Crude Drugs from Aquatic Plants. II.[1] On the Constituents of the Rhizome of *Alisma orientale* JUZEP. Originating from Japan, Taiwan, and China. Absolute Stereostructures of 11-Deoxyalisols B and B 23-Acetate

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Two new protostane-type triterpenes named 11-deoxyalisols B and B 23-acetate were isolated from the fresh rhizome of *Alisma orientale* JUZEP. originating from Japan, Taiwan, and China, together with known triterpenes and sesquiterpenes. The absolute stereostructures of 11-deoxyalisols B and B 23-acetate have been determined on the basis of chemical and physicochemical evidence. Sesquiterpene compositions in fresh rhizomes of *Alisma orientale* of the three different origins were examined and it was found that Japanese rhizome contained germacrene D as a major constituent, while fresh rhizomes from plants of Taiwanese and Chinese origin contained germacrene C and small amounts of alismol and alismoxide.

Keywords *Alisma orientale*; protostane-type triterpene; 11-deoxyalisol B; 11-deoxyalisol B 23-acetate; germacrene C; germacrene D

In search of biologically active constituents of crude drugs derived from aquatic plants, we have been investigating the constituents of various kinds of Alismatis Rhizoma (Takusha in Japanese), the dried rhizome of *Alisma orientale* JUZEPCZUK (Alismataceae).[2] From Chinese Alismatis Rhizoma from Szechwan Province (Japanese name: Sentaku, 川沢), we have so far isolated various then-new constituents, namely three protostane-type triterpenes, designated alisols E 23-acetate,[1] F[1] and G,[1] four sesquiterpenes, orientalols A,[3] B,[3] C[3] and D,[3b] and four water-soluble bioactive sesquiterpenes, sulfoorientalols a,[4] b,[4] c[4] and d,[4] together with five known protostane-type triterpenes, alisols A, A monoacetate, B (**1**), and B monoacetate (**2**), and 13,17-epoxyalisol A and two known sesquiterpenes, alismol and alismoxide, and described their structures, including revised structures of alismol (**7**)[3] and alismoxide (**8**).[3] The guaiane-type sesquiterpenes, orientalols, sulfoorientalols, alismol (**7**), and alismoxide (**8**), isolated from Chinese Alismatis Rhizoma showed no significant optical activity, so these sesquiterpenes were considered to have been formed during the processing of this crude drug. By means of HPLC, we have developed a quantitative analytical method for sesquiterpenes and triterpenes contained in various kinds of Alismatis Rhizoma.[5] Comparative analysis showed that the content of sesquiterpenes and triterpenes varied remarkably depending upon the habitat and the processing method. In order to characterize the variation of the constituents of Alismatis Rhizoma, we have analyzed the constituents of fresh rhizomes of various *Alisma orientale*. During these studies, two new protostane-type triterpenes named 11-deoxyalisols B (**3**) and B 23-acetate (**4**) were isolated

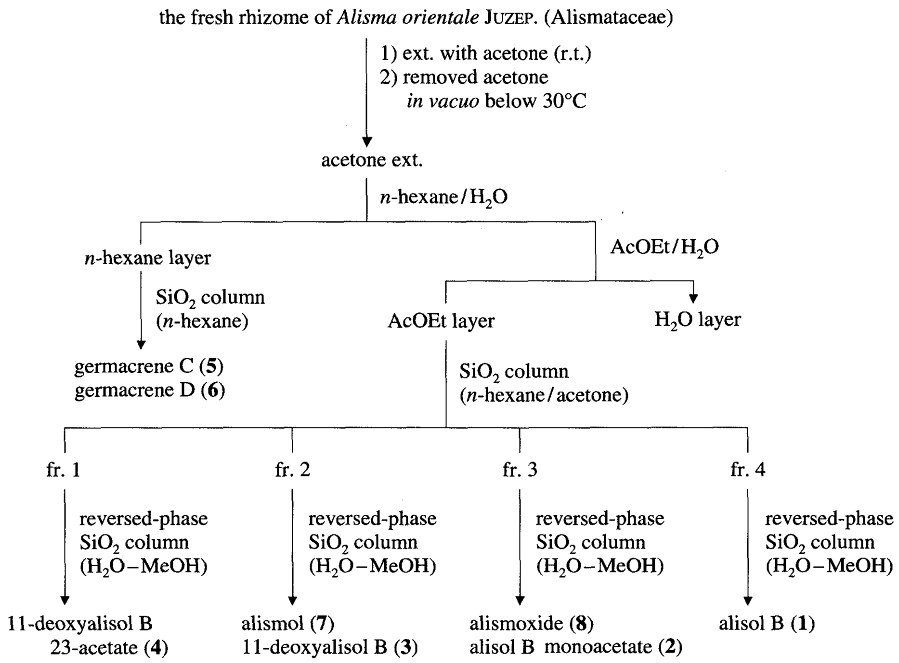
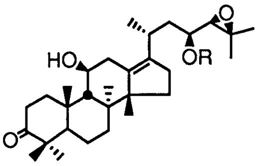
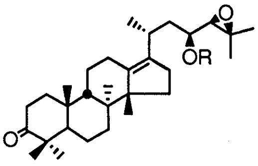


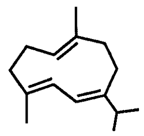
Fig. 1. Isolation Procedure for Sesquiterpenes and Triterpenes from the Fresh Rhizome of *Alisma orientale* JUZEP.



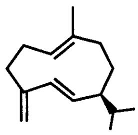
alisol B (**1**) : R=H
alisol B monoacetate (**2**) : R=Ac



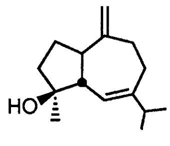
11-deoxyalisol B (**3**) : R=H
11-deoxyalisol B 23-acetate (**4**) : R=Ac



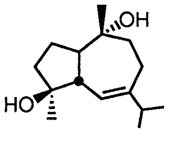
germacrene C (**5**)



germacrene D (**6**)



alismol (**7**)



alismoxide (**8**)

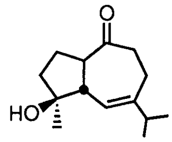


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Chart 1

TABLE I. Sesquiterpene and Triterpene Compositions of Fresh Rhizome of *Alisma orientale*

Sesquiterpene and triterpene	Fresh rhizome of *Alisma orientale* originating from		
	China	Taiwan	Japan
Alisol B (**1**)	0.08%	0.11%	0.09%
Alisol B monoacetate (**2**)	0.04%	0.06%	0.06%
11-Deoxyalisol B (**3**)	0.08%	0.04%	0.08%
11-Deoxyalisol B 23-acetate (**4**)	0.01%	0.004%	0.01%
Germacrene C (**5**)	0.03%	0.08%	0.006%[a]
Germacrene D (**6**)	N.D.	N.D.	0.06%[a]
Alismol (**7**)	0.003%	0.005%	Trace
Alismoxide (**8**)	0.003%	0.004%	Trace

a) The composition of **5** and **6** was determined by ^{1}H-NMR analysis.[13]

TABLE II. ^{13}C-NMR Data for Alisols B (**1**), B Monoacetate (**2**) and 11-Deoxyalisols B (**3**) and B 23-Acetate (**4**)

	1	2	3	4		1	2	3	4
1	30.9	31.0	31.7	31.7	16	29.0	29.2	28.8	28.7
2	33.7	33.7	33.7	33.7	17	134.8	134.2	133.7	132.7
3	220.3	220.3	220.1	220.2	18	23.3	23.2	23.6	23.4
4	46.9	47.0	46.9	47.0	19	25.5	25.7	22.8	22.8
5	48.5	48.5	48.1	48.1	20	27.6	27.9	27.7	27.7
6	20.0	20.0	20.0	20.0	21	20.2	20.1	20.2	20.1
7	34.3	34.2	34.0	33.9	22	38.7	37.0	38.9	36.8
8	40.5	40.8	40.6	40.6	23	69.1	71.5	69.2	71.6
9	49.5	50.1	43.9	43.8	24	67.9	65.1	67.8	65.1
10	36.9	36.8	36.2	36.2	25	59.2	58.5	59.0	58.3
11	69.8	70.3	22.5[a]	22.6[a]	26	19.1	19.4	19.1	19.3
12	34.4	34.6	22.8[a]	22.7[a]	27	24.9	24.7	24.9	24.7
13	138.1	138.1	140.3	140.7	28	29.5	29.6	29.2	29.2
14	56.9	57.1	57.3	57.3	29	20.0	20.1	19.6	19.7
15	30.6	30.7	31.1	31.1	30	23.9	23.9	23.6	23.5

a) Assignments may be interchangeable.

from fresh rhizomes of *Alisma orientale* originating from Japan, Taiwan and China. In this paper, we present a comparative analysis of the constituents of fresh rhizomes of *Alisma orientale* of these three origins and we describe the structure elucidation of 11-deoxyalisols B (**3**) and B 23-acetate (**4**).[6]

The chemical constituents in fresh rhizomes of *Alisma orientale* originating from Japan, Taiwan, and China were respectively separated through the procedure shown in Fig. 1. Thus, the rhizome was extracted with acetone at room temperature and the extract was partitioned into an *n*-hexane–water mixture. The water-soluble portion was further extracted with ethyl acetate. Silica gel column chromatography of the *n*-hexane-soluble portion furnished germacrene C (**5**) and/or germacrene D (**6**). The ethyl acetate-soluble portion was subjected to silica gel column chromatography and then reversed-phase silica gel column chromatography to give alisols B (**1**) and B monoacetate (**2**), 11-deoxyalisols B (**3**) and B 23-acetate (**4**), alismol (**7**) and alismoxide (**8**).

The compositions of sesquiterpenes and triterpenes from fresh rhizomes of these three origins are summarized in Table I. In regard to sesquiterpene constituents, it is noteworthy that the fresh rhizome of Japanese *Alisma orientale* contained germacrene D (**6**) as a major sesquiterpene constituent together with a small amount of germacrene C (**5**), whereas **6** was not detected in the fresh rhizomes of Taiwanese and Chinese *Alisma orientale*. On the other hand, the fresh rhizomes of Taiwanese and Chinese *Alisma orientale* were found to contain **5** as the major sesquiterpene constituent together with small amounts of alismol (**7**) and alismoxide (**8**).

It has been reported that germacrene C (**5**) is fairly unstable in air, and is readily converted to **7** and **8**.[7] Therefore, most of **7** and **8**, which were isolated from Alismatis Rhizoma, were considered to be secondary products formed during processing. Taking this evidence into consideration, we isolated the three sesquiterpenes (**5**, **7**, **8**) as quickly and mildly as possible from fresh rhizomes of Taiwanese and Chinese *Alisma orientale*. It was found that the extracts of the fresh rhizomes contained **7** and **8**, and that **7**, obtained in this way, showed an optical activity of $[\alpha]_D^{20}$ $+2.4°$ ($CHCl_3$). Furthermore, the ketone (**9**), which was prepared from **7** by oxidation with osmium tetroxide (OsO_4) in the presence of sodium periodate ($NaIO_4$), was found to show a negative Cotton effect ($\theta = -125$) at 282 nm in the CD spectrum. It is therefore likely that at least a part

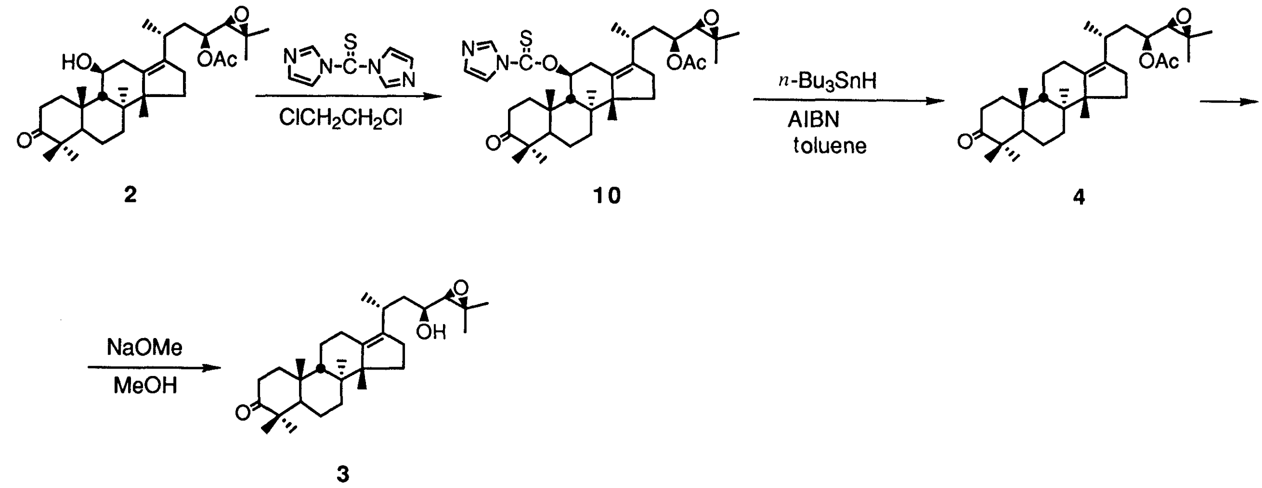

Chart 2

of **7** is biosynthesized in the rhizome, and the absolute stereostructure of genuine alismol (**7**) is presumed to be as shown.

Then, we investigated the triterpene constituents in the fresh rhizomes of *Alisma orientale* of the three origins. Two new protostane-type triterpenes named 11-deoxyalisols B (**3**) and B 23-acetate (**4**) were isolated from all of the fresh rhizomes, together with alisols B (**1**) and B monoacetate (**2**). But, several triterpenes such as alisols A, A monoacetate, E 23-acetate, and G, 13,17-epoxyalisol A which were reported to be present in various Alismatis Rhizoma as major constituents, were hardly detected in the fresh rhizomes.[8)]

11-Deoxyalisol B (**3**)[9)] was obtained as a white powder. The molecular formula $C_{30}H_{48}O_3$ has been determined from the quasimolecular ion $(M+Na)^+$ peak at *m/z* 479 observed in the positive FAB-MS and by high-resolution MS measurement. The IR spectrum of **3** suggested the presence of hydroxyl and ketone groups in its structure (3450, 1705 cm^{-1}). The proton NMR (^{1}H-NMR) spectrum of **3** showed signals due to five tertiary methyls, two tertiary methyls geminal to an oxygen function, and a secondary methyl, together with many other signals closely resembling those of alisol B (**1**), except for the signals due to the 11-hydroxy group in **1**. Detailed comparison of the carbon-13 NMR (^{13}C-NMR) data for **3** with those for **1** led us to presume that **3** is the 11-dehydroxyl derivative of **1**.

11-Deoxyalisol B 23-acetate (**4**)[9)] was obtained as a colorless oil and its molecular formula $C_{32}H_{50}O_4$, was clarified from the quasimolecular ion peak at *m/z* 521 observed in the positive FAB-MS and by high-resolution MS measurement. The IR spectrum of **4** showed the presence of ester and ketone absorptions at 1745 and 1705 cm^{-1}. The ^{1}H-NMR spectrum of **4** showed signals due to an acetyl group at δ 2.06 (3H, s) and an acetoxyl-bearing methine proton at δ 4.60 (ddd, $J=3$, 9, 11 Hz, 23-H), together with the signals of five tertiary methyls, two tertiary methyls geminal to an oxygen function, and a secondary methyl. In the ^{13}C-NMR spectrum of **4**, an acetylation shift[10)] around the C-23 position was observed (Table II) and consequently **4** was concluded to be the 23-acetyl derivative of **3**.

To verify these structures of **3** and **4**, a chemical conversion of alisol B monoacetate (**2**), of which absolute stereostructure has been determined on the basis of chemical evidence,[11)] to **3** and **4** was undertaken. Thus, treatment of **2** with *N*,*N*-thiocarbonyldiimidazole furnished **10**, which was subjected to reductive elimination reaction[12)] with tri-*n*-butyltinhydride (*n*-Bu_3SnH) in the presence of 2,2′-azobisisobutyronitrile (AIBN) to give **4**. Alkaline hydrolysis of **4** with sodium methoxide provided **3**. Based on above mentioned evidence, the absolute stereostructures of 11-deoxyalisols B (**3**) and B 23-acetate (**4**) were determined to be as shown.

Experimental

The instruments used for obtaining physical data and the conditions for chromatography were the same as described in our previous paper.[1)]

Isolation of Sesquiterpenes and Triterpenes from Fresh Rhizome of Japanese *Alisma orientale* The fresh rhizome of Japanese *Alisma orientale* (1.6 kg, cultivated at the Medicinal Plant Garden of Kyoto Pharmaceutical University) was cut finely and then extracted with acetone three times, with occasional stirring at room temperature (below 30 °C). After removal of the solvent from the acetone solution under reduced pressure at below 30 °C, the syrupy extract was partitioned into an *n*-hexane–water mixture and the water-soluble portion was further extracted with AcOEt. Removal of the solvent from the *n*-hexane-soluble portion and the AcOEt-soluble portion under reduced pressure below 30°C gave the *n*-hexane extract (7.0 g) and the AcOEt extract (8.0 g), respectively. Silica gel column chromatography (*n*-hexane) of the *n*-hexane extract furnished a mixture of germacrenes C (**5**) and D (**6**) (**5**:**6** = 19:81,[13)] 505 mg), and **6** {540 mg, $[\alpha]_D$ −235° (c=1.4, $CHCl_3$)}. The AcOEt extract was subjected to silica gel column chromatography [*n*-hexane–acetone (7:1—4:1)] to give fraction 1 (222 mg), fraction 2 (1.62 g), fraction 3 (1.75 g), fraction 4 (2.18 g) and fraction 5 (1.41 g, later eluates). Fraction 1 was further purified by reversed-phase silica gel column chromatography [water–MeOH (3:7)] to give 11-deoxyalisol B 23-acetate (**4**, 160 mg). Fraction 2 was also purified by reversed-phase silica gel column chromatography [water–MeOH (1:3)] to give 11-deoxyalisol B (**3**, 1.28 g). Reversed-phase silica gel column chromatography [water–MeOH (1:1)] of fraction 3 afforded alisol B monoacetate (**2**, 960 mg). Fraction 4 was subjected to reversed-phase silica gel column chromatography [water–MeOH (2:3)] to provide alisol B (**1**, 1.44 g). Sesquiterpenes and triterpenes were identified by TLC and ^{1}H-NMR ($CDCl_3$) spectral comparisons with authentic samples.[1,7,14)]

11-Deoxyalisol B (**3**): An amorphous powder, $[\alpha]_D^{22}$ +104.9° (c=1.0, MeOH). High-resolution FAB-MS: Calcd for $C_{30}H_{48}O_3Na$ $(M+Na)^+$, 479.3501. Found, 479.3481. IR (KBr): 3450, 1705, 1460, 1375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 1.01, 1.02, 1.06, 1.10, 1.26, 1.31 (3H, each, all s, 30, 19, 29, 28, 18, 26, 27-H_3). 1.04 (3H, d, J=7 Hz, 21-H_3), 2.70 (1H, d, J=8 Hz, 24-H), 3.23 (1H, ddd, J=3, 8, 10 Hz, 23-H). ^{13}C-NMR ($CDCl_3$) δ_C: see Table I. Positive FAB-MS (*m/z*): 479 $(M+Na)^+$.

11-Deoxyalisol B 23-Acetate (**4**): A colorless oil, $[\alpha]_D^{22}$ +97.2° (c=0.9, MeOH). High-resolution FAB-MS: Calcd for $C_{32}H_{50}O_4Na$ $(M+Na)^+$, 521.3607. Found, 521.3623. IR (KBr): 1745, 1705, 1455, 1375, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80, 0.99, 1.04, 1.06, 1.10, 1.31, 1.33 (3H each, all s, 30, 19, 29, 28, 18, 26, 27-H_3), 1.02 (3H, d, $J=7$ Hz, 21-H_3), 2.06 (3H, s, OAc), 2.73 (1H, d, $J=9$ Hz, 24-H), 4.60 (1H, ddd, $J=3$, 9, 11 Hz, 23-H). ^{13}C-NMR ($CDCl_3$) δ_C: 21.2, 167.0 and the others as given in Table I. Positive FAB-MS (m/z): 521 $(M+Na)^+$.

Isolation of Sesquiterpenes and Triterpenes from Fresh Rhizome of Taiwanese *Alisma orientale* The fresh rhizome of Taiwanese *Alisma orientale* (2.1 kg, cultivated at the Medicinal Plant Garden of Kyoto Pharmaceutical University) was cut finely and then extracted with acetone three times in the same manner as above. The syrupy extract, obtained after removal of the solvent under reduced pressure below 30 °C, was partitioned into *n*-hexane–water (1 : 1) mixture to give the *n*-hexane-soluble portion (5.1 g). The water-soluble portion was further extracted with AcOEt to afford the AcOEt-soluble portion (7.5 g). Silica gel column chromatography (*n*-hexane) of the *n*-hexane-soluble portion furnished germacrene C (**5**, 1.60 g). The AcOEt-soluble portion was subjected to silica gel column chromatography (*n*-hexane–acetone) and then reversed-phase silica gel column chromatography (water–MeOH) in the same manner as above to furnish 11-deoxyalisol B 23-acetate (**4**, 85 mg), 11-deoxyalisol B (**3**, 840 mg), alismol {**7**, 105 mg, $[\alpha]_D$ +2.4° ($c=0.2$, $CHCl_3$)}, alisol B monoacetate (**2**, 1.26 g), alismoxide (**8**, 83 mg) and alisol B (**1**, 2.31 g). These compounds were identical with authentic samples on the basis of TLC and ^{1}H-NMR data comparisons.

Isolation of Sesquiterpenes and Triterpenes from Fresh Rhizome of Chinese *Alisma orientale* The fresh rhizome of Chinese *Alisma orientale* (228 g, cultivated at Kyoto Herbal Garden, Takeda Chemical Industries, Ltd.) was cut finely and then extracted with acetone three times in the same manner as above. The acetone extract, obtained after removal of the solvent under reduced pressure at below 30 °C, was partitioned into *n*-hexane–water (1 : 1) mixture to give the *n*-hexane-soluble portion (0.9 g). The water-soluble portion was extracted with AcOEt to afford the AcOEt-soluble portion (1.1 g). Silica gel column chromatography (*n*-hexane) of the *n*-hexane-soluble portion furnished germacrene C (**5**, 75 mg). The AcOEt-soluble portion was subjected to silica gel column chromatography (*n*-hexane–acetone) and then reversed-phase silica gel column chromatography (water–MeOH) to give 11-deoxyalisol B 23-acetone (**4**, 23 mg), 11-deoxyalisol B (**3**, 178 mg), alismol (**7**, 6 mg), alisol B monoacetate (**2**, 91 mg), alismoxide (**8**, 7 mg), and alisol B (**1**, 190 mg). These compounds were identical with authentic samples on the basis of TLC and ^{1}H-NMR data comparisons.

Oxidation of 7 Leading to the Ketone 9 A solution of **7** (30 mg, obtained from the fresh rhizome of Taiwanese *Alisma orientale*) in CH_3CN–water (2 : 1, 3 ml) was treated with $NaIO_4$ (50 mg) and OsO_4 (1 mg) and the whole mixture was stirred at 20 °C for 30 h. The reaction mixture was treated with aqueous saturated Na_2SO_3 and the whole mixture was further stirred at 20 °C for 5 min, then extracted with AcOEt. The AcOEt extract was washed successively with 1% aqueous HCl and brine, and dried over $MgSO_4$. After removal of the solvent from the AcOEt extract under reduced pressure, the product was purified by silica gel column chromatography [benzene–acetone (50 : 1)] to give **9** (20 mg).

9: A colorless oil, $[\alpha]_D^{20}$ −2.0° ($c=0.4$, MeOH). High-resolution FAB-MS: Calcd for $C_{14}H_{21}O$ $(M+H-H_2O)^+$; 205.1593. Found; 205.1561. EI-MS (m/z): 222 (M^+, 4), 204 (M^+-H_2O, 7), 146 (100). Positive FAB-MS (m/z): 245 $(M+Na)^+$, 205 $(M+H-H_2O)^+$. CD ($c=0.25$, MeOH): $[\theta]_{282nm}$ −125 (neg. max.). IR (KBr): 3450, 1700, 1465 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, $J=7$ Hz, 12, 13-H_3), 1.22 (3H, s, 15-H_3), 2.12 (1H, m, 8-H), 2.32—2.54 (4H, m, 5, 8, 9, 11-H), 2.63 (1H, m, 9-H), 2.88 (1H, ddd, $J=7$, 10, 12 Hz, 1-H), 5.65 (1H, d, $J=2$ Hz, 6-H). ^{13}C-NMR (68 MHz. CD_3OD) δ_C: 53.1 (1-C), 19.1 (2-C), 39.4 (3-C), 80.5 (4-C), 51.9 (5-C), 120.6 (6-C), 148.6 (7-C), 25.7 (8-C), 42.2 (9-C), 211.9 (10-C), 37.4 (11-C), 21.2, 21.5 (12, 13-C), 22.1 (15-C).

Conversion of Alisol B Monoacetate (2) to 10 A solution of **2** (50 mg) in $ClCH_2CH_2Cl$ (0.5 ml) was treated with *N,N'*-thiocarbonyldiimidazole (30 mg) and the whole mixture was heated under reflux for 4 h. After removal of the solvent from the reaction mixture, the residue was purified by silica gel column chromatography [*n*-hexane–acetone (4 : 1)] to give **10** (30 mg). **10**: A yellow oil, $[\alpha]_D^{25}$ +120.5° ($c=0.4$, $CHCl_3$). IR (film): 1740, 1705, 1465, 1385, 1320, 1285, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.04, 1.08, 1.10, 1.23, 1.30, 1.33 (3H each, all s, *tert*-$CH_3\times 7$), 1.06 (3H, d, $J=7$ Hz, 21-H_3), 2.17 (3H, s, OAc), 2.71 (1H, d, $J=9$ Hz, 24-H), 4.58 (1H, m, 23-H), 5.70 (1H, ddd, $J=6$, 11, 11 Hz, 11-H), 7.06, 7.62, 8.37 (1H each, all s, thioimidazoyl part).

Conversion of 10 to 11-Deoxyalisol B 23-Acetate (4) A solution of **10** (10 mg) in toluene (0.6 ml) was treated with *n*-Bu_3SnH (29.1 μl) and AIBN (3 mg), and the whole mixture was heated under reflux for 5 min. Removal of the solvent from the reaction mixture furnished a residue, which was purified by silica gel column chromatography [*n*-hexane–acetone (4 : 1)] to give **4** (8.2 mg), which was identical with authentic 11-deoxyalisol B 23-acetate obtained from the fresh rhizome of Japanese *Alisma orientale*, by TLC, $[\alpha]_D$ and ^{1}H-NMR spectral comparisons.

Alkaline Hydrolysis of 11-Deoxyalisol B 23-Acetate (4) to 11-Deoxyalisol B (3) A solution of **4** (8 mg) in 1% NaOMe–MeOH (1.0 ml) was stirred at room temperature for 10 min and the whole mixture was neutralized with Amberlite IRA-400. After removal of the resin by filtration, the filtrate was worked up in the usual manner to give **3** (7 mg), which was identical with authentic 11-deoxyalisol B isolated from the fresh rhizome of Japanese *Alisma orientale*, by TLC, $[\alpha]_D$ and ^{1}H-NMR spectral comparisons.

References and Notes

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