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On the Constituents of *Linaria japonica* Miq. III.[1] The Structure of Linarienone, a New *cis*-Clerodane-type Diterpene

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A new diterpene named linarienone (**2**) was isolated from the ether-soluble portion of the fresh subterranean part of *Linaria japonica* Miq. (Scrophulariaceae). Linarienone (**2**) is a monoacetyl-monoangeloyl derivative of a 5β-methyl-*cis*-clerodane-type diterpene and the stereostructure including the absolute configuration has been established as **2** on the basis of the chemical and physicochemical evidence and the unequivocal conversion starting from linarienone (**2**) and linaridial (**1**) leading to a common 5β-methyl-*cis*-clerodane-type hydrocarbon (**18**).

Keywords——*Linaria japonica* Miq.; Scrophulariaceae; linarienone; linaridial; *cis*-clerodane-type diterpene; Horeau's method; CD; ORD; PMR; mass

In the initial study on the constituents of *Linaria japonica* Miq. (unran in Japanese, Scrophulariaceae), we isolated linarioside from the water-soluble portion of epigeous and subterranean parts of the plant and elucidated it to be the first naturally occurring chlorine-containing iridoid glucoside.[3] In a continuing study on the ether-soluble portion of the fresh subterranean part, we next elucidated the structure of a major diterpene of *cis*-clerodane-type named linaridial (**1**).[1] Further investigation on the ether-soluble portion has recently led to the isolation of a minor new diterpene designated as linarienone (**2**). This paper deals with the full account on the structure elucidation.[4]

Repeated silica gel chromatography of the ether extractive afforded oily linarienone (**2**), $C_{27}H_{40}O_5$,[5] in a 1% yield from the extractive. Linarienone (**2**) is a diacylated diterpene. It contains an acetoxyl function, an angelate group, and a β,β-disubstituted α,β-unsaturated six-membered ring ketone in its molecule as shown by its ultraviolet (UV), infrared (IR), and proton magnetic resonance (PMR) spectra. In the mass spectrum (MS), a series of fragment ions derived through eliminations of acetoxyl and angeloyloxyl groups are observed.

On mild alkaline treatment, linarienone (**2**) was converted to desacetyl-linarienone (**3**), $C_{25}H_{38}O_4$, while under more forced conditions, **2** was hydrolysed to afford the parent diterpene desdiacyl-linarienone (**4**), $C_{20}H_{30}O_2$, and angelic acid (identified as the methyl ester). Desacetyl-linarienone (**3**) lacks an acetyl group as compared with **2**, whereas both acetyl and angeloyl functions in **2** are lost in desdiacyl-linarienone (**4**).

The detailed PMR examinations including the double resonance experiments of **2**, **3**, and **4**, have disclosed that linarienone (**2**) possesses the partial structures i, ii, and iii as depicted in Chart 1. Some of the supporting PMR data of **2** or **3** (shown with *) are also given in Chart 1.[6] If a *cis*-clerodane-type carbon framework is presumed for linarienone (**2**) as in

1) Part II: *a*) I. Kitagawa, M. Yoshihara, T. Tani, and I. Yosioka, *Tetrahedron Lett.*, **1975**, 23; *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **24**, 294 (1976).
2) Location: *133–1, Yamada-kami, Suita, Osaka 565, Japan.*
3) *a*) I. Kitagawa, T. Tani, K. Akita, and I. Yosioka, *Tetrahedron Lett.*, **1972**, 419; *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **21**, 1978 (1973).
4) I. Kitagawa, M. Yoshihara, and T. Kamigauchi, *Tetrahedron Lett.*, **1977**, 1221 (preliminary report).
5) The elemental compositions of compounds and mass fragment ions given with the chemical formulae were confirmed by high resolution mass spectrometry.
6) Abbreviations for PMR signals and experiments: br.s=broad singlet, d=doublet, q=quartet, s=singlet, t=triplet, irr.=irradiation at. Chemical shifts and coupling constants (J values) in the parentheses are given in δ and Hz, respectively.

co-existing linaridial (**1**), the partial structures i, ii, and iii may be combined to iv and v, and the following evidence would provide further supports for iv.

In the mass spectra of **2**, **3**, and **4**, a prominent ion peak of $C_{14}H_{21}O$ (*m/e* 205)[5] is commonly observed. The PMR spectra of **2**, **3**, and **4** show, respectively, the signals due to two tertiary methyls and one each of olefinic methyl and secondary methyl. They also show

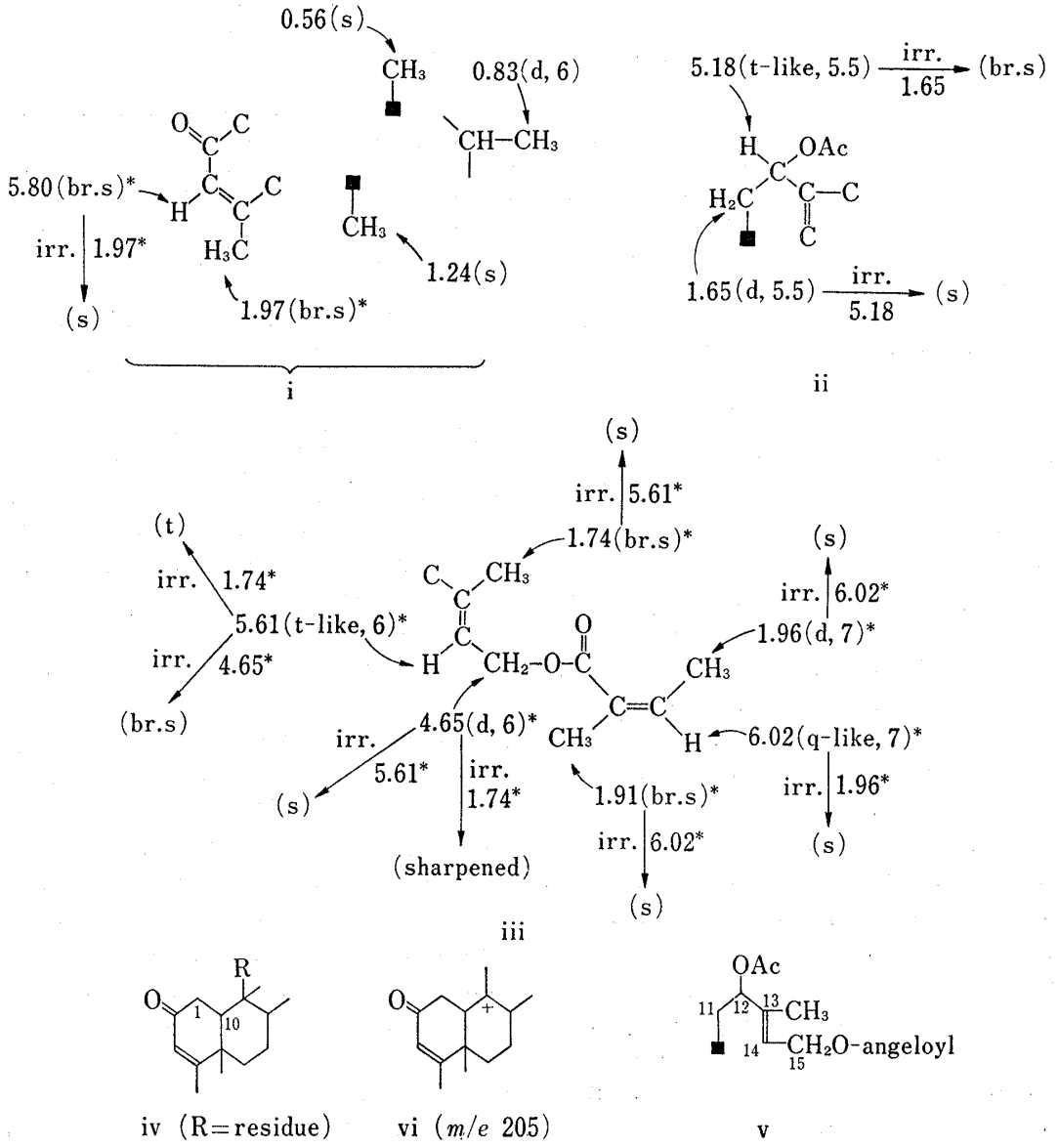


Chart 1. Partial Structures in Linarienone (**2**)[6]
(dark square (■): quaternary carbon)

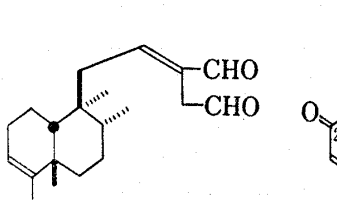
TABLE I. Comparison of Some PMR Data of **2**, **3**, and **4**[a]

	11-H_2	12-H	13-CH_3	14-H	15-H_2	$OCOCH_3$
2	1.65(d, 5.5)	5.18(t-like, 5.5)	1.74(br. s)	5.56(t-like, 6)	4.60(d, 6)	1.97
3	1.56(d, 5.5)	4.17(t-like, 5.5)	1.74(br. s)	5.61(t-like, 6)	4.65(d, 6)	—
4[b]	1.53(d, 6)	4.12[c]	1.69(br. s)	5.57(t-like, 6)	4.14(d, 6)	—

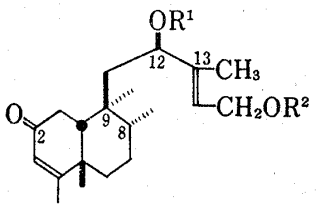
a) The assignments were confirmed by the double resonance experiments.
b) Only **4** lacks the signals due to an angelate group (see Experimental).
c) The signal pattern was unclear due to ovelapping with a doublet of 15-H_2.

the signals attributable to α-methylene protons of a carbonyl which are observed as an AB part signal in an ABX spin-system (*e.g.* in **2**, one proton each at δ 2.37 and δ 2.55 for 1-H_2). Therefore, the common mass fragment ion may be formulated as vi.

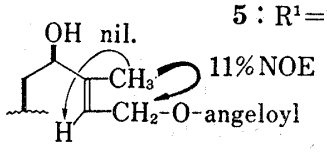
Based on the above-mentioned evidence and the consideration of the molecular composition, the structure **2** (stereochemistry undefined yet) has provisionally become consistent for linarienone and two derivatives, desacetyl-linarienone and desdiacyl-linarienone, would be expressed as **3** and **4**, respectively (without stereochemistry). The distinctive comparisons in the PMR data of **2**, **3**, and **4** are given in Table I.[6] These data figure out the mode of deacylation in **3** and **4** which has occurred in the side chain of **2**.



1 linaridial



2 : R^1=Ac, R^2=angeloyl: linarienone
3 : R^1=H, R^2=angeloyl: desacetyl-linarienone
4 : R^1=R^2=H: desdiacyl-linarienone
5 : R^1=α-phenylbutyryl, R^2=angeloyl



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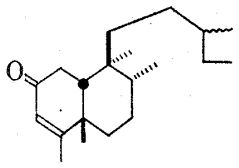
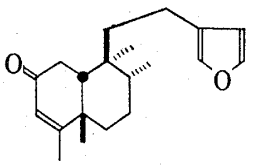
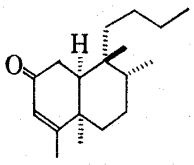


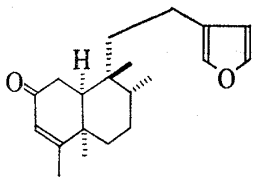
6 (a+64)[11]



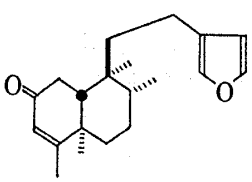
7 (a+65)[12]



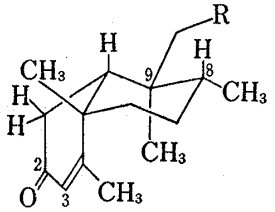
8 (a−33)[8]



9 (a−46)[9]



10 (a−58)[10]



vii

Chart 2

7) *a*)A. Horeau, *Tetrahedron Lett.*, **1961**, 506; *b*) *Idem, ibid.*, **1962**, 965.
8) T.J. King, S. Rodrigo, and S.C. Wallwork, *J. Chem. Soc. Chem. Comm.* **1969**, 683.
9) T. Anthonsen, M.S. Henderson, A. Martin, R.D.H. Murray, R. McCrindle, and D. McMaster, *Can. J. Chem.*, **51**, 1332 (1973).
10) M.S. Henderson, R. McCrindle and D. McMaster, *Can. J. Chem.*, **51**, 1346 (1973).
11) G. Berti, O. Livi, and D. Segnini, *Tetrahedron Lett.*, **1970**, 1401.
12) *a*) A.B. Anderson, R. McCrindle, and E. Nakamura, *J. Chem. Soc. Chem. Comm.*, **1974**, 453; *b*) R. McCrindle, E. Nakamura, and A.B. Anderson, *J. Chem. Soc. Perkin I*, **1976**, 1590.

In order to clarify the total stereostructure including the absolute configuration of linarienone (**2**), the following investigations have been undertaken. At first, the Horeau's method[7] has been applied for desacetyl-linarienone (**3**) to determine the absolute configuration at C-12. Treatment of **3** with (±)-α-phenylbutyric anhydride in pyridine at 32° afforded an oily α-phenylbutyrate (**5**) and recovered α-phenylbutyric acid. The specific rotations of α-phenyl-butyric acid recovered in two independent experiments showed +3.4° and +2.7° (in benzene), respectively, thus the absolute configuration at C-12 of **3** (consequently of **2**) being defined as R.

Secondly, the nuclear Overhauser effect (NOE) has been examined in the PMR spectrum of **3**. As illustrated in Chart 2, an 11% signal enhancement was observed for the 15-H_2 signal upon irradiation of the 13-CH_3 signal while no NOE was observed between 13-CH_3 and 14-H. Therefore, the geometry of Δ^{13} has been elucidated to be E.

Thirdly, the stereostructure of the decaline part in linarienone (**2**) has been examined by comparison of the optical rotatory dispersion (ORD) curves and circular dichroism (CD) spectra of **2**, **3**, and **4** with the ORD curves of five known clerodane-type diterpenes possessing a 3-en-2-one moiety. As shown in Chart 2, the 5α-methyl-*cis* derivatives (**8**,[8] **9**[9]) and the 5α-methyl-*trans* derivative (**10**)[10] give a negative Cotton effect curve, while the 5β-methyl-*cis* derivatives (**6**,[11] **7**[12]) give a positive curve. Among these, the molecular amplitudes of latter two compounds are very close to those of **2** (a +53), **3** (a +52), and **4** (a +67), thus the presence of a 5β-methyl-*cis*-clerodane structure having a 3-en-2-one moiety in linarienone (**2**) being suggested. At this stage of discussion, a 5β-methyl-*trans*-clerodane structure could not yet be excluded entirely. However, the 5β-methyl-*cis* structure for linarienone (**2**) has been further supported by the following resembled chemical shifts of methyl signals in the PMR spectra of **2** and **7**.[12b] As shown in Table II, the signals of 9-CH_3 in both compounds are observed at the shielded positions (probably due to a carbonyl at C-2) while the signals of 5-CH_3 of both appear similarly at the deshielded positions (in carbon tetrachloride (CCl_4)). Furthermore, it is noted that methyl chemical shifts in both compounds (especially the signals of 4-CH_3 and 5-CH_3) show the similar solvent-induced shifts (CCl_4→hexadeutero(d_6-)benzene). Since a steroid-like conformation (vii) in **7** has been already demonstrated by McCrindle, *et al.* on the basis of PMR studies of **7**[12b] and the X-ray analysis of a related lactonic compound,[13] a similar conformation of the decaline part in linarienone (**2**) has been presumed. It has thus been inferred that the stereostructure of linarienone is formulated as **2** except the configuration at C-8.

Table II. Comparison of Some PMR Data of **2** and **7** taken in Two Different Solvents

Compound	Solvent			
	CCl_4		d_6-Benzene	
	2	**7**[12b]	**2**	**7**[12b]
4-CH_3	1.97(br. s)	2.00(d, J=1.5)	1.5—1.7[a]	1.52(d, J=1.5)
5-CH_3	1.24(s)	1.32(s)	0.94(s)	0.92(s)
8-CH_3	0.83(d, J=6)	0.92(d, J=6)	0.77(d, J=6)	0.65(d, J=6)
9-CH_3	0.56(s)	0.68(s)	0.54(s)	0.56(s)

a) Unclear due to overlapping with the other signals.

13) G. Ferguson, W.C. Marsh, R. McCrindle, and E. Nakamura, *J. Chem. Soc. Chem. Comm.*, **1975**, 299.

Finally, the structure **2** has been established for linarienone by means of the following conversion starting from linarienone (**2**) and linaridial (**1**) leading to a common *cis*-clerodane-type hydrocarbon (**18**).

At the beginning, the direct isomerization of LJ-ester-aldehyde (**11**),[1] a derivative of linaridial (**1**), to a Δ^{13}-derivative was attempted under various acidic or alkaline conditions without success. Therefore, the following conversion was undertaken. Treatment of **11** with *p*-toluenesulfonylhydrazine in dry ethanol by heating yielded a tosylhydrazone (**12**). The IR and PMR spectra of 12 clearly demonstrate the correctness of the structure. On reduction of **12** with sodium cyanoborohydride in a dimethylformamide (DMF)–sulfolane (1:1) mixture under acidic conditions,[14] an unsaturated ester (**13**) was obtained. The presence of a terminal methylene moiety in **13** is shown by its IR (3080 (w), 901 cm^{-1}) and PMR (one proton each at δ 4.80 and δ 4.84, both broad singlet) spectra. Since a two-proton singlet due to allylic 14-H_2 is observed at δ 2.96, **13** has been proved to be an unconjugated methyl ester (IR: 1750 cm^{-1}; PMR: a three-proton singlet at δ 3.62). Isomerization of **13** giving a mixture of two conjugated methyl esters (**14** and **15** in a ratio of 4:1) was readily effected by treatment of **13** with 0.5 N methanolic sodium methoxide at room temperature. The IR spectra of **14** and **15**, respectively, show an absorption band due to a conjugated ester carbonyl (1727 and 1725 cm^{-1}). The PMR spectra of both distinguish the major (**14**) from the minor (**15**). A three-proton doublet (J=2 Hz) due to 13-CH_3 in **14** is observed at the deshielded

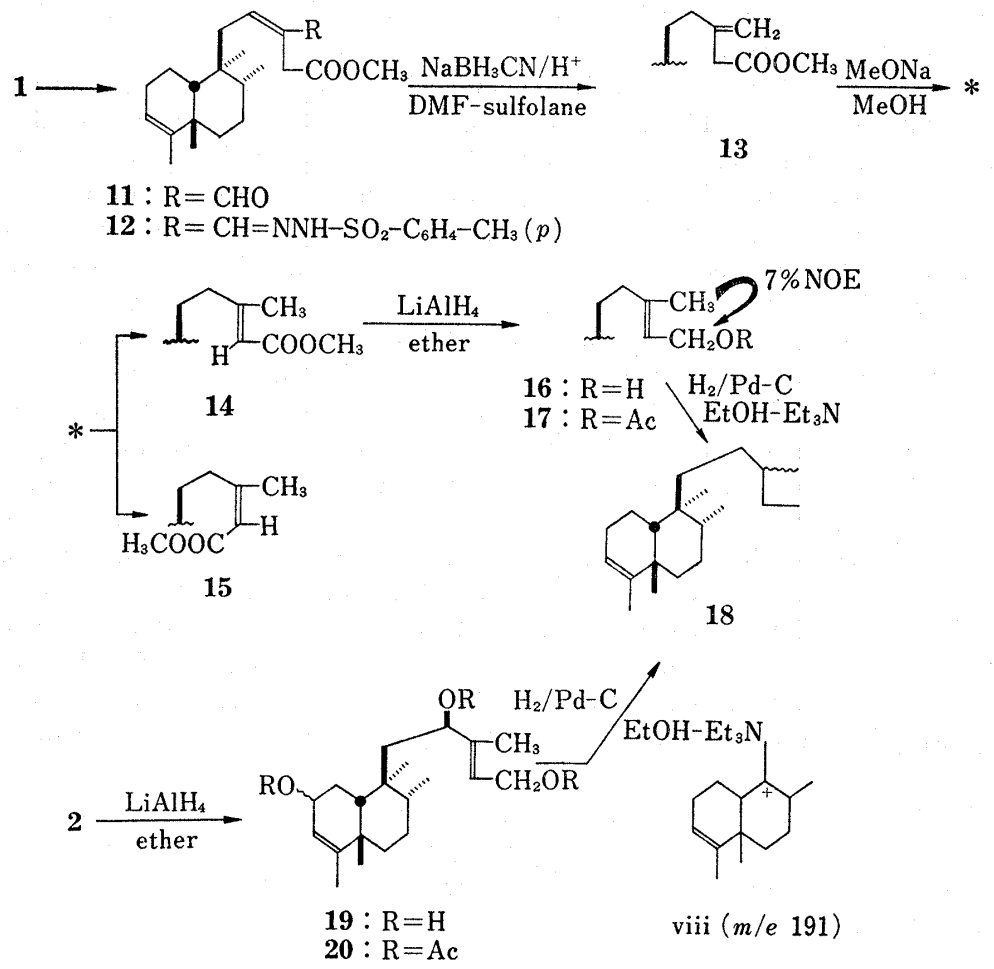


Chart 3

14) R.O. Hutchins, C.A. Milewski, and B.E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).

position (δ 2.14) while that (d, J=1.5 Hz) in **15** is found at δ 1.88, thus the major being assigned as the E-isomer and the minor as the Z-isomer. The long-range coupling between 13-CH_3 and 14-H in **14** and **15** was shown by the double resonance experiments and is responsible for the coupling pattern of the 13-CH_3 signal. The E geometry in **14** has been further supported by the NOE examinations of **16** as described below.

Lithium aluminum hydride ($LiAlH_4$) reduction of **14** under ice-cooled conditions furnished an allylic alcohol (**16**). The PMR spectrum of **16** shows a six-proton broad singlet at δ 1.67 which is assignable to two olefinic methyls at C-4 and C-13. In addition, it shows a one-proton triplet-like signal at δ 5.33 (J=7 Hz) due to 14-H and a two-proton doublet at δ 4.03 (J=7 Hz) attributable to 15-H_2.[15] The geometry of Δ^{13} in **16** has been substantiated by the NOE examinations between 13-CH_3 and 15-H_2 (a 7% enhancement of the 15-H_2 signal intensity upon irradiation of the 13-CH_3 signal). Acetylation of **16** through an ordinary procedure furnished a monoacetate (**17**) which was subsequently subjected to catalytic hydrogenation over 5% palladium–charcoal in an ethanol-triethylamine mixture. Hydrogenation accompanied by concomitant hydrogenolysis converted **17** to afford a desired hydrocarbon (**18**) having a 5β-methyl-*cis*-clerodane skeleton. The hydrocarbon is an unstable oil and is presumed to be a 1:1 mixture in regard to the C-13 configuration. The IR spectrum of **18** shows absorption bands at 2965, 2930, 2875, and 2855 cm^{-1} which are ascribable to methyls and methylenes. In the PMR spectrum of **18**, are observed the signals due to 3-H (m, δ 5.22), 4-CH_3 (br.s, δ 1.64), 5-CH_3 (s, δ 1.00), 8-CH_3 (d, J=6 Hz, δ 0.73), and 9-CH_3 (s, δ 0.76), together with a six-proton multiplet at δ 0.8—1.0 which is ascribable to 13-CH_3 and 14-CH_3. These physical properties along with a base peak at m/e 191 (viii)[1,16] in the mass spectrum of **18** corroborate the structure.

On the other hand, conversion of linarienone (**2**) leading to the hydrocarbon (**18**) has been accomplished as below. Thus, treatment of **2** with $LiAlH_4$ under ice-cooled conditions afforded a triol (**19**). The IR spectrum of **19** shows the hydroxyl absorption bands but it lacks the carbonyl absorption band. In the PMR spectrum of **19**, is observed at δ 2.91 a three-proton broad signal due to three hydroxyls, which disappears on addition of deuterium oxide. In addition, the signals due to 2-H, 12-H, and 15-H_2, which attach respectively to the carbons bearing a hydroxyl, are also observed.[15] Since the signal due to 3-H is observed at δ 5.28 as a broader signal than that in **2** ($W_{h/2}$: 3 Hz in **2**, 6 Hz in **19**), the carbonyl at C-2 in **2** has been found to be reduced to a secondary alcohol in **19**. Although the configuration of 2-OH in **19** is presumed to be α on the basis of the reaction mechanism for $LiAlH_4$ reduction, it has not yet been confirmed. Furthermore, in the PMR spectrum of **19** as compared with that of **2**, it is noted that, due to reduction of the carbonyl at C-2 in **2**, the signal of 9-CH_3 (δ 0.65) is shifted to a lower position while the signal of 5-CH_3 (δ 1.00) is observed at a higher position. Acetylation of **19** with acetic anhydride and pyridine gave a triacetate (**20**) (IR: no hydroxyl; PMR: three acetoxyls). The PMR spectrum of **20** shows the reasonable acetylation induced shifts of the signals due to 2-H, 12-H, and 15-H_2.[15] Hydrogenation accompanied by hydrogenolysis of **20** under the same reaction conditions as for **17** furnished a hydrocarbon which was found to be identical to **18** prepared above from linaridial (**1**) by thin-layer and gas-liquid chromatography (TLC, GLC), IR and PMR spectra, specific rotations, and mass spectrometry.

Consequently, the structure of linarienone has been established as **2**. Linarienone (**2**) seems to be the second example of *cis*-clerodane-type diterpene which has been isolated from the scrophulariaceous plant. The first example was linaridial (**1**) isolated by us previously from the same plant source.[1]

15) The assignments were confirmed by the double resonance experiments.
16) The same fragment ion of $C_{14}H_{23}$ (viii)[5] is also observed as a prominent ion (relative intensity to the base peak: 48—80%) in the mass spectra of **13**, **14**, **16**, and **17**.

Experimental[17]

Isolation of Linarienone (2)——Fresh subterranean part of *Linaria japonica* (cut, 6.9 kg, collected at Iwase in Toyama prefecture in the beginning of September) was extracted with ether (24 l) at room temperature four times for 2 days each. Evaporation of the solvent gave the ether extractive (180 g). The extractive (4 g) was mixed with silica gel (10 g) and purified by dry-column chromatography (silica gel 400 g) developing with *n*-hexane–AcOEt (9: 1) mixture for 12 hr in the ascending manner. Elution of four fractions (taken from bottom to top) with AcOEt (500 ml) gave Fr. 1 (2.1 g), Fr. 2 (710 mg), Fr. 3 (420 mg), and Fr. 4 (370 mg). Purification of Fr. 3 by preparative TLC (HF_{254}, *n*-hexane–AcOEt=9: 1) gave linaridial (**1**) (375 mg, 9% from the ether extractive).[1] Fr. 2 (3.5 g), which was obtained by repeated dry-column chromatography of the ether extractive (20 g), was further purified by column chromatography (silica gel 180 g, *n*-hexane–AcOEt=7: 1) to furnish crude linarienone (230 mg). Purification by preparative TLC (HF_{254}, *n*-hexane–AcOEt=6: 1) gave the analytical sample of linarienone (**2**) (190 mg, *ca.* 1% from the ether extractive) as colorless oil, $[\alpha]_D^{22}$ +30° (*c*=0.71, $CHCl_3$). High Resolution Mass Spectrum (High Mass) *m/e*: Calcd. for $C_{27}H_{40}O_5$ 444.288; Found: 444.288. UV λ_{max}^{EtOH} nm (*ε*): 219 (13000), 245 (11000) (conjugated ester, enone). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1737 (acetate), 1718, 1666, 1625 (sh) (angelate, enone), 1432, 1372. PMR (CCl_4, *δ*): 0.56 (3H, s, 9-CH_3), 0.83 (3H, d, *J*=6, 8-CH_3), 1.24 (3H, s, 5-CH_3), 1.65 (2H, d, *J*=5.5, 11-H_2), 1.74 (3H, br.s, $W_{h/2}$=3, 13-CH_3), 1.91 (3H, br.s), 1.96 (3H, d, *J*=7) (olefinic CH_3 in angelate), 1.97 (6H, br.s, 4-CH_3 and $OCOCH_3$), 2.37, 2.55 (1H each, AB in ABX, J_{AB}=18, 1-H_2), 4.60 (2H, d, *J*=6, 15-H_2), 5.18 (1H, t-like, *J*=5.5, 12-H), 5.56 (1H, t-like, *J*=6, 14-H), 5.70 (1H, br.s, $W_{h/2}$=3, 3-H), 5.96 (1H, q-like, *J*=7, olefinic H in angelate). PMR (d_6-benzene, *δ*): 0.54 (3H, s, 9-CH_3), 0.77 (3H, d, *J*=6, 8-CH_3), 0.94 (3H, s, 5-CH_3), 1.76 (3H, s, $OCOCH_3$), 1.8—2.0 (6H), 2.55 (2H, m, 1-H_2), 4.61 (2H, d, *J*=6, 15-H_2), 5.34 (1H, t-like, *J*=5.5, 12-H_2), 5.5—6.0 (3H). MS *m/e* (%): 444 (M^+, 3), 384 (M^+—AcOH, 8), 345 (M^+—$C_5H_7O_2$, 4), 301 (M^+—AcOH–C_5H_7O, 5), 285 (M^+—AcOH–$C_5H_7O_2$, 10), 205 (vi, 93), 83 (C_5H_7O, 86), 43 (CH_3CO, 100). CD (*c*=0.180, MeOH) $[\theta]^{15}$ (nm): +2900 (290), +1800 (302) (positive minimum), +4600 (330) (positive maximum), 0 (374). ORD (*c*=0.180, MeOH) $[M]^{15}$ (nm): 0° (298), −1800° (312) (trough), 0° (326), +3500° (350) (peak), +450° (450).

Desacetyl-linarienone (3) from 2——To a solution of **2** (50 mg) in dry MeOH (1 ml), was added 1% methanolic MeONa (0.5 ml). The total solution was kept stirring at room temperature for 3 hr, treated with Dowex 50 W×8 (10 ml), and evaporated under reduced pressure. Purification of the reaction product by preparative TLC (*n*-hexane–AcOEt=5: 1) furnished **3** (22 mg) and **2** (3 mg, recovered). Desacetyl-linarienone (**3**), colorless oil, $[\alpha]_D^{21}$ +38° (*c*=0.51, $CHCl_3$). High Mass *m/e*: Calcd. for $C_{25}H_{38}O_4$ 402.277; Found: 402.277. IR ν_{max}^{film} cm^{-1}: 3430 (br, hydroxyl), 1712, 1660 (angelate, enone), 1433, 1374, 1230, 1149, 1038. PMR ($CDCl_3$, *δ*): 0.58 (3H, s, 9-CH_3), 0.87 (3H, d, *J*=6, 8-CH_3), 1.23 (3H, s, 5-CH_3), 1.56 (2H, d, *J*=5.5, 11-H_2), 1.74 (3H, br.s, $W_{h/2}$=4, 13-CH_3), 1.91 (3H, br.s), 1.96 (3H, d, *J*=7) (olefinic CH_3 in angelate), 1.97 (3H, br.s, 4-CH_3), 2.50, 2.69 (1H each, AB in ABX, J_{AB}=18, 1-H_2), 4.17 (1H, t-like, *J*=5.5, 12-H), 4.65 (2H, d, *J*=6, 15-H_2), 5.61 (1H, t-like, *J*=6, 14-H), 5.80 (1H, br.s, $W_{h/2}$=3, 3-H), 6.02 (1H, q-like, *J*=7, olefinic H in angelate). The NOE experiments of **3**: the signal enhancement (11%) of 15-H_2 was observed on irradiation at *δ* 1.74 (13-CH_3), however the signal of 14-H was not affected. MS *m/e* (%): 402 (M^+, 0.5), 303 (M^+—$C_5H_7O_2$, 2), 302 (M^+—$C_5H_8O_2$, 1), 205 (vi, 35), 124 (100), 83 (97). CD (*c*=0.208, MeOH) $[\theta]^{20}$ (nm): +400 (290), +5000 (327) (positive maximum), 0 (382). ORD (*c*=0.239, MeOH) $[M]^{20}$ (nm): −1500° (280), −2500° (306) (trough), 0° (329), +2700° (352) (peak), +800° (450).

Desdiacyl-linarienone (4) from 2——To a solution of **2** (120 mg) in benzene (1 ml), was added 10% NaOH–MeOH (3 ml), and the total mixture was heated under reflux for 2 hr. After cooling, the mixture was acidified with aq. 10% H_2SO_4 and extracted with ether. The ether extract was washed successively with aq. sat. $NaHCO_3$ and water, and dried over $MgSO_4$. The product (80 mg), which was obtained by evaporation of the solvent, was purified by preparative TLC (*n*-hexane–AcOEt=1: 1) to afford desdiacyl-linarienone (**4**) (57 mg). The $NaHCO_3$ washings were combined, acidified with aq. 10% H_2SO_4, and extracted with ether. After the usual work-up, the ether extractive was treated with ethereal diazomethane to furnish methyl angelate (5 mg) (identified by GLC: 15% NPGS 3 mm×2 m, N_2 flow rate 30 ml/min, column temp.

17) The following instruments were used for obtaining the physical data. Specific rotations: Rex Photoelectric Polarimeter NEP-2 or JASCO DIP-181 Digital Polarimeter, measured with 1=1 dm; UV spectra: Shimadzu MPS-50L Spectrophotometer; IR spectra: Hitachi IR Spectrometer EPI-G3; ORD curves and CD spectra: JASCO UV/ORD-5 Spectropolarimeter; PMR spectra: Hitachi R-22 NMR Spectrometer (90 MHz), tetramethylsilane as the internal standard; Mass spectra: Hitachi RMU-6D or JEOL JMS-01SG Mass Spectrometer (for high resolution).

For GLC, Hitachi 063 or 163 Gas Chromatograph was used. Silica gel D-5 (Camag) and HF_{254} (Merck) were used for TLC and the detection was made by spraying aqueous 1% $Ce(SO_4)_2$ in 10% H_2SO_4 followed by heating. In the case of preparative TLC, the detection was made by a UV-lamp or by I_2 vapor.

For column chromatography, silica gel (Woelm for Dry-column Chromatography, Activity III/30 mm and silica gel (Merck, 0.05—0.2 mm) were used.

50°, retention time 2′11″) (*cf.* methyl tiglate 11′40″). Desdiacyl-linarienone (**4**), colorless oil, $[\alpha]_D^{21}$ +53° (c=0.25, $CHCl_3$). High Mass m/e: Calcd. for $C_{20}H_{30}O_2$ 320.235; Found: 320.234. IR ν_{max}^{film} cm^{-1}: 3410 (br, hydroxyl), 1652 (enone), 1438, 1380, 1008. PMR ($CDCl_3$, δ): 0.56 (3H, s, 9-CH_3), 0.86 (3H, d, J=6, 8-CH_3), 1.23 (3H, s, 5-CH_3), 1.53 (2H, d, J=6, 11-H_2), 1.69 (3H, br.s, $W_{h/2}$=3, 13-CH_3), 1.96 (3H, br.s, $W_{h/2}$=3, 4-CH_3), 2.46, 2.66 (1H each, AB in ABX, J_{AB}=18, 1-H_2), 2.93 (2H, br.s, OH×2, exchangeable with D_2O), 4.0—4.2 (3H, including a d-like signal (J=6) centered at δ 4.14, 12-H, 15-H_2), 5.57 (1H, t-like, J=6, 14-H), 5.82 (1H, br.s, $W_{h/2}$=3, 3-H). MS m/e (%): 302 (M^+, 4), 284 (M^+-H_2O, 6), 205 (vi, 56), 124 (100). CD (c=0.216, MeOH) $[\theta]^{20}$ (nm): +300 (288), +5600 (327) (positive maximum), 0 (392). ORD (c=0.505, MeOH) $[M]^{20}$ (nm): −3000° (290), −3600° (306) (trough), 0° (329), +3100° (356) (peak), +500° (500).

Treatment of 3 with (±)-α-Phenylbutyric Anhydride——A solution of **3** (49 mg) in pyridine (4 ml) was treated with (±)-α-phenylbutyric anhydride (110 mg). The total solution was left standing at 32° for 24 hr, treated with water (3 ml), and left standing again for 2 hr. The reaction mixture was extracted with AcOEt. The AcOEt extract was washed successively with aq. 5% $NaHCO_3$ and water. The $NaHCO_3$ washings were combined, acidified with aq. 5% H_2SO_4, and extracted with $CHCl_3$. After the usual work-up, the $CHCl_3$ extract gave recovered α-phenylbutyric acid (43 mg). The specific rotations (at 18°) of the recovered acid in two independent experiments were +3.4° (c=0.87, benzene) and +2.7° (c=0.25, benzene). The AcOEt extract, after removing α-phenylbutyric acid by $NaHCO_3$ treatment, was washed with water and dried over $MgSO_4$. The product, which was obtained by evaporation of the solvent, was purified by preparative TLC (n-hexane–AcOEt=7:1) to afford α-phenylbutyrate (**5**) (35 mg), colorless oil, $[\alpha]_D^{21}$ +8° (c=1.50, $CHCl_3$). High Mass m/e: Calcd. for $C_{35}H_{48}O_5$ 548.350; Found: 548.349. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1736, 1725, 1667 (ester, enone), 1622 (sh), 1601 (w), 1456, 1439, 1380, 1230, 1196, 1154. PMR (CCl_4, δ): 0.56 (3H, s, 9-CH_3), 0.7—1.0 (6H, including 8-CH_3), 1.22 (3H, s, 5-CH_3), 1.50 (3H, br.s, $W_{h/2}$=3, 13-CH_3), 1.60 (2H, d, J=5.5, 11-H_2), 1.84 (3H, br.s), 1.97 (3H, d, J=7) (olefinic CH_3 in angelate), 1.91 (3H, br.s, 4-CH_3), 2.37, 2.54 (1H each, AB in ABX, J_{AB}=18, 1-H_2), 3.36 (1H, t, J=8, Ph–C<u>H</u>–CH_2–CH_3), 4.45 (2H, d, J=6, 15-H_2), 5.13 (1H, t-like, J=5.5, 12-H), 5.27 (1H, t-like, J=6, 14-H), 5.71 (1H, br.s, $W_{h/2}$=4, 3-H), 6.08 (1H, q-like, J=7, olefinic H in angelate), 7.1—7.4 (5H, aromatic H). MS m/e (%): 548 (M^+, 1), 205 (vi, 56) (High Mass: Calcd. for $C_{14}H_{21}O$ 205.159; Found: 205.157), 180 (100).

Tosylhydrazone (12) from LJ-ester-aldehyde (11)——To a solution of **11** (740 mg)[1] in dry EtOH (15 ml), was added p-toluenesulfonylhydrazine (330 mg). The total mixture was heated in an oil bath (temp. 80—90°) for 40 min. After removing EtOH under reduced pressure, the residue was dissolved in AcOEt. The AcOEt solution was then washed with water, dried over $MgSO_4$, and evaporated to dryness. The product (1.06 g) was purified by column chromatography (silica gel 60 g) developing with n-hexane–AcOEt (7:1) to furnish tosylhydrazone (**12**) (580 mg), colorless oil, $[\alpha]_D^{21}$ +26° (c=0.67, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3190 (NH), 1743 (ester), 1598 (phenyl), 1322, 1165 (sulfonamide). PMR (CCl_4, δ): 0.73 (3H, d, J=6, 8-CH_3), 0.83 (3H, s, 9-CH_3), 0.95 (3H, s, 5-CH_3), 1.63 (3H, br.s, 4-CH_3), 2.38 (3H, s, –C_6H_5–C<u>H</u>$_3$), 3.53 (3H, s, $COOCH_3$), 3.26 (2H, s, 14-H_2), 5.22 (1H, br.s, $W_{h/2}$=7, 3-H), 5.96 (1H, t-like, J=7, 12-H), 7.20, 7.72 (2H, each, d, J=8, aromatic H), 7.46 (1H, s, =N–N<u>H</u>–SO_2–), 8.93 (1H, s, 16-H). The molecular ion was not obtained by high resolution mass spectrometry.

$NaBH_3CN$ Reduction of 12 giving 13——To a solution of **12** (240 mg) in a DMF-sulfolane (1:1) mixture (4 ml), was added a small amount of bromocresol green as an indicator (the solution colored yellow). After adding $NaBH_3CN$ (120 mg) (the solution turned blue), the stirred reaction mixture was heated in an oil bath (temp. 60—70°) and treated with conc. HCl until it became yellowish white. The reaction mixture was kept stirring for further 3 hr. After cooling, the mixture was treated with water and extracted with AcOEt. The AcOEt extract was then washed with water, dried over $MgSO_4$, and evaporated to dryness to give a residue. Purification of the residue by column chromatography (silica gel 50 g) developing with n-hexane furnished **13** (110 mg), colorless oil, $[\alpha]_D^{18}$ +28.6° (c=0.76, $CHCl_3$). High Mass m/e: Calcd. for $C_{21}H_{34}O_2$ 318.256; Found: 318.254. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3080, 1750 (ester), 1644, 901 (terminal methylene), 1195, 1160. PMR (CCl_4, δ): 0.77 (3H, d, J=6, 8-CH_3), 0.80 (3H, s, 9-CH_3), 1.01 (3H, s, 5-CH_3), 1.67 (3H, br.s, 4-CH_3), 2.96 (2H, s, 14-H_2), 4.80, 4.84 (1H each, br.s, 16-H_2), 3.62 (3H, s, $COOCH_3$), 5.22 (1H, m, $W_{h/2}$=9, 3-H). MS m/e (%): 318 (M^+, 19), 191 (viii, 60), 189 (68), 149 (100).

Isomerization of 13 giving 14 and 15——A solution of **13** (307 mg) in dry MeOH (8 ml) was treated with 1 N MeONa–MeOH (8 ml). After stirring for 2 hr at room temperature, the reaction mixture was diluted with water and evaporated under reduced pressure to remove MeOH. The resulting mixture was extracted with AcOEt. Working-up of the AcOEt extract in the usual manner furnished a product (268 mg), which was purified by preparative TLC (n-hexane–ether=5:1) to give **14** (116 mg) and **15** (29 mg). **14**, colorless oil, $[\alpha]_D^{22}$ +31° (c=0.77, $CHCl_3$). High Mass m/e: Calcd. for $C_{21}H_{34}O_2$ 318.256; Found 318.253. UV λ_{max}^{EtOH} nm (ε): 222 (12800) (conjugated ester). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1727 (ester), 1646, 1228, 1151. PMR (CCl_4, δ): 0.78 (3H, d, J=6, 8-CH_3), 0.81 (3H, s, 9-CH_3), 1.03 (3H, s, 5-CH_3), 1.67 (3H, br.s, $W_{h/2}$=7, 4-CH_3), 2.14 (3H, d, J=2, 13-CH_3), 3.61 (3H, s, $COOCH_3$), 5.24 (1H, m, $W_{h/2}$=8, 3-H), 5.57 (1H, m, $W_{h/2}$=5, 14-H). MS m/e (%): 318 (M^+, 23), 191 (viii, 58), 189 (100). **15**, colorless oil, $[\alpha]_D^{20}$ +23° (c=1.27, $CHCl_3$). High Mass m/e: Calcd. for $C_{21}H_{34}O_2$ 318.256; Found: 318.256. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725 (ester), 1645, 1251, 1151. PMR (CCl_4, δ): 0.79 (3H, d, J=6, 8-CH_3), 0.82 (3H, s, 9-CH_3), 1.04 (3H, s, 5-CH_3), 1.67 (3H, br.s, $W_{h/2}$=4, 4-CH_3), 1.88 (3H, d, J=1.5, 13-CH_3), 3.61 (3H, s, $COOCH_3$), 5.23 (1H, m, $W_{h/2}$=7, 3-H), 5.53 (1H, m, $W_{h/2}$=4,

14-H). MS *m/e* (%): 318 (M^+, 31), 191 (100) (High Mass: Calcd. for $C_{14}H_{23}$ 191.180; Found 191.180), 189 (78).

$LiAlH_4$ Reduction of 14 giving 16——To an ice-cooled stirred solution of **14** (137 mg) in dry ether (8 ml), was added dropwise a suspension of $LiAlH_4$ (100 mg) in dry ether (6 ml). After stirring for 1.5 hr, the reaction mixture was treated with aqueous ether, acidified with aq. 10% H_2SO_4, and extracted with ether. The usual work-up of the ether extract gave a product (127 mg) which was purified by preparative TLC (*n*-hexane–AcOEt=1:1) to furnish **16** (70 mg), colorless oil, $[\alpha]_D^{22}$ +34° (*c*=1.23, $CHCl_3$). High Mass *m/e*: Calcd. for $C_{20}H_{34}O$ 290.261; Found: 290.258. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (hydroxyl), 1668 (double bond), 1450, 1385. PMR (CCl_4, δ): 0.77 (3H, d, *J*=5, 8-CH_3), 0.79 (3H, s, 9-CH_3), 1.03 (3H, s, 5-CH_3), 1.67 (6H, br.s, 4-CH_3, 13-CH_3), 3.17 (1H, br.s, OH, exchangeable with D_2O), 4.03 (2H, d, *J*=7, 15-H_2), 5.25 (1H, m, 3-H), 5.33 (1H, t-like, *J*=7, 14-H). MS *m/e* (%): 290 (M^+, 19), 191 (viii, 62), 189 (56), 107 (99), 95 (100). The NOE experiments of **16**: the signal enhancement (7%) of 15-H_2 was observed on irradiation at δ 1.67 (13-CH_3).

Acetylation of 16 giving 17——**16** (270 mg) was treated with pyridine (4 ml) and acetic anhydride (4 ml) at room temperature for one hour. The reaction mixture was then treated with ice-water and extracted with AcOEt. The AcOEt extract was washed with aq. 3.5% HCl, neutralized with aq. sat. $NaHCO_3$, and treated in the usual manner to furnish **17** (270 mg), colorless oil, $[\alpha]_D^{22}$ +32° (*c*=1.07, $CHCl_3$). High Mass *m/e*: Calcd. for $C_{22}H_{36}O_2$ 332.271; Found: 332.270. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744 (acetate), 1644 (w), 1450, 1380, 1230, 1021. PMR (CCl_4, δ): 0.78 (3H, d, *J*=6, 8-CH_3), 0.81 (3H, s, 9-CH_3), 1.02 (3H, s, 5-CH_3), 1.6—1.8 (6H, br, 4-CH_3, 13-CH_3), 1.96 (3H, s, $OCOCH_3$), 4.49 (2H, d, *J*=7, 15-H_2), 5.28 (2H, m, 3-H, 14-H). MS *m/e* (%): 332 (M^+, 2), 191 (viii, 80), 189 (100).

Hydrogenation accompanied by Hydrogenolysis of 17 giving 18——To a solution of **17** (50 mg) in an EtOH–Et_3N (3 ml–1.5 ml) mixture, was added 5% Pd–C (40 mg). The stirred total mixture was hydrogenated at room temperature for 40 min. After removing the catalyst by filtration, the solution was concentrated under reduced pressure to give a residue. Purification of the product by preparative TLC (*n*-hexane) furnished **18** (30 mg), unstable oil, $[\alpha]_D^{21}$ +14.8° (*c*=0.45, $CHCl_3$). High Mass *m/e*: Calcd. for $C_{20}H_{36}$ 276.282; Found: 276.281. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2965, 2930, 2875, 2855, 1460, 1380. PMR (CCl_4, δ): 0.73 (3H, d, *J*=6, 8-CH_3), 0.76 (3H, s, 9-CH_3), 0.8—1.0 (6H, m, 13-CH_3, 14-CH_3), 1.00 (3H, s, 5-CH_3), 1.64 (3H, br.s, $W_{h/2}$=5, 4-CH_3), 5.22 (1H, m, $W_{h/2}$=8, 3-H). MS *m/e* (%): 276 (M^+, 65), 191 (viii, 100) (High Mass: Calcd. for $C_{14}H_{23}$ 191.180; Found: 191.179). GLC: 10% SE-30, 3 mm×1 m, N_2 flow rate 30 ml/min, column temp. 200°, retention time 5′40″.

$LiAlH_4$ Reduction of 2 giving 19——To an ice-cooled stirred solution of **2** (100 mg) in dry ether (3 ml), was added a suspension of $LiAlH_4$ (130 mg) in dry ether (5 ml). After stirring for 1.5 hr, the reaction mixture was treated with aqueous ether, acidified with aq. 10% H_2SO_4, and extracted with ether. The usual work-up of the ether extract gave a product (70 mg). Purification of the product by preparative TLC (benzene–AcOEt=2:3) furnished **19** (53 mg), colorless oil, $[\alpha]_D^{20}$ +31° (*c*=0.38, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400 (br) (hydroxyl), 1380, 1130, 1049. PMR ($CDCl_3$, δ): 0.70 (3H, s, 9-CH_3), 0.85 (3H, d, *J*=6, 8-CH_3), 0.93 (3H, s, 5-CH_3), 1.56 (2H, d, *J*=6, 11-H_2), 1.70 (6H, br.s, 4-CH_3, 13-CH_3), 2.91 (3H, br.s, OH×3, exchangeable with D_2O), 3.9—4.3 (4H, including a d-like signal (*J*=6) centered at δ 4.11, 2-H, 12-H, 15-H_2), 5.28 (1H, m, $W_{h/2}$=6, 3-H), 5.51 (1H, t-like, *J*=6, 14-H). MS *m/e* (%): 304 (M^+-H_2O) (High Mass: Calcd. for $C_{20}H_{32}O_2$ 304.240; Found: 304.241), 206 (76), 205 (72), 191 (18), 189 (25), 123 (100). The molecular ion was not obtained by high resolution mass spectrometry.

Acetylation of 19 giving 20——**19** (50 mg) was dissolved in pyridine (1.5 ml) and treated with acetic anhydride (1.5 ml) at room temperature for 2 hr. The reaction mixture was treated with ice-water and extracted with AcOEt. The AcOEt extract was then washed successively with aq. 3.5% HCl and aq. sat. $NaHCO_3$, and worked up in the usual manner. The product (47 mg) thus obtained was purified by preparative TLC (*n*-hexane–AcOEt=5:1) to furnish **20** (35 mg), colorless oil, $[\alpha]_D^{20}$ +24° (*c*=0.38, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1743 (acetate), 1665 (w), 1440, 1372, 1236, 1016. PMR (CCl_4, δ): 0.65 (3H, s, 9-CH_3), 0.86 (3H, d, *J*=6, 8-CH_3), 1.00 (3H, s, 5-CH_3), 1.62 (2H, d, *J*=7, 11-H_2), 1.73 (6H, br.s, 4-CH_3, 13-CH_3), 1.97 (3H, s, $OCOCH_3$), 1.99 (6H, s, $OCOCH_3$×2), 4.54 (2H, d, *J*=7, 15-H_2), 5.0—5.3 (3H, m, 2-H, 3-H, 12-H), 5.50 (1H, t-like, *J*=7, 14-H). MS *m/e* (%): 388 (M^+—AcOH, 1) (High Mass: Calcd. for $C_{24}H_{36}O_4$ 388.261; Found: 388.261), 329 (M^+—AcOH–AcO, 1), 189 (16), 149 (52), 43 (100). The molecular ion was not obtained by high resolution mass spectrometry.

Hydrogenation accompanied by Hydrogenolysis of 20 giving 18——A solution of **20** (30 mg) in EtOH–Et_3N (2 ml–1 ml) was added with 5% Pd–C (25 mg) and shaken in a hydrogen atmosphere at room temperature for one hour. After removing the catalyst by filtration, the solution was concentrated under reduced pressure to give a residue. Purification of the residue by preparative TLC (*n*-hexane) gave the reduction product (15 mg), colorless oil, $[\alpha]_D^{21}$ +15.6° (*c*=0.55, $CHCl_3$). High Mass *m/e*: Calcd. for $C_{20}H_{36}$ 276.282; Found: 276.279. The product was found to be identical to **18** by $[\alpha]_D$, IR, PMR, mass, and GLC.

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