Sesquiterpenes from *Acorus calamus* L.

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Three new sesquiterpenes, acoragermacrone (**1**), acolamone (**2**), and isoacolamone (**3**) were isolated from *Acorus calamus* L., and their structures were elucidated. In particular, acoragermacrone, a ten-membered ring sesquiterpene, is the most important precursor of the other sesquiterpenes included in the same plant. Acoragermacrone was converted into shyobunone, epi-shyobunone, preisocalamendiol, acolamone, and isoacolamone.

Many sesquiterpenes have been isolated from the plant *Acorus calamus* L. (Japanese name "Shyobu") growing in Japan.[1] However, such a key intermediate as acoragermacrone (**1**) has not been isolated. From a biogenetic point of view, our considerable efforts have been made to search for such an important precursor as **1**, and led us to the isolation of the expected ten-membered ring sesquiterpene, named "acoragermacrone", and two selinane-type compounds, acolamone (**2**) and isoacolamone (**3**). In this paper, we wish to describe the isolation and structures of these new sesquiterpenes. Furthermore, chemical correlation among them, including thermal and acid- or base-catalyzed isomerizations of acoragermacrone **1**, is also reported.

The Structures of Acoragermacrone (1). The pluverized raw rhizomes of *Acorus calamus* L. were carefully extracted with *n*-hexane to give a brown oil, which was directly chromatographed on silica gel. Rapid elution with *n*-hexane–ether (3 : 1) afforded a mixture of two ten-membered ring sesquiterpenes after elution of shyobunone and its isomers. Further separation of this mixture was successfully carried out by repeated preparative tlc using alumina in *n*-hexane–benzene (2 : 1) to give acoragermacrone **1** and preisocalamendiol (**4**) in 6 and 18% yields, respectively.[2]

Acoragermacrone **1** is a monocyclic sesquiterpene with a molecular formula $C_{15}H_{24}O$. The presence of an α,β-unsaturated cisoid carbonyl system (Me–C(=)CH–C(=)O) can be confirmed by its IR and UV spectra (ν_{max} 1680 and 1607 cm^{-1}; λ_{max} 242 nm (ε, 6590)] coupled with NMR spectrum which has two prominent signals at δ1.97 (3H, d, J=1.0 Hz) and 5.33 ppm (1H, q, J=1.0 Hz).[3] As found in the case of preisocalamendiol **4**,[1] furthermore, this new sesquiterpene also has an isopropyl group [δ 0.94 (3H, d, J=5.7 Hz) and 1.02 ppm (3H, d, J=5.7 Hz)] as well as a methyl group attached to a trisubstituted double bond [δ 1.12 (3H, d, J=1.5 Hz) and 4.60 ppm (1H, m)[4]]. In particular, the appearance of the methyl signal in unusually higher magnetic field (δ 1.12 ppm) seems to be due to the anisotropy effect of the α,β-unsaturated carbonyl system. This fact was supported by the following chemical evidence. When treated with sodium methoxide in MeOH (room temp., 30 min), acoragermacrone **1** was readily converted into the corresponding methoxy-ketone (**5**) in 48% yield, $C_{16}H_{28}O_2$ [*m/e* 252 (M^+)], which was proved to have a partial structure [Me–C(OMe)–CH_2–C(=)O] on the basis of its spectral data [ν_{max} 1705 cm^{-1}; δ 1.41 (3H, s), 2.46 (1H, d, J=17.7 Hz), 2.93 (3H, s) and 3.03 ppm (1H, d, J=17.7 Hz)]. Furthermore, it should be noted that the methyl signal at δ 1.12 ppm in **1** is shifted to δ 1.53 ppm in **5**.

From the above spectral and chemical data it is clear that acoragermacrone must be the most important ten-membered ring sesquiterpene (**1**) that has been expected to be present in the plant. Finally, the structure of acoragermacrone including its stereostructure (**1**) was established on the basis of some chemical evidences, namely thermal and base-catalyzed isomerizations.

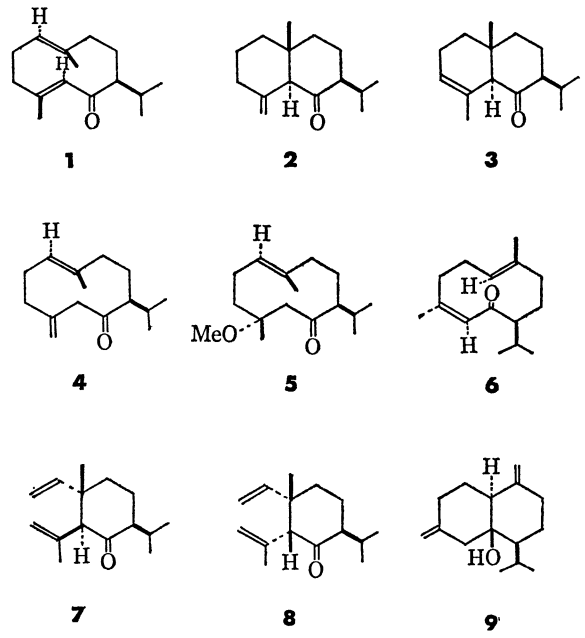
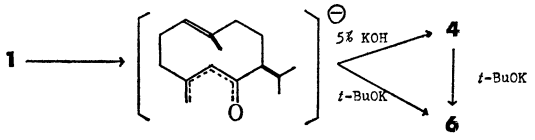


Fig. 1.

Base-catalysed Isomerization. As described earlier, action of MeONa on acoragermacrone **1** converted it into the corresponding addition product (**5**). When treated with *t*-BuOK in *t*-BuOH under N_2 (room temp., 30 min), **1** was readily converted into the known isomer (**6**)[5] in 95% yield through an enolate anion [A], as shown in Scheme 1. On the other hand, **1** reacted with 5% aq. KOH in *t*-BuOH (room temp., 24 hr) to give preisocalamendiol **4** in 84% yield, whose stereostructure had been already established in connection with shyobunone (**7**).[1] Further action of *t*-BuOK in *t*-BuOH on **4** also converted it into the most stable ten-membered ring compound, isoacoragermacrone (**6**), in almost quantitative yield.

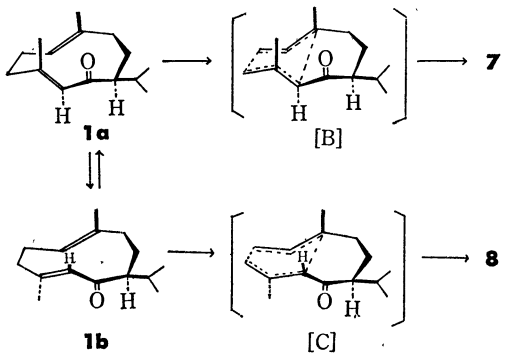


[A]

Scheme 1. Base-catalysed isomerization of acoragermacrone.

Thermal Isomerization of Acoragermacrone (1). In the cases of germacrones having an (*E*,*E*)-1,5-cyclodecadiene system, most of them have been known to adopt a crossed conformation.[6] In connection with the Cope rearrangement, conformations of these 1,5-cyclodecadienes have been also discussed by Takeda *et al.*[7]

The variable-temperature NMR spectrum of acoragermacrone was measured using benzene-d_6 as a solvent (24—106 °C). At 106 °C, it showed the new signal corresponding to those of shyobunone **7** in addition to the own signals, indicating that the Cope rearrangement took place to give **7**. When heated in a sealed tube at 110 °C for 30 min, acoragermacrone was completely converted into a mixture of shyobunone **7** and epi-shyobunone (**8**) (relative ratio **7**/**8**=21/4). In these experiments, shyobunone and epi-shyobunone both must be directly produced from acoragermacrone **1**, because these two elemene-type sesquiterpenes are quite stable under the same conditions. Therefore, this fact indicates that **1** has two possible conformational isomers (**1a** and **1b**) at least at higher temperature than 110 °C. Of two conformers, shyobunone **7** must be formed from the crossed conformer (**1a**) through a chair-like transition state [B], whereas epi-shyobunone **8** can be derived from the parallel one (**1b**) *via* a boat-like transition state [C]. In the above case, the chair-like one is much preferred as usual. However, it should be noted that the latter [C] leading to the formation of **8** can not be discarded, as shown in Scheme 2.[8] Under more vigorous conditions, in Scheme 2, the retro-Cope rearrangement of the elemene-type compounds takes place, leading to the formation of acoragermacrone **1** again, from which preisocalamendiol **4** and dehydroxyisocalamendiol (**9**) are readily produced.[1,5,9]



Scheme 2. Thermal isomerization of acoragermacrone (**1**).

The Structures of Acolamone (2) and Isoacolamone (3).[10] According to essentially the same procedure as that of acoragermacrone **1**, the *n*-hexane extracts were chromatographed repeatedly on different kinds of silica gel to afford acolamone **2** and isoacolamone **3** in each *ca.* 1.6% yield (from the *n*-hexane extracts) before elution of shyobunone **7** and its isomers.

Acolamone and isoacolamone both are bicyclic ketones ($C_{15}H_{24}O$; ν_{max} 1715 cm^{-1} in **2** as well as in **3**), and can be regarded as double bond isomers to each other on the basis of their NMR spectra, as shown in Table 1.

Table 1. NMR spectra of acolamone (**2**) and isoacolamone (**3**)

2	**3**
0.76(3H, s)	0.74(3H, s)
0.87(3H, d, J=6.5 Hz)	0.89(3H, d, J=6.3 Hz)
0.90(3H, d, J=6.5 Hz)	0.93(3H, d, J=6.3 Hz)
	1.76(3H, d, J=1.8 Hz)
2.90(1H, s)	3.10(1H, br. s)
5.00(1H, br. s)	
	5.42(1H, br. s)
5.95(1H, br. s)	

In the comparison of the NMR spectra between **2** and **3**, the former has two protons attached to an exocyclic double bond (δ 5.00 and 5.95 ppm), whereas **3** has one proton and the methyl group, both of which must be attached to a tri-substituted double bond (δ 5.42 and 1.76 ppm). The remaining signals are almost identical in both compounds. Furthermore, the structural relationship between acolamone and isoacolamone was established by the following thermal isomerization.

When heated in a sealed tube at 190 °C for 5 hr, acolamone **2** was converted into a mixture of two α,β-unsaturated ketones[11], whose spectral data were fairly close to each other [**10** (relative retention 2.30), ν_{max} 1690 and 1635 cm^{-1}; λ_{max} 248 nm (ε, 5600). **11** (relative retention 2.79), ν_{max} 1685 and 1638 cm^{-1}; λ_{max} 252 nm (ε, 4300)], in 60 and 27% yields, respectively. The former was completely identical with the selinane-type compound (**10**), which has been already derived from isoacoragermacrone **6** in several steps,[12] in respect of the glc and IR spectra. The compound (**10**) has also been derived from ajanol.[13] In the case of isoacolamone **3**, a mixture of **10** and **11** was also obtained in the same ratio as that of acolamone. Finally, the stereostructures of acolamone and isoacolamone were established as discussed below.

The ORD curve of acolamone showed a weak positive Cotton effect ($[\phi]^{P}_{325nm}+9°\times10^2$, $[\phi]^{T}_{280nm}-4°\times10^2$, $A=+13$), whereas that of isoacolamone has a weak negative Cotton effect ($[\phi]^{T}_{314nm}-10°\times10^2$, $[\phi]^{P}_{283nm}+7°\times10^2$, $A=-17$). In these cases, however, it is pretty dangerous to apply the octant rule to such $\beta\gamma$-unsaturated ketones as **2** and **3**. Therefore, the stereochemistry at C_5-position should be discussed in the case of the corresponding dihydro-compound (**12**, $C_{15}H_{26}O$, ν_{max} 1715 cm^{-1}),[14] which was readily

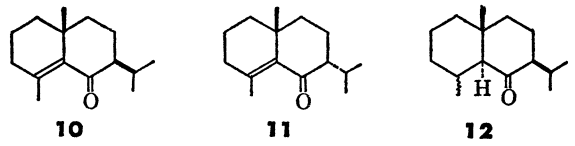
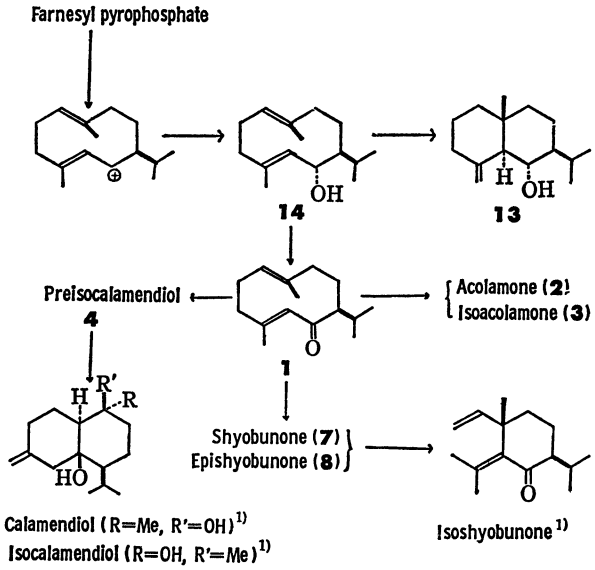


Fig. 2.

produced from acolamone as well as from isoacolamone on catalytic hydrogenation (H_2/PtO_2 in AcOEt) and has a positive Cotton effect in its ORD curve ($[\phi]^{P}_{312nm}+19°\times10^2$, $[\phi]^{T}_{274nm}-13°\times10^2$, $A=+32$), indicating that acolamone and isoacolamone should have the stereostructures (**2**) and (**3**), respectively.

From a structural view point, particularly, acolamone **2** is regarded as the higher oxidation product of junenol (**13**)[15], which must be derived from a plausible precursor (**14**). However, in consideration of the co-occurrence of acoragermacrone **1**, acolamone **2** and isoacolamone **3** both must be derived from **1** *in vivo*, as shown in Scheme 3. Thus, these two sesquiterpenes (**2** and **3**) were directly produced from acoragermacrone **1**.[16]

When treated with $AlCl_3$ in dry ether (0 °C, 1 hr), acoragermacrone afforded a pale yellow liquid, from which acolamone **2** and isoacolamone **3** were successfully separated, in each pure state, by preparative tlc in 55 and 23% yields, respectively.



Scheme 3. Biogenesis of acoragermacrone and related sesquiterpenes.

Experimental

All mps are uncorrected. Relative retentions *vs.* calamenene as an internal standard were recorded on Shimadzu GC-1C (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/cm²], unless otherwise stated. The IR spectra were recorded on a Hitachi-215 spectrophotometer. The UV spectra were recorded on a Hitachi 124 spectrophotometer using MeOH as solvent. The NMR spectra were recorded on a Varian Associates HA-100, a Varian A-60 or a Nihondenshi JNM-C60H NMR spectrometer using $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts are given in ppm relative to internal TMS, and only prominent signals are cited (d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet). The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy (70 eV). The ORD curves were recorded on a JASCO ORD/UV-5 spectrophotometer using MeOH as solvent.

*Isolation of Acoragermacrone (**1**).* As expected from the previous paper,[1] such ten-membered ring compounds as preisocalamendiol **4** and isoacoragermacrone **6** seem to be more polar than those of shyobunone and its isomers. Thus, our attentions were focused on searching for the much polar fraction similar to that of preisocalamendiol **4**.

Raw sliced rhizomes of *Acorus calamus* L. (7 kg) growing in Aichi-ken, which were collected late in November, were pluverized with a mixer, and immersed in *n*-hexane (*ca.* 35 l) at room temperature for two weeks, and then filtered. The filtrates were concentrated under reduced pressure below 35 °C to leave a brown residue. The above procedure was repeated three times, and total weight of the *n*-hexane extracts so far obtained is 92 g (*ca.* 13% yield). The brown oil (20 g) was chromatographed on silica gel (Kanto Chemical Co. Ltd., 100—200 mesh) (250 g), and eluted very rapidly with *n*-hexane -Et_2O (3 : 1). The first fraction eluted with the mixed solvent (*ca.* 400 ml) afforded a mixture of shyobunone, acolamone and their isomers and undetermined hydrocarbons. Further elution with the same solvent system (*ca.* 200 ml) gave the slightly brown oil (8.4 g) corresponding to the spot of preisocalamendiol on a tlc plate. This oil (150 mg) was directly separated by repeated preparative tlc using alumina [GF_{254} (Type E), E. Merck A. G., Darmstadt] in *n*-hexane–benzene (2 : 1). From the less polar fraction, preisocalamendiol (64 mg) was obtained. From the more polar fraction, acoragermacrone (22 mg) was isolated, whose physical data were shown below.

*Acoragermacrone (**1**).* A colorless liquid; ν_{max} (film) 1680 and 1607 cm^{-1}; λ_{max} 242 nm (ε, 6590); $\delta(C_6D_6)$ 0.94 (3H, d, J=5.7 Hz), 1.02 (3H, d, J=5.7 Hz), 1.12 (3H, d, J=1.5 Hz), 1.97 (3H, d, J=1.0 Hz), 4.60 (1H, br. m) and 5.33 ppm (1H, q, J=1.0 Hz); *m/e* 220 (M^+), 215, 177 and 150 (Found: *m/e* 220.1786. Calcd for $C_{15}H_{24}O$: *m/e* 220.1825).

Reaction of Acoragermacrone with MeONa. To a solution of acoragermacrone (22 mg) in anhydrous MeOH (1 ml) was added MeONa (6 mg) with stirring. The resulting solution was further stirred at 20 °C for 30 min, and then diluted by addition of water (1 ml) and extracted with *n*-hexane. The extract was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a colorless liquid (21 mg), which was purified by preparative tlc [Alumina (GF_{254} (Type E), E. Merck A. G., Darmstadt); *n*-hexane–benzene (4 : 1)] to give a colorless liquid (12 mg) of the methoxy-ketone (**5**); ν_{max} (film) 1705 and 1640 cm^{-1}; δ (C_6D_6) 0.79 (6H, d, J=6.0 Hz). 1.41 (3H, s), 1.53 (3H, s), 2.46 (1H, d, J=17.7 Hz), 2.98 (3H, s), 3.03 (1H, d, J= 17.7 Hz) and 5.40 ppm (1H, br. m); *m/e* 252 and 220 (Found: *m/e* 252.2137. Calcd for $C_{16}H_{28}O_2$: *m/e* 252.2088).

Action of t-BuOK on Acoragermacrone. To a solution of acoragermacrone (22 mg) in *t*-BuOH (1.5 ml) was added *t*-BuOK (11 mg) under N_2. The resulting solution was further stirred at room temperature for 30 min, and then diluted with saturated aqueous NaCl solution (5 ml) and extracted with *n*-hexane. The extract was washed with water, and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded a colorless liquid (21 mg),

an analytical tlc of which showed one spot corresponding to that of isoacoragermacrone **6**[5] (tlc and IR spectrum).

Conversion of Preisocalamendiol into Isoacoragermacrone. To a solution of preisocalamendiol (47 mg) in *t*-BuOH (2 ml) was added *t*-BuOK (24 mg) under N_2 with stirring. The resulting solution was continuously stirred at room temperature for 30 min and then extracted with *n*-hexane after addition of saturated aqueous NaCl solution (10 ml). The *n*-hexane extract was washed with water, and then dried over anhydrous Na_2SO_4. Removal of the solvent gave a colorless liquid (45 mg), which was identical with the authentic sample of isoacoragermacrone **6** (tlc and IR spectrum).[5]

Conversion of Acoragermacrone into Preisocalamendiol. To a solution of acoragermacrone (25 mg) in *t*-BuOH (2.5 ml) was added 5% aqueous KOH (0.5 ml). The resulting solution was stirred at room temperature for 24 hr, and then extracted with ether after addition of water (10 ml). The ethereal extract was washed with water and dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to give a colorless liquid (25 mg), whose glc showed two peaks (relative ratio; 84 : 16). The former was completely identical with preisocalamendiol **4**, (glc, tlc and IR spectrum).

Thermal Isomerization of Acoragermacron. Acoragermacrone **1** was heated in a sealed tube under various conditions as shown in Table 2, and the thermal reaction was stopped after the starting material was completely consumed.

Table 2. The Cope rearrangement of acoragermacrone

Temp. (°C)[a]	Time (min)	Relative ratio (%)[b]	
		7	**8**
110	30	83.8	16.2
120	25	82.6	17.4
130	12	81.9	18.1
140	6	80.5	19.5
150	3	80.1	19.9
160	2	77.5	22.5

a) Under more vigorous conditions, the retro-Cope rearrangement takes place, leading to the formation of acoragermacrone **1**, from which preisocalamendiol **4** can be produced.[1,5] b) Peak area of gas-liquid chromatogram (5% PEG 20 M on Celite 545, 95 °C, N_2) was served as an approximate value of content (%).

Isolation of Acolamone (2) and Isoacolamone (3). The *n*-hexane extract (36 g), which was described in the case of acoragermacrone **1**, was directly chromatographed on silica gel (Katayama Chemical Co. Ltd., 100—200 mesh) (500 g), and eluted rapidly with petroleum ether–Et_2O (9 : 1). After elution of a mixture of hydrocarbons (8.0 g), further elution with the same solvent system (*ca.* 240 ml) afforded a fraction (9.0 g) containing sesquiterpenic ketones as the main component, which was rechromatographed on silica gel (Kanto Chemical Co. Ltd., 100—200 mesh) (240 g), and eluted with *n*-hexane–benzene (1 : 1). After elution of hydrocarbons (1.0 g), a mixture of two new ketones (1.2 g) was obtained from the second fraction, which was checked by analytical tlc. Further elution with the same solvent afforded shyobunone (1.6 g), epishyobunone (0.7 g) and other undetermined ketones. The mixture of the second fraction (1.2 g) was carefully chromatographed on silica gel (Mallinckrodt, 100 mesh) (50 g) and eluted with *n*-hexane–benzene (1 : 1) to give acolamone (560 mg) and isoacolamone (570 mg), in each pure state*. Their physical data are shown below.

Acolamone (2). A colorless liquid; relative retention 2.70; λ_{max} (film) 1715 and 1645 cm^{-1}; *m/e* 220 (M^+), 205, 177 and 149 (Found: *m/e* 220.1825. Calcd for $C_{15}H_{24}O$: *m/e* 220.1825).

Isoacolamone (3). A colorless liquid; relative retention 2.30; ν_{max} (film) 1715, 1660 (w) and 1640 (w) cm^{-1}; *m/e* 220 (M^+), 205, 177 and 149 (Found: *m/e* 220.1863. Calcd for $C_{15}H_{24}O$: *m/e* 220.1825).

Thermal Isomerization of Acolamone. Acolamone (30 mg) in a sealed tube was heated at 190 °C for 5 hr, and then cooled. The resulting viscous oil was separated by preparative tlc [Wakogel B-5F; *n*-hexane–benzene (1 : 1)]. From the less polar fraction, an $\alpha\beta$-unsaturated keton (**10**) (18 mg) was obtained. On the other hand, an isomer (**11**) (8 mg) was separated from the more polar fraction.

10. A colorless liquid; relative retention 2.79; ν_{max} (film) 1690 and 1635 cm^{-1}; λ_{max} 248 nm (ε, 5600); δ 0.92 (3H, d, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 0.98 (3H, s) and 1.74 ppm (3H, s); *m/e* 220 (M^+), 205 and 178 (Found: *m/e* 220.1821. Calcd for $C_{15}H_{24}O$: *m/e* 220.1825).

11. A colorless liquid; relative retention 2.79; ν_{max} (film) 1685 and 1638 cm^{-1}; λ_{max} 252 nm (ε, 4300); δ 0.87 (3H, d, J=5.8 Hz), 0.93 (3H, d, J=5.8 Hz), 1.00 (3H, s) and 1.75 ppm (3H, s), *m/e* 220 (M^+), 205 and 178 (Found: *m/e* 220.1823. Calcd for $C_{15}H_{24}O$: *m/e* 220.1825).

Thermal Isomerization of Isoacolamone. Under the same conditions as that of acolamone, isoacolamone (30 mg) was heated in a sealed tube, and then the resulting viscous oil was proved to be a mixture of **10** and **11** in the same ratio as that of acolamone by its glc.

Catalytic Hydrogenation of Acolamone as well as of Isoacolamone. Catalytic hydrogenation of acolamone (30 mg) in AcOEt (3 ml) was carried out over PtO_2 (4 mg) at room temperature overnight, and then filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to give a colorless liquid (30 mg) of the dihydro-compound (**12**), which was also obtained, in almost quantitative yield, from isoacolamone **3** under the same conditions as that of **2**.

12. A colorless liquid; relative retention 2.32; ν_{max} (film) 1715 cm^{-1}; δ 0.86 (3H, d, J=6.8 Hz), 0.91 (3H, s), 0.92 (3H, d, J=6.8 Hz) and 1.15 ppm (3H, d, J=6.9 Hz); *m/e* 222 (M^+), 207, 138, 137 and 109 (Found: *m/e* 222.1980. Calcd for $C_{15}H_{26}O$: *m/e* 222.1982).

Conversion of Acoragermacrone into Selinane-type Sesquiterpenes (2 and 3). To a solution of acoragermacrone (50 mg) in anhydrous ether (2 ml) was added a solution of $AlCl_3$ (30 mg) in anhydrous ether (1 ml), with stirring, at 0 °C. The resulting solution was further stirred at 0 °C for 1 hr. and then diluted with ice–water and extracted with ether. The ethereal extract was washed with water, and then dried over anhydrous Na_2SO_4. Removal of the solvent afforded a pale yellow liquid (50 mg), which was separated by preparative tlc [Wakogel B-5F; *n*-hexane–benzene (1 : 1)] to give acolamone (22 mg) and isoacolamone (9 mg) in addition to the starting material (10 mg). These compounds were identified by comparing their tlc and IR spectra with those of the corresponding authentic samples.

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* Analytical glc of the original *n*-hexane extract has the peaks corresponding to those of these two ketons.

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2) M. Iguchi, A. Nishiyama, S. Yamamura, and Y. Hirata, *Tetrahedron Lett.*, **1973**, 2759.

3) Irradiation at δ 1.97 ppm caused the quartet at δ 5.33 ppm to collapse to a sharp singlet. In the case of irradiation at δ 5.33 ppm, the methyl doublet at δ 1.97 ppm became a sharp singlet.

4) Irradiation at δ 4.60 ppm caused the methyl doublet at δ 1.12 ppm to collapse to sharp singlet.

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7) K. Takeda, *Tetrahedron*, **30**, 1525 (1974) and references cited therein.

8) Usually, (*E*,*E*)-1,5-cyclodecadienes have been known to afford the corresponding Cope rearrangement products selectively *via* a chair-like transion state, but not *via* a boat-like one.[7] In the case of acoragermacrone which has an $\alpha\beta$-unsaturated carbonyl system, a boat-like transition state seems to be much stabilized by the conjugated carbonyl group, as seen from its molecular model.

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