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

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A new diterpene dialdehyde named linaridial was isolated from the ether extractive of fresh subterranean part of *Linaria japonica* Miq. (Scrophulariaceae), and the structure has been established as **1** on the basis of the physicochemical evidence and the chemical correlation with known 5β-methyl-*cis*-furano-clerodane (**7**). Linaridial (**1**) is the first example of a *cis*-clerodane-type diterpene isolated from the scrophulariaceous plant.

The examination of the MeOH extractive of the same plant has revealed the presence of two linaridial-analogues (LJ-1 (major) and LJ-2 (minor)) along with the small amount of linaridial (**1**). The structures, **11** and **12**, have been assigned to LJ-1 and LJ-2, which seem to be the artefacts formed secondarily from linaridial (**1**) during the hot MeOH extraction procedure.

Previously, we reported the structure elucidation of a new chlorinated iridoid glucoside named linarioside and two related glucosides from the hydrophilic portion of *Linaria japonica* Miq. (Scrophulariaceae), which was once used as a Japanese folk medicine.[1] Later on, a few flavonoid glycosides have been isolated from the same hydrophilic portion,[3a,b] whereas linarioside has been identified from another scrophulariaceous plant, *Cymbalaria mularis*.[3c] As a continuation of the work on *L. japonica*, we have been investigating the lipophilic portion and have isolated a new *cis*-clerodane-type diterpene dialdehyde named linaridial (**1**). This paper provides the full account on the structure elucidation.[4]

The ether extractive of fresh subterranean part of the plant was subjected to silica gel dry column chromatography[5] followed by preparative thin-layer chromatography (TLC) to furnish unstable oily linaridial (**1**), $C_{20}H_{30}O_2$ (high mass), $[\alpha]_D$ $+13°$, in a 9% yield from the extractive. Linaridial is quite labile and is hardly purified by the ordinary silica gel column chromatography due to ready decomposition. It seems worth to mention in this respect that linaridial is not detected in the air dried plant material. Linaridial reduces the Tollens reagent and 2,3,5-triphenyltetrazolium chloride[6] and is colored reddish-purple by the Ehrlich reagent on TLC.

The infrared (IR) spectrum of linaridial (**1**) shows the characteristic absorption band at 2750 cm^{-1} due to CHO and the bands at 1728, 1683, and 1638 cm^{-1} attributable to the saturated and conjugated CO groups, the presence of the latter CO being also suggested by the ultraviolet (UV) absorption maximum at 235 nm (ε=11300). The proton magnetic resonance (PMR) spectrum of **1** defines the presence of two CHO groups by a sharp singlet at δ 9.40 (1H) and a broad singlet at δ 9.51 (1H), and double resonance experiments of **1** have led us to formulate

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[1] Part I: I. Kitagawa, T. Tani, K. Akita, and I. Yosioka, *Tetrahedron Letters*, **1972**, 419; *idem*, *Chem. Pharm. Bull.* (Tokyo), **21**, 1978 (1973).

[2] Location: *133-1, Yamada-kami, Suita, Osaka, 565, Japan.*

[3] *a*) K. Takahashi, Y. Tanabe, and S. Kishihara, *Yakugaku Zasshi*, **93**, 707 (1973); *b*) N. Morita, M. Shimizu, M. Arisawa, and K. Kobayashi, *ibid.*, **94**, 913 (1974); *c*) S.K. Kapoor, J. Reisch, and K. Szendrei, *Phytochemistry*, **13**, 1018 (1974).

[4] Preliminary report on the structure of linaridial: I. Kitagawa, M. Yoshihara, T. Tani, and I. Yosioka, *Tetrahedron Letters*, **1975**, 23.

[5] B. Loev and M.M. Goodmann, *Chem.* & *Ind.*, **1967**, 2026.

[6] L.F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D.C. Heath and Company, Cambridge, 1959, p. 114.

the partial structures i, ii, and iii for linaridial (Chart 1). Thus, i) irradiation of the complex signal at δ 6.75, which is the X part of the ABX spin system, altered the AB part signal to a clear AB quartet (J_{AB}=16 Hz) at δ 2.21 and 2.51; ii) two-proton broad singlet at δ 3.33 was disclosed to couple with a broad CHO signal at δ 9.51; and iii) one-proton multiplet at δ 5.28 was shown to couple with a broad olefinic Me singlet at δ 1.68.

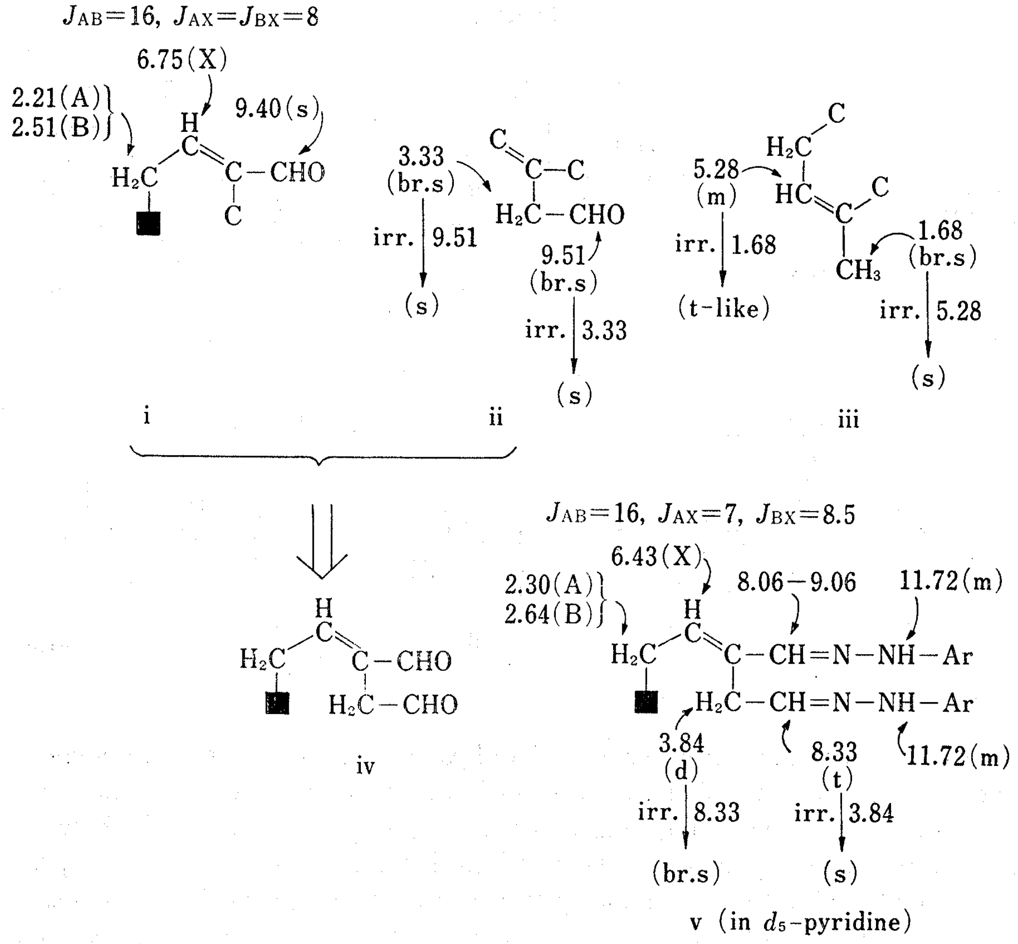

Chart 1

On treatment with 2,4-dinitrophenylhydrazine in aqueous sulfuric acid, linaridial (**1**) was converted to LJ-bis-2,4-dinitrophenylhydrazone (**2**), mp 207—209°, which is the sole crystalline derivative of linaridial. The IR spectrum of **2** shows no CO band but strong absorption band at 1620 cm^{-1} attributable to C=N as well as the absorption bands at 3430, 3310, 1595, and 1329 cm^{-1} due to N-H and aromatic NO_2. In the PMR spectrum of **2**, a low-field broad signal at δ 11.72 (2H) is indicative of the presence of two NH groups and in the δ 8.06—9.06 region are observed the signals due to two protons attached to C=N carbon and six ring protons of two 2,4-dinitrophenylhydrazone moieties. The spin decoupling experiments of **2** have figured out the side chain structure v (Chart 1) apart from the geometry at the C=C bond, and it has become certain that linaridial (**1**) possesses the grouping iv, which is made up from the two partial structures i and ii.

Elucidation of two partial structures iii and iv along with consideration of the degree of unsaturation in linaridial (**1**) has led to an assumption that linaridial possesses a bicarbocyclic diterpene skeleton. Among four hitherto known skeletons (A-D) as shown in Chart 2, the labdane-type skeleton (A) is ruled out since the PMR spectra of **1** and **2** show the presence of only two tertiary methyls. Of three remaining skeletons, the natural occurrence of perhydro-

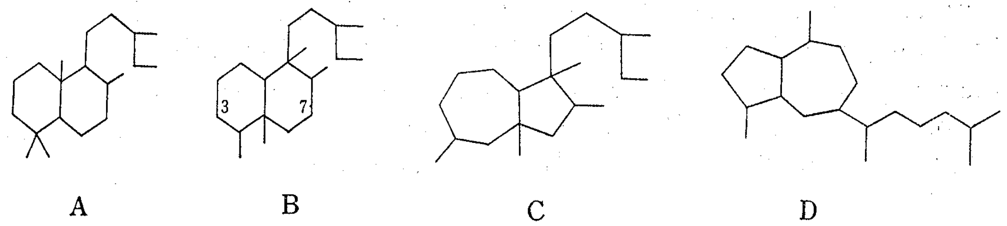

Chart 2

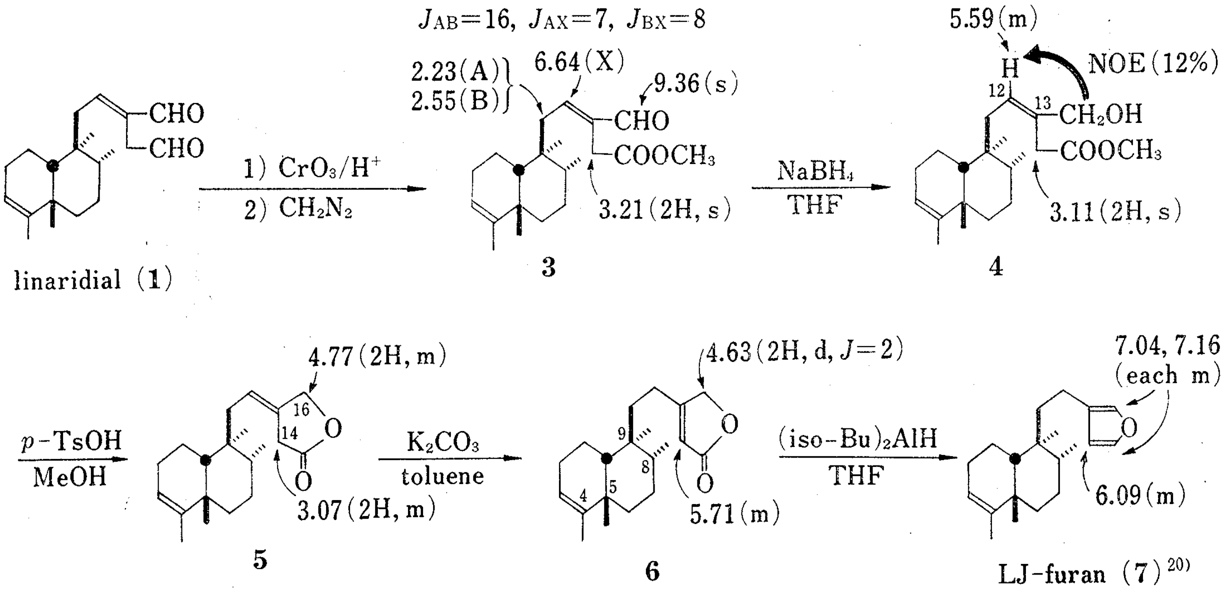

Chart 3

azulene-type diterpenes e.g. portulal-type (C)[7] and pachydictyol A-type (D),[8] is comparatively rare, and here again, the latter skeleton D is not in accord with **1** on the similar PMR basis as above. On the contrary, increasing number of clerodane-type diterpenes (B),[9] which possess the different stereochemistry of the A/B ring junction and/or at the C_8 and C_9 asymmetric centers, have been found in these years, for instance from *Solidago* species (Compositae),[10] and the clerodane-type framework (B) with a double bond at C_3 or C_7 has appeared plausible for linaridial.

On Jones oxidation followed by CH_2N_2 treatment, linaridial (**1**) furnished LJ-ester-aldehyde (**3**), which carries a COOMe function as shown by the IR (1746 cm^{-1}) and PMR (δ 3.63, 3H, s) spectra and retains the α,β-unsaturated CHO group as shown by the UV (λ_{max} 234.5 nm, $\varepsilon=13900$), IR (2710, 1690, 1640 cm^{-1}), and PMR (δ 9.36, 1H, s) spectra. On reduction with $NaBH_4$ in tetrahydrofuran (THF), **3** was converted to LJ-ester-ol (**4**) which exhibits the COOMe absorption band at 1747 cm^{-1} as well as a newly formed OH band at 3350 cm^{-1} in its IR spectrum. In order to establish the geometry of Δ^{12} in **4**, the nuclear Overhauser effect (NOE) experiments were undertaken. Thus, irradiation at δ 4.03, the signal due to C_{13}-$\underline{H}_2$OH, resulted in 12% enhancement of the signal due to C_{12}-$\underline{H}$ (δ 5.59), so that the *cis* relation of the former groups to the latter proton has been proved as depicted in **4**. Treatment of **4**

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7) S. Yamazaki, S. Tamura, F. Marumo, and Y. Saito, *Tetrahedron Letters*, **1969**, 359.

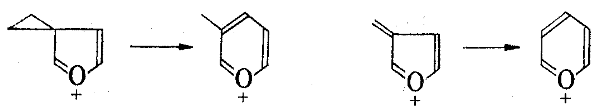
8) D.R. Hirschfeld, W. Fenical, G.H.Y. Lin, R.M. Wing, P. Radlick, and J.J. Sims, *J. Am. Chem. Soc.*, **95**, 4049 (1973).

9) R. McCrindle, and K.H. Overton, "Rodd's Chemistry of Carbon Compounds," 2nd ed. Vol. IIc, ed. by S. Coffey, Elsevier Publishing Company, Amsterdam, 1969, p. 387.

10) *a*) R. McCrindle, and E. Nakamura, *Canad. J. Chem.*, **52**, 2029 (1974); *b*) A. Ohsuka, S. Kusumoto, and M. Kotake, *Nippon Kagaku Zasshi*, **1973**, 590.

with *p*-TsOH in MeOH at room temperature smoothly yielded LJ-γ-lactone (**5**) which exhibits the CO absorption band at 1788 cm^{-1} indicative of the formation of γ-lactone moiety. Since **5** does not show the UV absorption maximum above 210 nm, Δ^{12} in **4** is retained in **5**. The unconjugated γ-lactone in **5** is further substantiated by two broad PMR signals at δ 3.07 (C_{14}-$\underline{H}_2$) and δ 4.77 (C_{16}-$\underline{H}_2$) attributable respectively to α- and γ-methylene protons in the γ-lactone moiety.

Treatment of **5** with K_2CO_3 in dry toluene under reflux[11] furnished isomeric LJ-butenolide (**6**). The UV (λ_{max} 222 nm, ε=8600) and IR (1780>1750, 1639 cm^{-1} in CCl_4; 1782<1745, 1636 cm^{-1} in $CHCl_3$)[12] spectra of **6** corroborate the formation of the conjugated butenolide possessing an α-olefinic proton, which is further supported by the PMR signals at δ 5.71 (narrow multiplet, C_{14}-$\underline{H}$) and δ 4.63 (d, J=2 Hz, C_{16}-$\underline{H}_2$), the assignment being confirmed by the double resonance experiments wherein the latter signal collapsed to a singlet on irradiation at the former signal. Reduction of **6** with $(iso\text{-}Bu)_2AlH$ in THF[13] gave LJ-furan (**7**) which shows the IR absorption band at 872 cm^{-1}. In the PMR spectrum of **7**, are observed three narrow multiplets at δ 6.09, 7.04, and 7.16 (1H each) attributable to the furan ring protons.[14] The mass spectrum of **7** agrees well with the reported fragmentation patterns for the β-substituted furan moiety[15]: the abundant ion peaks at *m/e* 95 (relative intensity: 82%) (vi)[16] and *m/e* 81 (77%) (vii) (Chart 4).



vi *m/e* 95 vii *m/e* 81

Chart 4

Based on the accumulated evidence, it has become clear so far that linaridial (**1**) possesses the above mentioned side chain iv, and finally the total stereostructure has been established as described below.

The mass spectra of linaridial (**1**) and its derivatives show the prominent ion peak at *m/e* 191 (viii) (Table I) derived from $M^{+\cdot}$ by the loss of side chain, which is common in the mass spectra of known clerodane-type diterpenes.[17] On comparison of the PMR data (especially Me chemical shifts) of LJ-butenolide (**6**) and LJ-furan (**7**) with those reported for solidagolactone (**8**),[13b] the 5α-methyl-*trans*-furano-clerodane derivative (**9**)[10a,13b,18] and 5α-methyl-*cis*-furano-clerodane derivative (**10**)[19] as given in Table II, it has been assumed that LJ-furan, $[\alpha]_D$ +32°, is identical with the 5β-methyl-*cis*-furano-clerodane derivative (**7**), $[\alpha]_D$ +33°,[20] the structure of which has been further confirmed by the X-ray structural studies of the related diterpenoid very recently.[21] The assumption has been verified by direct identification of

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[11] I. Kitagawa, Y. Yamazoe, H. Shibuya, R. Takeda, H. Takeno, and I. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), 22, 2662 (1974).

[12] R.N. Jones, C.L. Angell, T. Ito, and R.J.D. Smith, *Canad. J. Chem.*, **37**, 2007 (1959).

[13] *a*) H. Minato and T. Nagasaki, *J. Chem. Soc.* (*C*), **1966**, 377; *b*) T. Okazaki, A. Ohsuka, and M. Kotake, *Nippon Kagaku Zasshi*, **1973**, 584.

[14] *a*) E.J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E.R. Glazier, *J. Am. Chem. Soc.*, **80**, 1204 (1958); *b*) M.S. Henderson, R. McCrindle, and D. McMaster, *Canad. J. Chem.*, **51**, 1346 (1973).

[15] *a*) V.N. Aiyar and T.R. Seshadri, *Phytochemistry*, **11**, 1473 (1972); *b*) F. Bohlmann, M. Grenz, and H. Schwarz, *Chem. Ber.*, **106**, 2479 (1973).

[16] The ion of *m/e* 95 was observed as the base peak in the mass spectrum of linaridial (**1**). The high resolution mass analysis disclosed that the ion comprised of two fragments: vi and $C_7H_{11}^+$.

[17] P.R. Jefferies, J.R. Knox, and B. Scaf, *Aust. J. Chem.*, **26**, 2199 (1973).

[18] *a*) M. Ferrari, F. Pelizzoni, and G. Ferrari, *Phytochemistry*, **10**, 3267 (1971); *b*) M.S. Henderson, R.D.H. Murray, R. McCrindle, and D. McMaster, *Canad. J. Chem.*, **51**, 1322 (1973).

[19] T. Anthonsen, M.S. Henderson, A. Martin, R.D.H. Murray, R. McCrindle, and D. McMaster, *Canad. J. Chem.*, **51**, 1332 (1973).

[20] A.B. Anderson, R. McCrindle, and E. Nakamura, *J. C. S. Chem. Comm.*, **1974**, 453.

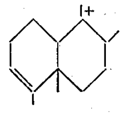
[21] G. Ferguson, W.C. Marsh, R. McCrindle, and E. Nakamura, *J. C. S. Chem. Comm.*, **1975**, 299.

Table I. High Resolution Mass Spectra

Compd.	Molecular formula (Calcd.)	Obsvd. $M^{+\cdot}$ (%)	Obsvd. *m/e* 191 (%)[a]
1	$C_{20}H_{30}O_2$ (302.225)	302.224(23)	191.179(84)
3	$C_{21}H_{32}O_3$ (332.235)	332.235(1)	191.180(71)
4	$C_{21}H_{34}O_3$ (334.250)	334.249(1)	191.179(50)
5	$C_{20}H_{30}O_2$ (302.225)	302.224(3)	191.180(81)
6	$C_{20}H_{30}O_2$ (302.225)	302.225(29)	191.180(50)
7	$C_{20}H_{30}O$ (286.230)	286.230(67)	191.179(100)
11	$C_{22}H_{36}O_3$ (348.266)	b) (0.08)	191.178(68)
12	$C_{22}H_{36}O_3$ (348.266)	348.267(1)	191.180(40)

a) calcd. for $C_{14}H_{23}$ (viii): 191.180

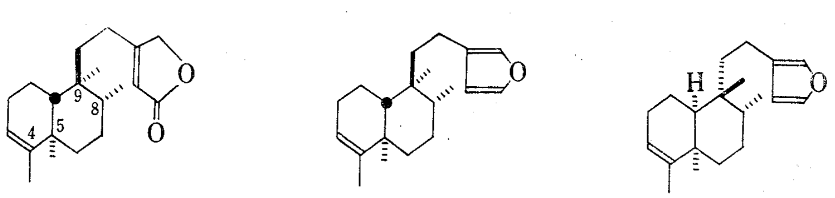
viii:



b) not measured due to weak intensity

Table II. Methyl Chemical Shifts (δ Values in CCl_4, *J* and $W_{h/2}$ Values in Hz)

Compound	4-Me	5-Me	8-Me	9-Me
LJ-butenolide (**6**)	1.68 (br. s) $W_{h/2}=6$	1.03(s)	0.78(d) $J=6$	0.84(s)
8[13b)]	1.57 (br. s)	1.01(s)	0.84(d) $J=6$	0.77(s)
LJ-furan (**7**)	1.65 (br. s) $W_{h/2}=6$	1.02(s)	0.78(d) $J=5.5$	0.80(s)
9[10a)]	1.56 (br. s)	0.99(s)	0.85(d) $J=5.5$	0.74(s)
9[13b)]	1.59(d) $J=2$	1.00(s)	0.84(d) $J=6$	0.74(s)
9[18a)]	1.57 (br. s)	1.00(s)	0.85(d) $J=7$	0.75(s)
9[18b)]	1.57 (br. s)	1.00(s)	0.86(d) $J=6$	0.74(s)
10[19)]	1.64 (br. s)	1.17(s)	0.92(d) $J=6$	1.08(s)



solidagolactone (8)[13b)] **9** [10a, 13b, 18)] **10** [19)]

Chart 5

LJ-furan with authentic **7** which was undertaken by Prof. McCrindle, thus the stereostructure of linaridial being established as **1**.

As described above, the ether extractive of fresh subterranean part of *L. japonica* contains linaridial (**1**) as the major component. However, TLC examinations of the MeOH extractive of fresh substerranean part have revealed the presence of two less polar substances designated as LJ-1 (major) and LJ-2 (minor) in addition to the minor presence of linaridial (**1**). The ether extraction of the MeOH extractive followed by purification as for linaridial gave oily LJ-1 (**11**) in a 3% yield from the MeOH extractive.

The mass spectrum of LJ-1 exhibits an abundant fragment ion peak at *m/e* 191 being suggestive of the clerodane-type skeleton (*vide supra*), in addition to the weak molecular ion peak at *m/e* 348. In the IR spectrum of LJ-1, neither the absorption band due to CHO nor the band due to conjugated CO group is observed, but are observed the weak absorption bands at 1670, 1085, and 1015 cm^{-1} due to C=C and C–O–C. Comparison of the PMR spectra of LJ-1 and linaridial (**1**) has disclosed that the Me signal regions of both are quite alike to each other, and the former lacks the CHO proton signal but possesses the MeO singlets at δ 3.30, 3.31, and 3.33 (combined intensity: 6H). The signal pattern of the MeO protons has shown that LJ-1 is a mixture of the isomeric cyclic hemiacetals which were presumably formed secondarily from linaridial (**1**) possessing the 1,4-dial structure iv during the hot MeOH extraction. The presumption has been substantiated by the hemiacetal cyclization of **1** on methanolic acid treatment under reflux (Chart 6), where LJ-1 as well as LJ-2 possessing a monoacetal structure (*vide infra*) was produced. The structure **11** for LJ-1 has finally been based on the direct correlation with linaridial. Thus, LJ-1, upon treatment with AcOH in ether under reflux, furnished a product being identical with linaridial (**1**). Furthermore, treatment of LJ-1 with 2,4-dinitrophenylhydrazine in an acidic solution gave the bis-2,4-dinitrophenylhydrazone which was identical with **2** prepared above similarly from linaridial (**1**).

LJ-2 (**12**), a minor component of the MeOH extractive, produced the red precipitate with 2,3,5-triphenyltetrazolium chloride and shows M^{+} peak at *m/e* 348 indicating the molecular formula ($C_{22}H_{36}O_3$) in its high resolution mass spectrum. The UV (λ_{max} 234.5 nm, ε=10800) and IR (2740, 1682, 1637 cm^{-1}) spectra of **12** resemble those of linaridial (**1**) in regard to the α,β-unsaturated CHO function, but **12** lacks the saturated CO absorption band in its IR spectrum. The presence of the partial structures i and iii in LJ-2 has been substantiated by the decoupling experiments. Comparison of the PMR data of **12** and **1** has revealed two characteristics: a) two methoxyls singlet at δ 3.26 (6H) is observed in the former; and b) a broad singlet (δ 3.33) due to $C_{14}-\underline{H}_2$ in the partial structure ii of **1** is varied in **12** to a doublet at δ 2.51 (J=5.5 Hz) which couples with a triplet at δ 4.31 (J=5.5 Hz) assignable to a methine proton on a carbon bearing two methoxyls. The above described PMR evidence has shown the presence of an acetal grouping $=\overset{|}{C}-CH_2-CH(OCH_3)_2$ in LJ-2 in place of the partial structure ii in linaridial (**1**). All the accumulated evidence for LJ-2 and the successful correlation between linaridial and LJ-2 (Chart 6) have finally led us to formulate the stereostructure **12** for LJ-2.

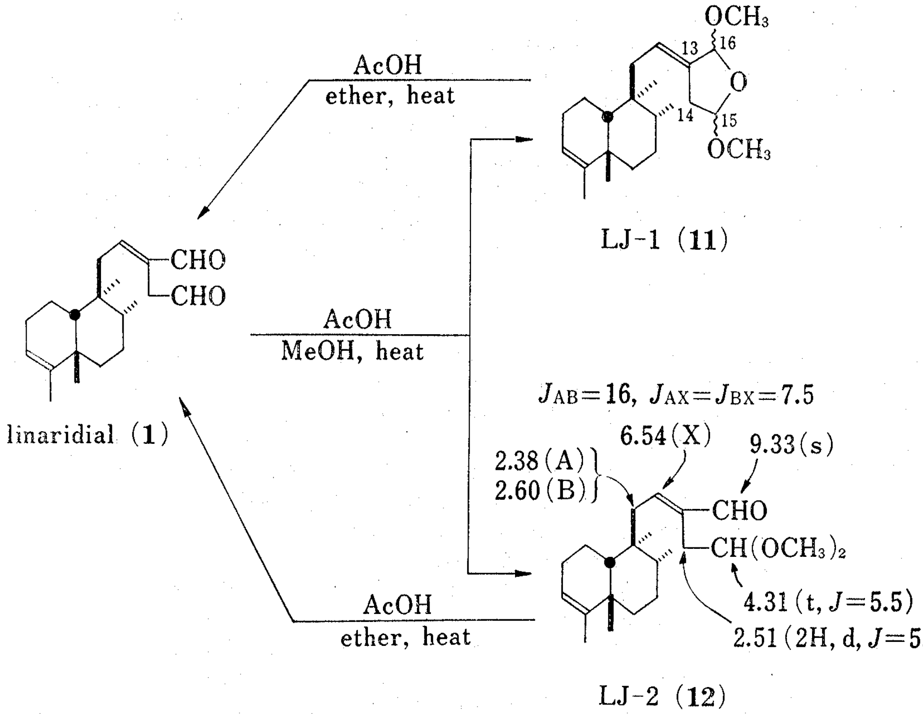


Chart 6

The detailed TLC examinations on the extractive of *L. japonica* have shown that LJ-1 (**11**) and LJ-2 (**12**) are present only in the MeOH extractive but absent in the ether extractive. On the other hand, linaridial (**1**), which is mainly present in the ether extractive, is transformed to LJ-1 and LJ-2 even under mild methanolic acid conditions. Consequently, it seems likely that LJ-1 (**11**) and LJ-2 (**12**) are formed secondarily from linaridial (**1**) during the MeOH extraction process catalized by vegetable organic acids.

Linaridial (**1**) appears to be the first example of the *cis*-clerodane-type diterpene isolated from the scrophulariaceous plant.

Experimental[22]

Isolation of Linaridial (1)——Fresh subterranean part of *Linaria japonica* (cut, 180 g, collected at Iwase in Toyama in Sep. 1973) was extracted with ether under reflux. The ether soluble portion, on evaporation of the solvent, gave a brown oily residue (9 g). The residue (4.2 g) was purified by silica gel (400 g) dry column chromatography developing with *n*–hexane–AcOEt (9: 1) mixture to afford crude linaridial (420 mg) which was further purified by preparative TLC to give unstable oily linaridial (**1**) (375 mg), $[\alpha]_D^{10}$ $+13°$ ($c=0.60$, $CHCl_3$). UV λ_{max}^{EtOH} nm (ε): 235 (11300). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2750, 1728, 1683, 1638, 1440, 1373. Mass Spectrum *m/e* (%): 302 (M^{+}, 23), 191 (84), 175 (36), 149 (91), 107 (44), 95 (100) (high mass: obsvd. 95.048, calcd. for C_6H_7O (vi): 95.050; obsvd. 95.086, calcd. for C_7H_{11}: 95.086), 81 (23) (high mass: obsvd. 81.034, calcd. for C_5H_5O (vii): 81.034; obsvd. 81.071, calcd. for C_6H_9: 81.070). PMR: 0.82 (3H, d, $J=6$, C_8–Me), 0.93 (3H, s, C_9–Me), 1.02 (3H, s, C_5–Me), and other signals as given in Chart 1. The molecular composition of **1** was confirmed by high resolution mass spectrometry as given in Table I.

LJ-Bis-2,4-dinitrophenylhydrazone (2) **from Linaridial** (1)——To a solution of **1** (255 mg) in EtOH (10 ml) was added a 2,4-dinitrophenylhydrazine solution (4 ml), prepared from 2,4-dinitrophenylhydrazine (3 g)–H_2O (20 ml)–EtOH (70 ml)–conc. H_2SO_4 (15 ml), and the mixture was left standing at room temperature for 1 hr and then filtered. The insoluble mass was washed with water and treated with hot AcOEt to give an orange precipitate (164 mg). The precipitate (100 mg) was subjected to silica gel (20 g) column chromatography (with pressure 2—3 Atm; flow rate: 1 ml/min) with the aid of *n*–hexane–benzene mixture to afford crude LJ-bis-2,4-dinitrophenylhydrazone (**2**) (45 mg), which was recrystallized from AcOEt giving yellow needles of **2**, mp 207—209°, $[\alpha]_D^{13}$ $-24°$ ($c=0.75$, pyridine). *Anal.* Calcd. for $C_{32}H_{38}O_8N_8$: C, 58.01; H, 5.74; N, 16.92. Found: C, 58.08; H, 6.03; N, 16.64. UV $\lambda_{max}^{dioxane}$ nm (ε): 258 (28000), 363 (39000). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3310, 1620, 1595, 1329. PMR (d_5-pyridine): 0.77 (3H, d, $J=6$, C_8–Me), 0.80 (3H, s, C_9–Me), 0.98 (3H, s, C_5–Me), 1.70 (3H, br.s, $W_{h/2}=5$, C_4–Me), 5.28 (1H, m, $W_{h/2}=7$, C_3–$\underline{H}$), 8.06, 8.12 (1H each, d, $J=9.5$), 8.27, 8.42 (1H each, d.d, $J=9.5$ & 2.5), 9.06 (2H, d, $J=2.5$), and other signals as given in Chart 1.

LJ-Ester-aldehyde (3) **from Linaridial** (1)——To an ice-cooled solution of **1** (236 mg) in acetone (4 ml) was added Jones reagent (4 ml) prepared from CrO_3 (7 g)–H_2O (30 ml)–conc. H_2SO_4 (11.2 g) and the solution was kept stirring at 0° for 2 hr and then diluted with ice-water, and extracted with $CHCl_3$. The $CHCl_3$ extractive (173 mg) obtained after usual work-up was treated with excess ethereal CH_2N_2. The reaction mixture was concentrated and purified by preparative TLC to afford unstable oily LJ-ester-aldehyde (**3**) (142 mg), $[\alpha]_D^{29}$ $+32.5°$ ($c=1.07$, $CHCl_3$). UV λ_{max}^{ether} nm (ε): 234.5 (13900); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2710, 1746, 1690, 1640, 1436, 1378, 1165. Mass Spectrum *m/e* (%): 332 (M^{+}, 1), 191 (71), 95 (100). PMR: 0.82 (3H, d, $J=6$, C_8–Me), 0.92 (3H, s, C_9–Me), 1.02 (3H, s, C_5–Me), 1.67 (3H, br.s, $W_{h/2}=6$, C_4–Me), 5.27 (1$\underline{H}$, m, $W_{h/2}=7$, C_3–H), and other signals as given in Chart 3. The composition of the molecular ion peak of **3** was confirmed by the accurate mass measurement as given in Table I.

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[22] The following instruments were used for obtaining the physical data. Melting-points: Yanagimoto Micro-meltingpoint Apparatus and recorded uncorrected; Specific Rotation: Rex Photoelectric Polarimeter NEP-2, measured with $l=1$ dm; IR Spectra: Hitachi IR Spectrometer EPI-G3 or EPI-S2; UV Spectra: Shimadzu MPS-50L or Hitachi EPS-3T Spectrophotometer; High Resolution Mass Spectra: JEOL JMS-OlSG Mass Spectrometer; PMR Spectra: Hitachi R-22 NMR Spectrometer, measured in CCl_4 unless otherwise stated and TMS as the internal standard. The chemical shifts are given in δ values at 90 MHz, and coupling constants (J) and half-height band width ($W_{h/2}$) are in Hz. Abbreviations: br.s= broad singlet, d=doublet, m=multiplet, s=singlet, t=triplet.

Silica gel D-5 (Camag) and HF_{254} (Merck) were used for TLC developing with *n*–hexane–AcOEt (9: 1) mixture unless otherwise stated, and detection by UV fluorescence and by spraying a solution of 1% $Ce(SO_4)_2$ in 10% H_2SO_4 or Ehrlich reagent followed by heating. For dry column chromatography, silica gel (Woelm for Dry-column Chromatography, Activity III/30 mm) was used. Silica gel (Merck, 0.05—0.2 mm) and silica gel (Merck, HF_{254}) were used for column chromatography (ordinary one and with pressure of 2—3 Atm).

LJ-Ester-ol (4) from LJ-Ester-aldehyde (3)——To an ice-cooled solution of 3 (210 mg) in dry THF (10 ml) was added $NaBH_4$ (100 mg) and the reaction mixture was kept stirring at 0° for 1.5 hr and then poured into ice-water. The total mixture was extracted with ether and the ether solution was washed, dried, and evaporated. The residue (200 mg) thus obtained was separated by preparative TLC to afford oily LJ-ester-ol (4) (92 mg) and 3 (83 mg). LJ-ester-ol (4), $[\alpha]_D^{15}$ $+30.4°$ ($c=1.73$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (w), 1747, 1636, 1440, 1376, 1165 (w). Mass Spectrum *m/e* (%): 334 (M^+, 1), 191 (60), 95 (100). PMR ($CDCl_3$): 0.78 (3H, d, $J=6$, C_8–Me), 0.82 (3H, s, C_9–Me), 1.00 (3H, s, C_5–Me), 1.66 (3H, br.d, $J=1.5$, C_4–Me), 4.03 (2H, br.s, C_{16}–$\underline{H}_2$), 5.26 (1H, m, $W_{h/2}=8$, C_3–H), and other signals as given in Chart 3. The molecular composition is given in Table I. The NOE experiments of **4**: the signal enhancement (12%) of C_{12}–$\underline{H}$ was observed on irradiation at δ 4.03 (C_{13}–$C\underline{H}_2OH$), and the enhancement (7%) of the latter signal was observed on saturation of the former.

LJ-γ-Lactone (5) from LJ-Ester-ol (4)——To a solution of **4** (55 mg) in MeOH (4 ml) was added a catalytic amount (3 microspatulafulls) of *p*–TsOH. After keeping for 10 min at room temperature with occasional stirring, the reaction mixture was purified by preparative TLC to give oily LJ-γ-lactone (**5**) (45 mg), $[\alpha]_D^{14}$ $+22°$ ($c=0.30$, $CHCl_3$). UV: transparent above 210 nm. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1788, 1440, 1376, 1150. Mass Spectrum *m/e* (%): 302 (M^+, 3), 191 (81), 107 (39), 95 (100). PMR: 0.81 (3H, d, $J=6$, C_8–Me), 0.83 (3H, s, C_9–Me), 1.02 (3H, s, C_5–Me), 1.68 (3H, br.d, $J=1.5$, C_4–Me), 5.27 (1H, m, C_3–$\underline{H}$), 5.40 (1H, m, C_{12}–$\underline{H}$), and other signals as given in Chart 3. The composition of M^+ of **5** is shown in Table I.

LJ-Butenolide (6) from LJ-γ-Lactone (5)——A mixture of **5** (37 mg) and K_2CO_3 (100 mg) in dry toluene (4 ml) was refluxed with stirring under N_2 atomosphere for 5 hr. After filtration, the filtrate was concentrated *in vacuo* giving a residue (35 mg) which was purified by preparative TLC with *n*–hexane–AcOEt (7: 1) mixture to furnish oily LJ-butenolide (**6**) (32 mg), $[\alpha]_D^{29}$ $+23.5°$ ($c=1.00$, EtOH). UV λ_{max}^{EtOH} nm (ε): 222 (8600); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780>1750, 1639, 1440, 1370, 1234, 1160, 1133, 1048, 880; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782<1745, 1636, 1440, 1373, 1166, 1138, 1048, 893, 858. Mass Spectrum *m/e* (%): 302 (M^+, 29), 287 (23), 191 (50), 107 (100), 95 (94) (high mass: obsvd. 95.050, calcd. for C_6H_7O (vi): 95.050; obsvd. 95.086, calcd. for C_7H_{11}: 95.086), 81 (48) (high mass: obsvd. 81.035, calcd. for C_5H_5O (vii): 81.034; obsvd. 81.071, calcd. for C_6H_9: 81.070). PMR: 5.25 (1H, m, $W_{h/2}=7$, C_3–$\underline{H}$), and other signals as given in Chart 3 and Table II. The molecular composition of **6** was confirmed by the exact mass determination (Table I).

LJ-Furan (7) from LJ-Butenolide (6)——To a solution of **6** (120 mg) in dry THF (6 ml) was added a reagent (0.32 ml) of $(iso–Bu)_2AlH$ in THF (19% solution, 1.1 eq.). The reaction mixture was kept at −89° for 1 hr and then acidified with 10% H_2SO_4 and the total solution was extracted with ether. The ether solution was washed with saturated aq. $NaHCO_3$ and water, dried and evaporated. The residue (93 mg) was chromatographed on silica gel (5 g) column eluting with light petroleum to give oily LJ-furan (**7**) (35 mg), $[\alpha]_D^{30}$ $+32°$ ($c=0.74$, EtOH). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1563 (w), 1500, 1445, 1378, 1160, 1065, 1026, 872. Mass Spectrum *m/e* (%): 286 (M^+, 67), 271 (29), 191 (100), 107 (72), 95 (82), 81 (77). PMR: 5.20 (1H, m, $W_{h/2}=7.5$, C_3–$\underline{H}$), and other signals as given in Chart 3 and Table II. The molecular composition was confirmed by the exact mass measurement (Table I). LJ-furan was identified with an authentic specimen (**7**) (PMR, TLC, SiO_2–$AgNO_3$) by Prof. R. McCrindle.

Isolation of LJ-1 (11)——Fresh subterranean part of *Linaria japonica* (cut, 380 g, collected at Iwase in Toyama in Sep. 1973) was extracted with MeOH under reflux. The brown residue (125 g) obtained by evaporation of MeOH was treated with ether and the ether soluble portion was concentrated to give the extractive (23 g). The extractive (4 g) was chromatographed on silica gel (400 g) dry column developing with *n*–hexane–AcOEt (9: 1) mixture to yield crude LJ-1 (380 mg) which was further purified by preparative TLC to furnish oily LJ-1 (**11**) (345 mg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (w), 1670 (w), 1450, 1432, 1370, 1205, 1085, 1015, 970, 897. Mass Spectrum *m/e* (%): 348 (M^+, 0.1), 191 (68), 95 (100) (high mass: obsvd. 95.048, calcd. for C_6H_7O (vi): 95.050; obsvd. 95.087, calcd. for C_7H_{11}: 95.086), 81 (8) (high mass: obsvd. 81.034, calcd. for C_5H_5O (vii): 81.034; obsvd. 81.071, calcd. for C_6H_9: 81.070). PMR: 0.79 (3H, d, $J=6$, C_8–Me), 0.82 (3H, s, C_9–Me), 1.00 (3H, s, C_5–Me), 1.65 (3H, br.s, $W_{h/2}=4$, C_4–Me), 3.30, 3.31, 3.33 (totally 6H, each s, $C_{15,16}$–OMe's), 4.9—5.5 (4H, m, $C_{3,12,15,16}$–$\underline{H}_4$).

Conversion of Linaridial (1) to LJ-1 (11) and LJ-2 (12)——To a solution of **1** (300 mg) in MeOH (11 ml) was added AcOH (0.7 ml) and the mixture was refluxed for 2.5 hr and then poured into ice-water (50 ml). The total solution was neutralized with aq. saturated $NaHCO_3$ and extracted with AcOEt. The residue (245 mg) obtained by evaporation of AcOEt was separated by preparative TLC to give LJ-1 (**11**) (135 mg) and LJ-2 (**12**) (98 mg), the former being identical with LJ-1 obtained above from the MeOH extractive of the plant.

LJ-2 (**12**), $[\alpha]_D^{14}$ $+20°$ ($c=1.06$, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1682, 1637, 1439, 1362, 1355, 1114, 1078. Mass Spectrum *m/e* (%): 348 (M^+, 1), 191 (40), 95 (64), 75 (100). PMR: 0.82 (3H, d, $J=6$, C_8–Me), 0.93 (3H, s, C_9–Me), 1.02 (3H, s, C_5–Me), 1.67 (3H, br.s, $W_{h/2}=5$, C_4–Me), 3.26 (6H, s, $C_{15\ 16}$–OMe's), 5.27 (1H, m, $W_{h/2}=7.5$, C_3–$\underline{H}$), and other signals as given in Chart 6. The composition of the molecular ion peak was confirmed by the exact mass measurement (Table I). Decoupling experiments of LJ-2: i) Upon irradiation of the olefinic proton signal at δ 6.54 (X part in ABX system, C_{12}–$\underline{H}$), the AB part signals were altered to a clear quartet ($J_{AB}=16$ Hz) centered at δ 2.49 (C_{11}–$\underline{H}_2$), and the reverse experiment caused the former signal to convert to a singlet. ii) The olefinic Me signal at δ 1.67 (C_4–Me) was sharpened by irradiating the other olefinic proton signal at δ 5.27 (C_3–$\underline{H}$).

Linaridial (1) from LJ-1 (11)——To a solution of **11** (200 mg) in ether (5 ml) was added AcOH (5 ml) and the reaction mixture was refluxed for 50 min and then poured into ice-water, and neutralized with aq. saturated $NaHCO_3$. The total solution was extracted with AcOEt, and the oily residue (187 mg) obtained from the AcOEt soluble portion was separated by preparative TLC to give linaridial (**1**) (160 mg) and LJ-1 (15 mg), the former being identical with natural linaridial.

Linaridial (1) from LJ-2 (12)——To a solution of **12** (50 mg) in ether (2 ml) was added AcOH (2 ml) and the reaction mixture was refluxed for 3 hr. After treatment as for LJ-1, the oily product (40 mg) was separated by preparative TLC to give linaridial (**1**) (28 mg) and LJ-2 (**12**) (6 mg), the former being identical with natural linaridial.

LJ-Bis-2,4-dinitrophenylhydrazone (2) from LJ-1 (11)——A solution of **11** (280 mg) in EtOH (10 ml) was treated with the 2,4-dinitrophenylhydrazine–H_2SO_4 reagent (5 ml, *vide supra*) under the same reaction conditions as for linaridial to yield the orange precipitate (180 mg). The crude product (100 mg) was purified by silica gel (20 g) column chromatography (with pressure of 2—3 Atm) to give a fraction mainly containing LJ-bis-2,4-dinitrophenylhydrazone, which was recrystallized from AcOEt to furnish yellow needles (36 mg) having the identical physical constants with those of **2** prepared from linaridial.

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