known as important precursors for γ-substituted γ-butyrolactones (**13**) as natural products.[16] According to the reported method of the hydrolysis of vinyl chloride to ketones,[17] treatment of **11b** with $TiCl_4$, MeOH, H_2O, and acetone in CH_2Cl_2 gave 4-oxononanoic acid (**12b**) in 82% accompanied with 8% yield of methyl 4-oxononanoate. The other acids **11** were also hydrolyzed to the corresponding keto acids **12** in good yields except for the cases of chlorodienoic acids such as **11f** and **11g**, which gave complex mixture. Moreover the transformation of **11** to 4-oxo-2-alkenoic acid **14**, which is incorporated in the macrolide antibiotics[18] such as A26771B, pyrenophorin, and vermiculine, was also achieved by the convenient method as follows. Hydrolysis of **11b** with refluxing 2 M NaOH (1 M=1 mol dm^{-3}) afforded 4-hydroxy-2-nonenoic acid (**15b**). Without any purification, **15b** was converted to 4-oxo-2-nonenoic acid (**14b**) by the Jones oxidation in a yield of 61% from **11b**. In this transformation, all of the other acids **11** were transformed to the corresponding keto alkenoic acids **14** in moderate yields. These results were summarized in Table 3.

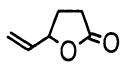
γ-Butyrolactone and δ-valerolactone do not react with diorganocuprate and these lactones have been used for the synthesis of keto alcohol by the addition of alkyllithium to the carbonyl carbon of the lactones.[19] Nevertheless the ring opening of γ-vinyl-γ-butyrolactone and δ-vinyl-δ-valerolactone using organocopper reagents proceeded in S_N2' reaction leading to 4- and 5-alkenoic acids in a similar way to the case of four-membered lactones. Several papers concerning the reactions of the related γ-lactones

Table 3. Transformation of **11** to 4-Oxoalkanoic Acids (**12**) and 4-Oxo-2-alkenoic Acids (**14**)

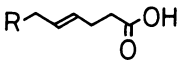
R	Product yield/%	
	12[a,b]	**14**[c]
Me	**12a** 66 (10)	**14a** 44
Bu	**12b** 82 (8)	**14b** 61
s-Bu	**12c** 77 (17)	**14c** 52
t-Bu	**12d** 71 (23)	**14d** 37
Ph	**12e** 71 (12)	**14e** 62
CH_2=CH	**12f** 0	**14f** 16
CH_2=$CHCH_2$	**12g** trace	**14g** 47

a) All reactions were performed at room temperature for 64 h. b) The values in parentheses indicate the yields of methyl ester of **12**. c) Hydrolysis of **11** to **15** was carried out with refluxing 2 M NaOH for 20 min and the following Jones oxidation of **15** was carried out at 0 °C for 10 min. The yields were calculated from **11**.

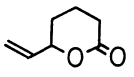
possessing γ-unsaturated substituent with organocopper reagents have been reported.[20]



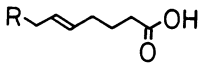
16



17



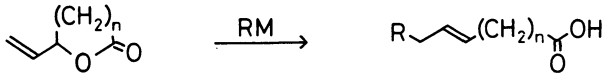
18



19

When γ-vinyl-γ-butyrolactone (**16**)[21] was treated with butylmagnesium bromide in THF–Me_2S in the presence of copper(I) iodide (2 mol%) at −30 °C, 4-decenoic acid (**17b**) was predominantly produced by

Table 4. Reactions of ω-Vinyllactones **16** and **18** with Organocopper Reagents[a]



RM	*n*=2 **16**			
	Temp/°C	Time/min	Yield/%	(*E*):(*Z*)
MeMgBr, cat. CuI[b]	−30	60	**17a** 87	92: 8
Me_2CuMgX[c]	−30	60	**17a** 87	88:12
BuMgBr, cat. CuI[b]	−30	60	**17b** 93	86:14
Bu_2CuMgX[c]	−30	60	**17b** 88	85:15
s-BuMgCl, cat. CuI[b]	−30	60	**17c** 90	83:17
s-Bu_2CuMgX[c]	−30	60	**17c** 90	78:22
t-BuMgCl, cat. CuI[b]	−30	60	**17d** 91	78:22
t-Bu_2CuMgX[c]	−30	60	**17d** 91	79:21
PhMgBr, cat. CuI[b]	−30	60	**17e** 75	62:38
Ph_2CuMgX[c]	−30, 30 →	rt, 30	**17e** 91	82:18
CH_2=CHMgBr, cat. CuI[b]	−30	60	**17f** 59	57:43
$(CH_2$=$CH)_2CuMgX$[c]	−30, 30 →	rt, 30	**17f** 70	82:18
CH_2=$CHCH_2$MgBr, cat. CuI[b]	−30	60	**17g** 9	92: 8
$(CH_2$=$CHCH_2)_2CuMgX$[c]	−30, 30 →	rt, 30	**17g** 41	86:14

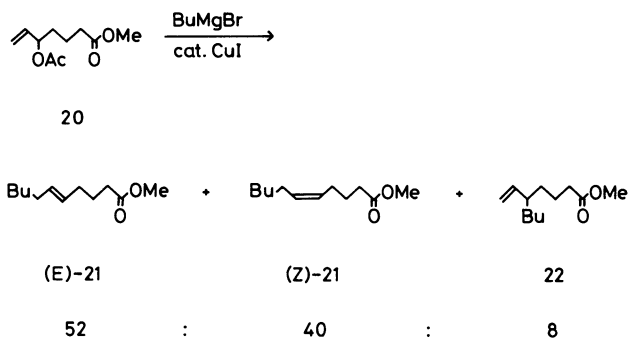
RM	*n*=3 **18**			
	Temp/°C	Time/min	Yield/%	(*E*):(*Z*)
MeMgBr, cat. CuI[b]	−45	60	**19a** 70	93: 7
Me_2CuMgX[c]	−45	60	**19a** 99	91: 9
BuMgBr, cat. CuI[b]	−45	60	**19b** 95	88:12
Bu_2CuMgX[c]	−45	60	**19b** 95	79:21
s-BuMgCl, cat. CuI[b]	−45	60	**19c** 94	83:17
s-Bu_2CuMgX[c]	−45	60	**19c** 89	72:28
t-BuMgCl, cat. CuI[b]	−45	60	**19d** 78	75:25
t-Bu_2CuMgX[c]	−45	60	**19d** 99	75:25
PhMgBr, cat. CuI[b]	−45	60	**19e** 56	67:33
Ph_2CuMgX[c]	−30	60	**19e** 57	71:29
CH_2=CHMgBr, cat. CuI[b]	−45	60	**19f** 28	67:33
$(CH_2$=$CH)_2CuMgX$[c]	−30	60	**19f** 67	78:22
CH_2=$CHCH_2$MgBr, cat. CuI[b]	−45	60	**19g** trace	—
$(CH_2$=$CHCH_2)_2CuMgX$[c]	−50	60	**19g** 51	92: 8

a) All products were isolated and the isomer ratios were determined by GLC analysis. b) Reactions were performed in THF–Me_2S (20:1). In the ring opening of **16** and **18**, 2 and 3 mol% of CuI were used, respectively. c) Reactions were performed in THF–Me_2S (10:1).

the S_N2' reaction. GLC analysis of the acid **17b** showed the predominance of the *E*-isomer (*E*:*Z*= 86:14). Both of copper-catalyzed Grignard reagents with primary, secondary, and tertiary alkyl groups and the corresponding dialkylcuprates attacked regioselectively the terminal vinyl carbon of the lactone to afford (*E*)-4-alkenoic acids **17a—d** in high yields. Diphenyl-, divinyl-, and diallylcuprates gave the acids **17e—g** in higher yields than the corresponding copper-catalyzed Grignard reagents. These results are summarized in Table 4.

δ-Vinyl-δ-valerolactone (**18**)[22] was also found to react regio- and stereoselectively with organocopper reagents as shown also in Table 4. In a similar way to the case of the reaction of vinylbutyrolactone **16**, (*E*)-5-alkenoic acids **19a—d** as the S_N2' products were predominantly obtained in the reaction of the lactone **18** with alkyl Grignard reagents in the presence of copper(I) iodide and with dialkylcuprates. The use of divinyl- and diallylcuprate resulted in increasing the yields and the geometrical purity of the dienoic acids **19f,g**.

In the synthetic methods of alkenoic acids described above, the cyclic structure of the lactones **3**, **8**, **10**, **16**, and **18** as the starting materials seems to be essential for high regio- and stereoselectivity as confirmed by the following control experiment. When methyl 5-acetoxy-6-heptenoate (**20**) was treated with butylmagnesium bromide in the presence of copper(I) iodide (3 mol%) in THF–Me_2S (20:1) at −45 °C for 1 h, methyl (*E*)- and (*Z*)-5-undecenoates (**21**) (S_N2' products) and methyl 5-vinylnonanoates (**22**) (S_N2 product) were obtained in 98% yield in the ratio of 52:40:8, while the reaction of the corresponding lactone **18** gave only S_N2' product with (*E*):(*Z*) ratio of 88:12. Anderson et al. reported that S_N2':S_N2 and (*E*)-S_N2':(*Z*)-S_N2' ratios of the substitution products of allylic esters were enhanced with leaving groups of lower acidity of the conjugate acid.[23] In also the above example, the acidity of the conjugate acids of ω-alkenyllactones is lower than that of methyl 5-acetoxy-6-heptenoate. Therefore the ring opening of three kinds of β-vinyllactones **3**, **16**, and **18** seemed to indicate almost similar selectivity regardless the number of the ring construction atoms, since it is thought that there is no large difference among the acidity of the conjugate acids of three kinds of β-vinyllactones **3**, **16**, and **18**.



The above description defines a new convenient synthetic method of (*E*)-3-, (*E*)-4-, and (*E*)-5-alkenoic acids by the reactions of β-, γ-, and δ-lactones possessing ω-alkenyl group with organocopper reagents. Advantages of these C_5—C_7 carbon homologation methods are specified as follows: (1) starting materials are easily accessible, (2) the reaction procedure is simple, (3) the introduction of various kinds of organic groups to the alkenoic acid is possible because of the easy availability of Grignard reagent, (4) carboxyl group and carbon–carbon double bond are easily transformed to other functional groups. Synthetic utilities of these methods were represented in previous communications on the synthesis of natural products.[1b-d,24]

Experimental

General. Boiling points were measured at the pressure indicated and are uncorrected. Infrared spectra were recorded on a Hitachi EPI-G2 spectrometer. ^1H NMR spectra were recorded on a Varian A-60 spectrometer and on a Jeol JNM-PMX60SI spectrometer and are reported in parts per million (δ) from TMS. Samples were dissolved in CCl_4 containing TMS as an internal standard. GLC analysis were performed on a Yanaco G-180 Gas Chromatograph using a 0.25 mm×50 m FFAP column. Preparative thin-layer chromatography (TLC) was performed on 20×20 cm glass plates coated with 1.5 mm of silica gel (Wakogel B-5F). Distillation of reaction products was performed on a Kugelrohr apparatus.

All reactions were run under a positive pressure of dry argon. Reactions requiring anhydrous conditions were performed in a flame-dried glassware that was cooled under argon. Anhydrous solvents were transferred by an oven-dried syringe. Solvents were distilled before use: diethyl ether from lithium aluminium hydride; tetrahydrofuran (THF) from sodium benzophenone ketyl. Dimethyl sulfide (Me_2S) was used without purification. Grignard reagents and butyllithium were standardized by titration with 2-butanol using 1,10-phenanthroline as an indicator.[25] Copper(I) iodide was purified by a known method.[26] All ω-alkenyllactones were prepared by published procedures.[11,21,22]

Procedure for the Reaction of Butylmagnesium Bromide in the Presence of 2 mol% CuI with β-Vinyl-β-propiolactone (3). In a typical experiment a flask equipped with a magnetic stirring bar and a septum was charged 9.3 mg (0.04 mmol) of CuI. After flushing with dry argon, 6 ml of anhydrous THF and 0.5 ml of Me_2S were added and the solution was chilled to −100 °C. A THF solution (2 ml) of 200 mg (2.00 mmol) of **3** was added to the flask. After stirring the mixture for 10 min, a solution of 2.40 mmol of BuMgBr in 2 ml of THF was added over 5 min. The reaction mixture was stirred for 15 min at −100 °C and then quenched with 2 ml of 3 M HCl and extracted with ether. The separated organic layer was extracted with three 5 ml

portions of 3 M NaOH. The alkaline solution was acidified with 3 ml of 6 M HCl, and then extracted with ether. The ethereal extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent followed by vacuum distillation gave 295 mg (94%) of clear oil. Regio- and stereoisomer ratios were determined by GLC analyses of the corresponding methyl ester using a FFAP 50 m column. Regioisomers were separated by TLC (hexane:AcOEt:AcOH=60:20:1).

The same procedure was used for the copper-catalyzed reactions of Grignard reagents with ω-alkenyllactones shown in Tables 2 and 4.

Procedure for the Reaction of Dibutylcuprate with the Lactone 3. In a typical experiment a flask equipped with a magnetic stirring bar and a septum was charged 420 mg (2.20 mmol) of CuI. After flushing with dry argon, 4 ml of anhydrous THF and 1 ml of Me_2S were added and the solution was chilled to −30 °C. A solution of 4.40 mmol of BuMgBr in 4 ml of THF was added. After stirring for 30 min at −30 °C, the mixture was chilled to −78 °C and a THF solution (2 ml) of 200 mg (2.00 mmol) of **3** was added to the flask. The reaction mixture was stirred for 60 min at −78 °C, worked up, purified, and analyzed as the case of copper-catalyzed reaction. The same procedure was used for the reactions of diorganocuprates with ω-alkenyllactones shown in Tables 2 and 4.

3-Hexenoic Acid (4a).[27] Bp 80 °C (bath temp)/1.5 mmHg (1 mmHg=133.322 Pa).

3-Nonenoic Acid (4b):[28] Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 965 (s) cm^{-1}; ^1H NMR δ=0.90 (t, J=6.5 Hz, 3 H), 1.07—1.80 (m, 6H), 1.80—2.30 (m, 2H), 2.83—3.17 (m, 2H), 5.33—5.68 (m, 2H), 10.84 (s, 1H).

3-Butyl-4-pentenoic Acid (5b). R_f=0.3 (Hexane:AcOEt:AcOH=60:20:1); IR (neat) 1710 (s), 995 (s), and 920 (s) cm^{-1}; ^1H NMR δ=0.87 (t, J=6.5 Hz, 3H), 1.05—1.52 (m, 6H), 2.13—2.76 (m, 3H), 4.69—5.84 (m, 3H), 10.83 (s, 1H); Anal. ($C_9H_{16}O_2$) C, H.

6-Methyl-3-octenoic Acid (4c). Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.86 (d, J=6.5 Hz, 3H), 0.88 (t, J=6.5 Hz, 3H), 1.08—1.77 (m, 3H), 1.77—2.25 (m, 2H), 2.90—3.24 (m, 2H), 5.28—5.68 (m, 2H), 10.93 (s, 1H); Anal. ($C_9H_{16}O_2$) C, H.

6,6-Dimethyl-3-heptenoic Acid (4d). Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.90 (s, 9H), 2.04—2.16 (m, 2H), 2.95—3.22 (m, 2H), 5.27—5.68 (m, 2H), 10.81 (s, 1H); Anal. ($C_9H_{16}O_2$) C, H.

5-Phenyl-3-pentenoic Acid (4e). Bp 200 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 965 (s), 740 (s), and 700 (s) cm^{-1}; ^1H NMR δ=2.85—3.15 (m, 2H), 3.15—3.50 (m, 2H), 5.44—5.70 (m, 2H), 7.08 (s, 5H), 11.30 (s, 1H); Anal. ($C_{11}H_{12}O_2$) C, H.

3,6-Heptadienoic Acid (4f). Bp 110 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (s), 965 (s), and 910 (s) cm^{-1}; ^1H NMR δ=2.58—2.93 (m, 2H), 2.93—3.20 (m, 2H), 4.78—6.25 (m, 5H), 11.56 (s, 1H); Anal. ($C_7H_{10}O_2$) C, H.

3,7-Octadienoic Acid (4g). Bp 120 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (s), 965 (s), and 915 (s) cm^{-1}; ^1H NMR δ=1.97—2.33 (m, 4H), 2.87—3.23 (m, 2H), 4.75—6.41 (m, 5H), 10.68 (s, 1H); Anal. ($C_8H_{12}O_2$) C, H.

4-Methyl-3-hexenoic Acid (9a). Bp 110 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 835 (w) cm^{-1}; ^1H NMR δ=1.00 (t, J=7 Hz, 3H), 1.63 (s, 1.8H), 1.72 (s, 1.2H), 2.03 (q, J=7 Hz, 2H), 3.00 (d, J=7 Hz,, 2H), 5.22 (t, J=7 Hz, 1H), 10.87 (s, 1H).

4-Methyl-3-nonenoic Acid (9b). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 830 (w) cm^{-1}; ^1H NMR δ=0.90 (t, J=6 Hz, 3H), 1.17—1.67 (m, 6H), 1.71 (s, 2.1H), 1.80 (s, 0.9H), 1.88—2.33 (m, 2H), 3.06 (d, J=7 Hz, 2H), 5.23 (t, J=7 Hz, 1H), 10.43 (s, 1H); Anal. ($C_{10}H_{18}O_2$) C, H.

4,6-Dimethyl-3-octenoic Acid (9c). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 840 (w) cm^{-1}; ^1H NMR δ=0.85 (t, J=6 Hz, 3H), 0.90 (d, J=6 Hz, 3H), 1.14—1.55 (m, 3H), 1.60 (s, 2.1H), 1.69 (s, 0.9H), 1.79—2.09 (m, 2H), 3.00 (d, J=7 Hz, 2H), 5.27 (t, J=7 Hz, 1H), 10.90 (s, 1H); Anal. ($C_{10}H_{18}O_2$) C, H.

4,6,6-Trimethyl-3-heptenoic Acid (9d). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 840 (w) cm^{-1}; ^1H NMR δ=0.90 (s, 6.3H), 0.93 (s, 2.7H), 1.67 (s, 2.1H), 1.76 (s, 0.9H), 1.94 (s, 2H), 3.00 (d, J=7 Hz, 2H), 5.23 (t, J=7 Hz, 0.7H), 5.42 (t, J=7 Hz, 0.3H), 11.30 (s, 1H); Anal. ($C_{10}H_{18}O_2$) C, H.

4-Methyl-5-phenyl-3-pentenoic Acid (9e). Bp 200 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 845 (w), 735 (s), and 700 (s) cm^{-1}; ^1H NMR δ=1.53 (s, 2.1H), 1.62 (s, 0.9H), 3.03 (d, J=7 Hz, 2H), 3.23 (s, 2H), 5.37 (t, J=7 Hz, 1H), 7.09 (s, 5H), 11.53 (s, 1H); Anal. ($C_{12}H_{14}O_2$) C, H.

4-Methyl-3,6-heptadienoic Acid (9f). Bp 120 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (m), 910 (s), and 830 (w) cm^{-1}; ^1H NMR δ=1.60 (s, 2.1H), 1.69 (s, 0.9H), 2.82 (d, J=7 Hz, 2H), 3.14 (d, J=7 Hz, 2H), 4.77—6.27 (m, 4H), 11.42 (s, 1H); Anal. ($C_8H_{12}O_2$) C, H.

4-Methyl-3,7-octadienoic Acid (9g). Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (m), 910 (s), and 830 (w) cm^{-1}; ^1H NMR δ=1.70 (s, 2.1H), 1.79 (s, 0.9H), 2.20 (br s, 4H), 3.10 (d, J=7 Hz, 2H), 4.77—6.25 (m, 4H), 10.81 (s, 1H); Anal. ($C_9H_{14}O_2$) C, H.

4,8-Dimethyl-3-nonenoic Acid (9h).[28] R_f=0.6 (CH_2Cl_2:AcOEt:AcOH=200:20:1); IR (neat) 1710 (s) and 830 (w) cm^{-1}; ^1H NMR δ=0.87 (d, J=5.5 Hz, 6H), 1.11—1.55 (m, 4H), 1.63—1.86 (m, 3H), 3.03 (d, J=7 Hz, 2H), 5.35 (t, J=7 Hz, 1H); 11.21 (s, 1H).

4,8-Dimethyl-3,7-nonadienoic Acid (9i).[30] R_f=0.6 (CH_2Cl_2:AcOEt:AcOH=200:20:1)

4,8,12-Trimethyl-3,7,11-tridecatrienoic Acid (9j).[14b] R_f=0.4 (CH_2Cl_2:AcOEt:AcOH=200:20:1); ^1H NMR δ=1.60 (br s,3H), 1.67 (br s, 9H), 2.05 (br s, 8H), 3.00 (d, J=7 Hz, 2H), 4.65—5.30 (m, 3H), 10.85 (s, 1H).

4-Chloro-3-hexenoic Acid (11a). Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s) and 820 (m) cm^{-1}; ^1H NMR δ=1.13 (t, J=7 Hz, 3H), 2.40 (q, J=7 Hz, 2H), 3.09 (d, J=6.5 Hz, 0.2H), 3.25 (d, J=6.5 Hz, 1.8H), 5.64 (t, J=6.5 Hz, 1H), 11.13 (s, 1H); Anal. ($C_6H_9ClO_2$) C, H.

4-Chloro-3-nonenoic Acid (11b). Bp 170 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) 850 (m), and 810 (m) cm^{-1}; ^1H NMR δ=0.91 (t, J=6 Hz, 3H), 1.07—2.00 (m, 6H), 2.00—2.67 (m, 2H), 3.08 (d, J=7 Hz, 0.2 H), 3.24 (d, J=6.5 Hz, 1.8H), 5.62 (t, J=6.5 Hz, 0.9H), 5.69 (t, J=7 Hz, 0.1H), 11.22 (s, 1H); Anal. ($C_9H_{15}ClO_2$) C, H.

4-Chloro-6-methyl-3-octenoic Acid (11c). Bp 170 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 830 (m), and 800 (m) cm^{-1}; ^1H NMR δ=0.93 (t, J=6 Hz, 3H), 0.98 (d, J=6 Hz, 3H), 1.05—2.00 (m, 3H), 2.00—2.65 (m, 2H), 3.06 (d, J=7 Hz, 0.2H), 3.22 (d, J=6.5 Hz, 1.8H), 5.61 (t, J=6.5 Hz, 0.9H), 5.69 (t, J=7 Hz, 0.1H), 11.49 (s, 1H); Anal. ($C_9H_{15}ClO_2$) C, H.

4-Chloro-6,6-dimethyl-3-heptenoic Acid (11d). Bp 150 °C

(bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 820 (m) cm^{-1}; ^1H NMR δ=0.98 (s, 9H), 2.27 (s, 2H), 3.07 (d, J=7 Hz, 0.2H), 3.26 (d, J=6.5 Hz, 1.8H), 5.57 (t, J=6.5 Hz, 0.9H), 5.85 (t, J=7 Hz, 0.1H), 11.32 (s, 1H); Anal. ($C_9H_{15}ClO_2$) C, H.

4-Chloro-5-phenyl-3-pentenoic Acid (11e). Bp 230 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 825 (m), 790 (m), 740 (s), and 700 (s) cm^{-1}; ^1H NMR δ=3.13 (d, J=7 Hz, 0.4H), 3.23 (d, J=6.5 Hz, 1.6H), 3.57 (s, 2H), 5.67 (t, J=6.5 Hz, 0.8H), 5.84 (t, J=7 Hz, 0.2H), 7.16 (s, 5H), 11.45 (s, 1H); Anal. ($C_{11}H_{11}COI_2$) C, H.

4-Chloro-3,6-heptadienoic Acid (11f). Bp 140 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (s), and 810 (m) cm^{-1}; ^1H NMR δ=3.08 (d, J=6.5 Hz, 2H), 3.24 (d, J=6.5 Hz, 2H), 4.60—6.23 (m, 5H), 11.41 (s, 1H); Anal. ($C_7H_9ClO_2$) C, H.

4-Chloro-3,7-octadienoic Acid (11g). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1710 (s), 990 (s), and 845 (m) cm^{-1}; ^1H NMR δ=2.40 (s, 4H), 3.08 (d, J=7 Hz, 0.2H), 3.26 (d, J=6.5 Hz, 1.8H), 4.77—6.12 (m, 4H), 11.41 (s, 1H); Anal. ($C_8H_{11}ClO_2$) C, H.

4-Heptenoic Acid (17a).[7] Bp 110 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.94 (t, J=7 Hz, 3H), 1.68—2.17 (m, 2H), 2.17—2.45 (m, 4H), 5.40—5.74 (m, 2H), 11.01 (s, 1H).

4-Decenoic Acid (17b).[31] Bp 150 °C (bath temp)/1.5 mmHg.

7-Methyl-4-nonenoic Acid (17c). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.86 (t, J=6 Hz, 3H), 0.91 (d, J=6 Hz, 3H), 1.01—1.70 (m, 3H), 1.70—2.17 (m, 2H), 2.20—2.53 (m, 4H), 5.25—5.59 (m, 2H), 11.62 (s, 1H); Anal. ($C_{10}H_{18}O_2$) C, H.

7,7-Dimethyl-4-octenoic Acid (17d). Bp 150 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.84 (s, 9H), 1.73—2.05 (m, 2H), 2.23—2.43 (m, 4H), 5.26—5.52 (m, 2H), 11.53 (s, 1H); Anal. ($C_{10}H_{18}O_2$) C, H.

6-Phenyl-4-hexenoic Acid (17e).[32] Bp 200 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 970 (s), 740 (s), and 700 (s) cm^{-1}; ^1H NMR δ=2.20—2.50 (m, 4H), 3.04—3.43 (m, 2H), 5.23—5.59 (m, 2H), 7.02 (s, 5H), 11.49 (s, 1H).

4,7-Octadienoic Acid (17f). Bp 120 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) 990 (s), 970 (s), and 915 (s) cm^{-1}; ^1H NMR δ=2.16—2.58 (m, 4H), 2.58—3.08 (m, 2H), 4.82—6.17 (m, 5H), 11.06 (s, 1H); Anal. ($C_8H_{12}O_2$) C, H.

4,8-Nonadienoic Acid (17g).[33] Bp 130 °C (bath temp)/1.5 mmHg.

5-Octenoic Acid (19a).[5b] Bp 120 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.96 (t, J=7 Hz, 3H), 1.42—2.50 (m, 8H), 5.20—5.50 (m, 2H), 10.21 (s, 1H).

5-Undecenoic Acid (19b).[34] Bp 170 °C (bath temp)/1.5 mmHg.

8-Methyl-5-decenoic Acid (19c). Bp 170 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.85 (t, J=6 Hz, 3H), 0.90 (d, J=6 Hz, 3H), 1.01—2.54 (m, 11H), 5.30—5.48 (m, 2H), 11.71 (s, 1H); Anal. ($C_{11}H_{20}O_2$) C, H.

8,8-Dimethyl-5-nonenoic Acid (19d). Bp 170 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s) and 970 (s) cm^{-1}; ^1H NMR δ=0.89 (s, 9H), 1.45—2.54 (m, 8H), 5.30—5.63 (m, 2H), 11.39 (s, 1H); Anal. ($C_{11}H_{20}O_2$) C, H.

7-Phenyl-5-heptenoic Acid (19e). Bp 220 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 970 (s), 740 (s), and 700 (s) cm^{-1}; ^1H NMR δ=1.45—2.57 (m, 6H), 3.12—3.41 (m, 2H), 5.21—5.64 (m, 2H), 7.08 (s, 5H), 9.97 (s, 1H); Anal. ($C_{13}H_{16}O_2$) C, H.

5,8-Nonadienoic Acid (19f). Bp 130 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 990 (s), 970 (s), and 915 (s) cm^{-1}; ^1H NMR δ=1.47—2.57 (m, 6H), 2.57—2.94 (m, 2H), 4.72—6.14 (m, 5H), 11.56 (s, 1H); Anal. ($C_9H_{14}O_2$) C, H.

5,9-Decadienoic Acid (19g). Bp 140 °C (bath temp)/1.5 mmHg; IR (neat) 1715 (s), 990 (s), 970 (s), and 910 (s) cm^{-1}; ^1H NMR δ=1.45—2.57 (m, 10H), 4.75—6.40 (m, 5H), 11.53 (s, 1H); Anal. ($C_{10}H_{16}O_2$) C, H.

Procedure for the Transformation of 4-Chloro-3-alkenoic Acids (11) to 4-Oxoalkanoic Acids (12). According to the reported method,[17] to a solution of $TiCl_4$ 1.95 g (10.3 mmol), MeOH 68.7 mg (2.14 mmol), H_2O 80.6 mg (4.47 mmol), and acetone 354 mg (6.09 mmol) in CH_2Cl_2 (4 ml), a solution of **11b** 385 mg (2.02 mmol) in 2 ml of CH_2Cl_2 was added at room temperature. The mixture was stirred at the same temperature for 64 h. Then the reaction was quenched by pouring into ice-water, and the organic layer was separated. The aqueous phase was washed twice with CH_2Cl_2 and the combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (CH_2Cl_2:AcOH=20:1) to give 4-oxononanoic acid (**12b**) 285 mg (1.66 mmol) (82%) and methyl 4-oxononanoate 30.1 mg (0.162 mmol) (8%).

In the exactly same manner as above, the other 4-oxoalkanoic acids were obtained.

4-Oxohexanoic Acid (12a).[16] Mp 37—40 °C.

4-Oxononanoic Acid (12b).[16] Mp 68—70 °C.

4-Methyl-4-oxooctanoic Acid (12c).[35] IR (neat) 1740 (s), 1720 (s), and 1710 (s) cm^{-1}; ^1H NMR δ=0.86 (d, J=2.5 Hz, 3H), 0.92 (br s, 3H), 1.08—1.58 (m, 2H), 1.58—2.14 (m, 1H), 2.14—2.48 (m, 2H), 2.63 (br s, 4H), 11.10 (s, 1H).

6,6-Dimethyl-4-oxoheptanoic Acid (12d). IR (neat) 1735 (s), 1720 (s), and 1710 (s) cm^{-1}; ^1H NMR δ=1.00 (s, 9H), 2.32 (s, 2H), 2.40—2.92 (m, 4H), 13.17 (br s, 1H); Anal. ($C_9H_{16}O_3$) C, H.

4-Oxo-5-phenylpentanoic Acid (12e).[36] Mp 53—55 °C; IR (neat) 1720 (s), 1700 (s), 740 (m), and 700 (m) cm^{-1}; ^1H NMR δ=2.55 (br s, 4H), 3.58 (s, 2H), 7.15 (s, 5H), 10.68 (s, 1H).

Procedure for the Transformation of 11 to 4-Oxo-2-alkenoic Acid (14). A solution of **11b** 502 mg (2.63 mmol) in 13 ml of 2 M NaOH was refluxed with stirring for 20 min. After the mixture was cooled to room temperature and acidified with concd HCl, the mixture was extracted twice with ether. The extracts were washed with water and brine, dried with $MgSO_4$, and concentrated to give viscous oil. The crude 4-hydroxy-2-nonenoic acid was used for the following oxidation without any purification. To a solution of the hydroxy acid in acetone (5 ml) was added a solution of CrO_3 263 mg (2.63 mmol) in concd H_2SO_4 (0.3 ml) and water (1.0 ml) at 0 °C. After the mixture was stirred at the same temperature for 10 min, the products were extracted with ether. The extracts were washed with water and brine, dried with $MgSO_4$, and concentrated. Purification of the residue by preparative TLC (CH_2Cl_2:AcOH=20:1) gave 4-oxo-2-nonenoic acid (**14b**) 272 mg (1.60 mmol) (61%).

In the exactly same manner as above, the other 4-oxo-2-

alkenoic acids were obtained.

4-Oxo-2-hexenoic Acid (14a).[37] Mp 110—112 °C; IR (KBr) 1720 (s), 1690 (s), and 1670 (s) cm^{-1}; ^1H NMR δ=1.13 (t, J=7 Hz, 3H), 2.72 (q, J=7 Hz, 2H), 6.82 (AB, H_A=6.60, H_B=7.05, J=16 Hz, 2H), 11.55 (s, 1H).

4-Oxo-2-nonenoic Acid (14b). Mp 115—117 °C; IR (KBr) 1720 (s), 1680 (s), and 1660 (s) cm^{-1}; ^1H NMR δ=0.90 (t, J=5 Hz, 3H), 1.12—1.97 (m, 6H), 2.65 (t, J=6 Hz, 2H), 6.90 (AB, J=16 Hz, 2H), 11.62 (br s, 1H); Anal. ($C_9H_{14}O_3$) C, H.

6-Methyl-4-oxo-2-octenoic Acid (14c). Mp 78—80 °C; IR (KBr) 1710 (s), 1680 (s), and 1660 (s) cm^{-1}; ^1H NMR δ=0.87 (br s, 3H), 0.97 (br s, 3H), 1.13—1.63 (m, 2H), 1.63—2.30 (m, 1H), 2.30—2.88 (m, 2H), 6.87 (AB, J=16 Hz, 2H), 11.52 (br s, 1H); Anal. ($C_9H_{14}O_3$) C, H.

6,6-Dimethyl-4-oxo-2-heptenoic Acid (14d). Mp 91—93 °C; IR (KBr) 1710 (s), 1685 (s), and 1670 (s) cm^{-1}; ^1H NMR δ=1.06 (s, 9H), 2.55 (s, 2H), 6.88 (AB, H_A=6.60, H_B=7.17, J=16 Hz, 2H), 10.71 (br s, 1H); Anal. ($C_9H_{14}O_3$) C, H.

4-Oxo-5-phenyl-2-pentenoic Acid (14e). Mp 95—97 °C; IR (KBr) 1705 (s), 1680 (s), 1675 (s), 735 (m), and 695 (m) cm^{-1}; ^1H NMR δ=3.87 (s, 2H), 6.88 (AB, J=16 Hz, 2H), 11.03 (br s, 1H); Anal. ($C_{11}H_{10}O_3$) C, H.

4-Oxo-2,6-heptadienoic Acid (14f). Mp 80—82 °C; IR (neat) 1720 (s), 1685 (s), 1665 (s), 1000 (s), and 915 (s) cm^{-1}; ^1H NMR δ=3.40 (d, J=7 Hz, 2H), 4.93—6.30 (m, 3H), 6.88 (AB, J=16 Hz, 2H), 10.88 (br s, 1H); Anal. ($C_7H_8O_3$) C, H.

4-Oxo-2,7-octadienoic Acid (14g). Mp 100—102 °C; IR (neat) 1710 (s), 1685 (s), 1665 (s), 1005 (s), and 910 (s) cm^{-1}; ^1H NMR δ=2.43 (t, J=5.5 Hz, 2H), 2.63—3.03 (m, 2H), 4.80—6.23 (m, 3H), 6.85 (AB, J=16 Hz, 2H), 11.56 (s, 1H); Anal. ($C_8H_{10}O_3$) C, H.

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