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Studies on Terpenoids and Related Alicyclic Compounds. XVIII.[1] Stereoselective Synthesis of (±)-Furanofukinol and (±)-Petasalbin

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A stereoselective synthesis of (±)-furanofukinol (**1a**) and (±)-petasalbin (**2**) starting from the diene adduct (**6**) is described. Reduction of the diketone (**8**) with $NaBH_4$ gave the 3β-ol (**9**) as a main product. Attempted synthesis of **1a** from **9**, by reduction of **9** with $LiAlH_4$ followed by catalytic reduction, was unsuccessful due to decomposition of **11**. Reduction of the diketone (**12**) gave the 3β-ol (**13**). The conformations of **13** and its acetate (**14**) were shown to be non-steroidal (**13b** and **14b**, Fig. 1) by nuclear magnetic resonance (NMR) and nuclear Overhauser effect (NOE) studies. Reduction of **13** with $LiAlH_4$ gave a mixture of **1a** and the 6α-ol (**15**), whereas reduction of **13** with Na metal dissolved in refluxing EtOH gave **1a** stereoselectively. On the basis of NMR and infrared (IR) spectral comparisons, **1a** and its diacetate (**1g**) were identical with the natural compounds (**1a** and **1g**, respectively). Reduction of (±)-ligularone (**4**) under thermodynamic conditions gave **2** stereoselectively. IR and NMR spectral comparisons showed (±)-**2** to be identical with petasalbin.

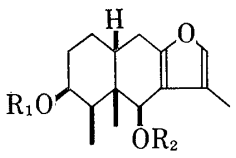
Keywords——sesquiterpenoid; synthesis; furanoeremophilane; furanofukinol; petasalbin; NMR; NOE; conformation

In the previous paper of this series, the authors reported[3–5] total syntheses of several furanoeremophilanes starting from the diene adduct (**6**) of 3-ethoxy-1,3-pentadiene and 3,5-dimethylbenzofuran-4,7-quinone.[3] In this paper, we report a stereoselective synthesis of (±)-furanofukinol (**1a**) and (±)-petasalbin (ligularol) (**2**).

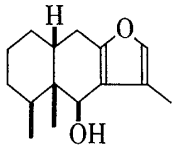
Furanofukinol (**1a**) and its esters (**1b**—**f**) have been found as main components of *Petasites japonicus* Maxim ("Fuki" in Japanese) by Naya *et al.*[6a] and in *Farfugium hiberniflorum* Kitamura ("Kantsuwabuki" in Japanese) by Takahashi *et al.*[7] The structure of furanofukinol was previously formulated as **3** by Naya *et al.*[6a] and the conformation of **3** was assumed to be steroidal. The 3α-OH stereochemistry was assigned from the width at half-height of the C-3H signal (14 Hz), which indicates an axial C-H bond at this position. However, very recently Naya *et al.*[6b] reported that the structure of furanofukinol should be revised to 3β-hydroxy (**1a**) on the basis of nuclear magnetic resonance (NMR) investigation and chemical transformation of **1a** to 3β-hydroxyeremophilanes. **1a** was shown to be non-steroidal 3β(eq), 6β(pseudo-eq)-dihydroxyfuranoeremophilane. The configuration of the 6β-hydroxyl group of **1a** was established by its conversion to petasalbin[8] (**2**), which was isolated from several *Petasites* and *Ligularia* spp. Petasalbin was known earlier as ligularol.[9]

1) Part XVII: K. Yamakawa, I. Izuta, H. Oka, R. Sakaguchi, M. Kobayashi, and T. Satoh, *Chem. Pharm. Bull.* (Tokyo), **27**, 331 (1979).
2) Location: *Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan.*
3) K. Yamakawa and T. Satoh, *Chem. Pharm. Bull.* (Tokyo), **25**, 2535 (1977).
4) K. Yamakawa and T. Satoh, *Heterocycles*, **8**, 221 (1977).
5) K. Yamakawa and T. Satoh, *Chem. Pharm. Bull.* (Tokyo), **26**, 3704 (1978).
6) *a*) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, *Tetrahedron Lett.*, **1971**, 2961; *b*) K. Naya, Y. Makiyama, T. Matsuura, N. Ii, H. Nagano, and T. Takahashi, *Chem. Lett.*, **1978**, 301.
7) H. Nagano and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **45**, 1935 (1972).
8) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965).
9) J. Shimoyama and G. Aikawa, *Yakugaku Zasshi*, **6**, 104 (1891); Y. Asahina, *ibid.*, **28**, 811 (1913).

Almost all naturally occurring furanoeremophilanes have a C-6 β-hydroxyl configuration. Ishii *et al.*[8] reported that reduction of 6-oxofuranoeremophilanes, ligularone (**4**) for example, with metal hydride reagent yielded only the 6α-hydroxy derivative (**5**), stereoselectively. The 6α-hydroxy compound may be formed by hydride attack from the less hindered β-face at the C-6 carbonyl group of **4**. Thus, a stereoselective reduction procedure for the C-6 carbonyl group to give a 6β-hydroxyl group is synthetically important.



	R_1	R_2
1a	H	H
1b	H	$COCH_3$ (Ac)
1c	H	$-CO$ with CH_3, CH_3, H (Ang)
1d	$-CO$ with SCH_3, H, H	Ang
1e	Ang	Ac
1f	Ang	H
1g	Ac	Ac



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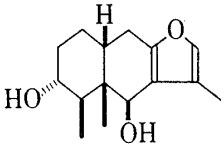

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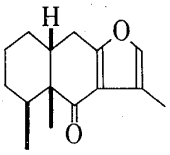

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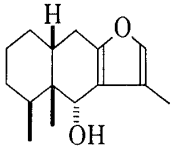

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As illustrated in Chart 1, **9a**, it was expected that on the reduction of furanoeremophil-9-en-6-on-3β-ol (**9**) with metal hydride reagent, the C-6 carbonyl group of **9** would probably be attacked from the less hindered α face due to the C-5 axial angular methyl group.

Reduction of **8** with sodium borohydride gave the 3β-ol (**9**), mp 119—119.5°, as a main product (91% yield) together with a small amount of 3α-ol (**10**), mp 144—145.5° (5% yield). Further reduction of **9** with lithium aluminum hydride yielded a diol (**11**), which was subjected to catalytic reduction with palladium catalyst. However, this was not successful because **11** was very unstable in air or on silica gel and alumina. Thus the attempt to synthesize furanofukinol (**1a**) by this route was abandoned.

Next, total synthesis of **1a** starting from furanoeremophilane-3,6-dione (**12**), derived from **7**, was investigated. The stereochemistry of **12** has been discussed in our previous paper.[3] The preferred conformation of **12** should be a steroidal form, and this was confirmed by NMR spectrometry.

Reduction of diketone (**12**) with sodium borohydride in methanol gave the 3β-hydroxy-6-one (**13a**) in 95% yield, whereas the 3α-epimer was not detected. The 3β(equatorial)-OH stereochemistry of **13a** was assigned from the width at half-height of the C-3H signal (15 Hz at δ 3.68), which indicates an axial C–H bond. Furthermore, Hα and Hβ at C-9 each appeared as a double doublet of J=18 and 2 Hz, and 18 and 6 Hz, at δ 2.59 and 3.11, respectively. From these data, the dihedral angles (*ca.* 47° and 68°) between C–10H and C–9Hβ,Hα (Fig. 1) could be calculated.[10] The conformation of **13** is indicated to be a non-steroidal form by

10) R.J. Abraham and J.S.E. Holker, *J. Chem. Soc.*, **1963**, 806.

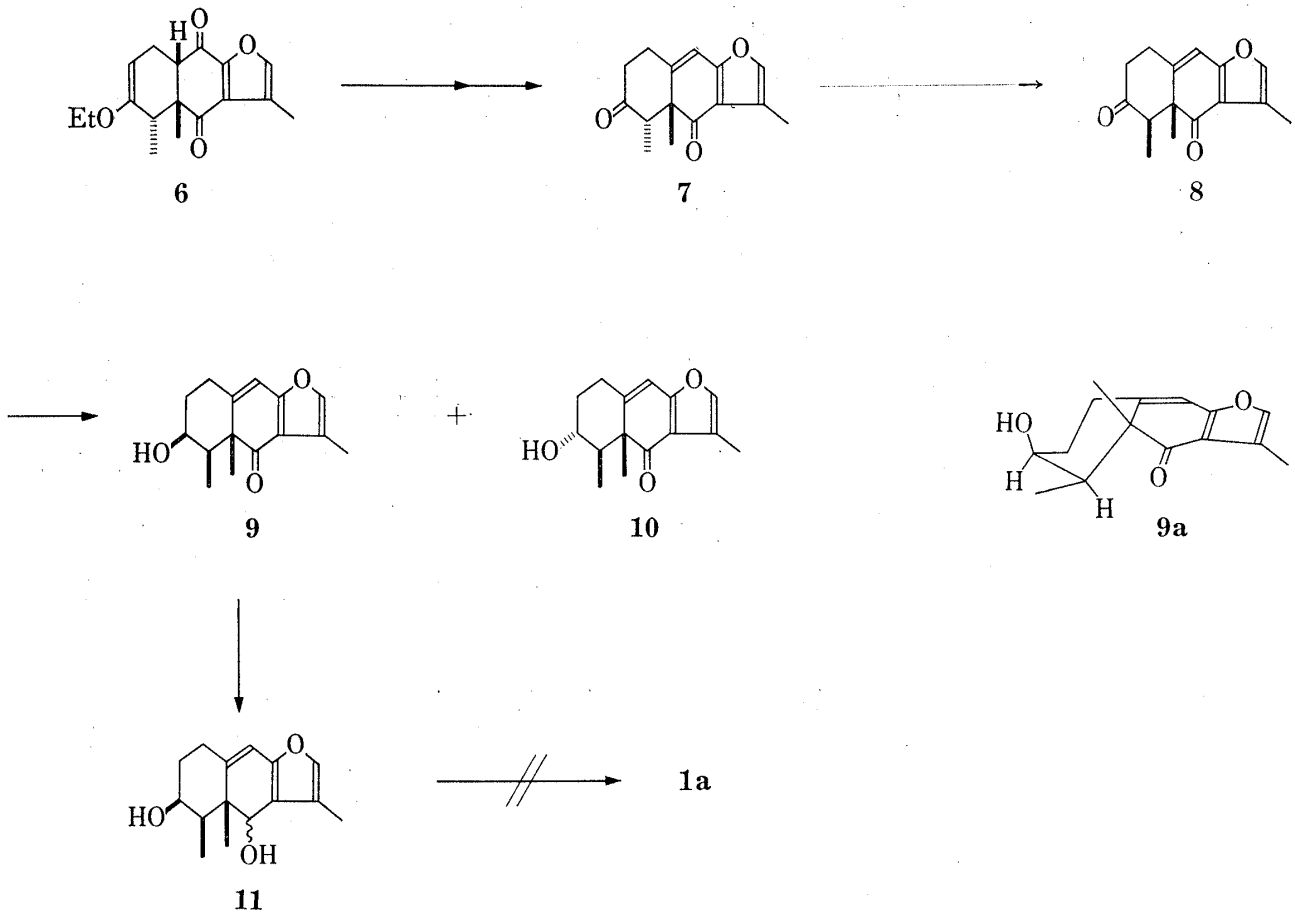

Chart 1

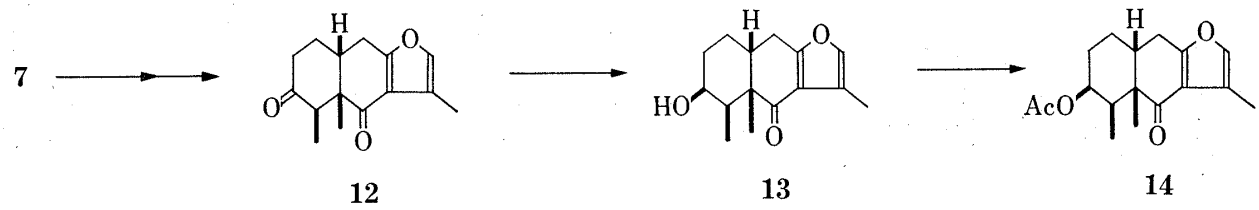

Chart 2

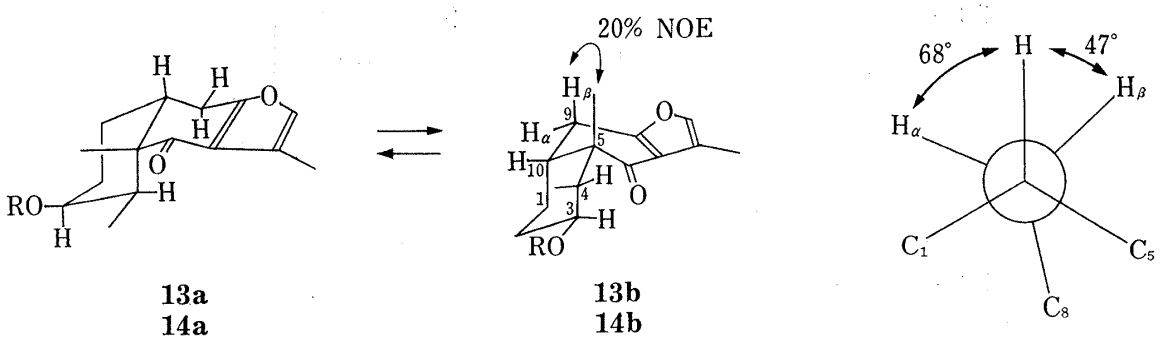

Fig. 1

the above NMR data. The corresponding 3β-acetate (**14**), mp 111—112°, also appears to take a non-steroidal conformation, judging from the NMR data. The signal due to C–3H of **14** appeared at δ 4.70 with a width at half-height of 13 Hz and those of Hα and Hβ at C-9 each appeared as a double doublet of J=18 and 2 Hz, and 18 and 6 Hz, at δ 2.60 and 3.15, respectively.

The non-steroidal conformation of the acetate (**14**) was confirmed by nuclear Overhauser effect (NOE) measurements in carefully degassed $CDCl_3$ solution. Irradiation of the C-5 methyl signal at δ 1.14 resulted in a 20% enhancement of the C-9 Hβ signal at δ 3.15, but no effect on the C-9 Hα signal at δ 2.60 was observed. Thus, the conformations of **13** and **14** must be non-steroidal chair–half chair (**13b** and **14b**, respectively).

Since the ketol (**13**) takes a non-steroidal form (**13b**) in the solution, it is expected that some of the 6β-hydroxy product will be formed by metal hydride reduction. Reduction of **13** with lithium aluminum hydride gave a product which was separated by preparative thin-layer chromatography (TLC) to give two products, (±)-**1a**, mp 155—160° (dec.) and (±)-6-epifuranofukinol (**15**), mp 200—202°, in 8% and 50% yield, respectively. The NMR spectra of (±)-**1a** and its diacetate (±)-(**1g**), mp 127—129°, were in good agreement with those of (—)-furanofukinol and diacetylfuranofukinol, respectively, which were reported by Naya *et al.*[6b]

For the stereoselective synthesis of (±)-furanofukinol (**1a**), several reductive procedures for **13** were investigated. On reduction of **13** under thermodynamic conditions, formation of a quasi-equatorial C-6β hydroxyl group is expected. In fact, reduction of **13** with sodium metal in refluxing ethanol gave (±)-**1a** in 52% yield, stereoselectively. Formation of a trace amount of the 6α-hydroxy epimer (**15**) under these conditions was found by TLC and gas-liquid chromatography (GLC).

The successful stereoselective reduction procedure developed for (±)-**1a** was next applied to (±)-ligularone[3] (**4**), which was derived from diketone (**12**). Reduction of **4** with lithium aluminum hydride gave (±)-6-epipetasalbin (**5**) as an oil in high yield, stereoselectively. The 6β-hydroxy product (**2**) was not detected by TLC and GLC. The spectral data for (±)-**5** were in good agreement with those of (—)-epipetasalbin derived from (—)-ligularone (**4**) reported by Ishii *et al.*[8] Reduction of **4** with dissolved sodium metal in refluxing ethanol under the conditions described for **13** gave (±)-petasalbin (**2**) as an oil in 58% yield, stereoselectively. The 6α-epimer (**5**) was not detected by TLC and GLC. The infrared (IR) and NMR data for (±)-**2** were in good agreement with those of (—)-petasalbin reported by Ishii *et al.*[8]

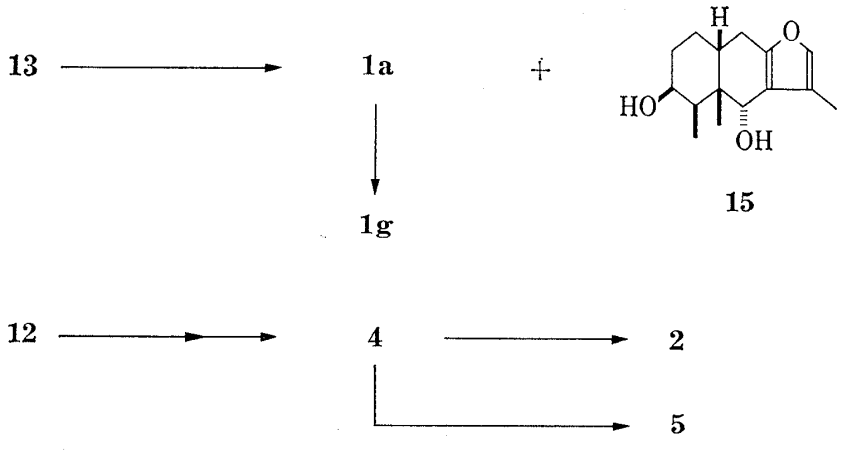

Chart 3

Experimental

Instrumentation was as described in reference 5.

Reduction of the Diketone (8) with $NaBH_4$——$NaBH_4$ (7 mg) was added to a solution of diketone[3] (**8**) (37 mg) in MeOH (20 ml) with stirring in an ice bath, and the stirring was continued for 15 min. NH_4Cl was added to the reaction mixture and then the solution was evaporated down *in vacuo*. The residue was extracted with ether, washed with H_2O, and dried. After removal of the solvent *in vacuo*, the residue was chromatographed over alumina. Elution with hexane–EtOAc (4: 1) first gave a band of 3β-OH (**9**) (34 mg; 91% yield) followed by a band of 3α-OH (**10**) (2 mg; 5% yield). Recrystallization of **9** from hexane–EtOAc gave pure **9**, mp 119—119.5°, as colorless plates. *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Mol. wt. 246.1255. Found: C, 73.18; H, 7.37. M$^+$, 246.1280. IR cm^{-1}: 3530 (OH), 1640 (CO), 1615, 1600 (C=C). UV λ_{max}^{EtOH} nm (ε): 240 (7500), 246.5 (7600), 256 and 265 (each shoulder), 332.5 (6100). NMR δ: 1.35 (3H, d, J=6 Hz, 4-CH_3), 1.45 (3H, s, 5-CH_3), 2.22 (3H, d, J=1 Hz, 11-CH_3), 3.88 (1H, m, $W_{1/2}$=7 Hz, 3-H), 6.42 (1H, d, J=1 Hz, 9-H), 7.03 (1H, m, $W_{1/2}$=3 Hz, 12-H). Mass Spectrum (MS) *m/e* (rel. intensity %): 246 (M$^+$, 85), 228 ([M−18]$^+$, 37), 213 (52), 199 ([M−47]$^+$, 27), 189 ([M−57]$^+$, 100). Recrystallization of **10** from hexane–EtOAc gave pure **10**, mp 144—145.5°, as colorless needles. High-resolution MS: Mol. wt. 246.1255 for $C_{15}H_{18}O_3$. Observed: M$^+$, 246.1273. IR cm^{-1}: 3440 (OH), 1641 (CO), 1612, 1594 (C=C). UV λ_{max}^{EtOH} nm: 240, 246, 256 and 266 (each shoulder), 333. NMR δ: 1.23 (3H, s, 5-CH_3), 1.25 (3H, d, J=6 Hz, 4-CH_3), 2.22 (3H, d, J=1 Hz, 11-CH_3), 3.66 (1H, m, $W_{1/2}$=22 Hz, 3-H), 6.42 (1H, bs, 9-H), 7.07 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 246 (M$^+$, 100), 228 ([M−18]$^+$, 58), 213 (89), 199 ([M−47]$^+$, 42), 189 ([M−57]$^+$, 84).

(±)-3β-Hydroxyfuranoeremophilan-6-one (13)——$NaBH_4$ (4 mg) was added to a solution of furanoeremophilane-3,6-dione[3] (**12**) (25 mg) in MeOH (10 ml) with stirring in an ice bath, and the stirring was continued for 10 min. After work-up as described for **9**, the crude product was purified by column chromatography over silica gel to afford 24 mg (95% yield) of 3β-OH (**13**), as a colorless oil. High-resolution MS of **13**: Mol. wt. 248.1411 for $C_{15}H_{20}O_3$. Observed: M$^+$, 248.1411. IR cm^{-1}: 3450 (OH), 1670 (CO). UV λ_{max}^{EtOH} 269.5 nm. NMR δ: 0.99 (3H, d, J=7 Hz, 4-CH_3), 1.15 (3H, s, 5-CH_3), 2.20 (3H, d, J=1 Hz, 11-CH_3), 2.59 (1H, dd, J=18, 2 Hz, 9α-H), 3.11 (1H, dd, J=18, 6 Hz, 9β-H), 3.68 (1H, m, $W_{1/2}$=15 Hz, 3-H), 7.09 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 248 (M$^+$, 24), 230 [(M−18]$^+$, 15), 176 ([M−72]$^+$, 38), 163 ([M−85]$^+$, 49), 122 ([M−126]$^+$, 100).

13 was converted to the acetate (**14**) by treatment with Ac_2O–pyridine. Recrystallization from hexane–EtOAc afforded 27 mg (92% yield) of **14**, mp 111—112°, as colorless needles. *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Mol. wt. 290.1516. Found: C, 70.52; H, 7.71. M$^+$, 290.1505. IR cm^{-1}: 1730, 1665 (CO), 1255 (OCOCH_3). UV λ_{max}^{EtOH} nm (ε): 270 (3300). NMR δ: 1.00 (3H, d, J=7 Hz, 4-CH_3), 1.14 (3H, s, 5-CH_3), 2.03 (3H, s, COCH_3), 2.20 (3H, d, J=1 Hz, 11-CH_3), 2.60 (1H, dd, J=18, 2 Hz, 9α-H), 3.15 (1H, dd, J=18, 6 Hz, 9β-H), 4.70 (1H, m, $W_{1/2}$=13 Hz, 3-H), 7.08 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 290 (M$^+$, 9), 230 ([M−60]$^+$, 23), 163 ([M−127]$^+$, 17), 122 ([M−168]$^+$, 100).

Reduction of 13 with $LiAlH_4$——$LiAlH_4$ (11 mg) was added to a solution of **13** (24 mg) in dry ether (15 ml) with stirring at room temperature, and the stirring was continued for 1.5 hr. After work-up in the usual manner, the crude product was separated by preparative TLC over silica gel to give two bands. Recrystallization of band 1 from EtOAc afforded 2 mg (8% yield) of (±)-furanofukinol (**1a**), mp 155—160° (dec.), as colorless crystals. High-resolution MS: Mol. wt. 250.1568 for $C_{15}H_{22}O_3$. Observed: M$^+$, 250.1580. IR cm^{-1}: 3390 (OH). NMR (DMSO-d_6) δ: 0.77 (3H, s, 5-CH_3), 0.84 (3H, d, J=7 Hz, 4-CH_3), 1.98 (3H, d, J=1 Hz, 11-CH_3), 3.97 (1H, m, $W_{1/2}$=18 Hz, 3-H), 4.24 (1H, d, J=4 Hz, 3-OH), 4.60 (1H, d, J=8 Hz, 6-OH), 4.75 (1H, d, J=8 Hz, 6-H; on addition of D_2O, the signal changed to a broad singlet), 7.15 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 250 (M$^+$, 5), 124 ([M−126]$^+$, 100). Recrystallization of band 2 from EtOAc gave 12 mg (50% yield) of (±)-6-epifuranofukinol (**15**), mp 200—202°, as colorless needles. High-resolution MS: Mol. wt. 250.1568 for $C_{15}H_{22}O_3$: Observed: M$^+$, 250.1572. IR cm^{-1}: 3350, 3250 (OH). NMR (DMSO-d_6) δ: 0.73 (3H, s, 5-CH_3), 0.91 (3H, d, J=7 Hz, 4-CH_3), 1.94 (3H, d, J=1 Hz, 11-CH_3), 4.05 (1H, d, J=7 Hz, 6-H; on addition of D_2O, the signal changed to a singlet), 4.09 (1H, d, J=5 Hz, 3-OH), 4.70 (1H, m, $W_{1/2}$=16 Hz, 3-H), 4.87 (1H, d, J=7 Hz, 6-OH), 7.18 (1H, m, $W_{1/2}$=3 Hz, 12-H).

(±)-Furanofukinol Diacetate (1g)——(±)-**1a** (15 mg) was dissolved in 10 ml of a solution of Ac_2O–pyridine (1: 4), and the solution was allowed to stand at room temperature for 24 hr. After removal of the solvent *in vacuo*, the residue was column chromatographed over silica gel to give 16 mg (80% yield) of (±)-**1g**. Recrystallization from EtOAc–hexane gave pure **1g**, mp 127—129°, as colorless prisms. High-resolution MS: Mol. wt. 334.1779 for $C_{19}H_{26}O_5$. Observed: M$^+$, 334.1799. IR cm^{-1}: 1750, 1735 (CO), 1240 (OCOCH_3). UV λ_{max}^{EtOH} nm: 218. NMR δ: 0.97 (3H, d, J=7 Hz, 4-CH_3), 1.01 (3H, s, 5-CH_3), 1.88 (3H, d, J=1 Hz, 11-CH_3), 2.03 (3H, s, 3-OCOCH_3), 2.13 (3H, s, 6-OCOCH_3), 5.32 (1H, m, $W_{1/2}$=17 Hz, 3-H), 6.37 (1H, bs, 6-H), 7.06 (1H, m, $W_{1/2}$=4 Hz, 12-H). MS *m/e* (rel. intensity %): 334 (M$^+$, 7), 292 ([M−42]$^+$, 16), 274 ([M−60]$^+$, 17), 232 ([M−102]$^+$, 18), 159 ([M−175]$^+$, 27), 124 ([M−210]$^+$, 100). IR and NMR spectra of (±)-**1g** were in good agreement with those of an authentic specimen of optically active **1g**.

(±)-Furanofukinol (1a)——Small pieces of Na (2 g) were added to a solution of **13** (25 mg) in refluxing EtOH (15 ml). When the sodium was completely dissolved in the solvent, the reaction mixture was cooled

to room temperature. NH_4Cl was added to the reaction mixture and then the solvent was evaporated off *in vacuo*. The residue was extracted with ether, and the organic layer was washed with sat. NH_4Cl and H_2O, and dried. After removal of the solvent, the residue was purified by preparative TLC on silica gel to give 13 mg (52% yield) of (±)-**1a**, mp 155—160° (dec.). All spectral data for (±)-**1a** were identical with those for (−)-furanofukinol, as described above.

(±)-6-Epipetasalbin (5)——$LiAlH_4$ (8 mg) was added to a solution of (±)-ligularone[3] (**4**) (16 mg) in dry ether (10 ml) with stirring at room temperature, and the stirring was continued for 30 min. After work-up in the usual manner, the crude product was purified by preparative TLC on silica gel to afford 15 mg (94% yield) of (±)-6-epipetasalbin (**5**), as a colorless oil. High-resolution MS: Mol. wt. 234.1618 for $C_{15}H_{22}O_2$. Observed: M^+, 234.1602. IR cm^{-1}: 3480 (OH). UV λ_{max}^{EtOH} nm: 219.5. NMR δ: 0.87 (3H, s, 5-CH_3), 1.05 (3H, d, J=7 Hz, 4-CH_3), 2.06 (3H, d, J=1 Hz, 11-CH_3), 4.31 (1H, bs, 6-H), 7.07 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 234 (M^+, 5), 124 ([M−110]$^+$, 100).

(±)-Petasalbin (2)——Using the procedure described for **1a**, Na (1.2 g) was added to a solution of (±)-**4** (15 mg) in refluxing EtOH (15 ml). After work-up in the manner described for **1a**, the product was purified by preparative TLC on silica gel to afford 3 mg of (±)-**4** and 7 mg (58% yield from converted **4**) of (±)-petasalbin, as a colorless oil. High-resolution MS: Mol. wt. 234.1618. for $C_{15}H_{22}O_2$. Observed: M^+, 234.1639. IR cm^{-1}: 3460 (OH). UV λ_{max}^{EtOH} 218.5 nm. NMR δ: 0.89 (3H, d, J=7 Hz, 4-CH_3), 1.01 (3H, s, 5-CH_3), 2.07 (3H, d, J=1 Hz, 11-CH_3), 4.72 (1H, s, 6-H), 7.07 (1H, m, $W_{1/2}$=3 Hz, 12-H). MS *m/e* (rel. intensity %): 234 (M^+, 5), 124 ([M−110]$^+$, 100).

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