The Structural Elucidation of Sesquiterpene Lactones from *Petasites japonicus* Maxim[1]

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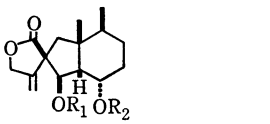
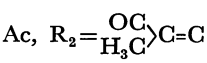
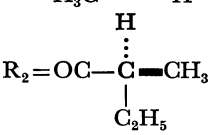
The structures and absolute configurations of five new sesquiterpenic lactones—fukinolide (**1**), dihydrofukinolide (**2**), homofukinolide (**3**), S-fukinolide (**4**), and fukinanolide (**5**)—isolated from the flower stalks of *Petasites japonicus* Maxim. have been established by a combination of spectroscopic and chemical methods, and by correlation with the known fukinone (**25**).

In a preliminary communication,[2] we reported the isolation and the structural proofs of three new lactones,[3] fukinolide (**1**), S-fukinolide (**4**), and fukinanolide (**5**), obtained from the flower stalks of wild butterburs, *Petasites japonicus* Maxim. ("Fuki" in Japanese). Our subsequent work has led to the isolation of two new sesquiterpenic lactones, named dihydrofukinolide (**2**)[4] and homofukinolide (**3**),[4] from the wild plant. The present paper will describe the isolation and structural determination of these five lactones. All of them belong to the class of novel skeletal sesquiterpenoids of the fukinane (**6**) type,[5,6] and all are shown to be ester derivatives of fukinolidol (**8**), which is the common sesquiterpenic moiety of these lactones.



1 R_1=Ac, R_2=  (ang)



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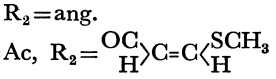
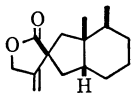
4 R_1=Ac, R_2= 



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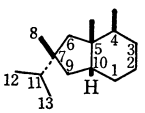

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Fig. 1. Formulas **1**—**6**.

Structure of Fukinolide (1). Fukinolide (**1**) ($C_{22}H_{30}O_6$, mp 101.5—102.0°C, $[\alpha]_D^{22}$ −126°) is the most abundant constituent of the flower stalks of the wild strain. In the UV spectrum, **1** showed only an end absorption (ε, 11300 at 215 mμ). The functional groups of **1** were inferred from the IR(KBr) absorption bands to be as follows (Fig. 2): 1775 (γ-lactone), 1737, 1706, 1693, 1263, 1230 (esters), 3090, 1666, 1643, 917 cm^{-1} (double bonds).

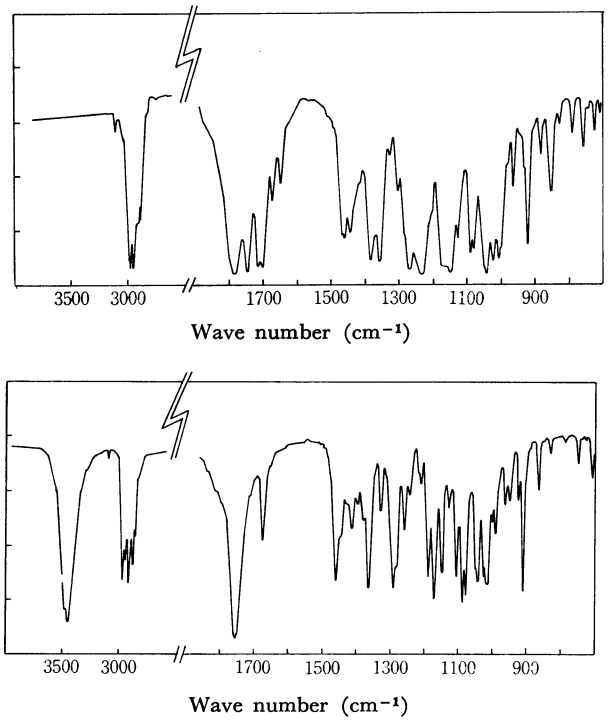


Fig. 2. IR spectra of fukinolide **1** and fukinolidol **8**.

The mild hydrolysis of fukinolide (**1**) with dilute hydrochloric acid gave deacetylfukinolide (**7**) ($C_{20}H_{28}O_5$, mp 167.0—167.5°C), which was then reconverted to **1** by acetylation with acetic anhydride-pyridine. The treatment of **1** with 2 N alcoholic potassium hydroxide afforded angelic acid,[7,8] and a doil, named fukinolidol (**8**) ($C_{15}H_{22}O_4$, mp 176.5—177.5°C). Thus, fukinolide (**1**) proved to be an acetate-angelate of fukinolidol (**8**).

The presence of a γ-lactone group in **1** was presumed from the reaction behavior of alkaline hydrolysis to **8**, as well as from its IR band at 1775 cm^{-1} (Fig. 2).

1) This work was supported in part by a grant from the Ministry of Education of Japan.

2) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, M. Kobayashi, and S. Katsumura, *Chem. Ind.* (London), **1968**, 318.

3) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, and M. Kobayashi, 11th Symposium on the Chemistry of Natural Products, Symposium Papers (1967), p. 88.

4) M. Hayashi, S. Nakamura, I. Takagi, and K. Naya, Annual Meeting of the Chemical Society of Japan (1968), Abstract of Paper, Vol. 3, p. 2152.

5) The numbering system is based on that of the presumed biogenetic precursor possessing eremophilane skeleton.

6) For the preparation of fukinane see: K. Naya and M. Kobayashi, This Bulletin, **44**, 258 (1971).

7) W. Herz and M. V. Laksmikantham, *Tetrahedron*, **21**, 1711 (1965).

8) A. Stoll, R. Morf. A. Rheiner, and J. Renz, *Experientia*, **12**, 360 (1956).

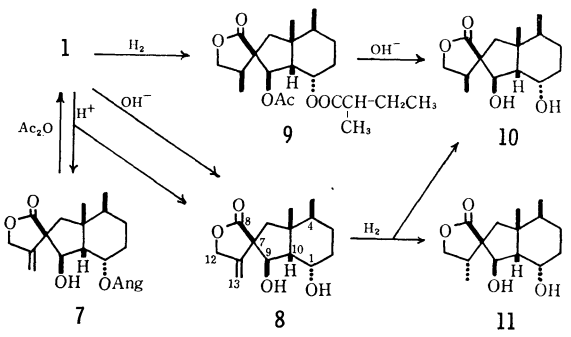


Fig. 3. Formulas **7**—**11**.

One of the two ethylenic double bonds clearly belongs to the angelyl group, as above, while the other seems to be an end-methylene group, judging from the IR bands at 3090, 1666, and 917 cm^{-1}. On hydrogenation with a platinum catalyst in acetic acid, **1** gave the tetrahydro derivative (**9**), which then afforded only dihydrofukinolidol (**10**) ($C_{15}H_{24}O_4$, mp 190.0—191.0 °C) on alkaline hydrolysis, while the similar hydrogenation of fukinolidol (**8**) gave dihydrofukinolidol (**10**) and its epimer, epidihydrofukinolidol (**11**) ($C_{15}H_{24}O_4$, mp 148.0—149.0°C). The IR spectra of **10** and **11** showed no band for an end-methylene group. It can readily be supposed that the above isomeric nature are caused by the hydrogenation of end-methylene groups by different steric environments depending on the existence of ester groups between fukinolide (**1**) and fukinolidol (**8**). The details of the stereochemistry will be described below.

The structure of fukinolidol (**8**) was established from the following evidence.

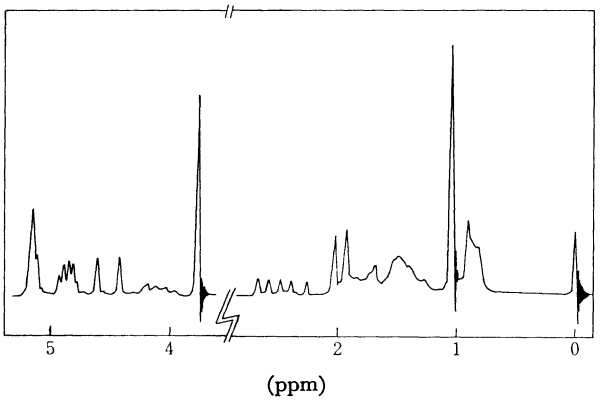


Fig. 4. NMR spectrum of fukinolidol **8**.

Spiro-lactone Group. Fukinolide (**1**) and fukinolidol (**8**) showed essentially similar NMR spectra,[9] except for the signals due to angelate and acetate groups in **1** (Fig. 4). The NMR spectra of **1** and **8** showed the presence of a $-O-CH_2-C=CH_2$ grouping with allyl coupling signals: *i. e.*, 5.20 (d, J=2.0 Hz, $-C=CH_2$) and 4.67 (t, J=1.5 Hz, $-O-CH_2-$) in **1**, and 5.12 (t, J=2.0 Hz, $-C=CH_2$) and 4.81 (m, $-O-CH_2-$) in **8**.

9) The NMR chart of fukinolide **1** was inserted in Ref. 2; NMR spectra in this paper were taken on a JEOL C-60 spectrometer with TMS as an internal reference. The values are reported in ppm.

The reduction of fukinolide (**1**) or fukinolidol diacetate (**12**) ($C_{19}H_{26}O_6$, mp 224.5—226.0°C) with lithium aluminum hydride afforded the same product, a tetrol (**13**) ($C_{15}H_{26}O_4$, mp 106.0—107.0°C), whose IR spectrum showed no C=O band, but the presence of an end-methylene group at 1649 and 906 cm^{-1}. The NMR spectrum of **13** exhibited the signals at 4.23 (slightly split s, 2H) and 5.28 (d, J=5.0 Hz, 2H) due to $HO-CH_2-$ and $-C=CH_2$ respectively, and newly-appeared signals at 3.84 and 3.51 (ABq, J=11.0 Hz, 2H) assignable to the $HO-CH_2-$ group, which was probably derived from the lithium aluminum hydride reduction of the lactone C=O group of **1** or **12**.

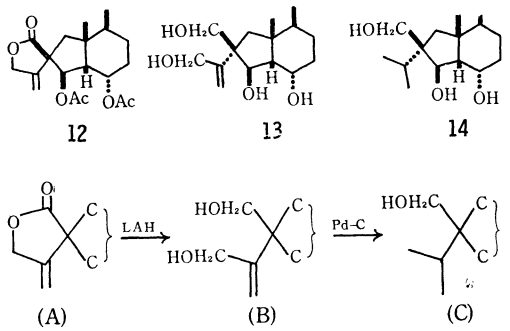


Fig. 5. Formulas **12**—**14**, Partial structure A, B and C.

The above data led to the conclusion that a partial structure (A) was present in **1**. The allylic hydroxyl group in the partial formula (B) was confirmed by the following chemical method.

On the hydrogenation of tetrol (**13**) with palladium charcoal in ethanol, the allylic hydroxyl group was eliminated by hydrogenolysis to yield a triol (**14**) ($C_{15}H_{28}O_3$, mp 88.5—89.5°C). The NMR spectrum of **14** showed signals at 0.97 and 1.07 (each d, J=6.5 Hz) due to a newly-introduced isopropyl group, as in the partial structure (C).

Carbon-ring System and 1,3-Diol Relationship. The NMR spectrum to fukinolidol (**8**) showed signals at 0.86 (d, J=5.0 Hz), 1.04 (s) assignable to a secondary methyl and a tertiary methyl respectively. Accordingly, considering the presence of a spiro-lactone group, two methyls, and the lack of saturation of fukinolidol (**8**) ($C_{15}H_{22}O_4$), the remaining nine carbon atoms seems to consist of a bicyclononane, most probably

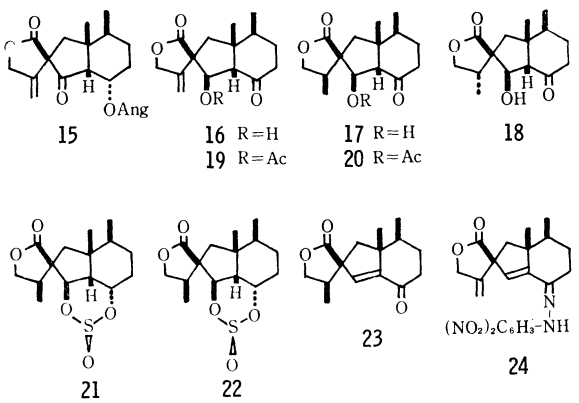


Fig. 6. Formulas **15**—**24**.

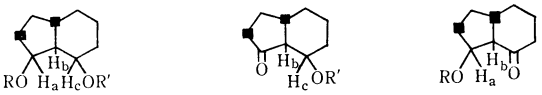
a 5-6 fused ring system. This assumption was verified chemically as follows.

The oxidation of deacetylfukinolide (**7**) with Jones' reagent gave a ketone (**15**) ($C_{20}H_{26}O_5$, mp 96.0—97.0°C), whose IR spectrum showed C=O bands for γ-lactone (1770 cm^{-1}), 5-membered ring ketone (1751 cm^{-1}), and α,β-unsaturated ester (1715, 1646, 1239 cm^{-1}). Similarly, Jones' oxidations of fukinolidol (**8**), dihydrofukinolidol (**10**), and epidihydrofukinolidol (**11**) gave three ketols, **16** ($C_{15}H_{20}O_4$, mp 141.5—142.0°C), **17** ($C_{15}H_{22}O_4$, mp 184.0—186.0°C), and **18** ($C_{15}H_{22}O_4$, mp 137.0—138.0°C) respectively, whose IR spectra showed bands at 3490 and 3365 (H-bonded OH), 1773 and 1755 (γ-lactone), and 1702sh and 1680 cm^{-1} (H-bonded 6-membered ring ketone) in **16**, at 3350 (H-bonded OH), 1767 (γ-lactone), and 1680 cm^{-1} (H-bonded 6-membered ring ketone) in **17**, and at 3470sh and 3405 (H-bonded OH), 1755 (γ-lactone), and 1680 cm^{-1} (H-bonded 6-membered ring ketone) in **18**. The IR spectra of both **16**-acetate (**19**) and **17**-acetate (**20**) showed C=O bands at *ca.* 1700 cm^{-1} attributable to 6-membered ring ketones, but no OH bands. Thus, the two hydroxyl functions of the above ketol derivatives are apparently located on the 5- and 6-membered ring respectively. Furthermore, the 1,3-relationship of the diols in fukinolidol (**8**) and dihydrofudkinoliol (**10**) was defined as will be described below.

The treatment of dihydrofukinolidol (**10**) with thionyl chloride–pyridine gave a mixture of two isomeric cyclic sulfites,[10] $C_{15}H_{22}O_5S$, which were separated by column chromatography to afford **21** (mp 190.5—191.5°C) and **22** (mp 187.5—188.5°C). These isomers were assigned to the **21** and **22** formulas from an examination of both the physical and chemical properties previously reported.[11] On the other hand, the treatment of the ketol **17** with phosphorus oxychloride–pyridine readily provided a dehydration product (**23**) ($C_{15}H_{20}O_3$, mp 103.0—103.5°C), whose IR, UV, and NMR spectra showed the presence of an α,β-unsaturated ketone; IR(KBr): 1681, 1629 cm^{-1}, λ_{max}^{EtOH} 250 mμ (ε, 7100), δ^{CDCl_3}: 6.07 (s) due to C–CH=C–CO. An alcoholic solution of the 2,4-dinitrophenylhydrazone of the **16** ketol was refluxed in the presence of a few drops of 85% phosphoric acid to give a dehydration product, **24** (mp 209.5—210.0°C), which showed the presence of a C–CH=C–C=N– grouping by the following data: λ_{max}^{EtOH} 373 mμ (ε, 31600),[12] δ^{CDCl_3}: 5.80 (s). The ease of dehydration suggests strongly that the **16** and **17** compounds both possess β-hydroxyketone groups. In the NMR spectra of **23** and **24**, the sharp singlets at both 6.07 and 5.80 indicate that the adjacent carbon atom of the ethylenic double bond bears no proton.

From the above results, all the two hydroxyl groups in fukinolidol (**8**), dihydrofukinolidol (**10**), and epidihydrofukinolidol (**11**) were confirmed to be in a 1,3-relationship. Subsequently, the outlines of H_a, H_b, and H_c in the 1,3-diol system, and the further expanded grouping $-CH_a(OH)-CH_b-CH_c(OH)-CH_2-$ in fukinolidol (**8**) could be drawn from the NMR data in Table 1.

Table 1. Chemical shifts (ppm as δ-values) of protons in 1,3-diol systems



D E F

■: bears no proton.

Compounds	H_a	H_b	H_c
Fukinolide **1**	5.79 d	2.82 dd	5.15 m
D: R=Ac R'=angelyl	J=10.5	J=5.0, 10.5	W ½=13.5
Deacetylfukinolide **7**	4.58 d	2.60 dd	5.20 m
D: R=H R'=angelyl	J=10.5	J=5.0, 10.5	W ½=13.5
Fukinolidol **8**	4.49 d	2.55 dd	4.08 m
D: R=R'=H	J=11.0	J=5.5, 11.0	W ½=13.5
Ketone **15**		3.02 d	5.05 m
E: R'=angelyl		J=5.0	
Ketone **16**	4.38 d	2.86 d	
F: R=H	J=11.0	J=11.0	
Ketone **17**	4.36 d	2.90 d	
F: R=H	J=11.0	J=11.0	

In addition, the NMR spectra of fukinolide (**1**) and fukinolidol (**8**) showed a pair of signals at 2.26 and 1.93 (ABq, J=14 Hz, 2H) and at 2.14 and 1.84 (ABq, J=14.5 Hz, 2H) respectively, indicating the presence of an isolated methylene group. If fukinolide (**1**) is genetically derived from eremophilane derivatives as those of the main constituents isolated from the *Petasites* species,[13,14] the summary of the above evidence leads to the carbon-ring system of fukinolidol (**8**) and also implies its stereochemistry; *i. e.*, two methyls on the carbon-ring system should be situated at at C-4 and C-5 with β-configurations, and the 5-6 ring juncture should be a *cis*-fused ring system, as in Formulas **1** and **8**. Accordingly, the H_a, H_b, and H_c in **8** may be assignable to the α-, β-, and β-configurations respectively, as is shown in Formula **8** on the basis of the coupling constants, J_{ab}=11.0 Hz, and J_{bc}=5.0 Hz, in the NMR spectra of the **15**, **16**, and **17** ketones

10) For the isomeric cyclic sulfites of 1,3-diol: *e. g.* see: A. T. Rowland, T.B. Adams, H. W. Atland, W. S. Creasy, S. A., Dressner and T. M. Dyott, *Tetrahedron Lett.*, **1970**, 4405; E. L. Eliel and N. L. Allinger, "Topics in Stereochemistry," Vol. 4, Willey-Interscience, New York (1967), p. 48.

11) K. Naya, I. Takagi, and T. Kasai, This Bulletin, **44**, 3204 (1971).

12) E. S. Stern and C. J. Timmons, "Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold, London (1970), p. 200.

13) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).

14) K. Naya and I. Takagi, *Tetrahedron Lett.*, **1968**, 629; A. Aebi, T. Waaler, and J. Buchi, *Pharm. Weekblad*, **93**, 397 (1958); C. Djerassi, M. Mauli, and L. H. Zalkow, *J. Amer. Chem. Soc.*, **81**, 3429 (1959); L. Novotný, J. Jizba, V. Herout, F. Sorm, L. H. Zalkow, S. Hu, and C. Djerassi, *Tetrahedron*, **19**, 1101 (1963); L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 6354 (1960); L. H. Zalkow, A. M. Shaligram, S. Hu, and C. Djerassi, *Tetrahedron*, **22**, 337 (1966).

(Table 1). Therefore, the configurations of the two hydroxyl groups in fukinolidol (**8**) can be assigned to the 1α(eq) and 9β orientations respectively. Further evidence of the stable 1α(eq) orientation was provided by the reduction of the ketol acetate (**20**) with sodium] borohydride, giving dihydrofukinolidol (**10**). The chemical shifts of the C–15 methyls in the NMR spectra of fukinolidol (**8**) ($CDCl_3$, 1.04; pyridine, 0.97) and dihydrofukinolidol (**10**) ($CDCl_3$, 1.03; benzene, 0.99) showed the anisotropic effect of of the spiro-lactone carbonyl group, suggesting that the lactone and 15β-methyl are located on the same side of the *cis*-fused 5-6 carbon-ring system. The ORD curves of the three ketones, **15**, **16**, and **17**, are in good agreement with the above stereochemistry (**15**: +Cotton; **16** and **17**: −Cotton effects).[15]

Thus, the above results lead to the stereoformulas of **8** and **1** for fukinolidol and fukinolide respectively.

The final evidence for the structure and stereochemistry of fukinolidol (**8**) was provided by the following chemical method for correlation to the known eremophilane derivative, fukinone (**25**),[13] *via* fukinan-8-ol (**26**).

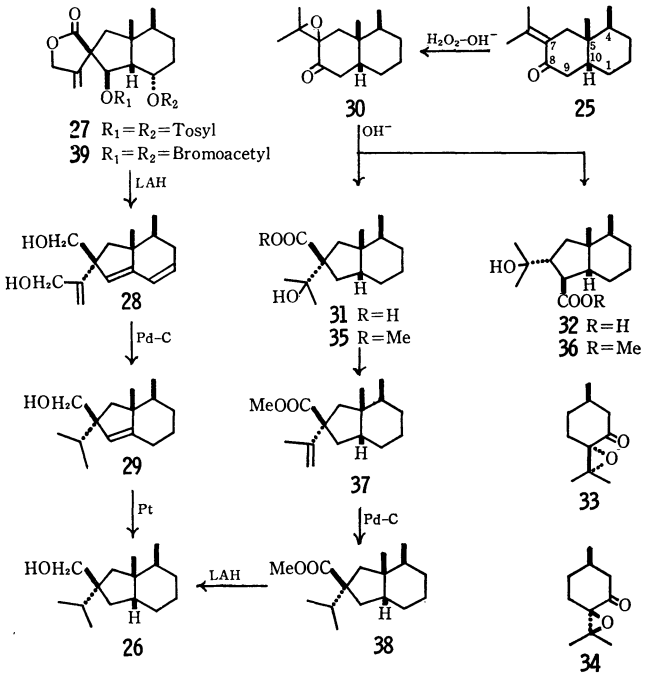


Fig. 7. Formulas **25**—**39**.

The treatment of fukinolidol ditosylate (**27**) (mp 179.5—180.0°C dec) with lithium aluminum hydride gave a diol, **28** ($C_{15}H_{22}O_2$, mp 119.5—120.0°C), whose spectra indicate the presence of a conjugated diene; λ_{max}^{EtOH} 237 mμ (ε, 18700); δ^{CDCl_3}: 6.21 (d, J=9.5 Hz, C–1 H), 5.75 (dt, J=9.5, 2.0 Hz, C–2 H) and 5.50 (s, C–9 H). The subsequent hydrogenation of **28** with palladium charcoal in ethanol afforded a product, **29**, by the hydrogenolysis of the allylic hydroxyl group, as has been described before. The IR and NMR spectra of **29** still showed the existence of an ethylenic bond; IR (film): 1662 cm^{-1}; δ^{CCl_4}: 4.95 (s, C–9 H). Subsequent hydrogenation with a platinum catalyst in acetic acid gave a saturated monol, fukinan-8-ol (**26**) ($C_{15}H_{28}O$, mp 38.0—39.0°C).

On the other hand, fukinan-8-ol (**26**) was prepared from the eremophilane-type, known fukinone (**25**), which is supposed to be a precursor for the genesis of fukinolide (**1**) and its homologues.

The treatment of a mixture of fukinone epoxides (**30**)[16] with an aqueous sodium hydroxide–ethanol solution gave mainly a mixture of a spiro-acid (**31**) and a nonspiro-acid (**32**), similar to the products of the Favorskii rearrangements of the two pulegone epoxides **33** and **34**.[17] The spiro-acid (**31**) was isolated as its ester, **35** ($C_{16}H_{28}O_3$, mp 63.5—64.5°C) by column chromatography. The stereochemistry of the spiro-acid can be properly described by Formula **31** in accordance with the known mechanism demonstrated for the rearrangement of the pulegone epoxides, **33** and **34**.[17] The spiro-ester (**35**) was dehydrated with phosphorus oxychloride-pyridine to afford an unsaturated ester (**37**); subsequent hydrogenation with 10% palladium charcoal in ethanol gave an oil (**38**). The reduction of the saturated alcohol (**38**) with lithium aluminum hydride gave a monol ($C_{15}H_{28}O$, mp 38.0—39.0°C), which was identical in all respects

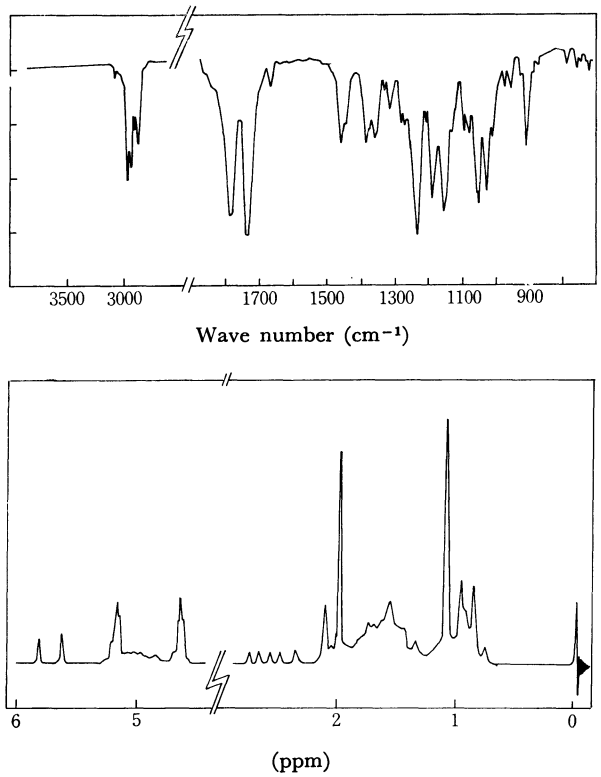


Fig. 8. IR and NMR spectra of dihydrofukinolide **2**.

15) G. V. Baddeley, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, **1960**, 1715; C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362 (1956); C. Djerassi, W. Closson, and E. Lippman, *ibid.*, **78**, 3163 (1956).

16) Recently α- and β-epoxides of fukinone have been separated and examined their stereospecific natures for Favorskii rearrangement. The details will be published soon.

17) G. W. K. Cavill and C. D. Hall, *Tetrahedron*, **23**, 1119 (1967); W. Reusch and P. Mattison, *ibid.*, **23**, 1953 (1967); S. A. A. Achmad and G. W. K. Cavill, *Aust. J. Chem.*, **16**, 858 (1963).

with the fukinan-8-ol (**26**) prepared from fukinolide (**1**).

At this stage, the structures and absolute configurations of fukinolidol and fukinolide can be represented as in Formulas **8** and **1**. In conjunction with this study, an X-ray analysis[18] has been performed with fukinolidol dibromoacetate (**39**); this also secured the molecular structure of fukinolidol (**8**).

Structure of Dihydrofukinolide (2). Dihydrofukinolide (**2**) ($C_{22}H_{32}O_6$, mp 125.0—126.0°C, $[\alpha]_D^{22}$ −105.5°) was named on the basis of having two hydrogens more than fukinolide (**1**) ($C_{22}H_{30}O_6$). Its IR and NMR spectra resemble those of fukinolide (**1**) except for the absorptions and signals attributable to the angelyl group[7] in **1**. Dihydrofukinolide (**2**) was deduced to be an ester of fukinolidol (**8**) from its IR spectrum; IR(KBr): 1788 (γ-lactone), 1734, 1236 (saturated ester), 3085, 1667, 909 cm^{-1} (end-methylene). In fact, the **2** compound afforded fukinolidol (**8**), acetic acid, and *d*-(S)-α-methylbutyric acid (**40**)[19] upon alkaline hydrolysis. These acids were identified as *p*-phenylphenacyl esters by comparison with authentic sample (tlc, mixed-melting-point determination, and IR spectra). Therefore, dihydrofukinolide (**2**) proved to be the acetate and *d*-(S)-α-methylbutyrate of fukinolidol (**8**).

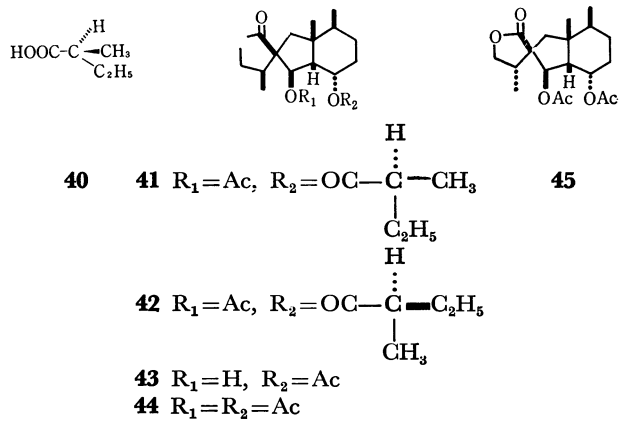


Fig. 9. Formulas **40**—**45**.

The final evidence for the structure of dihydrofukinolide (**2**) was obtained by the correlation with fukinolide (**1**) through its hydrogenated derivatives as follows.

The reduction of fukinolide (**1**) with a platinum catalyst in acetic acid afforded a mixture of two diastereomers, **41** and **42** ($C_{22}H_{34}O_6$), each of which was separated by repeated recrystallization with aqueous methanol, **41**, colorless needles, mp 112.0—113.0°C, $[\alpha]_D^{22}$ −52.25°; **42**, colorless prisms, mp 121.5—122.5°C, $[\alpha]_D^{22}$ −67.5°. The lower-melting isomer, **41**, was identical with tetrahydrofukinolide (mp 116.5—117.0°C, $[\alpha]_D^{22}$ −51.0°), which was obtained exclusively by the hydrogenation of dihydrofukinolide (**2**) with palladium charcoal in ethanol. On the other hand, the higher-melting isomer, **42**, showed a depression of the mixed-melting-point on admixture with tetrahydrofukinolide (**41**) prepared from dihydrofukinolide (**2**), and a different IR spectrum from that of **41**. The above diastereomers are only concerned with an asymmetric center derived from the hydrogenation of the angelyl moiety of fukinolide (**1**). This fact indicates that the addition of hydrogens to the end-methylene group of **1** proceeds preferentially from one side of the lactone ring, namely, from the opposite, less-hindered side to the attaching site of ester groups. The epimeric mixture of **41** and **42**, therefore, upon alkaline hydrolysis afforded only dihydrofukinolidol (**10**). On the other hand, the hydrogenation of fukinolidol (**8**) with palladium charcoal in ethanol gave two diastereomers connected with the configuration of C-13 methyl, $C_{15}H_{24}O_4$—namely, dihydrofukinolidol (**10**) (mp 190.0—191.0°C, $[\alpha]_D^{22}$ −14.5°) and epidihydrofukinolidol (**11**) (mp 148.0—149.0°C, $[\alpha]_D^{22}$ −69.5°), as has been described above. The above results apparently demonstrate that the the absence of ester groups facilitates the addition of hydrogens to the end-methylene group from both sides

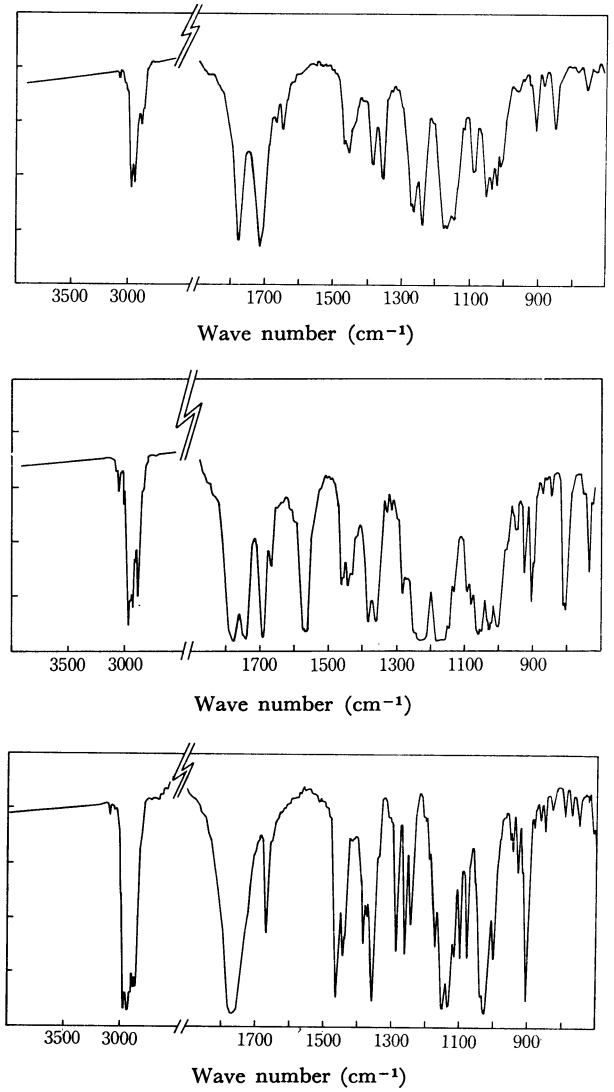


Fig. 10. IR spectra of homofukinolide **3**, S-fukinolide **4**, and fukinanolide **5**.

18) C. Katayama, A. Furusaki, I. Nitta, M. Hayashi, and K. Naya, This Bulletin, **43**, 1976 (1970).

19) A. Yagi and T. Kawasaki, *Yakugaku Zasshi*, **82**, 210 (1962).

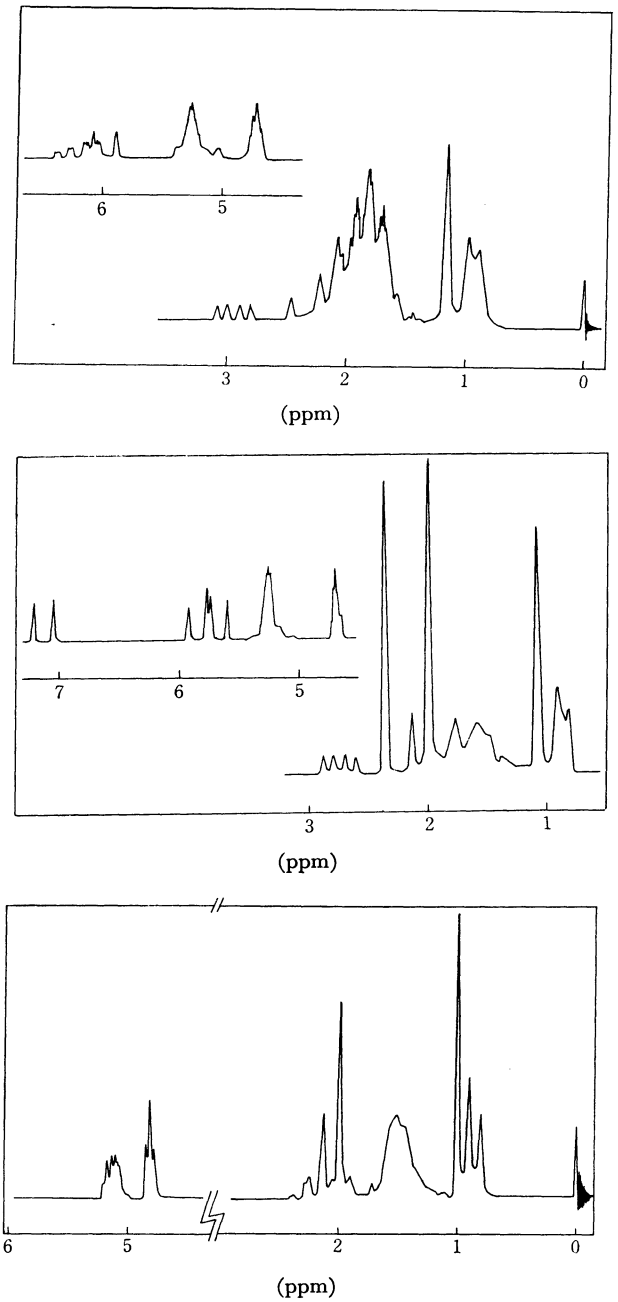
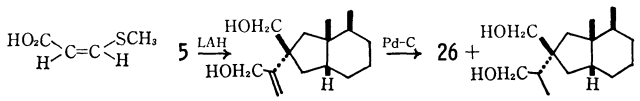


Fig. 11. NMR spectra of homofukinolide **3**, S-fukinolide **4**, and fukinanolide **5**.

of the lactone ring. Thus, the epimer can be represented by Formula **11** in connection with Fomula **10**, with 13β-methyl for dihydrofukinolidol. This configurational postulation at the C-13 methyl group was also supported by the following chemical behavior in response to the steric hindrance caused by 13β-methyl: the acetylation of dihydrofukinolidol (**10**) containing 13β-methyl with acetic anhydride–pyridine gave a mixture of monoacetate (**43**) ($C_{17}H_{26}O_5$, mp 194.0—196.0°C) and diacetate (**44**) ($C_{19}H_{28}O_6$, mp 246.0—248.0°C, $[\alpha]_D^{22}$ −42.5°), while the acetylation of epidihydrofukinolidol (**11**) containing 13α-methyl under conditions similar to the above readily afforded only the diacetate (**45**) (mp 214.0—215.0°C, $[\alpha]_D^{22}$ −50.5°) quantitatively.

Homofukinolide (3). The spectroscopic absorption of homofukinolide (**3**) ($C_{25}H_{34}O_6$, mp 184.0—186.0°C, $[\alpha]_D^{22}$ −127°) were also similar to those of fukinolide (**1**). The NMR spectrum of **3** showed the signals at 6.13 attributable to two vinyl protons, and four vinyl methyl signals between 1.70—1.95 due to the two angelyl groups. The intensity of the UV maximum, ε, 23500 at 215 mμ supported the above assignment.[20] Homofukinolide (**3**) was hydrolysed with alcoholic potassium hydroxide to give fukinolidol (**8**) (mp 177.0—178.0°C) and angelic acid.[8] Those results led to the conclusion that homofukinolide (**3**) is the diangelate of fukinolidol (**8**).

S-Fukinolide (4). Compound **4** ($C_{21}H_{28}O_6S$, mp 200.0—201.0°C, $[\alpha]_D^{22}$ −161°) shows spectroscopic absorptions closely similar to those of fukinolide (**1**), except for the IR band at 1568 cm^{-1} and the NMR signals at 7.00 (d, J=9.5 Hz, 1H), 5.60 (d, J=9.5 Hz, 1H), 2.38 (s, 3H) instead of 5.96 (q, J=7.0 Hz, 1H), 1.80 (d, J=7.0 Hz, 3H) and 1.78 (s, 3H) due to the angelate group in **1**. Further, besides the above spectra, the UV spectra (λ_{max}^{EtOH} 287.5 mμ (ε, 15700)) suggest that Compound **4** may include an isolated disubstituted ethylenic acid residue containing a β-*S*-alkyl group. The hydrolysis of **4** with alcoholic potassium hydroxide gave fukinolidol (**8**) and *cis*-β-methylthioacrylic acid (**46**) ($C_4H_6O_2S$, mp 119.0—120.0°C).[8,21] Thus, S-fukinolide can be represented by Formula **4**.



46 **47** **48**

Fig. 12. Formulas **46**—**48**.

Fukinanolide (5). Fukinanolide (**5**) ($C_{15}H_{22}O_2$, mp 80.5—80.6°C, $[\alpha]_D^{22}$ +17.0°) showed IR bands indicating the presence of a γ-lactone (1770 cm^{-1}) and an end-methylene group (1665, 898 cm^{-1}). From a comparison of the NMR spectra of **5** and fukinolidol (**8**), this compound was readily inferred to possess the **5** structure.

The above conclusion was ascertained by the chemical method as follows.

The reduction of **5** with lithium aluminum hydride gave a diol, **47** ($C_{15}H_{26}O_2$, mp 81.5—82.0°C). Compound **47** was hydrogenated with 10% palladium charcoal to afford a monol ($C_{15}H_{28}O$) and another diol, **48** ($C_{15}H_{28}O_2$, mp 121.0—122.0°C). The monol is identical in all respects with fukinan-8-ol (**26**), as is to be expected.

Therefore, the structure and absolute configuration of fukinanolide can be represented by Formula **5**.

Fukinolide (**1**), *S*-fukinolide (**4**), and fukinanolide (**5**) have also been isolated from the flower stalks of *Petasites japonicus* subsp. *giganteus* Kitam. and named bakkenolide-B, -D, and -A respectively by Kitahara

20) A. T. Nielsen, *J. Org. Chem.*, **22**, 1539 (1957).
21) L. Novotný, V. Herout and F. Sorm, *Collect. Czech. Chem. Commun.*, **2**, 2182 (1964).

and his colleagues. They have independently reached the same conclusions.[22]

Experimental

All the melting and boiling points are uncorrected. The IR spectra were recorded with a JASCO DS-402G spectrophotometer, and the UV spectra were obtained with a Cary Model 14 spectrophotometer. The optical rotations were measured with a Hitachi EPU-2A spectrophotometer, and the ORD curves were taken with a JASCO spectrophotometer, Model ORD-5. The mass spectra were measured with a Hitachi RMU-6 mass spectrometer. The analytical and preparative glc were performed with a Shimadzu GC-1C apparatus on a stainless steel column (ϕ=3 mm). The tlc were run on silica gel (Merck Kieselgel G). The microanalyses were carried out in the microanalytical section of the Shionogi Research Laboratory, Shionogi and Co., Ltd.

*Isolation of Fukinolide (**1**), Dihydrofukinolide (**2**), Homofukinolide (**3**), S-Fukinolide (**4**), and Fukinanolide (**5**).* The dried flower stalks of *P. japonicus* Maxim. collected near the northern margin of Lake Biwa, at the foot of Mt. Ibuki, in Shiga Prefecture, and at Mt. Shirouma in Nagano Prefacture, were extracted in the cold with methanol for 20 days. The solvent was then removed under reduced pressure, and the residue was dissolved in benzene. The solution was washed with a saturated sodium hydrogen carbonate aqueous solution and then with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*, thus leaving a dark oil (95 g). This oil was repeatedly chromatographed on silica gel, and elution with benzene, benzene–ethyl acetate (50 : 1), or light petroleum–ethyl ether (50 : 1) gave fukinanolide (**5**) (tlc: R_f, 0.77, benzene–ethyl acetate, 15 : 1), homofukinolide (**3**) (R_f, 0.64), dihydrofukinolide (**2**) (R_f, 0.47), fukinolide (**1**) (25 g; R_f, 0.45), and S-fukinolide (**4**) (3 g; R_f, 0.34).

*Fukinolide (**1**)*: mp 101.5—102.0°C, colorless prisms (from light petroleum), $[\alpha]_D^{22}$ −126.0° (*c*, 1.0, MeOH), −117.5° (*c*, 1.0, $CHCl_3$); MS: *m/e* 390 M^+; IR (KBr): 1775 (γ-lactone), 1737, 1706, 1693, 1263, 1230 (ester), 3090, 1666, 1643, 917 cm^{-1} (double bond), (CCl_4): 1788 (γ-lactone), 1744, 1716, 1235 (ester), 3080, 1667, 1645, 900 cm^{-1} (double bond); NMR($CDCl_3$): 5.96 (q, *J*=7.0 Hz, =CH- in angelate), 5.79 (d, *J*=10.5 Hz, 9-CH), 5.20 (d, *J*=2.0 Hz, 13-CH_2), ca 5.15 (m, 1-CH), 4.67 (t, *J*=1.5 Hz, 12-CH_2), 2.82 (dd, *J*=5.0, 10.5 Hz, 10-CH), 2.26, 1.93 (ABq, *J*=14.0 Hz, 6-CH_2), 1.93 (s, AcO), 1.80 (d, *J*=7.0 Hz, β-CH_3 in angelate), 1.78 (s, α-CH_3 in angelate), 1.13 (s, 15-CH_3), 0.90 (d, *J*=7.0 Hz, 14-CH_3).

Found: C, 67.62; H, 7.83%. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74%.

*Dihydrofukinolide (**2**)*: mp 125.0—126.0°C, colorless prisms (from light petroleum), $[\alpha]_D^{22}$ −105.5° (*c*, 1.0, MeOH); IR-(KBr): 1788 (γ-lactone), 1734, 1236 (ester), 3085, 1667, 909 cm^{-1} (double bond); UV: λ_{max}^{EtOH} end absorption; NMR-($CDCl_3$): 5.80 (d, *J*=11.5 Hz, 9-CH), 5.20 (t, *J*=1.0 Hz, 13-CH_2), 5.09 (m, 1-CH), 4.69 (t, *J*=2.0 Hz, 12-CH_2), 2.66 (dd, *J*=5.5, 11.5 Hz, 10-CH), 2.30, 1.71 (ABq, *J*=14.0 Hz, 6-CH_2), 2.07 (s, AcO), 1.12 (s, 15-CH_3), 1.07 (d, *J*=6.5 Hz, 3H), 0.94 (d, *J*=6.5 Hz, 14-CH_3), ca 0.90 (m, 3H); (C_6H_6): 5.87 (d, *J*=11.0 Hz, 9-CH), 5.18 (m, 1-CH), 4.90 (t, *J*=0.5 Hz, 13-CH), 4.70 (t, *J*=0.5 Hz, 13-CH), 4.32 (m, 12-CH_2), 2.84 (dd, *J*=5.5, 11.0 Hz, 10-CH), 2.19, 1.66 (ABq, *J*=14.0 Hz, 6-CH_2), 1.83 (s, AcO), 1.05 (d, *J*=6.5 Hz, 3H), 0.91 (d, *J*=6.5 Hz, 14-CH_3), 0.84 (s, 15-CH_3), 0.62 (m, 3H).

Found: C, 67.20; H, 8.26%. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22%.

*Homofukinolide (**3**)*: mp 184.0—186.0°C, colorless needles (from light petroleum), $[\alpha]_D^{22}$ −127.0° (*c*, 1.0, $CHCl_3$); IR-(KBr): 1773 (γ-lactone), 1723sh, 1708, 1233 (ester), 3080, 1668, 1648, 905, 850 cm^{-1} (double bond); (CCl_4): 1785 (γ-lactone), 1717, 1235 (ester), 3080, 1670sh, 1645, 902, 845 cm^{-1} (double bond); UV: λ_{max}^{EtOH} 215 mμ (ε, 23500); NMR($CDCl_3$): 6.13 (q, *J*=8.0 Hz, 2H, β-CH in angelate), 5.90 (d, *J*=11.5 Hz, 9-CH), 5.20 (d, *J*=2.5 Hz, 13-CH_2), 5.16 (m, 1-CH), 4.65 (t, *J*=2.0 Hz, 12-CH_2), 2.92 (dd, *J*=4.5, 11.5 Hz, 10-CH), 2.35, 1.97 (ABq, *J*=14.0 Hz, 6-CH_2), 1.95—1.70 (4×CH_3), 1.18 (s, 15-CH_3), 0.96 (d, *J*=5.5 Hz, 14-CH_3).

Found: C, 69.68; H, 8.05%. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96%.

*S-Fukinolide (**4**)*: mp 200.0—201.0°C, colorless needles (from light petroleum), $[\alpha]_D^{22}$ −161.0° (*c*, 1.0, $CHCl_3$); IR-(KBr): 1778 (γ-lactone), 1743, 1693, 1234 (ester), 3090, 1668, 1568, 903, 803 cm^{-1} (double bond); UV: λ_{max}^{EtOH} 287.5 mμ (ε, 15700); NMR($CDCl_3$): 7.00 (d, *J*=9.5 Hz, β-CH in an acid residue), 5.73 (d, *J*=11.0 Hz, 9-CH), 5.60 (d, *J*=9.5 Hz, α-CH in an acid residue), 5.16 (d, *J*=2.0 Hz, 13-CH_2), 5.15 (m, 1-CH), 4.64 (t, *J*=2.0 Hz, 12-CH_3), 2.77 (dd, *J*=4.5, 11.0 Hz, 10-CH), 2.38 (s, S-CH_3), 2.28, 1.91 (ABq, *J*=14.0 Hz, 6-CH_2), 2.01 (s, AcO), 1.12 (s, 15-CH_3), 0.90 (d, *J*=5.5 Hz, 14-CH_3).

Found: C, 62.09; H, 6.99; S, 8.04%. Calcd for $C_{21}H_{28}O_6S$: C, 61.74; H, 6.91; S, 7.83%.

*Fukinanolide (**5**)*: mp 80.5—80.6°C, colorless leaflets (from light petroleum), $[\alpha]_D^{22}$ +17.0° (*c*, 1.0, MeOH); IR-(KBr): 1770 (γ-lactone), 1665, 898 cm^{-1} (end-methylene); NMR($CDCl_3$): 5.11 (dd, *J*=2.0, 2.0 Hz, 13-CH), 5.02 (dd, *J*=2.0, 2.0 Hz, 13-CH), 4.75 (ABq, *J*=2.0 Hz, 12-CH_2), 1.00 (s, 15-CH_3), 0.87 (d, *J*=6.0 Hz, 14-CH_3).

Found: C, 76.94; H, 9.53%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

*Acid Hydrolysis of Fukinolide (**1**).* A mixture of fukinolide (**1**) (1.0 g) in ethanol (10 m*l*) and a 6N hydrogen chloride solution (10 m*l*) was refluxed for 2.5 hr. The reaction mixture was then poured into water and extracted with ether. The ethereal extract was washed with a saturated sodium hydrogen carbonate solution and water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue (850 mg) was chromatographed on silica gel (25 g); subsequent elution with benzene–ethyl acetate (50 : 1) gave the crude deacetylfukinolide (**7**) (540 mg), which was then recrystallized from light petroleum as colorless needles, mp 167.0—167.5°C, $[\alpha]_D^{22}$ −144.0° (*c*, 1.0, MeOH); IR(KBr): 3530, 3440, 1752, 1709, 1695, 1669, 1642, 1233, 895 cm^{-1}; NMR ($CDCl_3$): 6.18 (q, *J*=7.0 Hz, β-CH in angelate), 5.17 (t, *J*=2.0 Hz, 13-CH_2), *ca.* 5.20 (m, 1-CH, partly superimposed with 13-methylene), 4.86 (m, 12-CH_2), 4.58 (d, *J*=10.5 Hz, 9-CH), 2.75 (OH), 2.60 (dd, *J*=5.0, 10.5 Hz, 10-CH), 2.25, 1.94 (ABq, *J*=14.0 Hz, 6-CH_2), 1.94 (d, *J*=7.0 Hz, β-CH_3 in angelate), 1.85 (s, α-CH_3 in angelate), 1.11 (s, 15-CH_3), 0.90 (d, *J*=5.5 Hz, 14-CH_3).

Found: C, 68.68; H, 8.11%. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10%.

Further elution with benzene–ethyl acetate (5 : 1) gave fukinolidol (**8**) (75 mg), which was recrystallized from ethyl acetate–light petroleum as colorless prisms; mp 174.0—176.0 °C, $[\alpha]_D^{22}$ −79.0° (*c*, 1.0, MeOH).

22) N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, and Y. Kitahara, *Tetrahedron Lett.*, **1968**, 369; 11th Symposium on the Chemistry of Natural Products, Symposium Paper (1967), p. 96; N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, K. Ro, and T. Kurihara, *Tetrahedron Lett.*, **1968**, 1993.

Found: C, 67.81; H, 8.53%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%. This is identical with the specimen of fukinolidol (**8**) obtained by the alkaline hydrolysis of fukinolide (**1**), as determined by a mixed-melting-point determination and a comparison of the IR spectra.

*Regeneration of Fukinolide (**1**).* Deacetylfukinolide (**7**) (50 mg) was acetylated in the usual manner with acetic anhydride–pyridine. The product (47 mg) was recrystallized from light petroleum as colorless prisms; mp 101.5—102.0°C, $[\alpha]_D^{22}$ −137.0° (*c*, 1.0, MeOH).

Found: C, 67.94; H, 7.88%. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74%. This was found to be identical with an authentic sample of natural fukinolide (**1**) by a mixed-melting-point determination and by a comparison of the IR spectra.

*Alkaline Hydrolysis of Fukinolide (**1**).* Fukinolide (**1**) (3 g) was dissolved in 2N potassium hydroxide–menthanol (20 m*l*), and the mixture was allowed to stand at room temperature for 3 days. After the removal of the solvent and acidification with 2N sulfuric acid, the reaction mixture was extracted with ethyl acetate. The extract was washed with a saturated sodium hydrogen carbonate solution and water, and dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent gave fukinolidol (**8**) (1.54 g) (mp 176.5—177.5°C) as colorless prisms (from ethyl acetate–light petroleum). $[\alpha]_D^{22}$ −75.5° (*c*, 1.0, MeOH); IR(KBr): 3440 (OH), 1755 (γ-lactone), 3100, 1675, 910 cm^{-1} (double bond); NMR($CDCl_3$): 5.12 (t, J=2.0 Hz, 13-CH_2), 4.81 (m, 12-CH_2), 4.49 (d, J=11.0 Hz, 9-CH), 4.08 (m, 1-CH), 3.77 (2×OH), 2.55 (dd, J=5.5, 11.0 Hz, 10-CH), 2.14, 1.84 (ABq, J=14.5 Hz, 6-CH_2), 1.04 (s, 15-CH_3), 0.86 (d, J=5.0 Hz, 14-CH_3); (pyridine): 5.60 (s, 2H), 5.08 (d, J=3.0 Hz, 2H), 4.84 (m, 2H), 4.67 (d, J=11.0 Hz, 1H), ca 4.15 (m, 1H), 2.80 (dd, J=6.0, 11.0 Hz, 1H), 2.17, 1.81 (ABq, J=14.5 Hz, 2H), 0.97 (s, 3H), 0.77 (d, J=6.0 Hz, 3H).

Found: C, 67.42; H, 8.42%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

The above sodium hydrogen carbonate solution was acidified with 2N sulfuric acid and extracted with ether. The extract was washed with water and dried. The solvent was removed to give a residue (600 mg). The residue (200 mg) was then transformed to the *p*-phenylphenacyl ester in the usual manner, using *p*-phenylphenacyl bromide (356 mg). The product was chromatographed on silica gel (10 g); subsequent elution with light petroleum–ether (50 : 1) gave *p*-phenylphenacyl angelate (104 mg) (mp 89.5—90.5°C) as leaflets (from ethanol).

Found: C, 77.52; H, 6.19%. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%.

The *p*-bromophenacyl ester of angelic acid was obtained in a similar manner (mp 64.0—66.0°C) as leaflets (from ethanol).

Found: C, 52.32; H, 4.34%. Calcd for $C_{13}H_{13}O_3Br$: C, 52.54; H, 4.41%.

*Acetylation of Fukinolidol (**8**).* Fukinolidol (**8**) (100 mg) was dissolved in acetic anhydride (1 m*l*) and pyridine (0.5 m*l*), and the mixture was left at room temperature for 48 hr. The reaction mixture was then worked up in the usual manner to give, quantitatively, crude diacetate (**12**) as an amorphous solid which was crystallized from ethanol as prisms; mp 224.5—226.0°C, $[\alpha]_D^{22}$ −120.0° (*c*, 1.0, $CHCl_3$); IR(KBr): 3080, 1773, 1746, 1741, 1668, 1241, 1231, 913 cm^{-1}; NMR($CDCl_3$): 5.78 (d, J=11.0 Hz, 9-CH), 5.20 (m, 13-CH_2), 5.00 (m, 1-CH), 4.68 (t, J=2.0 Hz, 12-CH_2), 2.71 (dd, J=5.0, 11.0 Hz, 10-CH), 2.27, 1.93 (ABq, J=14.0 Hz, 6-CH_2), 2.06 (s, AcO), 1.94 (s, AcO), 1.11 (s, 15-CH_3), 0.90 (d, J=5.5 Hz, 14-CH_3).

Found: C, 65.06; H, 7.50%. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48%.

*Dihydrofukinolidol (**10**).* A solution of fukinolide (**1**) (10.7 g) in acetic acid (30 m*l*) was hydrogenated with Adams' catalyst (626 mg) at room temperature. Hydrogen uptake (2 mol) ceased after 3 hr. After the filtration of the catalyst, the solvent was removed *in vacuo* to give crude tetrahydrofukinolide (**9**), which was used for the next step without any further purification. A solution of the above product in 2N potassium hydroxide–methanol was allowed to stand at room temperature for 2 days. The solvent was then removed, and the residue was diluted with water, and extracted with ether to take off the neutral part. The aqueous layer was acidified with 5N sulfuric acid and extracted with ethyl acetate. The extract was washed with a saturated sodium hydrogen carbonate solution and water, and then dried. The solvent was removed to give dihydrofukinolidol (**10**) (5.6 g); mp 190.0—191.0°C, colorless prisms (from ethyl acetate–light petroleum), $[\alpha]_D^{22}$ −14.5° (*c*, 1.0, MeOH); IR(KBr): 3525, 3445, 1766 cm^{-1}; NMR($CDCl_3$): 4.60 (d, J=11.0 Hz, 9-CH), 4.23 (t, J=8.5 Hz, 12-CH), 4.12 (m, 1-CH), 3.92 (dd, J=8.5, 10.0 Hz, 12-CH), 3.19 (s, 2×OH), 2.55 (dd, J=5.5, 11.0 Hz, 10-CH), 2.01, 1.49 (ABq, J=14.0 Hz, 6-CH_2), 1.13 (d, J=7.0 Hz, 13-CH_3), 1.03 (s, 15-CH_3), 0.80 (d, J=4.5 Hz, 14-CH_3); (C_6H_6): 4.54 (d, J=11.0 Hz, 1H), ca 4.0 (m, 1H), 3.92 (m, 2H), 3.78 (s, 2H), 2.79 (dd, J=5.5, 11.0 Hz, 1H), 1.97, 1.23 (ABq, J=14.0 Hz, 2H), 0.99 (s, 3H), 0.79 (d, J=7.0 Hz, 3H), 0.61 (d, J=5.0 Hz, 3H).

Found: C, 67.12; H, 9.20%. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

*Reduction of Fukinolide (**1**) with Lithium Aluminum Hydride.* A solution of fukinolide (**1**) (600 mg) in dry ether (20 m*l*) was stirred, drop by drop, into a suspension of lithium aluminum hydride (280 mg) in dry ether (30 m*l*), and then the mixture was refluxed for 5 hr. The excess reagent was destroyed by the careful addition of ethyl acetate and water, followed by treatment with a saturated sodium sulfate solution. The organic layer was separated, and the aqueous layer was extracted with ether. The combined extracts were washed with water, and dried. The solvent was removed to leave an oily residue (543 mg), which was then chromatographed on silica gel (8 g). Elution with ethyl acetate–benzene (3 : 2) gave a tetrol (**13**) (300 mg); mp 106.0—107.0°C, $[\alpha]_D^{22}$ −14.0° (*c*, 1.0, MeOH); IR(KBr): 3390, 3275, 1649, 906 cm^{-1}; NMR($CDCl_3$): 5.28 (d, J=5.0 Hz, 13-CH_2), 4.86 (d, J=11.0 Hz, 9-CH), 4.23 (slightly split s, 12-CH_2), 4.00 (m, 1-CH), 3.84, 3.51 (ABq, J=11.0 Hz, 8-CH_2), 3.56 (s, 4×OH), 2.20 (dd, J=5.5, 11.0 Hz, 10-CH), 2.00, 1.34 (ABq, J=14.0 Hz, 6-CH_2), 0.91 (s, 15-CH_3), 0.76 (d, J=4.0 Hz, 14-CH_3); (pyridine): 0.87 (s, 15-CH_3), 0.67 (d, J=5.0 Hz, 14-CH_3).

Found: C, 66.96; H, 9.74%. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%.

Tetrol-acetate. Tetrol (**13**) (65 mg) was acetylated with acetic anhydride (0.3 m*l*) and pyridine (0.2 m*l*) at room temperature for 40 hr. Working up in the usual manner gave the tetraacetate (95 mg) as a viscous oil; IR(film): 3090, 1742, 1642, 1245, 907 cm^{-1}; NMR($CDCl_3$): 6.10 (d, J=10.5 Hz, 9-CH), 5.38 (d, J=8.0 Hz, 13-CH_2), 5.05 (m, 1-CH), 4.10 (slightly split s, 12-CH_2), 4.20, 3.95 (ABq, J=11.5 Hz, 8-CH_2), 2.08 (s, 1×AcO), 2.03 (s, 2×AcO), 1.96 (s, 1×AcO), 1.00 (s, 15-CH_3), 0.80 (d, J=5.0 Hz, 14-CH_3).

*Reduction of Fukinolidol Diacetate (**11**) with Lithium Aluminum Hydride.* A solution of fukinolidol diacetate (**11**) (380 mg) in dry ether (45 m*l*) and dry benzene (5 m*l*) was stirred into a suspension of lithium aluminum hydride (310 mg) in dry ether (10 m*l*). After refluxing for 7 hr, working up as above afforded a crude tetrol (**13**) (84 mg). This was chro-

matographed on silica gel (5 g) and eluted with ethyl acetate-benzene (3 : 2). Mp 106.0—107.0°C, colorless leaflets (from ethyl acetate-light petroleum).

Found: C, 66.62; H, 9.51%. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%.

This substance is identical with the tetrol (**13**) described above.

*Hydrogenation of Tetrol (**13**).* A solution of tetrol (**13**) (690 mg) in ethanol (5 m*l*) was shaken with hydrogen at room temperature in the presence of 10% palladium charcoal (68 mg) for 4 hr, until the hydrogen-uptake (1.37 mol) had ceased. After the subsequent filtration of the catalyst, the solvent was removed *in vacuo* to leave an oily residue (700 mg). The crude product was chromatographed on silica gel (20 g); elution with benzene-ethyl acetate (15 : 1) then gave triol (**14**); mp 88.5—89.5°C, colorless needles (from cyclohexane); $[\alpha]_D^{22}$ −5.5° (*c*, 1.0, MeOH); IR(KBr): 3430, 3330, 1386, 1370, 1088, 1047 cm^{-1}; NMR($CDCl_3$): 4.58 (d, J=11.0 Hz, 9-CH), 4.10 (m, 1-CH), 3.80, 3.54 (ABq, J=11.5 Hz, 8-CH_2), 3.30 (s, 3×OH), 2.78 (dd, J=5.5, 11.0 Hz, 10-CH), 1.88, 1.47 (ABq, J=10.5 Hz, 6-CH_2), 1.07 (d, J=6.5 Hz, 12- or 13-CH_3), 0.97 (d, J=6.5 Hz, 12- or 13-CH_3), 0.90 (s, 15-CH_3), 0.77 (d, J=5.0 Hz, 14-CH_3).

Found: C, 70.91; H, 11.25%. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%.

*Oxidation of Deacetylfukinolide (**7**).* Jones' reagent (1.9 m*l*) was added to a solution of deacetylfukinolide (**7**) (1.0 g) in acetone (15 m*l*) under ice-salt cooling at −8— −12°C over a period of 3 hr with stirring. After stirring for a further 4 hr under the same conditions, the mixture was concentrated *in vacuo* and extracted with ether. The extract was washed with water and dried. The solvent was then removed to give a crude product (880 mg), which was subsequently crystallized from light petroleum to yield the pure ketone (**15**) (320 mg) as colorless needles; mp 96.0—97.0°C, $[\alpha]_D^{22}$ −110° (*c*, 1.0, MeOH), ORD (*c*, 0.1, MeOH): $[\alpha]_{589}$−90°, $[\alpha]_{380}$−220°, $[\alpha]_{342}$ 0°, $[\alpha]_{323}$+1340°, $[\alpha]_{312}$ 0°; (*c*, 0 01, MeOH): $[\alpha]_{268}$ −5800°, $[\alpha]_{262}$−5600°, $[\alpha]_{226}$−12400°; IR(KBr): 3095, 1770, 1751, 1715, 1672, 1646, 1239, 902 cm^{-1}; NMR($CDCl_3$): 6.08 (q, J=7.0 Hz, β-CH in angelate), 5.22 (d, J=2.5 Hz, 13-CH), *ca.* 5.05 (m, 1-CH), 5.00 (d, J=2.5 Hz, 12-CH_2), 4.86 (d, J=2.5 Hz, 13-CH), 3.02 (d, J=5.0 Hz, 10-CH), 2.46, 2.17 (ABq, J=14.0 Hz, 6-CH_2), 1.96 (d, J=7.0 Hz, β-CH_3 in angelate), 1.90 (s, α-CH_3 in angelate), 1.23 (s, 15-CH_3), 0.98 (d, J=2.0 Hz, 14-CH_3).

Found: C, 69.47; H, 7.38%. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57%.

*Oxidation of Fukinolidol (**8**).* A solution of chromium trioxide (235 mg) in water (0.55 m*l*) and concentrated sulfuric acid (0.16 m*l*) was stirred, drop by drop over a 1-hr period, into a solution of fukinolidol (**8**) (560 mg) in acetone (3.5 m*l*) under a nitrogen atmosphere at 5°C. After stirring for a further 30 min, the reaction mixture was worked up as has been described above to yield a crude product (376 mg). Recrystallization from ethyl acetate–light petroleum gave monoketone (**16**) as colorless leaflets; mp 141.5—142.0°C, $[\alpha]_D^{22}$ −232° (*c*, 1.0, MeOH); ORD (*c*, 0.10, MeOH): $[\alpha]_{598}$ −170°, $[\alpha]_{315}$ −5000°, $[\alpha]_{296}$0°, $[\alpha]_{276}$+3670°, $[\alpha]_{250}$0°; (*c*, 0.005, MeOH): $[\alpha]_{228}$−8220°, $[\alpha]_{219}$0°; IR(KBr): 3490, 3365, 3085, 1773, 1755, 1680, 1675sh, 1666sh, 1190, 1162, 1096, 920, 913 cm^{-1}; NMR($CDCl_3$): 5.20 (t, J=2.0 Hz, 13-CH_2), 4.78 (m, 12-CH_2), 4.38 (d, J=11.0 Hz, 9-CH), *ca.* 3.5 (broad signal, OH), 2.86 (d, J=11.0 Hz, 10-CH), 1.00 (s, 15-CH_3), 0.97 (d, J=5.5 Hz, 14-CH_3).

Found: C, 68.20; H, 7.65%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

*Acetate (**19**).* The above monoketone (**16**) (50 mg) was acetylated with acetic anhydride (0.2 m*l*) and pyridine (0.2 m*l*) at room temperature for 50 hr. Working up in the usual manner gave an oil (42 mg), which was then chromatographed on silica gel (5 g); subsequent elution with benzene afforded the acetate (**19**) (24 mg), mp 132.5—133.0 °C, $[\alpha]_D^{24}$ −210° (*c*, 1.0, $CHCl_3$); IR(KBr): 1770, 1744, 1698, 918 cm^{-1}; NMR($CDCl_3$): 5.50 (d, J=11.0 Hz, 9-CH), 5.28 (d, J=2.7 Hz, 13-CH_2), 4.72 (t, J=3.0 Hz, 12-CH_2), 3.01 (d, J=11.0 Hz, 10-CH), 1.98 (s, AcO), 1.05 (s, 15-CH_3), 0.98 (d, J=6.0 Hz, 14-CH_3).

Found: C, 66.75; H, 7.31%. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24%.

*2,4-Dinitrophenylhydrazone of Monoketone (**16**).* The 2,4-dinitrophenylhydrazone was prepared by Brady's method and crystallized from aqueous ethanol as yellow needles; mp 220.0—221.0°C.

Found: C, 56.63; H, 5.45; N, 12.50%. Calcd for $C_{21}H_{24}O_7N_4$: C, 56.75; H, 5.44; N, 12.61%.

Dehydration of Monoketone 2,4-Dinitrophenylhydrazone. The above 2,4-dinitrophenylhydrazone (20 mg) in ethanol was refluxed with 85% phosphoric acid (3 drops) for 10 hr. The reaction mixture was concentrated *in vacuo*, poured into water, and extracted with ether. The extract was washed with a saturated sodium hydrogen carbonate solution and water, and dried. The subsequent evaporation of the solvent gave a crude product which was chromatographed on silica gel (3 g). Elution with benzene gave a dehydration product (**24**) (13 mg), which was then crystallized from ethanol as orange-red needles; mp 209.5—210.0°C; IR(KBr): 3090, 1775, 1673 cm^{-1}; NMR($CDCl_3$): 11.18 (m, 1H), 9.11 (d, J=2.5 Hz, 1H), 8.30 (dd, J=2.5, 9.5 Hz, 1H), 8.01 (d, J=9.5 Hz, 1H), 5.80 (s, 9-CH), 5.14 (m, 13-CH_2), 4.89 (t, J=2.0 Hz, 12-CH_2), 2.52, 1.95 (ABq, J=14.0 Hz, 6-CH_2), 1.28 (s, 15-CH_3), 0.97 (d, J=6.0 Hz, 14-CH_3).

Found: C, 59.02; H, 5.20%. Calcd for $C_{21}H_{22}O_6N_4$: C, 59.15; H, 5.20%.

*Oxidation of Dihydrofukinolidol (**10**).* A solution of chromium trioxide (1.44 g) in acetone (21 m*l*), water (3.3 m*l*) and concentrated sulfuric acid (1 m*l*) was stirred, drop by drop over 70 min under a nitrogen atmosphere at 3—5°C, into a solution of dihydrofukinolidol (**10**) (2.91 g) in acetone (35 m*l*). After stirring for a further 20 min, the excess reagent was decomposed with methanol (3 m*l*), diluted with water, and extracted with ether. The extract was washed with a 5% potassium hydroxide solution and then water, and dried. The removal of the solvent gave a crude product as a solid (2.4 g). The product was chromatographed on silica gel (80 g); subsequent elution with benzene-ethyl acetate (9 : 1) gave dihydromonoketone (**17**) (1.8 g); mp 184.0—186.0°C, colorless prisms (from acetone-light petroleum), $[\alpha]_D^{22}$ −79.0°(*c*, 1.0, MeOH); ORD (*c*, 0.1, MeOH): $[\alpha]_{589}$ −60°, $[\alpha]_{315}$−2100°, $[\alpha]_{297}$0°, $[\alpha]_{275}$+2100°, $[\alpha]_{236}$+690°, $[\alpha]_{220}$+2100°; IR(KBr): 3350, 1767, 1680 cm^{-1}, (CCl_4): 3540, 1765, 1690 cm^{-1}; NMR($CDCl_3$): 4.36 (d, J=11.0 Hz, 9-CH), 4.33 (t, J=8.5 Hz, 12-CH), 4.02 (dd, J=8.5, 10.0 Hz, 12-CH), 2.90 (d, J=11.0 Hz, 10-CH), 2.80 (OH), 1.97, 1.61 (ABq, J=14.0 Hz, 6-CH_2), 1.21 (s, 15-CH_3), 1.15 (d, J=6.5 Hz, 13-CH_3), 0.93 (d, J=5.5 Hz, 14-CH_3).

Found: C, 67.71; H, 8.41%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

*Acetate (**20**).* Dihydromonoketone (**17**) (140 mg) in pyridine (0.4 m*l*) was treated with acetic anhydride (0.5 m*l*) at room temperature for 32 hr. Working up in the usual manner yielded the acetate (**20**) (120 mg); mp 158.5—159.5°C, colorless needles (from ethyl acetate-light petroleum), $[\alpha]_D^{22}$ −93° (*c*, 1.0, MeOH); IR(KBr): 1764, 1738, 1696 cm^{-1}; NMR($CDCl_3$): 5.67 (d, J=11.0 Hz, 9-CH), 4.38

(t, J=8.5 Hz, 12-CH), 3.73 (dd, J=8.5, 10.5 Hz, 12-CH), 2.94 (d, J=11.0 Hz, 10-CH), 1.98 (s, AcO), 1.16 (d, J=6.0 Hz, 13-CH_3), 1.07 (s, 15-CH_3), 0.97 (d, J=6.0 Hz, 14-CH_3).

Found: C, 65.93; H, 7.88%. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85%.

*Reduction of Dihydromonoketone Acetate (**20**) with Sodium Borohydride.* The acetate (**20**) (370 mg) in methanol (3 ml) was treated with sodium borohydride (200 mg) in methanol (7 ml) at room temperature for 19 hr. The reaction mixture was then diluted with water (3 ml) and allowed to stand at room temperature for 24 hr. Working up in the usual manner gave a solid (320 mg), which was subsequently crystallized from ethyl acetate; mp 190.0—191.0°C, colorless prisms, $[\alpha]_D^{22}$ −14.0° (c, 1.0, MeOH).

Found: C, 67.33; H, 9.01%. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

The above substance was found to be identical in all respects with the dihydrofukinolidol (**10**) obtained from tetrahydrofukinolide (**9**) by mixed-melting-point determination and a comparison of the IR spectra.

*Oxidation of Epidihydrofukinolidol (**11**).* Jones' reagent (2.2 ml) was stirred, over a 45-min period at −15°C under a nitrogen atmosphere, into a solution of epidihydrofukinolidol (**11**) (1.0 g) in acetone (15 ml). After stirring for a further 30 min under the same conditions, the reaction mixture was treated with a little methanol and concentrated *in vacuo*. Extraction with chloroform gave ketone (**18**) (850 mg), which was then crystallized from ethyl acetate-light petroleum; mp 137.0—138.0°C, colorless needles, $[\alpha]_D^{22}$ −125° (c, 1.0, MeOH); ORD (c, 0.108, MeOH): $[\alpha]_{589}$ −140°, $[\alpha]_{400}$ −440°, $[\alpha]_{350}$ −880°, $[\alpha]_{311}$ −2580°, $[\alpha]_{293}$0°, $[\alpha]_{274}$ +1680°, $[\alpha]_{232}$ +690°, $[\alpha]_{220}$ +790°; IR(KBr): 3470sh, 3405, 1755, 1714, 1689sh, 1680 cm^{-1}; NMR($CDCl_3$): 4.53 (dd, J=7.0, 8.5 Hz, 12-CH), 4.34 (dd, J=6.0, 11.0 Hz, 9-CH), 3.80 (dd, J=7.0, 9.5 Hz, 12-CH), 3.31 (d, J=6.0 Hz, OH), 2.87 (d, J=11.0 Hz, 10-CH), 1.99, 1.70 (ABq, J=14.0 Hz, 6-CH_2), 1.13 (s, 15-CH_3), 1.11 (d, J=7.0 Hz, 13-CH_3), 0.95 (d, J=6.0 Hz, 14-CH_3).

Found: C, 67.81; H, 8.46%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.

*Dehydration of Dihydromonoketone (**17**).* The ketone (**17**) (120 mg) in pyridine (1.0 ml) was treated with phophorus oxychloride (0.4 ml) at room temperature for 30 hr. The reaction mixture was poured onto ice and extracted with ether. The extract was washed successively with dilute hydrochloric acid, a saturated sodium hydrogen carbonate solution and water, and dried. The removal of the solvent gave a crude product (90 mg) which was chromatographed on silica gel (5 g). Elution with benzene-ethyl acetate (50 : 1) afforded the dehydration product, **23** (80 mg); mp 103.0—103.5°C, colorless needles (from light petroleum); $[\alpha]_D^{22}$ −36° (c, 1.0, MeOH); ORD (c, 0.09, MeOH): $[\alpha]_{589}$ −70°, $[\alpha]_{360}$ −920°, $[\alpha]_{335}$0°, $[\alpha]_{310}$ +1220°, $[\alpha]_{282}$0°; (c, 0.009, MeOH): $[\alpha]_{262}$ −1330°, $[\alpha]_{254}$0°, $[\alpha]_{232}$ +20440°; IR(KBr): 1776, 1681, 1629 cm^{-1}; λ_{max}^{EtOH} 250 mμ (ε, 7100); NMR($CDCl_3$): 6.07 (s, 9-CH), 4.45 (dd, J=8.5, 9.5 Hz, 12-CH), 3.93 (t, J=9.5 Hz, 12-CH), 2.38, 1.79 (ABq, J=14.0 Hz, 6-CH_2), 1.24 (s, 15-CH_3), 1.00 (d, J=7.0 Hz, 13- and 14-CH_3).

Found: C, 72.54; H, 8.23%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

*Tosylation of Fukinolidol (**8**).* Fukinolidol (**8**) (2 g) was treated with *p*-toluenesulfonyl chloride (6.3 g) in pyridine (10 ml) and left for 72 hr at room temperature. The reaction mixture was diluted with water to deposit a solid. The collected precipitates (4.3 g) were chromatographed on silica gel (50 g); subsequent elution with benzene-ethyl acetate (30 : 1) gave ditosylate (**27**) (3.5 g); mp 179.5—180.0°C decomp., colorless prisms (from ethyl acetate-light petroleum); IR(KBr): 3060, 1774, 1673, 1600, 1498, 1179, 923 cm^{-1}.

Found: C, 60.65; H, 5.91; S, 11.19%. Calcd for $C_{29}H_{34}O_8S_2$: C, 60.60; H, 5.94; S, 11.16%.

*Reduction of Ditosylate (**27**) with Lithium Aluminum Hydride.* Ditosylate (**27**) (4.05 g) in dry tetrahydrofuran (30 ml) was added, drop by drop over a 2-hr period under refluxing, to a suspension of lithium aluminum hydride (3.0 g) in dry tetrahydrofuran (20 ml). After refluxing for 20 hr, the excess reagent was decomposed with tetrahydrofuran-water (1 : 1, 14 ml) and diluted with water (30 ml), and then 6N sulfuric acid (40 ml) was added. This mixture was extracted with ether to give an oily product (1.64 g). The chromatography of the product on silica gel (60 g) and elution with benzene-ethyl acetate (50 : 1) gave a fraction (422 mg) as the main product on tlc; this product was crystallized from light petroleum to afford diol (**28**); mp 119.5—120.0°C, colorless needles; IR(KBr): 3290, 1642, 1068, 1037, 1028, 901, 882 cm^{-1}; λ_{max}^{EtOH} 237 mμ (ε, 18700); NMR($CDCl_3$): 6.21 (d, J=9.5 Hz, 1-CH), 5.75 (dt, J=9.5, 2.0 Hz, 2-CH), 5.50 (s, 9-CH), 5.11 (d, J=9.0 Hz, 13-CH_2), 4.15 (s, 12-CH_2), 3.73 (s, 8-CH_2), 2.85 (2×OH), 2.02, 1.68 (ABq, J=11.0 Hz, 6-CH_2), 1.00 (s, 15-CH_3), 0.91 (d, J=6.0 Hz, 14-CH_3).

Found: C, 76.82; H, 9.52%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

*Hydrogenation of Diol (**28**).* A solution of diol (**28**) (631 mg) in ethanol was hydrogenated over 10% palladium charcoal (303 mg) at room temperature until the hydrogen-uptake had ceased (2.08 mol). After working up as usual, the chromatography of the crude product (509 mg) on silica gel (10 g) and elution with benzene-ethyl acetate (50 : 1) gave a fraction, an unsaturated monol (**29**) (110 mg) which showed the existence of an ethylenic linkage in the IR and NMR spectra; IR(film): 3330, 1662, 1380, 1365, 1038 cm^{-1}; NMR(CCl_4): 4.95 (s, 9-CH), 3.38 (s, 8-CH_2), 2.85 (s, OH), 0.93 (d, J=6.0 Hz, 12- and 13-CH_3), 0.88 (s, 15-CH_3), 0.82 (d, J=6.0 Hz, 14-CH_3).

The above sample in acetic acid (5.0 ml) was further hydrogenated with Adams' catalyst (20 mg) by the standard method. Working up as usual gave a monol, fukinan-8-ol (**26**), which was then purified by preparative glc (PEG 6000, 2.6 m; column temperature, 180°C; H_2, flow-rate, 150 ml/min), mp 38.0—39.0°C, $[\alpha]_D^{22}$ +15.6° (c, 1.6, MeOH); IR(KBr): 3300, 1387, 1375, 1049, 1041, 1023 cm^{-1}; NMR(CCl_4): 3.37 (s, 8-CH_2), 2.71 (OH), 0.89 (d, J=6.0 Hz, 12- and 13-CH_3), 0.84 (s, 15-CH_3), 0.75 (d, J=6.5 Hz, 14-CH_3).

Found: C, 80.23; H, 12.66%. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58%.

*Favorskii Rearrangement of Fukinone Epoxide (**30**).* A solution of fukinone (**25**) (9.92 g) in methanol (300 ml) was treated with a mixture of 30% hydrogen peroxide (70 ml) and 2N sodium hydroxide-methanol (70 ml) at room temperature. After the removal of the solvent under reduced pressure, the mixture was diluted with water and extracted with ether to give a colorless oil, **30** (10.03 g); IR(film): 1722 cm^{-1}.

The above epoxide (**30**) in ethanol (42 ml) was refluxed with a 4N sodium hydroxide solution (34 ml) under a nitrogen atmosphere for 11 hr. The reddish-brown solution was then concentrated *in vacuo* and extracted with ether to remove the neutral part. The aqueous layer was acidified under ice-cooling with dilute sulfuric acid and then extracted with ether. The product was separated into neutral and acidic parts. The acidic part was treated with diazomethane-etherate overnight at room temperature, and then the reac-

tion mixture was evaporated to leave a yellow oil (8.12 g). Chromatography of the oil on silica gel (240 g) and elution with benzene–ethyl acetate (100 : 1) gave a spiro-ester, **35** (2.26 g, tlc: R_f, 0.37, benzene–ethyl acetate, 20 : 1); mp 63.5—64.5°C, colorless needles (from *n*-pentane), $[\alpha]_D^{22}$ +23.5° (*c*, 1.0, MeOH); IR(KBr): 3480, 1725, 1705, 1195, 1150 cm^{-1}; NMR(CCl_4): 3.68 (s, CH_3O-CO), 3.07 (s, OH), 1.13 (slightly split s, 12- and 13-CH_3), 0.88 (s, 15-CH_3), 0.77 (d, J=6.5 Hz, 14-CH_3).

Found: C, 80.23; H, 12.66%. Calcd for $C_{16}H_{28}O_3$: C, 80.29; H, 12.58%.

Further elution with the same solvent afforded a nonspiro-ester, **36**[16] (3.78 g, tlc: R_f, 0.18, benzene–ethyl acetate, 20 : 1), mp 52.0—54.0°C, colorless needles (from aqueous methanol), $[\alpha]_D^{22}$ +14.0° (*c*, 1.0, MeOH); IR(KBr): 3560, 3250, 1735, 1725, 1190 cm^{-1}.

*Dehydration of the **35** Ester.* A solution of the **35** ester (2.26 g) in dry pyridine (7 m*l*) was treated with phosphorus oxychloride (7.7 m*l*) under cooling and then left at room temperature for 46 hr. The mixture was subsequently poured onto ice and extracted with ether. After working up as usual, the product was chromatographed on silica gel (38 g); elution with light petroleum gave an unsaturated ester **37** (1.776 g); bp 87.0—95.0°C (bath temperature)/1 mmHg; IR(film): 1720, 1630 cm^{-1}; NMR(CCl_4): 4.77 (d, J=6.0 Hz, 12-CH_2), 3.59 (s, CH_3O-CO), 1.68 (s, 13-CH_3), 0.90 (s, 15-CH_3), 0.78 (d, J=6.0 Hz, 14-CH_3).

Found: C, 76.71; H, 10.57%. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.

*Hydrogenation of the Unsaturated Ester (**37**).* The above ester in ethanol (13 m*l*) was hydrogenated with 10% palladium charcoal (70 mg) at room temperature and atmospheric pressure to afford a saturated ester **38** as an oil; bp 66.0—86.0°C (bath temperature)/1 mmHg; $[\alpha]_D^{22}$ +23.8° (*c*, 1.51, MeOH); IR(film): 1720, 1235, 1180, 1141 cm^{-1}. The pure sample was obtained by glc (PEG 6000, 2.8 m; column temperature, 150°C; H_2-flow rate, 67 m*l*/min, retention time 10.7 min).

Found: C, 76.57; H, 11.16%. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18%.

*Reduction of the Saturated Ester (**38**) with Lithium Aluminum Hydride to Fukinan-8-ol (**26**).* The above ester (**38**) (1.7 g) in dry ether (15 m*l*) was stirred, drop by drop over a 50 min period at room temperature, to a suspension of lithium aluminum hydride (800 mg) in dry ether (20 m*l*), and then the mixture was refluxed for 2 hr. Working up as usual gave a colorless oil (1.51 g) which was subsequently purified by preparative glc (PEG 6000, 2.6 m; column temperature, 180°C; H_2-flow rate, 150 m*l*/min), mp 38.0—39.0°C, $[\alpha]_D^{22}$ +18.5° (*c*, 1.6, MeOH); MS: *m/e* 206 (M^+—18), 193 (base peak). This sample was identical in all respects with the fukinan-8-ol (**26**) prepared from fukinolide (**1**) and fukinanolide (**5**).

*Alkaline Hydrolysis of Dihydrofukinolide (**2**).* Dihydrofukinolide (**2**) (800 mg) was dissolved in 2 N potassium hydroxide–methanol (30 m*l*), and then the mixture was left for 90 hr at room temperature. After removal of the solvent and acidification with 2 N sulfuric acid, the reaction mixture was extracted with chloroform, and the extract washed with a saturated sodium hydrogen carbonate solution and then water. The dried extract was evaporated *in vacuo* to give fukinolidol (**8**) (340 mg); colorless prisms (from ethyl acetate), mp 177.0—178.0°C; $[\alpha]_D^{22}$ −83.0° (*c*, 1.0, MeOH).

Found: C, 67.74; H, 8.33%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%. This sample was identified with the authentic sample of fukinolidol (**8**) obtained from fukinolide (**1**) by a comparison of their IR spectra and by a mixed-melting-point determination.

The sodium hydrogen carbonate solution was acidified with dilute sulfuric acid and extracted with ether. The acidic extract was transformed to the *p*-phenylphenacyl esters in the usual way and gave a product. This was chromatographed on silica gel; subsequent elution with light petroleum–ether (50 : 1) afforded the *p*-phenylphenacyl ester of *d*-(S)-α-methylbutyric acid (**40**);[19] colorless needles, mp 71.0—72.0°C (from ethanol), $[\alpha]_D^{22}$ +16.5° (*c*, 1.0, $CHCl_3$); IR(KBr): 1746, 1694, 1605, 1244, 1183, 1158 cm^{-1}.

Found: C, 77.01; H, 6.84%. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%.

*Hydrogenation of Dihydrofukinolide (**2**).* Dihydrofukinolide (**2**) (100 mg) was dissolved in ethanol (6 m*l*) and hydrogenated with 10% palladium charcoal (20 mg) at room temperature. After hydrogen-uptake (2 mol), the filtrate was evaporated *in vacuo* to furnish tetrahydrofukinolide (**41**) (95 mg); mp 116.5—117.0°C, colorless needles (from aqueous methanol); $[\alpha]_D^{22}$ −51.0° (*c*, 1.0, MeOH); IR(CCl_4): 1785 (γ-lactone), 1741, 1721sh, 1244 cm^{-1} (ester), (KBr): 1783 (γ-lactone), 1735, 1236 cm^{-1} (ester).

Found: C, 67.25; H, 8.65%. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69%. This sample was found to be identical with the lower-melting isomer (**41**) of tetrahydrofukinolide (**9**) obtained by the hydrogenation of fukinolide (**1**) by a mixed-melting-point determination and by a comparison of the IR spectra.

*Hydrogenation of Fukinolide (**1**).* Fukinolide (**1**) (200 mg) was hydrogenated with platinum oxide (20 mg) in acetic acid (10 m*l*) at room temperature. Hydrogen-uptake (25 m*l*, 2 mol) ceased after 45 min. The catalyst was then filtered off, and the solvent was evaporated *in vacuo* to afford a crystalline mass. The product was recrystallized from light petroleum to deposit a mixture of two crystals, each of which was separated mechanically and recrystallized from aqueous methanol.

One isomer (**41**) (50 mg) was in the form of colorless needles; mp 112.0—113.0°C, $[\alpha]_D^{24}$ −52.25° (*c*, 0.95, MeOH); IR(CCl_4): 1785 (γ-lactone), 1741, 1244 cm^{-1} (ester); (KBr): 1783 (γ-lactone), 1735, 1236 cm^{-1} (ester); NMR($CDCl_3$): 5.99 (d, J=11.5 Hz, 9-CH), 5.05 (m, 1-CH), 4.25 (t, J=8.5 Hz, 12-CH), 3.51 (dd, J=8.5, 10.5 Hz, 12-CH), 2.68 (dd, J=5.0, 11.5 Hz, 10-CH), 2.04 (s, AcO), 2.18, 1.62 (ABq, J=14.0 Hz, 6-CH_2), 1.23 (d, J=7.5 Hz, 13-CH_3), 1.10 (s, 15-CH_3), 1.08 (d, J=7.0 Hz, α-CH_3 in α-methylbutyrate), 0.88 (t, J=7.0 Hz, β-CH_3 in α-methylbutyrate), 0.85 (d, J=6.5 Hz, 14-CH_3).

Found: C, 66.89; H, 8.72%. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69%.

The other isomer (**42**) (70 mg) was in the form of colorless prisms; mp 121.5—122.5°C, $[\alpha]_D^{24}$ −67.5° (*c*, 1.0, MeOH); IR(CCl_4): 1785, 1741, 1244 cm^{-1}; (KBr): 1779, 1751, 1732, 1242 cm^{-1}.

Found: C, 66.79; H, 8.78%. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69%.

*Fukinolidol Dibromoacetate (**39**).* A mixture of dry benzene (25 m*l*), bromoacetyl bromide (2 m*l*), and fukinolidol (**8**) (500 mg) was refluxed for 5 hr. After working up as usual, the crude product (700 mg) was chromatographed on silica gel (11 g). Elution with benzene–ethyl acetate (80 : 1) gave dibromoacetate (**39**) (270 mg), which was then crystallized from ethyl acetate–light petroleum as colorless needles; mp 156.5—158.0°C, $[\alpha]_D^{22}$ −77.5° (*c*, 1.0, $CHCl_3$); IR(KBr): 1767, 1748, 1742sh, 1666, 1272, 910, 688, 604, 553, 530 cm^{-1}; NMR($CDCl_3$): 5.82 (d, J=11.0 Hz, 9-CH), 5.25 (t, J=2.0 Hz, 13-CH_2), *ca.* 5.1 (m, 1-CH), 4.75 (t, J=2.0 Hz, 12-CH_2), 3.87 (s, CH_2 in bromoacetate), 3.70

(s, CH_2 in bromoacetate), 2.82 (dd, J=5.0, 11.0 Hz, 10-CH), 2.32, 1.95 (ABq, J=14.0 Hz, 6-CH_2), 1.12 (s, 15-CH_3), 0.91 (d, J=5.0 Hz, 14-CH_3).

Found: C, 44.80; H, 4.77; Br, 31.25%. Calcd for $C_{19}H_{24}O_6Br_2$: C, 44.90; H, 4.75; Br, 31.45%.

*Hydrogenation of Fukinolidol (**8**).* Fukinolidol (**8**) (2.0 g) in ethanol (20 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium charcoal (200 mg). After the absorption of hydrogen (195 ml), the catalyst was filtered and the solvent was evaporated *in vacuo*. The product was chromatographed over silica gel (50 g); subsequent elution with benzene–ethyl acetate (5 : 1) afforded dihydrofukinolidol (**10**) (1.20 g), which was then crystallized from ethyl acetate as colorless prisms; mp 190.0—191.0°C, $[\alpha]_D^{22}$ −14.5° (*c*, 1.0, MeOH). This was identical with the dihydrofukinolidol (**10**) obtained by the alkaline hydrolysis of tetrahydrofukinolide (**9**) (mixed-melting-point determination and a comparison of their IR spectra).

Further elution with the same solvent gave epidihydrofukinolidol (**11**) (600 mg), which was crystallized from ethyl acetate as colorless prisms; mp 148.0—149.0°C, $[\alpha]_D^{22}$ −69.5° (*c*, 1.0, MeOH); IR(KBr): 3365, 3330, 1758 cm^{-1}; NMR-($CDCl_3$): 4.52 (dd, J=7.0, 8.5 Hz, 12-CH), 4.47 (d, J=10.5 Hz, 9-CH), 4.05 (OH), *ca.* 3.95 (m, 1-CH), 3.81 (dd, J=2.5, 8.5 Hz, 12-CH), 3.65 (OH), *ca.* 2.50 (m, 1H), 2.32 (dd, J=5.0, 10.5 Hz, 10-CH), 1.83 (s, 6-CH_2), 1.06 (d, J=6.0 Hz, 13-CH_3), 0.98 (s, 15-CH_3), 0.81 (d, J=3.5 Hz, 14-CH_3).

Found: C, 67.06; H, 9.03%. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

*Acetylation of Dihydrofukinolidol (**10**).* Dihydrofukinolidol (**10**) (100 mg) was treated with acetic anhydride (0.5 ml) and pyridine (0.3 ml) at room temperature for 48 hr. The reaction mixture was then worked up in the usual manner. The crude product (130 mg) was chromatographed on silica gel (5 g); subsequent elution with benzene–ethyl acetate (80 : 1) gave diacetate (**44**) (70 mg), mp 246.0—248.0°C, colorless prisms (from ethyl acetate), $[\alpha]_D^{22}$ −42.5° (*c*, 1.0, $CHCl_3$); IR(KBr): 1769, 1738sh, 1733, 1241sh, 1233 cm^{-1}; NMR($CDCl_3$): 5.95 (d, J=11.5 Hz, 9-CH), 5.00 (m, 1-CH), 4.24 (t, J=8.0 Hz, 12-CH), 3.50 (dd, J=8.0, 11.0 Hz, 12-CH), 2.68 (dd, J=5.5, 11.5 Hz, 10-CH), 2.15, 1.59 (ABq, J=14.0 Hz, 6-CH_2), 2.03 (s, AcO), 1.92 (s, AcO), 1.20 (d, J=7.0 Hz, 13-CH_3), 1.07 (s, 15-CH_3), 0.83 (d, J=4.5 Hz, 14-CH_3).

Found: C, 64.59; H, 8.04%. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01%. This was identical with the diacetate prepared by the hydrogenation of fukinolidol diacetate (**12**).

Further elution with the same solvent gave monoacetate (**43**) (30 mg); mp 194.0—196.0°C, colorless prisms (from ethyl acetate–light petroleum); IR(KBr): 3445, 1760, 1715sh, 1702, 1265 cm^{-1}.

Found: C, 66.00; H, 8.64%. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44%.

*Acetylation of Epidihydrofukinolidol (**11**).* Epidihydrofukinolidol (**11**) (150 mg) was acetylated under conditions similar to those above to furnish, quantitatively, diacetate (**45**) (190mg). The product was crystallized from ethyl acetate as colorless prisms; mp 214.0—215.0°C, $[\alpha]_D^{22}$ −50.5° (*c*, 1.0, $CHCl_3$); IR(KBr): 1768, 1731, 1235 cm^{-1}; NMR-($CDCl_3$): 5.75 (d, J=10.5 Hz, 9-CH), 5.02 (m, 1-CH), 4.27 (dd, J=6.5, 9.0 Hz, 12-CH), 3.82 (dd, J=2.5, 9.0 Hz, 12-CH), 2.50 (dd, J=5.5, 10.5 Hz, 10-CH), 2.04 (s, AcO), 1.98 (s, 6-CH_2), 1.92 (s, AcO), 1.06 (d, J=7.0 Hz, 13-CH_3), 1.05 (s, 15-CH_3), 0.88 (d, J=3.0 Hz, 14-CH_3).

Found: C, 65.00; H, 7.93%. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01%.

*Hydrogenation of Fukinolidol Diacetate (**12**).* Fukinolidol diacetate (**12**) (193 mg) in acetic acid (2 ml) was hydrogenated in the presence of platinum oxide (24.8 mg) at room temperature and atmospheric pressure. Working up in the usual manner afforded the dihydro compound (**44**); mp 246.0—248.0°C, colorless needles (from ethyl acetate–light petroleum).

Found: C, 64.48; H, 8.01%. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01%. This was identical with the dihydrofukinolidol diacetate (**44**) obtained by the acetylation of dihydrofukinolidol (**10**).

*Hydrolysis of Homofukinolide (**3**).* Homofukinolide (**3**) (0.4 g) was dissolved in 2 N alcoholic potassium hydroxide (20 ml), and then the mixture was left for 70 hr at room temperature. After the removal of the solvent and acidification with dilute sulfuric acid, the reaction mixture was extracted with chloroform. The extract was washed with a saturated sodium hydrogen carbonate solution and water, and dried. The subsequent evaporation of the solvent gave fukinolidol (**8**) (180 mg) as colorless prisms (from ethyl acetate); mp 177.0—180.0°C, $[\alpha]_D^{22}$ −79.5° (*c*, 1.0, MeOH).

Found: C, 67.78; H, 8.37%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%. This was identical with the sample of fukinolidol (**8**) obtained by the hydrolysis of fukinolide (**1**).

Acidification of the sodium hydrogen carbonate solution with dilute sulfuric acid and extraction with ether gave a crude acidic part (150 mg), which was then transformed into the *p*-phenylphenacyl ester in the usual manner. The product (450 mg) was chromatographed over silica gel (10 g) and eluted with light peroleum–ether (50 : 1) to afford *p*-phenylphenacyl angelate (130 mg) as colorless leaflets (from ethanol); mp 89.0—90.0°C.

Found: C, 77.54; H, 6.29%. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%. This was identical with the authentic sample of *p*-phenylphenacyl angelate.

*Hydrolysis of S-Fukinolide (**4**).* S-Fukinolide (**4**) (300 mg) was dissolved in 2 N methanolic potassium hydroxide (10 ml), and then the mixture was left overnight at room temperature. The solvent was removed *in vacuo*, and the residue was acidified with dilute sulfuric acid and extracted with ether. The extract was washed with a saturated sodium hydrogen carbonate solution and water, and dried. The subsequent evaporation of the solvent gave a product (110 mg) which was crystallized from ethyl acetate as colorless prisms; mp 176.0—178.0°C, $[\alpha]_D^{22}$ −78.5° (*c*, 1.0, MeOH), −75.0° (*c*, 1.0, $CHCl_3$).

Found: C, 67.84; H, 8.42%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%. This was identical with the fukinolidol (**8**) obtained by the alkaline hydrolysis of fukinolide (**1**) according to a mixed-melting-point determination and a comparison of their IR spectra.

The sodium hydrogen carbonate solution was concentrated *in vacuo*, acidified with dilute sulfuric acid, and extracted with ether. The extract was washed with water and dried. After the removal of the solvent, the residue (100 mg) was crystallized from ethanol–cyclohexane to give an acid (**46**) as colorless prisms; mp 119.0—120.0°C, NMR($CDCl_3$): 11.10 (s, COOH), 7.20 (d, J=10.0 Hz, β-CH=), 5.85 (d, J=10.0 Hz, α-CH=), 2.39 (s, S-CH_3).

Found: C, 40.54; H, 5.19%. Calcd for $C_4H_6O_2S$: C, 40.66; H, 5.12%.

The above acid was transformed into the *p*-phenylphenacyl ester, which was then crystallized from ethanol as colorless needles; mp 132.5—133.5°C.

Found: C, 69.19; H, 5.20; S, 10.46%. Calcd for $C_{18}H_{16}O_3S$: C, 69.20; H, 5.16; S, 10.26%. The acid (**46**) was identified as *cis*-β-methylthioacrylic acid from the above

data.

*Reduction of Fukinanolide (**5**) with Lithium Aluminum Hydride.* A solution of fukinanolide (**5**) (662 mg) in dry ether (20 m*l*) was added, drop by drop, to a suspension of lithium aluminum hydride (264 mg) in dry ether (35 m*l*) at room temperature over a 1-hr period, and then the mixture was refluxed for 4hr. Working up as usual gave a crude diol (**47**) (657 mg), which was then crystallized from light petroleum; mp 81.5—82.0°C, colorless leaflets, $[\alpha]_D^{22}+22.0°$ (*c*, 1.0, MeOH); IR(KBr): 3280, 1638, 1063, 1040, 903 cm^{-1}.

Found: C, 75.61; H, 11.08%. Calcd for $C_{15}H_{26}O_2$: C, 75.84; H, 11.00%.

*Hydrogenation of Diol (**47**).* The diol (**47**) (410 mg) was hydrogenated with 10% palladium charcoal (70 mg) in ethanol (15 m*l*) at room temperature and atmospheric pressure. Working up in the usual manner gave a crude product (400 mg) which was subsequently chromatographed on silica gel (10 g). Elution with benzene afforded fukinan-8-ol (**26**) (78 mg); this was followed by purification on glc (PEG 6000, 2.6 m; column temperature, 180°C; H_2-flow rate, 150 m*l*/min; retention time, 29.5 min), mp 38.0—39.0°C, $[\alpha]_D^{22}+18.0°$ (*c*, 1.01, MeOH).

Found: C, 80.04; H, 12.52%. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58%. This was identical with the fukinan-8-ol (**26**) obtained from fukinone epoxide (**30**) and fukinolidol (**8**) as shown by a comparison of their IR spectra and by a mixed-melting-point determination.

Further elution with ethyl acetate afforded diol (**48**) (290 mg), which was subsequently crystallized from light petroleum; mp 121.0—122.0°C, colorless needles, $[\alpha]_D^{22}+11.7°$ (*c*, 0.94, MeOH); MS: *m/e* 240 M^+: IR(KBr): 3230, 1250, 1135, 1100, 1070, 1045 cm^{-1}.

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