Regio- and Stereospecific Cyclizations of Germacrones

Masatake NIWA, Masanobu IGUCHI, and Shosuke YAMAMURA*

Faculty of Pharmacy, Meijo University, Showa-ku, Nagoya 468

(Received April 21, 1976)

From a biogenetic point of view, the acid-catalyzed cyclizations of germacrones (**1**, **2**, and **3**) were carried out, using several kinds of reagents and solvents (80% aq AcOH, 80% aq HCOOH, $AlCl_3$ in absolute ether, AcOH in PhSH, 100% HCOOH in PhSH, and concd H_2SO_4 in PhSH). In all cases, the stereospecific cyclizations of these germacrones took place to give cadinane-type, selinane-type or guaiane-type compounds depending on the kinds of reagents and solvents. The formation process of each compound will be presented in detail.

From a biogentic point of view, many sesquiterpenes are known to be derived from germacrenes or germacrones, which are regarded as an important precursor. Our interests are focused on the biogenetic-type reactions of these ten-membered ring sesquiterpenes and their derivatives. In the present paper, we describe the regio- and stereospecific cyclizations of these germacrones with some acids, leading to the formation of cadinane-type, selinane-type or guaiane-type compounds. In addition, some naturally occurring sesquiterpenes were synthesized from these germacrones.

As described in the previous papers,[1,2] many sesquiterpenes have been isolated from the plant *Acorus calamus* L. and their structures also been established. Of these sesquiterpenes, acoragermacrone (**1**) is regarded as the most important compound, which has been chemically converted into isoacoragermacrone (**2**), preisocalamendiol (**3**) and other sesquiterpenes.[2] In our experiments, mainly, three germacrones **1**, **2** and **3** were used for the biogenetic-type reactions.

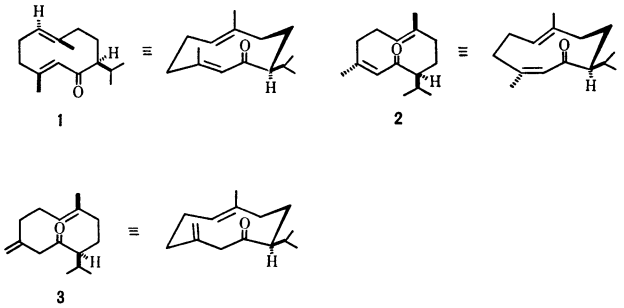
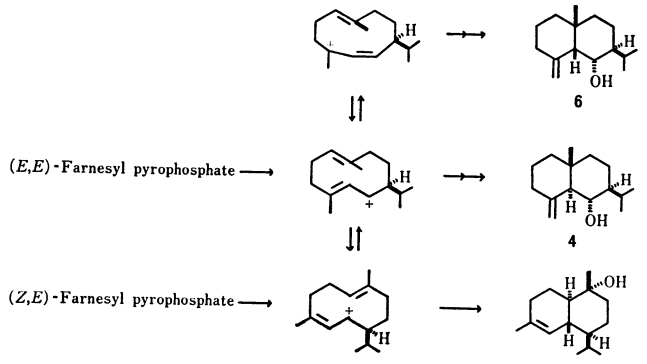


Fig. 1.

Acid-catalyzed Cyclizations of Acoragermacrone (1). Biogenetically, *trans*-selinane-type sesquiterpenes are produced from the corresponding germacrenes with an (*E*,*E*)-1,5-cyclodecadiene system, while cadinane-type compounds must be stereochemically produced from the corresponding ten-membered ring compounds with an (*E*,*Z*)-1,5-cyclodecadiene system which may be directly derived from a (*Z*,*E*)-farnesyl pyrophosphate or produced on *cis-trans* isomerization of the corresponding (*E*,*E*)-1,5-cyclodecadienes: the formation process of junenol (**4**)[3] as well as of α-cadinol (**5**)[4] is demonstrated in Scheme 1. Quite recently, 5-epi-junenol (**6**) was isolated from *Ferula galbaniflua*.[5] Probably, this sesquiterpene is produced on double-bond isomerization of the (*E*,*E*)-1,5-cyclodecadienyl cation, followed by acid-catalyzed cyclization together with simultaneous hydration, as shown in Scheme 1.



Scheme 1. Biogenesis of *cis*- and *trans*-selinane-type and cadinane-type sesquiterpenes.

It is interesting to examine the acid-catalyzed cyclization of acoragermacrone (**1**), because the protonated form (A) of **1** is expected to show the same behavior as that of the (*E*,*E*)-1,5-cyclodecadienyl cation (B), as shown in Scheme 1. Thus, the acid-catalyzed reactions of acoragermacrone (**1**) were carried out under various conditions.[6]

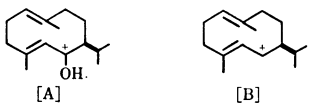


Fig. 2.

As described earlier,[2] $AlCl_3$ converted **1** into two *trans*-selinane-type sesquiterpenes, acolamone (**7**) and isoacolamone (**8**), in 55 and 23% yields, respectively. Both of them are included in the plant together with acoragermacrone (**1**).

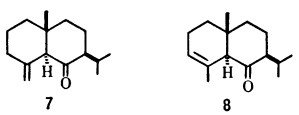
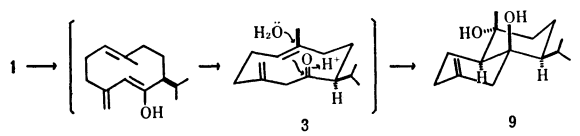


Fig. 3.

Acoragermacrone (**1**) is fairly stable toward 80% aq AcOH at room temperature. However, when heated at 75°C for 50 min, the compound **1** afforded isocalamendiol (**9**),[1] in a 28% yield. Clearly, acoragermacrone with an (*E*,*E*)-1,5-cyclodecadiene system must be converted into preisocalamendiol (**3**) which is further subjected to the regio- and stereospecific cyclization giving the

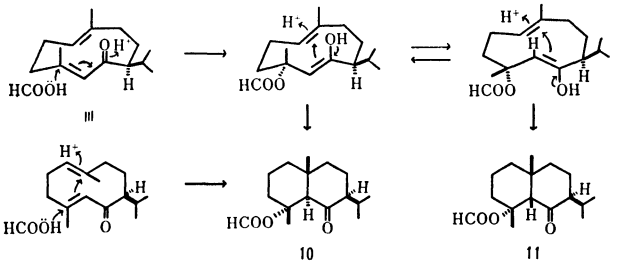
* To whom all correspondence should be addressed.



Scheme 2. Conversion of acoragermacrone into isocalamendiol.

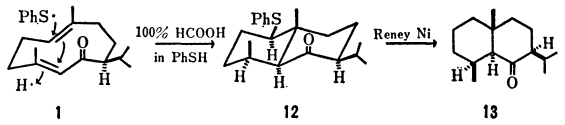
cadinane-type compound (**9**), as shown in Scheme 2.

Furthermore, the acid-catalyzed cyclization of acoragermacrone (**1**) was carried out using 80% aq HCOOH instead of 80% aq AcOH. In this case, the cyclization reaction takes place under much milder conditions (room temp, 10 min) to give three cyclization products **9**, **10** and **11**, in 19, 17 and 17% yields, respectively, one of which is identical with isocalamendiol (mp and IR spectrum). Other two compounds both are selinane-type compounds (**10**, mp 45—48 °C; **11**, mp 83—85 °C) with the same molecular formula ($C_{16}H_{26}O_3$), whose structures are based on their spectral data, as will be discussed below. Both cyclization compounds show an IR absorption band at 1720 cm^{-1}, and an intense fragment peak at *m/e* 220 (M^+—HCOOH). The NMR spectra of both compounds are also quite similar to each other: they have two methyl singlets (δ 0.90 and 1.88 ppm in **10**; δ 0.96 and 1.91 ppm in **11**) in addition to one isopropyl group. Furthermore, these compounds have two singlets due to a C_5-methine proton and a HCOO-grouping (δ 2.87 and 8.04 ppm in **10**; δ 2.93 and 8.03 ppm in **11**). From the above data, these two products must be selinane-type compounds and stereoisomers to each other. In fact, a remarkable difference is observed in their ORD curves: the *trans*-selinane-type compound (**10**) has a positive Cotton effect ($[\phi]^{P}_{320nm}$ $+14°\times10^2$, $[\phi]^{T}_{277nm}$ $-28°\times10^2$, $A=+42$), while the *cis*-isomer (**11**) has a negative Cotton effect $[(\phi]^{T}_{324nm}$ $-56°\times10^2$, $[\phi]^{P}_{278nm}$ $+61°\times10^2$, $A=-117$). In particular, the formation of the *cis*-selinane-type compound (**11**)is interesting in connection with Scheme 1. As seen in Scheme 3, two possible pathways from **1** to the *trans*-isomer (**10**) are suggested, and any of them can not be ruled out. The *cis*-isomer (**11**) seems to be derived directly from one of the ten-membered ring conformers, since these two selinane-type compounds are not interconvertible under mild reaction conditions. We further examined the acid-catalysed cyclization of acoragermacrone (**1**) using 100% HCOOH in thiophenol, as follows.



Scheme 3. Acid-catalyzed cyclization of acoragermacrone with 80% aq HCOOH.

When treated with 100% HCOOH in thiophenol (room temp, 1 h), the compound **1** was readily converted into a selinne-tyape compound (**12**), in *ca.* 60% yield. This compound (**12**) is a colorless oil with molecular formula $C_{21}H_{30}OS$, whose structure has been elucidated on the basis of its spectral data and chemical evidence: desulfurization of **12** with Raney Ni(W-4) gave dihydroacolamone (**13**)[2] in a 26% yield. In particular, the NMR signal at δ 3.01 (1H, dd, J=6.5 and 8.8 Hz) ppm indicates that the PhS group should be in an equatorial configuration. As shown in Scheme 4, the regio- and stereospecific cyclization of **1** may not take place in an ionic mechanism, but probably in a radical manner.[7]



Scheme 4. Regio- and sterespecific cyclization of acoragermacrone with 100% HCOOH in thiophenol.

Acid-catalyzed Cyclization of Isoacoragermacrone (2). It is quite reasonable to suppose that the protonated form(C) of isoacoragemacrone (**2**) is equivalent to the (*Z,E*)-1,5-cyclodecadienyl cation (D) in their chemical behavior. Furthermore, from a stereochemical aspect, isoacoragermacrone, which has been obtained from acoragermacrone (**1**) as well as from preisocalamendiol (**3**),[2] seems to be converted into cadinane-type compounds, as shown in Scheme 1. In fact, when treated with 80% aq AcOH at room temperature for 5 min, **2** was readily converted into two dienes **14** and **15**, in 43 and 23% yields, respectively.[8] The structures of these products are based on their spectral data [**14**,

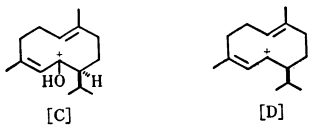
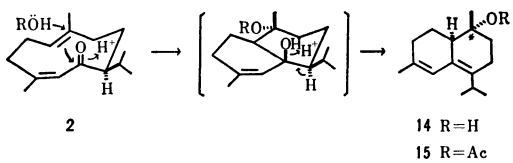


Fig. 4.

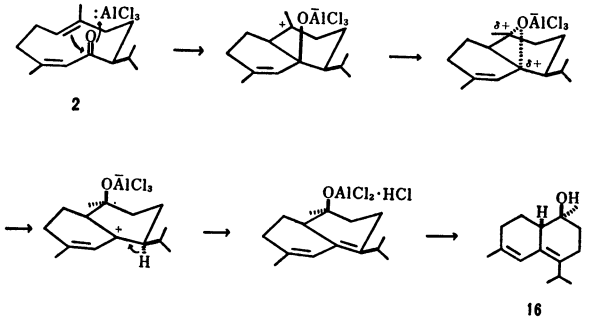
$C_{15}H_{24}O$; ν_{max} 3350 (br) cm^{-1}; λ_{max} 247 and 241 nm (ε, 11100 and 10900, respectively); δ 1.06 (3H, s), 1.80 (3H, br.s) and 6.24 (1H, br.s) ppm. **15**, $C_{17}H_{26}O_2$; ν_{max} 1730 cm^{-1}; λ_{max} 247 and 241 nm (ε, 10500 and 10300, respectively); δ 1.35 (3H, s), 1.79 (3H, br.s), 1.99 (3H, s) and 6.25 (1H, br.s) ppm], in which the configuration of the asterisked carbon atom will be discussed later. The different point between **14** and **15** is that the former has a hydroxyl group, while an acetoxyl group is present in **15**. Thus, treatment of the latter with $LiAlH_4$ afforded **14** in a high yield. In the above experiment, the regio- and stereospecific cyclization of isoacoragermacrone (**2**) takes place in a concerted



Scheme 5. Reaction of isoacoragermacrone (**2**) with 80% aq AcOH.

manner, leading to the formation of **14** and **15**, as shown in Scheme 5.

On the other hand, when treated with $AlCl_3$ in absolute ether (0 °C, 10 mil), isoacoragermacrone (**2**) was converted into an isomer of **14** in a 72% yield. The spectral data of this isomer (**16**) are quite similar to those of **14** except for the chemical shift of the tertiary methyl signal (δ 1.06 ppm in **14**; δ 1.28 ppm in **16**). Clearly, the axial methyl signal in the former should be observed in higher magnetic field than that of the equatorial isomer.[8,9] In the case of $AlCl_3$, the stereospecific reaction of **2** takes place in a stepwise manner, as demonstrated in Scheme 6, which includes an intramolecular oxygen-transfer.[8]



Scheme 6. Reaction of isoacoragermacrone (**2**) with $AlCl_3$.

We further examined the acid-catalyzed cyclization of isoacoragermacrone (**2**) in thiophenol.[10] Interestingly, when treated with AcOH in thiophenol (room temp, 24 h), isoacoragermacrone (**2**) was converted into a guaiane-type compound (**17**, mp 90—91 °C; $C_{21}H_{30}OS$), in a 50% yield, whose structure was determined by its spectral data and the following chemical evidence. This compound has a CO group (ν_{max} 1700 cm^{-1}) and each one of secondary and tertiary methyl groups [δ (CCl_4) 0.95 (3H, d, J=7.5 Hz) and 1.22 (3H, s) ppm] in addition to the original isopropyl group. Treatment of **17** with MeI in acetone (under reflux, 8 h) afforded an α,β-unsaturated ketone in a 66% yield [**18**, $C_{15}H_{24}O$; ν_{max} 1670 and 1610 cm^{-1}; λ_{max} 256 nm (ε, 8270); δ 2.05 (3H, s) ppm]. On desulfurization with Raney Ni (W-4) in EtOH, the guaiane-type compound **17** was readily converted, in an 86% yield, into the corresponding reduction product (**19**, mp 55—57.5 °C; $C_{15}H_{26}O$) which has a newly formed secondary methyl group in addition to the three secondary methyl groups (δ 0.83, 0.87, 0.92 and 1.13 ppm). In addition, a methine doublet at δ 2.92 (1H, d, J= 8.5 Hz) ppm in **17** became double doublets at δ 2.86 (1H, dd, J=7.8 and 4.8 Hz) ppm in **19**. Finally, this reduction product **19** was converted into the more stable *trans*-isomer (**20**) on treatment with NaOMe–MeOH (under reflux, 3 h).[11] The stereostructures of these two isomers (**19** and **20**) are also supported by measurements of their ORD curves: the *cis*-isomer (**19**) has a positive Cotton effect ($[\phi]^{P}_{321nm}$ +14°×10², $[\phi]^{P}_{276nm}$ −39°×10², A=+53), while the *trans*-isomer (**20**) has a negative Cotton effect ($[\phi]^{T}_{312nm}$ −46°×10², $[\phi]^{P}_{272nm}$ +57°×10², A=−103).

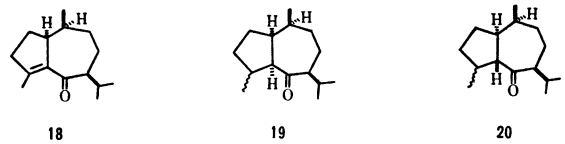
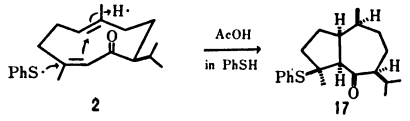


Fig. 5.

The formation process of the guaiane-type compound (**17**) is shown in Scheme 7, indicating that the regio- and stereospecific cyclization of **2** takes place in a radical mechanism.

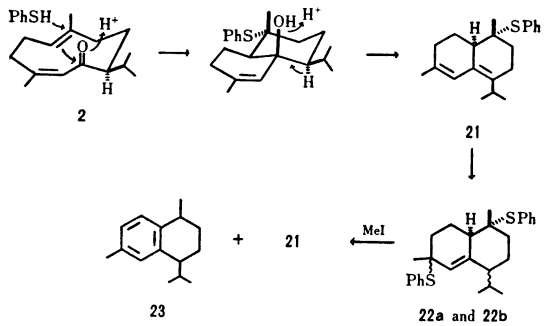


Scheme 7. Reaction of isoacoragermacrone with AcOH in thiophenol.

In the case of 100% HCOOH in thiophenol (room temp, 15 h), four cyclization products were obtained from isoacoragermacrone (**2**), in low yields (**17**, 15%; **21**, 5%; **22a**+**22b**, 12%). One of them is completely identical with the guaiane-type compound (**17**) which has been already obtained in the case of AcOH in thiophenol, as described earlier (mp and IR spectrum). The other three products (**21**, **22a** and **22b**) are cadinane-type compounds, whose structures are based on their spectral data and chemical evidences. The compound **21** is a colorless viscous liquid ($C_{21}H_{28}S$) and has two methyl groups [δ 1.09 (3H, s) and 1.76 (3H, br.s) ppm] in addition to the original isopropyl group. In addition, one broad singlet at δ 6.13 ppm due to an olefinic proton is observed in the NMR spectrum of **21**.

The compound **22**, a colorless viscous liquid, is an inseparable mixture consisting of two epimers (**22a** and **22b**), both of which have two PhS groups [δ 7.10—7.70 (10H, complex) ppm] and one olefinic proton (δ 5.35 and 5.43 ppm). Finally, these compounds (**21**, **22a** and **22b**) were chemically interconvertible, as follows.

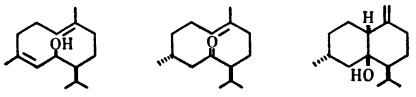
When treated with conc. H_2SO_4 in thiophenol (0 °C, 30 min), the compound **21** was readily converted into the mixture of **22a** and **22b**, in a 75% yield. On the other hand, the mixture (**22a** and **22b**) reacted with excess amounts of MeI (under reflux, 4 h) to give **21** and calamenene (**23**), in 45 and 29% yields, respectively.



Scheme 8. The formation of cadinane-type compounds (**21**, **22a** and **22b**) from isoacoragermacrone (**2**).

We further examined the acid-catalyzed cyclization of isoacoragermacrone (**2**) in thiophenol using concd H_2SO_4 instead of 100% HCOOH (0 °C, 30 min). In this case, the cadinane-type compounds were only isolated from the reaction mixture (**21**, 4%; **22a**+**22b**, 67%). In the above experiment using such a strong acid as concd H_2SO_4, clearly, the regio- and stereospecific cyclization of **2** giving these cadinane-type compounds must take place in an ionic mechanism (see Scheme 8) in contrast to the formation process of the guaiane-type compound (**17**).

From a biogenetic point of view, such an allyl alcohol as **24** is also attractive to us for the biogenetic model reactions (see Scheme 1). However, reduction of isoacoragermacrone (**2**) with diisobutylaluminium hydride (0—5 °C, 2 h) did not afford the desired alcohol (**24**), but a saturated ketone (**25**) in a 72% yield, which could be converted into the known cadinane-type compound (**26**)[1] in a 20% yield on treatment with 80% aq AcOH (room temp, 5 min).



24 25 26

Fig. 6.

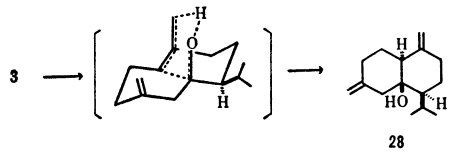
Regio- and Stereospecificity in the Cyclizations of Preisocalamendiol (3) and its Derivatives. As reported in the previous paper,[1] action of 80% aq AcOH on preisocalamendiol (**3**) converted it into isocalamendiol (**9**) in a good yield. However, any amount of calamendiol (**27**), an isomer of **9**, has not been obtained.[8] We further examined the acid-catalyzed cyclization of **3** with $AlCl_3$ in absolute ether, which was carried out at 0 °C for 10 min to give the dienol (**28**)[1] in a 54% yield. The compound **28** was also obtained, in a high yield, by thermal reaction of **3** at 180 °C, as described in Table 1. Probably, a chair-like transition state must be included in the course of the stereospecific cyclization, as demonstrated in Scheme 9.[12]

Table 1. Thermal isomerization of preisocalamendiol (**3**)

Time (min)	**3** (%)	**28** (%)	Other products (%)
0	100	0	0
7.5	99	1	0
22	83	17	0
42	48	46	6
90	3	86	11

Peak-heights in gas chromatogram (PEG 20 M, N_2, 115 °C, flame-ionizer detector) were served as approximate values of the content (%)

The Formation of ε-Cadinene. Preisocalamendiol (**3**) is quite stable toward $NaBH_4$. However, when treated with excess amounts of $LiAlH_4$ (room temp, 30 h), **3** was converted into the corresponding hydroxy compound in a quantitative yield [**29**, $C_{15}H_{26}O$; ν_{max} 3360 br·cm^{-1}; δ 3.60—3.92 (1H, m) ppm]. Further

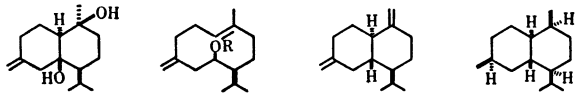


28

Scheme 9. Thermal isomerization of preisocalamendiol (**3**) to the dienol (**28**).

treatment of **29** with 80% aq HCOOH (0 °C, 2 h) did not afford any cyclization product, but the corresponding formate in a high yield [**30**, ν_{max} 1720 cm^{-1}; δ 3.66—3.90 (1H, m) and 8.11 (1H, s) ppm]. On reduction with $LiAlH_4$, this formate was reconverted into the original alcohol (**29**).

Finally, dehydration of **29** with mesyl chloride–pyridine (room temp, 7 h) afforded ε-cadinene (**31**) in a 35% yield, which was further subjected to catalytic hydrogenation (PtO_2 in AcOEt) giving the corresponding tetrahydro compound (**32**).[13] The IR spectrum of **32** was completely identical with that of an authentic sample of tetrahydrocadinene.[14]



27 29 R=H 31 32

30 R=CHO

Fig. 7.

Experimental

All the mps are uncorrected. GLC were recorded on a Shimadzu GC-1C gas chromatograph with a flame-ionizer detector [stationary phase: 5% PEG 20M on Celite 545 (100 mesh); column [ϕ 3 mm × 1.5 m (stainless steel)] temp: 90 °C; carrier gas: nitrogen (85 ml/min); inlet pressure: 1.2 kg/cm^2], unless otherwise stated. IR spectra were recorded on a Hitachi-215 spectrophotometer. UV spectra were taken on a Hitachi-124 spectrophotometer, using MeOH as the solvent. NMR spectra were recorded on a Varian Associate A-60 (60 MHz), a JEOL JNM-C60H (60 MHz) or JNM-PS 100 (100 MHz), using $CDCl_3$ as the solvent, unless otherwise stated. The chemical shifts are given in ppm relative to the internal TMS, and only prominent signals are recorded (d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet). Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating at an ionization energy of 70 eV. ORD curves were recorded on a JASCO ORD/UV-5 spectrophotometer, using MeOH as the solvent. Preparative TLC were carried out on Kieselgel PF_{254} (E. Merck, A. G.), unless otherwise stated.

Reaction of Acoragermacrone (1) with 80% aq AcOH. A solution of **1** (27 mg) in 80% aq AcOH (0.5 ml) was heated at 75 °C for 50 min with stirring, and then diluted with water (2 ml). The solution was neutralized with a dil. $NaHCO_3$aq solution, and then extracted with ether. The ethereal extract was washed with water, and then dried over anhydrous Na_2SO_4. Removal of the solvent gave a colorless viscous liquid, which was subsequently separated by preparative TLC using benzene–ether (4: 1) to give isocalamendiol (**9**) (8 mg) (mp and IR spectrum).

Reaction of Acoragermacrone (1) with 80% aq HCOOH. A solution of **1** (90 mg) in 80% aq HCOOH (0.9 ml) was

stirred at room temperature for 10 min, and then diluted with water (5 ml). The solution was neutralized with a sat. $NaHCO_3$ aq solution, and then extracted with ether. The ethereal extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a pale yellow liquid (106 mg), which was separated by preparative TLC using benzene–ether (4: 1) to give three main fractions in the following order: **9** (18 mg), **10** (19 mg), and **11** (19 mg). The compound **9** was identical with an authentic sample of isocalamendiol (mp and IR spectrum). The physical data of the other two products are shown below.

trans-*Selinane-type Compound (10)*: mp 45—48 °C (from hexane); ν_{max} (film) 1720 cm^{-1}; δ 0.88 (3H, d, J=6.5 Hz), 0.92 (3H, d, J=6.5 Hz), 0.90 (3H, s), 1.88 (3H, s), 2.87 (1H, s) and 8.04 (1H, s) ppm; *m/e* 266 (M^+) and 220 (Found: *m/e* 266.18862. Calcd for $C_{16}H_{26}O_3$: *m/e* 266.18818).

cis-*Selinane-type Compound (11)*: mp 83—85 °C (from hexane); ν_{max} (film) 1720 cm^{-1}; δ 0.85 (3H, d, J=6.0 Hz), 0.98 (3H, d, J=6.0 Hz), 0.96 (3H, s), 1.91 (3H, s), 2.93 (1H, s), and 8.03 (1H, s) ppm; *m/e* 266 (M^+) and 220 (Found: *m/e* 266.19067. Calcd for $C_{16}H_{26}O_3$: *m/e* 266.18818).

Reaction of Acoragemacrone (1) with 100% HCOOH in Thiophenol. To a solution of **1** (125 mg) in thiophenol (2 ml) was added 5 drops of 100% HCOOH with stirring. The resulting solution was further stirred at room temperature for 1 h, and then diluted with a lot of ether. The ethereal solution was washed successively with 10% NaOH aq solution and water, and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left a pale yellow liquid (190 mg), which was purified by preparative TLC using hexane–benzene (1:1) to give a pale yellow liquid of **12** (109 mg), ν_{max} (film) 3060, 1710, 1580, 735, and 690 cm^{-1}; δ 0.83 (3H, s), 0.85—1.00 (9H, complex), 3.01 (1H, dd, J=6.5 and 8.8 Hz) and 7.18—7.69 (5H, complex) ppm; *m/e* 330 (M^+) and 220 (Found: *m/e* 330.20388. Calcd for $C_{21}H_{30}OS$: *m/e* 330.20173).

Desulfurization of 12. To a solution of **12** (80 mg) in EtOH (3 ml) was added Raney Ni (W-4) (100 mg), and then the reaction mixture was refluxed for 3 h under a nitrogen atmosphere. After removal of the catalyst, the filtrate was concentrated under reduced pressure to give a colorless viscous liquid (51 mg) which was purified by preparative GLC at 120 °C to give a colorless liquid of dihydroacolamone (14 mg) (GLC, TLC and IR spectrum).

Reaction of Isoacoragermacrone (2) with 80% aq AcOH. Isoacoragermacrone (40 mg) was dissolved in 80% aq AcOH (5 ml) with stirring. The resulting solution was further stirred at room temperature for 5 min, and then diluted with ice–water (*ca.* 10 ml). After neutralization with $NaHCO_3$ powder, the solution was extracted with ether. The ethereal extract was washed with a sat. NaCl aq solution and dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a colorless oil, which was separated by preparative TLC using petroleum ether–ether (1: 3) to give two fractions. From the more polar fraction, the alcohol **14** (17 mg) was isolated as a colorless viscous liquid. From the less polar fraction, the acetate **15** (11 mg) was also obtained as a colorless viscous liquid.

14: ν_{max} (film) 3350 br. and 1640 br. cm^{-1}; λ_{max} 247 and 241 nm (ε, 11100 and 10900, respectively); δ 0.96 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.06 (3H, s), 1.80 (3H, br. s) and 6.24 (1H, br. s) ppm; *m/e* 220 (M^+), 187 and 159 (Found: *m/e* 220.18096. Calcd for $C_{15}H_{24}O$: *m/e*220.18270).

15: ν_{max} (film) 1730 and 1660 br. cm^{-1}; λ_{max} 247 and 241 nm (ε, 10500 and 10300, respectively); δ 0.96 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.35 (3H, s), 1.79 (3H, br. s), 1.99 (3H, s), 4.77 (1H, br. s) and 6.25 (1H, br. s) ppm; *m/e* 262 (M^+), 220, 202, 187, 177, and 159 (Found: *m/e* 262.19634. Calcd for $C_{17}H_{26}O_2$: *m/e* 262.19327).

Reduction of the Acetate 15 with $LiAlH_4$. To a solution of **15** (18 mg) in anhydrous ether (5 ml) was added $LiAlH_4$ (4 mg) with stirring, and then the reaction mixture was heated under reflux for 4 h. After decomposition of an excess of the reagent with water, 20% potassium sodium tartarate aq solution was added to the reaction mixture, which was extracted with ether. The ethereal extract was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a colorless oil (14 mg), which was purified by preparative TLC using petroleum ether–ether (1: 3) to give the alcohol **14** (GLC, TLC, and IR spectrum).

Reaction of Isoacoragermacrone (2) with $AlCl_3$. To a solution of **2** (39 mg) in absolute ether (5 ml) was added a solution of $AlCl_3$ (24 mg) in absolute ether (1.5 ml) at 0 °C, with stirring. The resulting solution was further stirred at 0 °C for 10 min, and then poured into ice water and extracted with ether several times. The combined ethereal extracts were washed with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded a colorless oil,* which was purified by preparative TLC using alumina [GF_{254} (type E), E. Merck A. G.] and benzene to give **16** as a colorless viscous liquid (20 mg); ν_{max} (film) 3570 sh., 3450 and 1640 cm^{-1}; λ_{max} 246 and 241 nm (ε, 16300 and 16200, respectively); δ 1.00 (6H, d, J=7.0 Hz), 1.28 (3H, s), 1.77 (3H, br. s) and 6.27 (1H, br. s) ppm; *m/e* 220 (M^+), 202, 187, and 159 (Found: *m/e* 220.18247. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271).

The Formation of the Guaiane-type Compound (17). To a solution of isoacoragermacrone (245 mg) in thiophenol (2 ml) was added, with stirring, 10 drops of AcOH at room temperature, and then the resulting solution was further stirred at room temperature for 24 h. After addition of a cooled 10% NaOH aq solution, the solution was extracted with ether. The ethereal extract was washed successively with a cooled 10% NaOH aq solution and water, and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave an almost colorless liquid, which was chromatographed on silica gel (20 g) and eluted with benzene to give **17** as colorless crystals (184 mg); mp 90—91 °C (from hexane); ν_{max} (KBr) 3060, 1700, 1580, 745, and 690 cm^{-1}; δ (CCl_4) 0.91 (3H, d, J=6.4 Hz), 0.95 (3H, d, $J\simeq$7.5 Hz), 0.96 (3H, d, J=6.4 Hz), 1.22 (3H, s), 2.92 (1H, d, J=8.5 Hz) and 7.08—7.57 (5H, m) ppm; *m/e* 330 (M^+) and 221 (Found: C, 76.53; H, 9.26%. Calcd for $C_{21}H_{30}OS$: C, 76.31; H, 9.15%).

Formation of the α,β-Unsaturated Ketone (18). A solution of **17** (100 mg) and freshly distilled MeI (1 ml) in acetone (4 ml) was refluxed under a nitrogen atmosphere for 8 h, and then concentrated under reduced pressure to give a crude residue which was purified by preparative TLC using hexane–benzene (1: 1) to give **18** as a colorless liquid (44 mg); ν_{max} (film) 1670 and 1610 cm^{-1}; λ_{max} 256 nm (ε, 8270); δ 0.72 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=6.4 Hz), 0.92 (3H, d, J=6.4 Hz), 2.05 (3H, br. s) and 3.24 (1H, m) ppm; *m/e* 220 (M^+) and 215 (Found: 220.18108. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271).

Desulfurization of 17. To a solution of **17** (137 mg) in absolute EtOH (5 ml) was added, with stirring, Raney Ni (W-4) (*ca.* 1 g) at room temperature, and then the reaction mixture was refluxed under a nitrogen atmosphere for 6 h. After filtration of the catalyst, the filtrate was concentrated

* Peak-area of analytical GLC was served as approximate values of the content (%), indicating that this oil contained the alcohol **16** (28.2 mg).

under reduced pressure to give a crystalline solid (79 mg), the sublimation of which afforded **19** as colorless needles; mp 55—57.5 °C; ν_{max} (KBr) 1700 cm^{-1}; δ 0.83 (3H, d, J=6.7 Hz), 0.87 (3H, d, J=6.5 Hz), 0.92 (3H, d, J=6.5 Hz), 1.13 (3H, d, J=6.3 Hz) and 2.86 (1H, dd, J=7.8 and 4.8 Hz) ppm; *m/e* 222 (M^+), 207 and 166 (Found: *m/e* 222.19849. Calcd for $C_{15}H_{26}O$: *m/e* 222.19836).

Epimerization of ***19***. A solution of **19** (44 mg) and NaOMe (27 mg) in absolute MeOH (3 ml) was refluxed for 3 h under a nitrogen atmosphere, and then concentrated under reduced pressure. After addition of water (5 ml), the reaction mixture was extracted with ether. The ethereal extract was dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a colorless liquid (39 mg), which was separated by preparative TLC using hexane–benzene (1: 1) to give two fractions. From the less polar fraction, the starting material of **19** (8 mg) was recovered (mp and IR spectrum). From the polar fraction, a colorless viscous liquid **20** (28 mg) was isolated; ν_{max} (film) 1695 cm^{-1}; δ 0.84—1.06 (12H, complex) ppm; *m/e* 222 (M^+), 207 and 166 (Found: *m/e* 222.19846. Calcd for $C_{15}H_{26}O$: *m/e* 222.19836).

Reaction of Isoacoragermacrone (2) with 100% HCOOH in Thiophenol. To a solution of **2** (480 mg) in thiophenol–benzene [30 ml (1: 1)] was added, with stirring, 20 drops of 100% HCOOH at room temperature. The resulting solution was further stirred at room temperature for 15 h, and then washed successively with 10% NaOH aq solution and water, and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded a viscous liquid which was chromatographed on silica gel. Elution with hexane–benzene (1: 1) gave a colorless oil (347 mg), which was rechromatographed on silica gel and eluted with hexane and then with hexane–benzene (9: 1) to give **21** (33 mg) and **22** (110 mg), respectively.

Further elution of the above viscous liquid with hexane–benzene (1: 1) gave a colorless viscous liquid (179 mg) of undetermined structure. Continuous elution with the same solvent system afforded the guaiane-type compound **17** (110 mg) (mp and IR spectrum).

21. A colorless viscous liquid; ν_{max} (film) 3070 sh., 3060, 1580 br., 745 and 690 cm^{-1}; δ (CCl_4) 0.93 (6H, d, J=7.0 Hz), 1.09 (3H, s), 1.76 (3H, br. s), 2.99 (1H, m, J=7.0 Hz), 6.13 (1H, br. s) and 7.30 (5H, complex) ppm; *m/e* 312 (M^+), 202, 187, and 159 (Found: *m/e* 312.19197. Calcd for $C_{21}H_{28}S$: *m/e* 312.19116).

22. A colorless viscous liquid; ν_{max} (film) 3070, 1585 br., 750 and 695 cm^{-1}; δ (CCl_4) 0.76—0.98 (6H, complex), 1.12 (3H, s), 1.24 and 1.26 (total 3H), 5.35 and 5.43 (total 1H) and 7.10—7.70 (10H, complex) ppm; *m/e* 312 (M^+—110), 202 and 159 (Found: *m/e* 312.19105. Calcd for $C_{27}H_{34}S_2$–C_6H_6S; *m/e* 312.19116).

Reaction of Isoacoragermacrone (2) with concd H_2SO_4 in Thiophenol. To a solution of **2** (380 mg) in thiophenol (12 ml) was added, with stirring, 10 drops of conc. H_2SO_4 at 0 °C, and the solution was further stirred at 0 °C for 30 min, and then extracted with ether after addition of a cooled 10% NaOH aq. solution (40 ml). The ethereal extract was washed successively with 10% NaOH aq solution and water, and then dried over anhydrous $MgSO_4$. Removal of the solvent afforded a pale yellow liquid, which was chromatographed on silica gel (15 g) and eluted with hexane to give a colorless viscous liquid of **21** (22 mg) (TLC and IR spectrum). Further elution with hexane–benzene (9: 1) also gave a colorless viscous liquid **22** (491 mg) (TLC and IR spectrum).

Formation of the Dithio Compounds (22a and 22b) from the Conjugated Diene (21). To a solution of **21** (12 mg) in thiophenol (1 ml) was added, with stirring, one drop of concd H_2SO_4 at 0 °C. The solution was further stirred at 0 °C for 30 min, and then extracted with hexane after addition of a cooled 10% NaOH aq solution. The extract was washed successively with a cooled 10% NaOH aq solution and water, and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative TLC using hexane to give a mixture of dithio compounds (**22a** and **22b**) as a colorless viscous liquid (9 mg) (TLC and IR spectrum).

Conversion of the Dithio Compounds (22a and 22b) into the Conjugated Diene (21). A solution of the dithio compounds (100 mg) in acetone containing MeI (2 ml) was refluxed for 4 h under a nitrogen atmosphere, and then concentrated under reduced pressure to give a pale yellow liquid which was separated by preparative TLC using hexane to give two fractions. From the first fraction, calamenene (14 mg) was isolated (GLC, TLC, and IR spectrum). From the second fraction, **21** (39 mg) was obtained (TLC and IR spectrum) as a colorless viscous liquid.

Reduction of Isoacoragermacrone (2) with Diisobutylaluminium Hydride (DBAH). To a solution of **2** (27 mg) in absolute benzene (2 ml) was added, with stirring, a solution of DBAH (100 mg) in heptane at 0 °C under a nitrogen atmosphere. The solution was further stirred at 0 °C for 1.5 h and at 5 °C for 30 min, and then cooled to 0 °C again. After addition of MeOH–benzene (1: 1) (5 ml), the solution was concentrated under reduced pressure to dryness. The residue was diluted with benzene with shaking, and then filtered. The filtrate was concentrated under reduced pressure to give a colorless oil (26 mg),** which was purified by preparative TLC using alumina [GF_{254} (type E), E. Merck A. G.] and benzene to give the corresponding dihydro compound **25** (7.5 mg) as a colorless viscous liquid; ν_{max} (film) 1700 cm^{-1}; δ 0.87 (3H, d, J=6.9 Hz), 0.92 (3H, d, J=6.9 Hz), 0.96 (3H, d, J=6.9 Hz), 1.45 (3H, br. s) and 5.16 (1H, t, J=6.5 Hz) ppm; *m/e* 222 (M^+) and 207 (Found: *m/e* 222.19837. Calcd for $C_{15}H_{26}O$: *m/e* 222.19836).

Reaction of the Dihydro Compound (25) with 80% aq AcOH. A solution of **25** (54 mg) in 80% aq AcOH (4 ml) was stirred at room temperature for 5 min, and then diluted with ice–water (*ca.* 10 ml). After neutralization with $NaHCO_3$ powder, the solution was extracted with ether. The ethereal extract was washed with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded a colorless oil which was separated by preparative TLC using alumina [GF_{254} (type E), E. Merck A. G.] and benzene to give **26** (11 mg) as a colorless viscous liquid, which was identical with an authentic sample of dihydro-dehydroisocalamendiol.[1]

Reaction of Preisocalamendiol (3) with $AlCl_3$. To a solution of **3** (27 mg) in absolute ether (5 ml) was added, with stirring, a solution of $AlCl_3$ (23 mg) in absolute ether (1.5 ml) at 0 °C. The resulting solution was further stirred at 0 °C for 10 min, and then poured into ice–water. After separation of the ethereal layer, the aqueous solution was extracted with ether. The combined extracts were washed with a sat. NaCl aq. solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded a yellow oil***, which was subjected to preparative TLC using alumina [GF_{254} (type E), E. Merck A. G.] and benzene, giving a colorless viscous liquid, the dienol **28** (6.6 mg) (GLC, TLC, and IR spectrum).[1]

** Peak-area of analytical GLC was served as approximate values of the content (%), indicating that this oil contained the dihydro compound (19.6 mg).

*** Peak-area of analytical GLC was served as an approximate value of the content (%), indicating that this oil contained the dienol (14.6 mg).

Thermal Isomerization of Preisocalamendiol (3). A colorless viscous liquid of **3** (*ca.* 10 mg) in a sealed tube was heated at 180 °C, and the composition of the reaction mixture was checked by analytical GLC, as already described in Table 1.

Reduction of Preisocalamendiol (3) with $LiAlH_4$. To a solution of **3** (220 mg) in absolute ether (20 ml) was slowly added, with stirring, $LiAlH_4$ (40 mg) at room temperature, and then the reaction mixture was further stirred at room temperature for 30 h. After decomposition of an excess of the reagent with water, 20% potassium sodium tartarate aq solution was added to the reaction mixture, which was extracted with ether. The ethereal extract was washed with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded **29** (220 mg)† as a colorless liquid; ν_{max} (film) 3360 br. and 1640 cm^{-1}; δ 0.95 (6H, d, J=6.8 Hz), 1.60 (3H, br. s), 3.60—3.92 (1H, m), 4.92 (2H, br. s) and 5.25 (1H, m) ppm; *m/e* 222 (M^+), 204 and 161 (Found: *m/e* 222.19700. Calcd for $C_{15}H_{26}O$: *m/e* 222.19836).

Reaction of 29 with 80% aq HCOOH. The alcohol **29** (36 mg) was dissolved in 80% aq HCOOH (1 ml) at 0 °C. The resulting solution was stirred at 0 °C for 2 h, and then poured into a cooled sat. $NaHCO_3$ aq solution and extracted with ether. The ethereal extract was washed with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent gave a colorless oil (39 mg) in an almost pure state, which was purified by preparative GLC at 110 °C to afford a pure sample of the formate **30** (13 mg); ν_{max} (film 1720 and 1645 cm^{-1}; δ 0.93 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=6.9 Hz), 1.66 (3H, d, J=1.3 Hz), 3.66—3.90 (1H, m), 4.97 (2H, br. s), 5.28 (1H, br. m) and 8.11 (1H, s) ppm; *m/e* 204 (M^+—46) and 161. Elemental analysis of this formate has not been carried out, but its structure (**30**) is supported by the above-mentioned spectral data coupled with the next experimental results.

Recoversion of the Formate (30) into the Alcohol (29). To a solution of **30** (13 mg) in absolute ether (3 ml) was added, with stirring, $LiAlH_4$ (4 mg). The reaction mixture was further stirred at room temperature for 3 h, and then an excess of the reagent was decomposed by addition of ether saturated with water. The reaction mixture was diluted with 20% potassium sodium tartarate aq solution (5 ml), and then extracted with ether. The ethereal extract was washed with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded a colorless oil (11 mg) which was purified by preparative TLC using petroleum ether–ether (5:3) to give **29** (6 mg) in a pure state (GLC and IR spectrum).

Formation of ε-Cadinene (31). To a solution of **29** (164 mg) in absolute pyridine (10 ml) was slowly added, with stirring, a solution of mesyl chloride (100 mg) in pyridine (5 ml) at 0 °C. The resulting solution was further stirred at 0 °C for 1 h, and then at room temperature for 7 h. The solution was poured into ice water, and then extracted with ether. The ethereal extract was washed throughly with a sat. NaCl aq solution, and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an almost colorless oil (135 mg), which was purified by preparative TLC using hexane to give ε-cadinene (51 mg) as a colorless viscous liquid; ν_{max} (film) 3070 and 1645 cm^{-1}; δ 0.71 (3H, d, J=6.7 Hz), 0.91 (3H, d, J=6.7 Hz) and 4.72—4.48 (4H, complex) ppm; *m/e* 204 (M^+ for $C_{15}H_{24}$), 176 and 161.

Catalytic Hydrogenation of ε-Cadinene (31). Catalytic hydrogenation of **31** (10 mg) in AcOEt (1 ml) was carried out over PtO_2 (3 mg) at room temperature for 2 h. After filtration of the catalyst, the solvent was evaporated under reduced pressure to give a colorless oil (10.1 mg) in a pure state; δ 0.73 (3H, d, J=6.6 Hz), 0.82 (6H, d, J=7.0 Hz) and 0.97 (3H, d, J=6.6 Hz) ppm; *m/e* 208 (M^+ for $C_{15}H_{28}$), 165 and 109. The IR spectrum of this oil was completely identical with that of an authentic sample of tetrahydrocadinene.[14]

† GLC of this liquid showed only one peak.

The authors wish to thank Professor Yoshimasa Hirata (Nagoya University) for his invaluable suggestion. Thanks are also due to Drs. Masayasu Kurono and Masaaki Toda (Ono Pharmaceutical Co. Ltd.) for measurements of high resolution mass spectra. This research has been supported in part by grants from the Ministry of Education, to which greatful acknowledgement is made.

References

1) S. Yamamura, M. Iguchi, A. Nishiyama, M. Niwa, H. Koyama, and Y. Hirata, *Tetrahedron*, **27**, 5419 (1971) and references cited therein.

2) M. Niwa, A. Nishiyama, M. Iguchi, and S. Yamamura, *Bull. Chem. Soc. Jpn.*, **48**, 2930 (1975).

3) V. Herout, O. Motl, and F. Sǒrm, *Coll. Czech. Chem. Commun.*, **22**, 785 (1957); S. C. Bhattacharyya, A. S. Rao, and A. M. Shaligram, *Chem. Ind.*, **1960**, 469, and *Tetrahedron*, **18**, 969 (1962); D. W. Theobald, *Tetrahedron*, **20**, 2593 (1964).

4) O. Motl, V. Sykora, V. Herout, and F. Sǒrm, *Coll. Czech. Chem. Commun.*, **23**, 1297 (1958).

5) A. F. Thomas, M. Ozainne, R. Decorzant, F. Näf, and C. Lukacs, *Tetrahedron*, in press.

6) M. Iguchi, M. Niwa, and S. Yamamura, *Tetrahedron Lett.*, **1973**, 4367.

7) J. G. Traynham, G. R. Frauzen, G. A. Knesel, and D. J. Northington Jr., *J. Org. Chem.*, **32**, 3285 (1967); J. G. Traynham, and H. H. Hsieh, *ibid.*, **38**, 868 (1973); J. K. Sutherland, *Tetrahedron*, **30**, 1651 (1974).

8) M. Iguchi, M. Niwa, and S. Yamamura, *J. Chem. Soc., Chem. Commun.*, **1971**, 974.

9) M. Ōki, "Jikken Kagaku Koza," Supplement Vol. XII, ed. by The Chemical Society of Japan, Maruzen Publishing Co. Ltd., Tokyo (1967), p. 252.

10) M. Iguchi, M. Niwa, and S. Yamamura, *Tetrahedron Lett.*, **1973**, 1687.

11) G. Büchi, W. Hofheinz, and J. V. Paukstelis, *J. Am. Chem. Soc.*, **91**, 6473 (1969) and references cited therein.

12) M. Iguchi, A. Nishiyama, S. Yamamura, and Y. Hirata, *Tetrahedron Lett.*, **1970**, 855.

13) L. Westfelt, *Acta Chem. Scand.*, **20**, 2865 (1966).

14) We are most grateful to Drs. Y. Hirose and Y. Ohta (The Institute of Food Chemistry) for their discussion, and identification of the synthetic tetrahydrocadinene with an authentic sample.