The Photosensitized Oxygenation of Furanoeremophilanes. III.[1,2] The Transformations to the Skeletally Isomeric Lactones from Furanofukinol[3]

Keizo NAYA,* Mitsuaki SHIMIZU, Hideki NISHIO, Motonori TAKEDA, Shogo OKA, and Keiji HIROTA
Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, Hyogo 662
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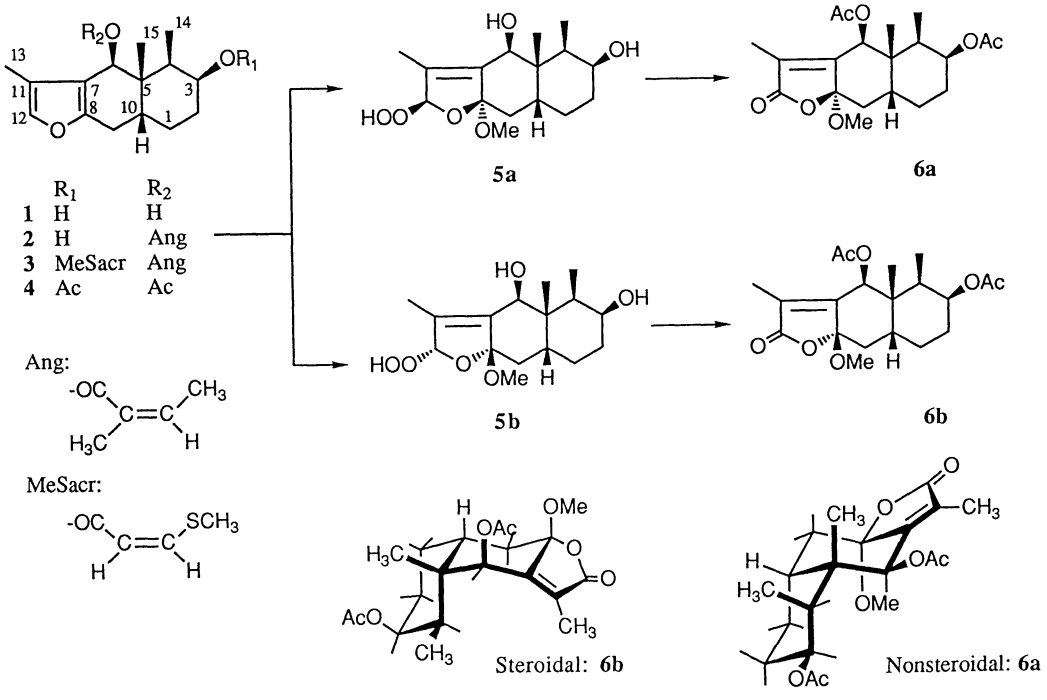
Pairs of the skeletal isomers of eremophilane-type lactones were synthesized from furanofukinol via photosensitized oxygenation, followed by lactone cleavage and reformation. Their stereochemistry has been clarified so as to be consistent with a classification method outlined in our earlier papers.[1,2]

Most of the naturally occurring eremophilane-type lactones possessing *cis*-decalin rings have 8β-substituents,[4,5] except for quite a few recent examples;[6] consequently, the synthesis of 8α-substituted lactone would not, hitherto, be attempted.[7] In previous papers[1,2] we reported on the photosensitized oxygenation of furanoeremophilanes in MeOH, followed by dehydration with Ac_2O-pyridine to yield, quantitatively, an epimeric mixture of 8α- and 8β-methoxylactones, in a ratio of ca. 1 : 1.[8] We have also proposed a procedure to distinguish the stereochemistry of the epimers, that is, 8α-nonsteroidal or 8β-steroidal A/B *cis* chair/chair configurations, according to the substitution mode at C-8.

The present paper deals with syntheses of novel nonsteroidal 8α-substituted eremophilenolides, termed epieremophilenolides, by the photosensitized oxygenation of furanofukinol (**1**) followed by dehydration, as well as by hydrolytic cleavage of lactones, recyclization and further chemical modifications. Recyclization to a nonsteroidal-type 8α-substituted lactone was achieved for the first time by a steric effect due to the 3β-hydroxyl group in furanofukinol (**1**).

Thus, the most simple lactone pair **13a,b** and the four 3-hydroxy skeletal diastereomers, **9a,b** and **16a,b,** were synthesized by recyclization; a further detailed comparison of the spectral data (cf. Tables 1 and 2) between the corresponding pairs was made in order to ascertain the classification procedure[1,2] proposed previously.

Furanofukinol (**1**) was isolated as a minor component from *Petasites japonicus* Maxim. rhizomes,[9] and the major components were its esters, 6-*O*-angeloylfuranofukinol: 6-*O*-[(*Z*)-2-methyl-2-butenoyl] furanofukinol (**2**) and *S*-furanopetasitin: 6-*O*-[(*Z*)-2-methyl-2-butenoyl]-3-*O*-[(*Z*)-3-methylthioacryloyl]furanofukinol (**3**). Hence, the starting material **1** was prepared by the alkaline hydrolysis of **2** and **3**. The stereochemis-



Scheme 1.

try of **1**, possessing a nonsteroidal conformation, has been unambiguously established by a combination of spectroscopic and chemical methods.[10]

A mixture of **1** and methylene blue in MeOH was irradiated with a circular fluorescent lamp (30 W×2) under bubbling air through the solution, affording quantitatively a crystalline product. The product showed two spots on TLC (R_f 0.09 and 0.29, benzene–AcOEt 2 : 1); the mixture was separated on the basis of solubilities in benzene, followed by careful recrystallization which afforded two isomeric hydroperoxides, a less soluble, polar isomer **5a**, mp 165.0—165.5 °C (decomp) and a soluble, less polar isomer **5b**, mp 94.0—96.0 °C (decomp), in a ratio of 2 : 1. Both were positive to peroxide tests, KI–AcOH and $Fe(SCN)_2$.

A mixture of **5a,b** was subsequently treated with Ac_2O–pyridine to give quantitatively an epimeric mixture, which was separated to afford the less polar (R_f 0.60, light petroleum–ether 1 : 1) 3β,6β-diacetoxy-8α-methoxyepieremophilenolide (**6a**), mp 132.5—133.0 °C and the polar (R_f 0.51) 3β,6β-diacetoxy-8β-methoxyeremophilenolide (**6b**), mp 139.0—140 °C, in a ratio of 3 : 1. Meanwhile, **5a** alone was exclusively converted to **6a** in the similar manner as described above (cf. Scheme 1).

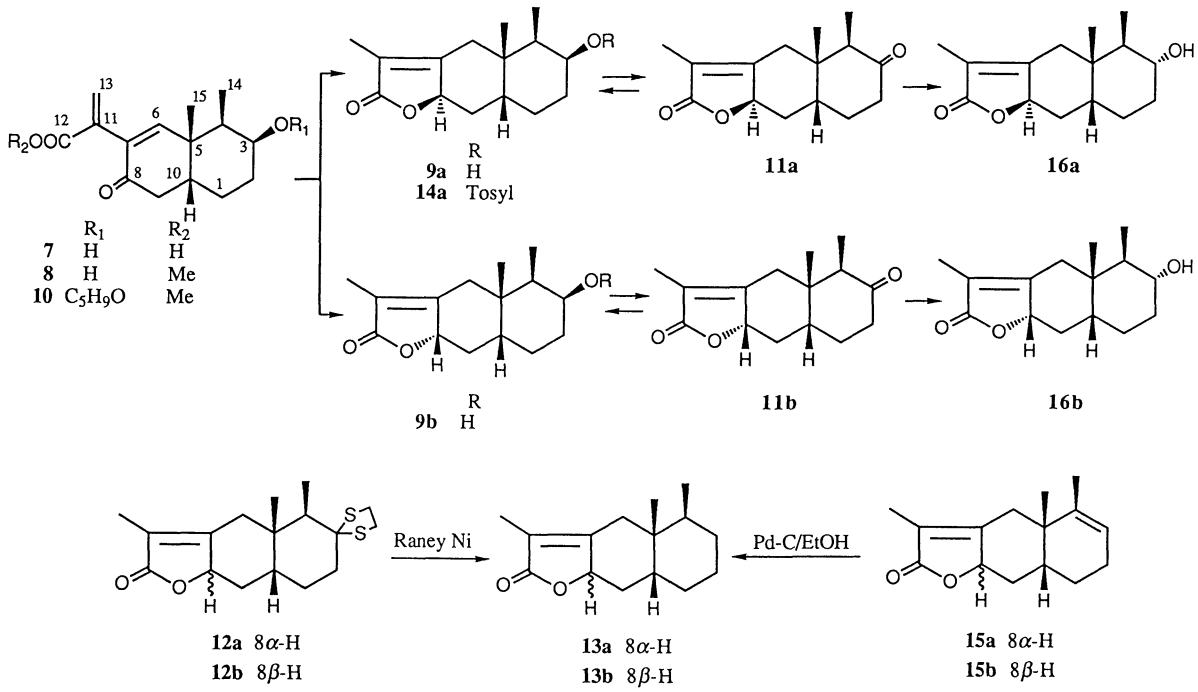
The assigned stereoformulas of pairs of **5a,b** and **6a,b** were readily drawn from the coupling pattern of 3α-H in ^{1}H NMR and, furthermore, from the physical properties along with the generalization reported before.[1,2] Only the nonsteroidal **5a** and **6a** showed homoallylic couplings[2,11] between 13-Me and 6α-H (the mutual dihedral angle=ca. 90°), indicating 8α-configuration (cf. Scheme 1 and Exptl.).

An alkaline hydrolysis of a mixture of **6a,b** gave an 8-oxodienoic acid **7**, mp 163.5—164.0 °C, as a sole product in 85% yield. The Na salt of **7** in MeOH was refluxed with MeI to furnish an ester **8**, mp 114.5—115.5 °C, in 83% yield. Reduction of the ester **8** with $NaBH_4$ in MeOH gave an oily mixture, which was separated by chromatography upon silica gel, followed by recrystallization, to give 3β(*equatorial*)-hydroxyepieremophilenolide (**9a**), mp 167.0—168.0 °C, and 3β(*axial*)-hydroxyeremophilenolide (**9b**), mp 169.5—170.5 °C, in a ratio of 1 : 1; the more bulky 3-*O*-tetrahydropyranyl ether **10** prepared from **8** was subjected to a similar reduction with $NaBH_4$ as mentioned above, giving **9a** and **9b** in a ratio of 5 : 2 (cf. Scheme 2).

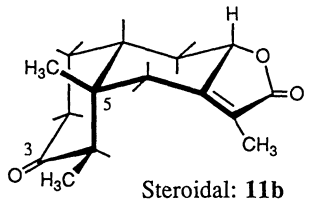
Jones' and PDC oxidations of **9a** and **9b** furnished the 3-oxo derivatives, **11a** mp 131.5—132.5 °C and **11b** mp 155.5—156.5 °C in good yields, respectively. However, product **11a** prepared by a Jones oxidation exhibited signals due to 14-Me (δ=1.06 and 1.20, each d, J=6.5 Hz) and 15-Me (δ=0.91 and 1.03, each s). This might be caused by epimerization of 14-Me in an acidic medium.

The dithioacetalization of **11a** and **11b**, and the subsequent desulfurization of dithioacetals **12a** and **12b** with Raney nickel furnished epieremophilenolide (**13a**), mp 86.0—86.5 °C, and eremophilenolide (**13b**), mp 123.5—124.5 °C, respectively.

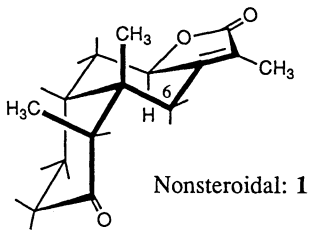
In additional routes to **13a** and **13b**, the tosylation of **9a** and a subsequent treatment with NaI in acetone resulted in an elimination of the tosyl group, while affording a 3,4-dehydro compound **15a**. The mesylation of **9a** or **9b** also caused dehydration, directly



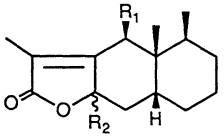
Scheme 2.



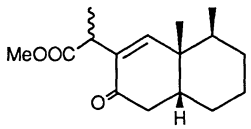
Steroidal: **11b**



Nonsteroidal: **11a**



	R_1	R_2
17b	OH	β-H
19a,b	H	α,β-OMe
20b	H	β-OH



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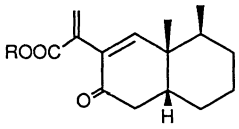

	R
21	H
22	Me

17b $\xrightarrow{(i)}$ **18** $\xrightarrow{(ii)}$ **13b** $\xleftarrow{(ii)}$ **22** $\xleftarrow{(iii)}$ **21** **19a,b** $\xrightarrow{(iv)}$ **20b**

Scheme 3. (i) 2 M KOH–MeOH, CH_2N_2–ether; (ii) $NaBH_4$; (iii) NaOMe–MeOH, MeI; (iv) 1.5 M KOH–MeOH, 10% H_2SO_4 (1M=1 mol dm^{-3}).

affording 3,4-dehydro compounds, **15a** or **15b**. The hydrogenation of **15a** and **15b** furnished **13a** and **13b** as predominant products, respectively. This result revealed that the addition of hydrogen to the double bond proceeded preferentially from the concave side of the *cis*-decalin ring.

A further approach to the syntheses of all four possible diastereomers of the 3-hydroxy lactones was attempted in order to explore the stereoselectivity upon reduction of the prochiral 3-oxo groups with $NaBH_4$ in MeOH as follows. Thus, **11a** gave a nonsteroidal 3α(*axial*)-OH isomer **16a**, mp 138.5—139.5 °C (56.3%), and the regenerated 3β(*equatorial*)-OH isomer **9a** (36.9%). Similarly, **11b** gave a new steroidal 3α(*equatorial*)-OH isomer **16b**, mp 158.0—159.0 °C (10%) together with the original 3β(*axial*)-OH isomer **9b** (80%). The above-mentioned results can be predicted by an observation of stereoformulas **11a** and **11b**. The 3-oxo groups in **11a** and **11b** were preferentially attacked with $NaBH_4$ from the convex and concave sides of the *cis*-decalin ring, so as to avoid 1,3-diaxial interactions with the 6-CH_2 and 15-Me groups, respectively (cf. stereoformulas **11a** and **11b** in Scheme 3).

For a comparison of the stereoselectivity upon recyclization to lactones, the natural 6β-hydroxyeremophilenolide (**17b**)[1] was subjected to alkaline hydrolysis followed by esterification with CH_2N_2 in diethyl ether, and then by reduction with $NaBH_4$ in a similar manner as in the transformation from 3β-hydroxydienoic ester **8** to **9a** and **9b**. Thus, only eremophilenolide **13b** was obtained via an enoic ester **18**, bp 116—118 °C/0.3 mmHg (40 Pa), in 86% overall yield. In a previous study,[2] 8β-hydroxyeremophilenolide (**20b**) was quantitatively synthesized from a mixture of 8α- and 8β-methoxy lactones **19a,b** by alkaline lactone cleavage, followed by acidic recyclization.

In addition, dienoic acid **21**[1,2] prepared previously from petasalbin (6β-hydroxyfuranoeremophilane) and furanofukinin (6β-methoxyfuranoeremophilane) was transformed into the methyl ester **22**, followed by a treatment with $NaBH_4$ in MeOH in a similar manner as that for ester **8** to furnish only steroidal **13b** (92%).

Therefore, the above-mentioned successful methods for the first preparation of epieremophilenolides by recyclization could be achieved by a steric effect based on the greater stability of the 3β(*equatorial*)-hydroxy group in a nonsteroidal conformation, more than the 3β(*axial*)-hydroxy group in a steroidal conformation, where 3β-substituent has a 1,3-diaxial interaction with 15β-methyl.

Now, the stereochemistry of the above-mentioned products can be clearly assigned by means of a general procedure.[1,2] In Table 1,[12] the 8α-substituted lactones (suffix a-series) showed chemical shifts due to 14-methyls at a lower field than those due to 15-methyls; this relation of the chemical shifts between 14- and 15-methyls is reversed in the 8β-series (suffix b-series). These variations in the chemical shifts could be accounted for in terms of an alteration in the geometric orientations of the 14- and 15-methyls, accompanied by a skeletal change between the steroidal and nonsteroidal conformations.[13] Also, the coupling patterns[14] of the protons at C-3 in the 3-hydroxy lactones, consisting of rigid[15] chair forms, practically serve to define the absolute configuration of 3-hydroxy substituents as well as a determination of the nonsteroidal and steroidal conformations of the

Table 1. Comparison of ^{1}H NMR Chemical Shifts (δ), Specific Rotations, CD Maxima and R_f Values of the Corresponding Isomers

Compound [mp/°C]	15-Me	14-Me $CDCl_3$	13-Me	3-H	$[\alpha]_D$/° $CHCl_3$	CD MeOH λ/nm ($\Delta\varepsilon$)	R_f	C_6H_6 : AcOEt
6a	0.92s	0.93d	1.87d	4.85ddd	−198	244 (−5.15)[a]	0.60	
[133]		J=7	J=1.8	J=6,6,12				1 : 1[c]
6b	1.24s	0.92d	2.01s	4.99ddd	+180	263 (+1.06)[a,b]	0.51	
[140]		J=7		J=3,3,3				
9a	0.85s	0.97d	1.79t	4.10ddd	−157	253 (+0.10)	0.27	
[168]		J=7	J=1.6	J=5.5,5.5,11				2 : 1
9b	1.29s	1.01d	1.80t	3.81ddd	+196	248 (+3.09)	0.60	
[170.5]		J=6.8	J=1.8	J=4,4,5				
11a	0.89s	1.20d	1.79t		−157	241 (−0.20)	0.70	
[132.5]		J=6.5	J=1.8					2 : 1
11b	1.00s	0.96d	1.83t		+154	245 (+2.05)	0.75	
[156.5]		J=7	J=1.3					
13a	0.88s	0.92d	1.80t		−127	248 (−0.54)	0.57	
[86.5]		J=6.6	J=1.5					30 : 1
13b	1.04s	0.80d	1.80t		+163	248 (+2.40)	0.55	
[124.5]		J=5.9	J=1.4					
16a	0.80s	0.95d	1.78t	3.97ddd	−138	248 (−0.04)	0.43	
[139.5]		J=7.3	J=1.5	J=3,3,3				2 : 1
16b	1.05s	1.01d	1.81t	3.61ddd	+214	252 (+0.38)	0.45	
[159]		J=8.5	J=1.5	J=5,10.3,10.3				

a) Measured with JASCO J-600 spectropolarimeter. b) Hexane. c) Light petroleum : ether, 1 : 1.

Table 2. The ^{13}C NMR Chemical Shifts of the Corresponding Isomers

C	**6a**	**6b**	**9a**	**9b**	**16a**	**16b**	**11a**	**11b**	**13a**	**13b**
1	24.9	21.0	27.3	21.7	22.8	25.0	28.1	26.9	29.1	30.7
2	26.6	24.6	29.2	28.3	28.9	30.1	34.0[a]	35.0[a]	26.6	20.6
3	71.5	73.2	68.6	71.6	73.9	72.4	213.6	211.0	27.1	26.7
4	34.9	32.1	44.7	33.9	44.7	38.1	55.4	45.6	41.4	30.0
5	45.8	42.0	41.0	39.9	38.9	41.0	42.6	44.5	40.3	39.8
6	71.0	70.7	34.7	37.4	35.1	36.6	34.4[a]	36.8[a]	31.0	36.5
7	154.8	150.0	162.1	161.0	163.3	160.5	160.2	159.1	163.0	161.0
8	106.6	106.6	77.7	80.2	78.1	80.2	77.1	79.6	78.0	80.3
9	37.8	38.0	33.7	35.0	35.1	35.1	36.9	36.1[a]	36.1	35.2
10	35.2	34.5	35.5	39.9	36.8	39.6	35.3	39.5	42.9	40.3
11	126.3	130.8	122.0	120.4	121.0	120.9	122.7	121.8	121.6	120.6
12	170.7	170.2	174.7	174.8	175.2	174.8	174.1	174.1	175.0	174.8
13	8.2	8.9	8.0	8.2	8.0	8.2	8.0	8.4	8.0	8.2
14	8.4	12.3	7.5	12.3	15.2	11.1	13.9	7.6	16.0	16.0
15	20.5	18.0	25.0	25.1	25.4	22.9	23.1	23.2	24.4	21.6
3-MeCO	19.2	20.7								
6-MeCO	21.2	21.3								
3-MeCO	170.2	170.4								
6-MeCO	170.3	170.4								
OMe	50.3	50.5								

a) Assignments may be interchanged in each column.

chair-chair *cis*-decalins in 8α- and 8β-isomers, respectively.

The paired lactones exhibited CD spectra with opposite signs (Table 1), which can be rationalyzed by the opposite helicities in the α,β-unsaturated carbonyl moieties caused by lactone ring fusion. Thus, the 8β-isomers possessing a right-handed helix showed positive Cotton effects centered near 240—260 nm corresponding to the π-π^* transition,[16] while the 8α-isomers with a left-handed helix showed negative Cotton effects in the same region, except for the compound **9a** (cf. Table 1).

In the ^{13}C-chemical shifts (Table 2), the comparative chemical shifts between the paired isomers proved, on the whole, to be qualitatively in accord with the empirical calculation presented by Beierbeck et al.,[17] except for the chemical shifts of 9-C and the olefinic carbons, 7-C and 11-C. The chemical shifts of 7-C could not also be rationalized by the diamagnetic γ-effect[18] of the 15(*axial*)-Me group in the 8α-H

isomers. The chemical shifts of the olefinic carbons, 7-C and 11-C, at a higher field in the 8β-H isomers are clearly reflected by shielding of the carbon atoms in the steroidal *cis*-type (*cis-syn-cis*) ring relative to its nonsteroidal *trans*-type (*cis-anti-cis*) ring in 8α-H isomers[19] (cf. stereoformulas **6a,b** and **11a,b**).

Experimental

All of the melting points are uncorrected. The IR, UV, CD, and MS spectra were taken with Hitachi EPI-G3, Cary 118, JASCO Model ORD/CD-5, and JEOL JMS-D300 spectrophotometers, respectively. The ^{1}H and ^{13}C NMR spectra were recorded with a JEOL FX-90Q (90 and 22.5 MHz) spectrometer, and the chemical shifts are reported in δ values (with TMS as the internal reference). The optical rotations were measured with a Perkin-Elmer 141 polarimeter. The TLC were run on a Kieselgel G (Merck).

Isolation of Furanofukinol (1), 6-*O*-Angeloylfuranofukinol (2), and *S*-Furanopetasitin (3). The dried rhizomes of *Petasites japonicus* Maxim. ("Aichiwasebuki" cultivated in Osaka Prefecture) (36 kg) were extracted with benzene (85 l) at room temperature for 12 days. The extract was concentrated in vacuo in order to remove the solvent. The residue was dissolved in ether, washed with saturated $NaHCO_3$ aqueous solution, then with water, dried over anhydrous Na_2SO_4 and evaporated in vacuo, leaving a dark oil (473 g). This oil (100 g) was chromatographed on deactivated alumina (1 kg, grade III). Elution with benzene, and then benzene-ethyl acetate (2:1), afforded a mixture of *S*-furanopetasitin (**3**) and 6-*O*-angeloylfuranofukinol (**2**) (45 g), as well as furanofukinol (**1**) (120 mg). The mixture of **2** and **3** was repeatedly chromatographed on alumina (grade III), and elution with light petroleum-ether (20:1) gave both **3** (11 g, 11% yield based on the crude extract) and **2** (16 g, 16% yield).

Furanofukinol (1): Mp 178.0—180 °C (decomp), colorless needles (from MeOH); $[\alpha]_D^{25}$ −18° (*c* 0.97, dioxane); UV (EtOH) 219 nm (ε 6720); IR (KBr) 3367, 3323 (OH), 1648, 1569 cm^{-1} (furan); ^{1}H NMR ($CDCl_3$) δ=7.06 (q, *J*=1.3 Hz, 12-H), 4.90 (br s, 6α-H), 4.21 (ddd, *J*=5, 5, 10 Hz, 3α-H), 2.07 (d, *J*=1.3 Hz, 13-Me), 0.97 (d, *J*=7.3 Hz, 14-Me), 0.95 (s, 15-Me); ^{13}C NMR (pyridine-d_5) δ=27.0 (t, 1-C), 28.2 (t, 2-C), 68.1 (d, 3-C), 39.3 (d, 4-C), 43.0 (s, 5-C), 66.8 (d, 6-C), 121.4 (s, 7-C), 149.5 (s, 8-C), 30.4 (t, 9-C), 37.0 (d, 10-C), 119.5 (s, 11-C), 138.4 (d, 12-C), 7.7 (q, 13-C), 9.1 (q, 14-C), 20.1 (q, 15-C).

Found: C, 71.82; H, 8.75%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

6-*O*-Angeloylfuranofukinol: 6-*O*-[(*Z*)-2-Methyl-2-butenoyl]furanofukinol (2): A colorless oil (purified by HPLC, μ-Bondapak C_{18}, MeOH-H_2O 8:1); $[\alpha]_D^{25}$ −41.4° (*c* 0.91, $CHCl_3$); UV (EtOH) 215 nm (ε 17150); IR (film) 3440 (OH), 1700, 1640, 1230 cm^{-1} (α,β-unsaturated ester); ^{1}H NMR ($CDCl_3$) δ=7.07 (q, *J*=1.2 Hz, 12-H), 6.50 (s, 6α-H), 6.14 (slightly splitted q, *J*=7.0 Hz, 3-H in butenoyl), 4.40 (ddd, *J*=5.5, 5.5, 10.5 Hz, 3α-H), 2.02 (br d, *J*=7.5 Hz, 4-Me in butenoyl), 1.98 (br s, 2-Me in butenoyl), 1.83 (d, *J*=1.2 Hz, 13-Me), 1.03 (s, 15-Me), 0.95 (d, *J*=6.0 Hz, 14-Me); ^{13}C NMR ($CDCl_3$) δ=27.5 (t, 1-C), 26.9 (t, 2-C), 68.9 (d, 3-C), 39.2 (d, 4-C), 42.0 (s, 5-C), 68.5 (d, 6-C), 115.2 (s, 7-C), 150.4 (s, 8-C), 28.9 (t, 9-C), 36.9 (d, 10-C), 119.6 (s, 11-C), 138.8 (d, 12-C), 7.0 (q, 13-C), 8.5 (q, 14-C), 20.4 (q, 15-C), butenoyl: 168.1 (s, CO), 127.8 (s, 2-C), 138.4 (d, 3-C), 16.0 (q, 2-Me), 20.7 (q, 4-Me).

Found: *m/z* 333.2045 (MH^+). Calcd for $C_{20}H_{28}O_4$: MH, 333.2058.

***S*-Furanopetasitin: 6-*O*-[(*Z*)-2-Methyl-2-butenoyl]-3-*O*-[(*Z*)-3-methylthioacryloyl]furanofukinol (3):** Mp 107.0—108.0 °C, colorless prisms (from ethyl acetate-diisopropyl ether), $[\alpha]_D^{24}$ −60.5° (*c* 1.0, $CHCl_3$); UV (EtOH) 216 (ε 21000), 287.5 nm (14340); IR ($CHCl_3$) 1704, 1694, 1644, 1230—1215 br (two α,β-unsaturated esters), 1603, 1573 cm^{-1} (furan); ^{1}H NMR ($CDCl_3$) δ=7.08 (q, *J*=1.0 Hz, 12-H), 7.03 (d, *J*=11.0 Hz, Me-S-C<u>H</u>=), 6.50 (s, 6α-H), 6.12 (slightly splitted q, *J*=8.0 Hz, 3-H in butenoyl), 5.82 (d, *J*=11.0 Hz, Me-S-CH=C<u>H</u>-), 5.40 (ddd, *J*=4.5, 4.5, 9.0, 3α-H), 2.38 (s, <u>Me</u>-S-), 2.03 (d, *J*=8.0 Hz, 4-Me in angelate), 1.96 (br s, 2-Me in angelate), 1.87 (d, *J*=1.0 Hz, 13-Me), 1.07 (s, 15-Me), 0.98 (d, *J*=7.0 Hz, 14-Me); ^{13}C NMR ($CDCl_3$) δ=25.8 (t, 1-C), 26.3 (t, 2-C), 72.3 (d, 3-C), 35.9 (d, 4-C), 41.7 (s, 5-C), 68.4 (d, 6-C), 115.6 (s, 7-C), 150.5 (s, 8-C), 30.0 (t, 9-C), 36.5 (d, 10-C), 119.8 (s, 11-C), 138.3 (d, 12-C), 8.5 (q, 13-C), 8.8 (q, 14-C), 19.9 (q, 15-C), butenoyl: 167.5 (s, CO), 127.9 (s, 2-C), 138.1 (d, 3-C), 15.8 (q, 2-Me), 20.7 (q, 4-Me); 3-MeS-acryloyl: 165.6 (s, CO), 113.5 (d, α-C), 151.0 (d, β-C), 19.0 (q, S-Me).

Found: C, 66.88; H, 7.39: S, 7.64%. Calcd for $C_{24}H_{32}O_5S$: C, 66.64; H, 7.46; S, 7.41%.

Preparation of Furanofukinol (1). a) Alkaline Hydrolysis of the Mixture of 2 and 3. Aqueous 20% NaOH (134 ml) was added, drop by drop, to a stirred mixture of **2** and **3** (37 g) in DMSO (240 ml). The mixture was then warmed at 60—65 °C for 9 h under N_2. After dilution with ice-water and acidification with 6 M H_2SO_4 aqueous solution (1 M=1 mol dm^{-3}), the reaction mixture was adjusted to pH 7—8 with a saturated $NaHCO_3$ aqueous solution and kept under cooling to deposit a brownish solid. After working up using the usual method, the crude furanofukinol (**1**) (23 g) was crystallized from MeOH as colorless prisms (11 g), mp 178—180 °C (decomp).

b) To a stirred solution of 1M *t*-BuOK (1 M=1 mol dm^{-3}) in anhydrous DMSO (100 ml) was added a solution of **2** (15 g) in anhydrous DMSO (150 ml) at room temperature over a 0.5 h period under N_2. After stirring for further 12 h, the reaction mixture was diluted with ice-water (300 g) and acidified with 1 M H_2SO_4 to deposit a solid, which was worked up in the usual manner. The crude product **1** was recrystallized from MeOH as colorless prisms (8.7 g); mp 178.0—180.0 °C (decomp). Both of the above-mentioned products were identical in all respects with the natural furanofukinol **1**.

Furanofukinol Diacetate (4). Furanofukinol **1** (100 mg) was treated with pyridine (1 ml) and acetic anhydride (1 ml) at room temperature for 48 h. The usual workup yielded the diacetate **4** (130 mg); mp 144.0—145.0 °C, colorless prisms (MeOH); $[\alpha]_D^{22}$ −53.7° (*c* 0.95, $CHCl_3$); UV (EtOH) 217.5 nm (ε 7720); IR (KBr) 1720, 1253, 1230 (acetate), 1640, 1565 cm^{-1} (furan); ^{1}H NMR ($CDCl_3$) δ=6.98 (q, *J*=1.1 Hz, 12-H), 6.28 (s, 6α-H), 5.28 (ddd, *J*=5.5, 5.5, 10 Hz, 3α-H), 2.11 (s, OAc), 2.00 (s, OAc), 1.82 (d, *J*=1.1 Hz, 13-Me), 0.98 (s, 15-Me), 0.93 (d, *J*=6.0 Hz, 14-Me); ^{13}C NMR ($CDCl_3$) δ=25.6 (t, 1-C), 26.0 (t, 2-C), 72.1 (d, 3-C), 36.0 (d, 4-C), 41.7 (s, 5-C), 68.9 (d, 6-C), 115.8 (s, 7-C), 150.1 (s, 8-C), 26.5 (t, 9-C), 36.4 (d, 10-C), 119.5 (s, 11-C), 138.9 (d, 12-C), 8.5 (q, 13-C), 8.5 (q, 14-C), 19.6 (q, 15-C), 170.3 and 169.1 (each s, Me<u>C</u>OO), 21.2 and 20.8 (each q, <u>C</u>H$_3$COO).

Found: C, 68.24; H, 7.82%. Calcd for $C_{19}H_{26}O_5$: C, 68.24;

H, 7.84%.

Photosensitized Oxygenation of Furanofukinol (1). A stirred solution of **1** (487 mg) and Methylene Blue (2 mg) in anhydrous MeOH (80 ml) was irradiated with two circular fluorescent lamps (30 W×2) for 55 min under air bubbling. After evaporation of the solvent in vacuo, the crystalline residue (603 mg, quantitative yield) showed two spots on TLC (R_f 0.29 and 0.09, benzene-ethyl acetate 2:1), and was positive to peroxide tests: KI-AcOH and $Fe(SCN)_2$ reagents. The above-mentioned crystalline mixture was separated into less and readily soluble hydroperoxides, (**5a**, R_f 0.09) (337 mg, 55%) and (**5b**, R_f 0.29) (157 mg, 27%), according to the solubility in benzene, followed by fractional crystallization.

8α-Methoxy-12β-hydroperoxide (5a): Mp 165.0—165.5 °C (decomp), colorless prisms (MeOH-acetone); $[\alpha]_D^{25}$ −20.0° (*c* 0.92, MeOH); positive to peroxide tests; IR (KBr) 3530, 3410 (OH), 1085, 1030 cm^{-1} (ether); ^1H NMR (acetone-d_6) δ=11.40 (s, OOH); (pyridine-d_5) δ=6.20 (s, 12-H), 5.12 (q, *J*=1.8 Hz, 6α-H), 4.47 (ddd, *J*=5.5, 5.5, 10.5 Hz, 3α-H), 3.29 (s, OMe), 2.33 (d, *J*=1.8 Hz, 13-Me), 1.23 (d, *J*=7.0 Hz, 14-Me), 1.11 (s, 15-Me).

Found: C, 61.12; H, 8.50%. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34%.

8β-Methoxy-12α-hydroperoxide (5b): Mp 94.0—96.0 °C (decomp), colorless needles (benzene-pentane); $[\alpha]_D^{22}$ +57° (*c* 0.93, MeOH); positive to peroxide tests; IR (KBr) 3430, 3200sh (OH), 1045 cm^{-1} (ether); ^1H NMR ($CDCl_3$) δ=10.08 (s, OOH), 5.80 (s, 12-H), 4.27 (br m, 6-H and H_2O), 3.79 (ddd, *J*=3, 3, 3 Hz, 3α-H), 3.30 (s, OMe), 1.81 (s, 13-Me), 1.31 (s, 15-Me), 0.95 (d, *J*=6.0 Hz, 14-Me).

Found: C, 60.90; H, 8.35%. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34%.

Acetylation of Hydroperoxides, 5a,b. a) A mixture of hydroperoxides, **5a,b** (3.4 g) prepared from **1** (2.7 g), was dissolved in pyridine (35 ml) and acetic anhydride (45 ml). The mixture was left overnight at room temperature. The usual type workup gave quantitatively a crude oily product (4.0 g), which showed two spots on TLC (R_f 0.51 and 0.60, light petroleum-ether 1:1). The crude product (1 g) was chromatographed on silica gel (20 g) with light petroleum-ether (10:1) to afford a less polar isomer **6a** (772 mg, 60% yield) and a polar isomer **6b** (245 mg, 20% yield), each of which was crystallized from diisopropyl ether.

b) Hydroperoxide **5a** (50 mg) was treated with pyridine (5 ml) and acetic anhydride (5 ml), as mentioned above, to afford an oily product (74 mg, quantitatively). Recrystallization from diisopropyl ether gave **6a**, mp 132.0—133.0 °C (34 mg), which was identical with the above-mentioned sample **6a**, obtained by acetylation of the hydroperoxides mixture (mixed-melting point determination and a comparison of IR spectra).

3β,6β-Diacetoxy-8α-methoxyepieremophilenolide (6a): Mp 132.5—133.0 °C, colorless prisms; $[\alpha]_D^{23}$ −198° (*c* 1.045, $CHCl_3$); UV (MeOH) 220.6 nm (ε 13900); CD (*c* 3.96×10^{-5}, MeOH, 25°) $[\theta]_{244}$ −17000; IR (CCl_4) 1770, 1695 (α,β-unsaturated γ-lactone), 1750, 1730, 1236 cm^{-1} (OAc); ^1H NMR ($CDCl_3$) δ=5.89 (d, *J*=1.8 Hz, 6-H), 4.85 (ddd, *J*=6, 6, 12 Hz, 3α-H), 3.22 (s, OMe), 2.23 and 2.02 (each s, OAc), 1.87 (d, *J*=1.8 Hz, 13-Me), 0.93 (d, *J*=7 Hz, 14-Me), 0.92 (s, 15-Me); ^{13}C NMR (Table 2).

Found: C, 63.08; H, 7.64%. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42%.

3β,6β-Diacetoxy-8β-methoxyeremophilenolide (6b): Mp 139.0—140.0 °C, colorless needles; $[\alpha]_D^{26}$ +180° (*c* 1.0, $CHCl_3$); UV (MeOH) 219.9 nm (ε 11540); CD (*c* 1.43×10^{-4}, hexane, 25°) $[\theta]_{263}$ +3500; IR (CCl_4) 1770, 1695 (α,β-unsaturated γ-lactone), 1735, 1233 cm^{-1} (OAc); ^1H NMR ($CDCl_3$) δ=5.65 (s, 6-H), 4.99 (ddd, *J*=3, 3, 3 Hz, 3α-H), 3.08 (s, OMe), 2.12 and 2.08 (each s, OAc), 2.01 (s, 13-Me), 1.24 (s, 15-Me), 0.92 (d, *J*=7 Hz, 14-Me); ^{13}C NMR (Table 2).

Found: C, 63.20; H, 7.65%. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42%.

Alkaline Hydrolysis of a Mixture of Lactones, 6a,b. A mixture (9.30 g) of 8α- and 8β-methoxy lactones, **6a,b** was dissolved in a 1.685 M KOH-MeOH solution (190 ml) and then left at room temperature for 16 h. After evaporation of the solvent in vacuo and dilution with water, the solution was acidified with aqueous 10% H_2SO_4, and then extracted with ethyl acetate. The usual workup gave an unsaturated acid (5.50 g, 85%) as the sole product, which was crystallized from ethyl acetate to afford a pure acid **7**, mp 163.5—164.0 °C, colorless prisms; $[\alpha]_D^{20}$ −42.5° (*c* 0.89, MeOH); UV (MeOH) 218 (ε 8250), 243 nm (9140); IR (KBr) 3650—2250, 3360, 1703, 1670 (α,β-unsaturated acid), 1618, 945 cm^{-1} (conjugated diene); ^1H NMR (acetone-d_6) δ=6.98 (m, COOH and OH), 6.69 (d, *J*=1.5 Hz, 6-H), 6.11 (d, *J*=1.5 Hz, 13-H), 5.68 (d, *J*=1.5 Hz, 13-H), 3.76 (ddd, *J*=5.5, 6, 6 Hz, 3α-H), 1.28 (s, 15-Me), 0.98 (d, *J*=7.4 Hz, 14-Me); ^{13}C NMR (pyridine-d_5) δ=26.9 (1-C), 28.5 (2-C), 69.9 (3-C), 44.9 (4-C), 40.4 (5-C), 156.7 (6-C), 141.1 (7-C), 197.0 (8-C), 40.7 (9-C), 36.7 (10-C), 136.6 (11-C) , 168.7 (12-C), 125.6 (13-C), 8.2 (14-C), 25.0 (15-C).

Found: C, 68.00; H, 7.84%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

Esterification of the Unsaturated Acid 7. The above-mentioned dienoic acid **7** (1.235 g) in MeOH (1 ml) was neutralized by a dropwise addition of a 1 M NaOMe-MeOH solution using phenolphthalein as the indicator, followed by the addition of MeI (15 g) over a 5 min period. The solution was refluxed for 9 h, and concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The usual workup gave the crude methyl ester **8** (1.081 g, 83%), which was crystallized from ethyl acetate-diisopropyl ether as colorless needles (670 mg, 51.6%), mp 114.5—115.5 °C; $[\alpha]_D^{25}$ −40° (*c* 1.04, $CHCl_3$); UV (MeOH) 242 nm (ε 8870); IR ($CHCl_3$) 3420 (OH), 1715 (ester), 1670 (ketone), 1610, 942 cm^{-1} (conjugated diene); ^1H NMR ($CDCl_3$) δ=6.64 (d, *J*=1.5 Hz, 6-H), 6.20 (d, *J*=1.5 Hz, 13-H), 5.65 (d, *J*=1.5 Hz, 13-H), 3.72 (s, CO_2Me), ca. 3.7 (m, $W_{1/2}$=15 Hz, 3α-H), 1.29 (s, 15-Me), 1.00 (d, *J*=7 Hz, 14-Me); ^{13}C NMR ($CDCl_3$) δ=26.5 (t, 1-C), 27.9 (t, 2-C), 70.6 (d, 3-C), 44.5 (d, 4-C), 40.3 (s, 5-C), 156.9 (d, 6-C), 138.2 (s, 7-C), 197.3 (s, 8-C), 40.2 (t, 9-C), 36.0 (d, 10-C), 135.7 (s. 11-C), 166.8 (s, 12-C), 127.0 (t, 13-C), 7.5 (q, 14-Me), 25.0 (q, 15-C), 52.1 (q, OMe).

Found: C, 69.01; H, 8.19%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

Reduction of Dienoic Ester 8 with Sodium Borohydride. A solution of $NaBH_4$ (700 mg) in MeOH (10 ml) was added over a 5 min period at 60 °C into a solution of dienoic ester **8** (1.0 g) in MeOH (20 ml). After stirring for an additional 1.5 h under the same conditions, the reaction mixture was concentrated in vacuo and diluted with water. Extraction with ethyl acetate gave a colorless oil (1.166 g, quantitatively), which showed two spots on TLC (R_f 0.27 and 0.60, benzene-ethyl acetate 2:1), and was chromatographed on silica gel (21 g). Elution with benzene-ethyl acetate (15:1)

afforded the less polar **9b** (308 mg, 33.8%) and the polar isomer **9a** (305 mg, 33.5%), each of which was recrystallized from the ethyl acetate-diisopropyl ether.

Reduction of 3-*O*-Tetrahydropyran-2-yl Ether 10 with Sodium Borohydride. a) Preparation of 10: A mixture of *p*-toluenesulfonic acid (20 mg) and dienoic ester **8** (357 mg) in CH_2Cl_2 (2 ml) was stirred for 5 min; 2*H*-3,4-dihydropyran (276 mg) was then added into the stirred solution. After stirring for 18 h the reaction mixture was extracted with CH_2Cl_2, and the extract washed with a saturated aqueous $NaHCO_3$ and water. The usual workup gave a colorless oily product **10** (430 mg, 93%): IR (film) 1670, 1610, 1240, 1010, 950 cm^{-1}.

b) Reduction with $NaBH_4$: Into a stirred solution of the above-mentioned ester **10** (240 mg) in MeOH (5 ml) was added $NaBH_4$ (122 mg) over a 5 min period. After stirring for 2 h, the reaction mixture was adjusted to pH 2; stirring was then continued for additional 2 h. The usual workup gave a crude product (163 mg, quantitative yield), which was chromatographed on silica gel (20 g) with benzene-ethyl acetate (15 : 1) to afford the less polar isomer **9b** (46 mg, 28%) and the polar isomer **9a** (109 mg, 66%).

3β(eq)-Hydroxyepieremophilenolide (9a): Mp 167.0—168.0 °C as colorless needles; $[\alpha]_D^{27}$ −157° (*c* 0.99, $CHCl_3$); UV (MeOH) 217.5 nm (ε 5600); CD (*c* 4.010×10⁻³, MeOH, 22 °C) $[\theta]_{253}$ +350; IR ($CHCl_3$) 3600, 3450 (OH), 1735, 1680, 1095 cm^{-1} (α,β-unsaturated γ-lactone); ^1H NMR ($CDCl_3$) δ=4.80 (br m, $W_{1/2}$=15.8 Hz, 8α-H), 4.10 (ddd, *J*=5.5, 5.5, 11 Hz, 3α-H), 2.78 (d, *J*=14.5 Hz, 6α-H), 1.79 (t, *J*=1.6 Hz, 13-Me), 0.97 (d, *J*=7 Hz, 14-Me), 0.85 (s, 15-Me); ^{13}C NMR (Table 2).

Found: C, 71.82; H, 9.19%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

3β(ax)-Hydroxyereemophilenolide (9b): Mp 169.5—170.5 °C as colorless needles; $[\alpha]_D^{27}$ +196° (*c* 1.04, $CHCl_3$); UV (MeOH) 217.5 nm (ε 15200); CD (*c* 4.140×10⁻³, MeOH, 22 °C) $[\theta]_{248}$ +10200; IR ($CHCl_3$) 3600, 3470 (OH), 1740, 1690, 1095 cm^{-1} (α,β-unsaturated γ-lactone); ^1H NMR ($CDCl_3$) δ=4.72 (m, *W*1/2=18 Hz, 8β-H), 3.81 (ddd, *J*=4, 4, 5 Hz, 3α-H), 2.89 (d, *J*=14.6 Hz, 6α-H), 1.80 (t, *J*=1.8 Hz, 13-Me), 1.29 (s, 15-Me), 1.01 (d, *J*=6.8 Hz, 14-Me); ^{13}C NMR (Table 2).

Found: C, 72.01; H, 8.89%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

Oxidation of 3β(eq)-Hydroxyepieremophilenolide (9a). a) Jones' Oxidation: Jones' reagent (0.8 ml) was added into a stirred solution of **9a** (150 mg) in acetone (3 ml) over a period of 5 min under ice cooling. After stirring for additional 10 min at room temperature, the excess reagent was decomposed with MeOH and the reaction mixture extracted with ethyl acetate. Working up as usual gave a crude crystalline product (114 mg, quantitatively), mp 130.5—132.5 °C, which showed the presence of a pair of epimers concerning the configuration of 14-methyl in its ^1H NMR spectrum (δ=0.91 and 1.03, each s, 15-Me; 1.06 and 1.20, each d, *J*=6.5 Hz, 14-Me). Recrystallization from ethyl acetate gave a pure specimen of 3-oxoepiermophilenolide (**11a**), mp 131.5—132.5 °C (55 mg, 37%).

b) PDC (Pyridinium Dichromate) Oxidation. PDC (1.0 g) was gradually added into a stirred solution of **9a** (118 mg) in CH_2Cl_2 (20 ml). After stirring for additional 2 h, the reaction mixture was shaken with Celite (5 g) and filtered. Evaporation of the filtrate in vacuo gave **11a** (109 mg, 93%).

3-Oxoepieremophilenolide (11a): Mp 131.5—132.5 °C, colorless needles (ethyl acetate-diisopropyl ether); $[\alpha]_D^{26}$ −157° (*c* 1.08, $CHCl_3$); UV (MeOH) 224 nm (ε 9000); CD (c 3.670×10⁻³, MeOH, 22 °C) $[\theta]_{241}$ −655, $[\theta]_{288}$ −3410; IR ($CHCl_3$) 1740, 1685 (α,β-unsaturated γ-lactone), 1710 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ=4.82 (br m, $W_{1/2}$=14 Hz, 8α-H), 1.79 (d, *J*=1.8 Hz, 13-Me), 1.20 (d, *J*=6.5 Hz, 14-Me), 0.89 (s, 15-Me). ^{13}C NMR (Table 2).

Found: C, 72.44; H, 8.13%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Oxidation of 3β(ax)-Hydroxyeremophilenolide 9b. a) Jones' Oxidation. Jones' reagent (1 ml) was added into a stirred solution of **9b** (100 mg) in acetone (2 ml) over a period of 5 min under ice cooling. After stirring for additional 30 min, the reaction mixture was worked up in a similar manner to that mentioned above, giving a crude crystalline product (101 mg, quantitatively), which was recrystallized from ethyl acetate-diisopropyl ether to afford 3-oxoeremophilenolide (**11b**) (126 mg, 95.5%).

b) PDC Oxidation. PDC (1.8 g) was gradually added into a solution of **9b** (153 mg) in CH_2Cl_2 (20 ml) at room temperature. After stirring for additional 2.5 h, the mixture was worked up in a similar manner as to that mentioned above, giving **11b** (148 mg, 97.5%).

3-Oxoeremophilenolide (11b). Mp 155.5—156.5 °C, colorless needles (ethyl acetate-diisopropyl ether); $[\alpha]_D^{26}$ +154° (*c* 0.99, $CHCl_3$); UV (MeOH) 224 nm (ε 11800); CD (*c* 4.301×10⁻³ MeOH, 22 °C) $[\theta]_{245}$ +6790, $[\theta]_{284}$ −10600; IR ($CHCl_3$) 1740, 1695, 1205 (α,β-unsaturated γ-lactone), 1705 cm^{-1} (ketone); ^1H NMR ($CDCl_3$) δ=4.87 (br m, $W_{1/2}$=15.2 Hz, 8β-H), 2.88 (d, *J*=14.0 Hz, 6α-H), 1.83 (t, *J*=1.3 Hz, 13-Me), 1.00 (s, 15-Me) , 0 96 (d, *J*=7 Hz, 14-Me); ^{13}C NMR (Table 2).

Found: C, 72.39; H, 8.14%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Reduction of 3-Oxoepieremophilenolide (11a) via Ethylene Dithioacetal 12a. Ten drops of BF_3-diethyl ether (1/1) were added into a stirred solution of **11a** (55 mg) in 1,2-ethanedithiol (0.5 ml) under ice-cooling. After stirring for 6 h at room temperature and the addition of MeOH (5 drops), the reaction mixture was concentrated in vacuo, diluted with water, and then extracted with ethyl acetate. The usual workup gave an oily product (75 mg, quantitatively), which was crystallized from ethyl acetate-light petroleum to afford ethylene dithioacetal **12a**, mp 129.5—131.5 °C, as colorless needles; $[\alpha]_D^{26}$ −157° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 1742, 1682, 1096, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.80 (m, $W_{1/2}$=14 Hz, 8α-H), 3.4—3.1 (m, acetal methylene), 1.79 (t, *J*=1.5 Hz, 13-Me), 1.31 (d, *J*=6.8 Hz, 14-Me), 0.91 (s, 15-Me)

A suspension of dithioacetal **12a** (153 mg) and Raney nickel (500 mg) in ethanol (10 ml) was refluxed for 3 h and then filtered. The filtrate was concentrated in vacuo to leave a colorless oil (110 mg, 90%). Purification by PTLC (benzene-ethyl acetate, 30 : 1) followed by recrystallization from pentane gave epieremophilenolide (**13a**) (32 mg, 26%).

Epieremophilenolide (13a): Mp 86.0—86.5 °C, colorless prisms; $[\alpha]_D^{26}$ −127° (*c* 1.00, $CHCl_3$); CD (*c* 4.22×10⁻³, MeOH, 22 °C) $[\theta]_{248}$ −1800; IR ($CHCl_3$) 1750, 1675, 1080 cm^{-1} (α,β-unsaturated γ-lactone); ^1H NMR ($CDCl_3$) δ=4.82 (br m, $W_{1/2}$=13.6 Hz, 8α-H), 1.80 (t, *J*=1.5 Hz, 13-Me), 0.92 (d, *J*=6.6 Hz, 14-Me), 0.88 (s, 15-Me); ^{13}C NMR (Table 2).

Found: C, 76.86; H, 9.52%. Calcd for $C_{15}H_{22}O_2$: C,76.88; H, 9.46%.

Reduction of 3-Oxoepieremophilenolide (11b) via Eth-

ylene Dithioacetal 12b. The 3-ketone **11b** (54 mg) was treated with 1,2-ethanedithiol (0.5 ml) and BF_3-diethyl ether (1/1) (7 drops), as described above. A similar type workup gave a crude product (64 mg, 90%), which was crystallized from ethyl acetate as colorless needles to afford the dithioacetal **12b**, mp 195.5—196.5 °C, $[\alpha]_D^{22}$ +133° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1735, 1685, 1090 cm^{-1} (α,β-unsaturated γ-lactone); ^1H NMR ($CDCl_3$) δ=4.65 (br m, $W_{1/2}$=13.3 Hz, 8β-H), 3.5—3.0 (m, acetal methylene), 1.82 (t, *J*=1.4 Hz, 13-Me), 1.20 (s, 15-Me), 1.16 (d, *J*=5.7 Hz, 14-Me).

The dithioacetal **12b** (50 mg) was treated with Raney nickel (250 mg) in ethanol (5 ml) in a similar manner as that stated above to give an oily product (34 mg, 94%), which was crystallized from diisopropyl ether or light petroleum to afford eremophilenolide (**13b**).

Eremophilenolide (13b): Mp 123.5—124.5 °C, colorless needles; $[\alpha]_D^{21}$ +163° (*c* 1.00, $CHCl_3$); UV (MeOH) 224 nm (ε 13500); CD (*c* 8.74×10^{-3}, MeOH, 22 °C) $[\theta]_{248}$ +7950; IR ($CHCl_3$) 1755, 1690 cm^{-1} (α,β-unsaturated lactone); ^1H NMR ($CDCl_3$) δ=4.67 (br m, $W_{1/2}$=16.5 Hz, 8β-H), 2.90 (d, *J*=14.5 Hz, 6α-H), 1.80 (t, *J*=1.4 Hz, 13-Me), 1.04 (s, 15-Me), 0.80 (d, *J*=5.9 Hz, 14-Me); ^{13}C NMR (Table 2). This lactone was found to be identical with the natural specimen by a comparison of the IR and ^1H NMR spectra, and by a mixed-melting point determination.

Tosylation of 3β(eq)-Hydroxyepieremophilenolide (9a). Into a solution of **9a** (55 mg) in pyridine (1.5 ml) was added tosyl chloride (200 mg) at −5 °C; the mixture was left for 24 h at room temperature. The usual workup gave a crystalline product (75 mg, 84.4%), which was recrystallized from ethyl acetate-light petroleum to afford the tosylate **14a** as colorless leaflets, mp 156.5—158.0 °C (decomp); IR ($CHCl_3$) 1740, 1685 (α,β-unsaturated lactone), 1190, 1180, 1040, 885 cm^{-1} (tosylate); ^1H NMR ($CDCl_3$) δ=7.85—7.25 (q, aromatic 4H), 4.83 (ddd, *J*=5.5, 5.5, 11.5 Hz, 3α-H), 2.46 (s, tosyl Me), 1.76 (t, *J*=1.5 Hz, 13-Me), 0.96 (d, *J*=7.2 Hz, 14-Me), 0.80 (s, 15-Me).

Found: C, 65.16; H, 7.19%. Calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98%.

Treatment of Tosylate 14a with Sodium Iodide. A suspension of **14a** (85 mg) and NaI (300 mg) in dry acetone (3 ml) was stirred for 5 min at room temperature and then left for 1 week. The usual workup gave a crystalline product (40 mg, 82%), which was crystallized from ethyl acetate-light petroleum to afford 3,4-dehydroepieremophilenolide (**15a**).

3,4-Dehydroepieremophilenolide (15a): Mp 134.0—135.5 °C as colorless leaflets; IR ($CHCl_3$) 1750, 1680, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.34 (br s, 3-H), 4.71 (br m, $W_{1/2}$=15.2 Hz, 8α-H), 1.73 (t, *J*=1.7 Hz, 13-Me), 1.63 (d, *J*=1.3 Hz, 14-Me), 0.89 (s, 15-Me); ^{13}C NMR ($CDCl_3$) δ=25.7 (t, 1-C), 26.1 (t, 2-C), 122.6 (d, 3-C), 139.6 (s, 4-C), 40.8 (s, 5-C), 36.7 (t, 6-C), 160.8 (s, 7-C), 77.8 (d, 8-C), 40.4 (t, 9-C), 36.7 (d, 10-C), 121.0 (s, 11-C), 174.5 (s, 12-C), 7.9 (q, 13-C), 18.6 (q, 14-C), 22.7 (q, 15-C).

Found: C, 77.29; H, 8.97%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

Mesylation of 9a. Methanesulfonyl chloride (1 ml) was added into a solution of **9a** (134 mg) in pyridine (1 ml) at 0 °C; the mixture was left for 15 h. The usual workup gave **15a** (116 mg, 93%), which was crystallized from ethyl acetate-light petroleum as colorless leaflets, mp 134.0—135.0 °C. This compound was identical in all respects to the above-mentioned sample **15a** derived by tosylation of **9a**, followed by treatment with NaI.

Hydrogenation of 15a. Compound **15a** (67 mg) in ethanol (6 ml) was hydrogenated over 10% Pd-C (35 mg) for 1 h at room temperature. The filtrate was evaporated in vacuo to leave a crystalline product (65 mg, 96%), which was recrystallized from pentane to afford epieremophilenolide (**13a**) as colorless prisms, mp 84.0—85.0 °C. This compound was identical to the above-mentioned sample **13a**, transformed from **11a** via dithioacetal **12a** by a mixed-melting-point determination and a comparison of the IR and ^1H NMR spectra.

Mesylation of 9b. Methanesulfonyl chloride (1 ml) was added into a solution of **9b** (163 mg) in pyridine (1 ml) over a period of 2 min at 0 °C, and then left at room temperature for 14 h. The usual workup gave 3,4-dehydroeremophilenolide (**15b**) (137 mg, 91%), which was crystallized from ethyl acetate-light petroleum.

3,4-Dehydroeremophilenolide (15b): Mp 138.9—139.5 °C as colorless needles; IR ($CHCl_3$) 1755, 1685, 1335, 1090, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.23 (br s, 3-H), 4.61 (br m, $W_{1/2}$=16.3 Hz, 8β-H), 3.03 (d, *J*=14 Hz, 6α-H), 1.83 (d, *J*=1.3 Hz, 13-Me), 1.60 (d, *J*=1.1 Hz, 14-Me), 1.24 (s, 15-Me); ^{13}C NMR ($CDCl_3$) δ=23.1 (t, 1-C), 21.5 (t, 2-C), 122.5 (d, 3-C), 135.8 (s, 4-C), 41.3 (s, 5-C), 35.7 (t, 6-C), 160.6 (s, 7-C) , 80.2 (d, 8-C), 34.8 (t, 9-C), 38.6 (d, 10-C), 119.2 (s, 11-C), 174.9 (s, 12-C), 8.7 (q, 13-C), 19.5 (q, 14-C), 25.7 (q, 15-C).

Hydrogenation of 15b. A solution of **15b** (85 mg) in EtOH (7 ml) was hydrogenated with 10% Pd-C (53 mg) for 45 min. The filtrate was evaporated to give a crude eremophilenolide (**13b**) (85 mg, 99%), which was crystallized from light petroleum as colorless needles, mp 123.0—124.0 °C. This compound was identical in all respects with the natural specimen by a mixed-melting point determination, and by a comparison of the IR and ^1H NMR spectra.

Reduction of 3-Oxoepieremophilenolide (11a) with Sodium Borohydride. A solution of **11a** (51 mg) in MeOH (5 ml) was added into a solution of $NaBH_4$ (163 mg) in MeOH (2 ml) over a 3 min period at room temperature. After stirring for additional 35 min and acidification with 0.1 M HCl, the mixture was extracted with ether. The usual workup gave a reduction product (52 mg, quantitatively), which showed 2 spots on TLC (R_f 0.29 and 0.43; benzene-ethyl acetate 2:1). The product was chromatographed on silica gel (5 g) with benzene-ethyl acetate (5:1) to 3α(*ax*)-hydroxyepieremophilenolide (**16a**) (R_f 0.43, 29 mg, 56.3%) and **9a** (R_f 0.29, 19 mg, 36.9%). Both were crystallized from ethyl acetate-light petroleum; the polar product, mp 167.0—168.0 °C, was identified as **9a** (described above) by a mixed-melting point determination and a comparison of the spectral data.

3α(ax)-Hydroxyepieremophilenolide (16a): Mp 138.5—139.5 °C, as colorless prisms; $[\alpha]_D^{24}$ −138° (*c* 0.98, $CHCl_3$); CD (*c* 4.522×10^{-3}, MeOH, 22 °C) $[\theta]_{248}$ −150; IR ($CHCl_3$) 3450 (OH), 1745, 1680 cm^{-1} (α,β-unsaturated lactone); ^1H NMR ($CDCl_3$) δ=4.88 (br t, *J*=9.7 Hz, 8α-H), 3.97 (ddd, *J*=3, 3, 3 Hz, 3β-H), 3.70 (d, *J*=14.5 Hz, 6α-H), 2.16 (d, *J*=14.5 Hz, 6β-H), 1.78 (t, *J*=1.5 Hz, 13-Me), 0.95 (d, *J*=7.3 Hz, 14-Me), 0.80 (s, 15-Me); ^{13}C NMR (Table 2).

Found: C, 71.95; H, 8.71%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

Reduction of 3-Oxoepieremophilenolide (11b) with Sodium Borohydride. A solution of the ketone **11b** (152 mg) in MeOH (4 ml) was added into a stirred solution of

$NaBH_4$ (193 mg) in MeOH (5 ml) over a 10 min period at room temperature. After stirring for an additional 30 min, the mixture was acidified with 0.1 M HCl and extracted with ether. The usual workup gave a crude product (135 mg, 90%), which showed 2 spots on TLC (R_f 0.60 and 0.45; benzene-ethyl acetate 2:1). The product was chromatographed on silica gel (12 g) by elution with benzene-ethyl acetate (10:1) to give a less polar compound (R_f 0.60, 120 mg, 80%), which was crystallized from ethyl acetate-diisopropyl ether to afford **9b**, mp 169.5—170.5 °C, as colorless needles. This compound was identified as 3β(*ax*)-hydroxyeremophilenolide (**9b**), as described above. Further elution with the same solvent gave a polar compound, 3α(*eq*)-hydroxyeremophilenolide (**16b**) (R_f 0.45, 15 mg, 10%).

3α(eq)-Hydroxyeremophilenolide (16b): Mp 158.0—159.0 °C, colorless needles (ethyl acetate-light petroleum); $[\alpha]_D^{24}$ +214° (*c* 1.12, $CHCl_3$); CD (*c* 4.312×10^{-3}, MeOH, 22 °C) $[\theta]_{252}$ +1250; IR ($CHCl_3$) 3440 (OH), 1745, 1690 cm^{-1} (α,β-unsaturated lactone); ^1H NMR ($CDCl_3$) δ=4.70 (br m, 8β-H), 3.61 (ddd, *J*=5, 10.3, 10.3 Hz, 3β-H), 2.90 (d, *J*=14.6 Hz, 6α-H), 1.81 (t, *J*=1.5 Hz, 13-Me), 1.05 (s, 15-Me), 1.01 (d, *J*=8.5 Hz, 14-Me); ^{13}C NMR (Table 2).

Found: C, 71.67; H, 9.04%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

Preparation of Eremophilenolide (13b) from the Natural 6β-Hydroxyeremophilenolide (17b). A 2 M KOH-MeOH solution (4 ml) was added into a solution of natural **17b** (300 mg) in MeOH (3 ml); the mixture was left overnight. After removing the solvent in vacuo and dilution with water, the solution was acidified with aqueous 10% H_2SO_4 and extracted with ether. Without isolation of the free acid, the ethereal extract was treated with CH_2N_2 in diethyl ether. The usual workup gave an oil (302 mg, 95%), which was purified by vacuum distillation to furnish an enoic ester **18** as a colorless oil (263 mg), bp 116—118 °C/0.3 mmHg (40 Pa); $[\alpha]_D^{25}$ +15.5° (*c* 0.99, $CHCl_3$); UV (MeOH) 238 nm (ε 14300); IR (film) 1730, 1670, 1635, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.63 (br s, 6-H), 3.65 (s, OMe), 1.27 (d, *J*=7.2 Hz, 13-Me), 1.12 (s, 15-Me), 0.91 (d, *J*=6.5 Hz, 14-Me); ^{13}C NMR ($CDCl_3$) δ=20.4 (t, 1-C), 27.0 (t, 2-C), 30.2 (t, 3-C), 36.1 (d, 4-C), 38.9 (s, 5-C), 156.4 (d, 6-C), 136.6 (s, 7-C), 198.4 (s, 8-C), 39.4 (t, 9-C), 37.9 (d, 10-C), 38.2 (d, 11-C), 175.0 (s, 12-C), 16.5 (q, 13-C), 15.8 (q, 14-C), 20.8 (q, 15-C), 51.8 (q, OMe).

A solution of $NaBH_4$ (98 mg) in MeOH (6 ml) was added into a solution of the ester **18** (267 mg) in MeOH (3 ml) and left at room temperature for 4 h to deposit a crystalline product. The usual workup gave crude crystals (213 mg, 90%). Recrystallization from light petroleum furnished eremophilenolide (**13b**, 87 mg) as colorless needles, mp 123.5—124.5 °C. This compound was identical in all respects with the natural specimen as well as the above-mentioned synthesized **13b**.

Reduction of Ester 22 with Sodium Borohydride. a) Preparation of Ester 22: Dienoic acid **21**[1,2] (323 mg) was subjected to esterification in a similar method as that used in the preparation of ester **8** to furnish ester **22** as an oily product (273 mg, 80%), which was purified by vacuum distillation, bp 100—120 °C (bath temperature)/10^{-2} mmHg (2.7 Pa); $[\alpha]_D^{23}$ +16.5° (*c* 1.24, $CHCl_3$); IR (film) 1725, 1680, 1620, 1200, 1150, 1050, 945, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.78 (s, 6-H), 6.21 (d, *J*=1.5 Hz, 13-H), 5.65 (d, *J*=1.3 Hz, 13-H), 3.73 (s, $COOCH_3$), 2.75 (dd, *J*=17, 11 Hz, 9α-H), 1.16 (s, 15-Me), 0.94 (d, *J*=6.6 Hz, 14-Me).

b) Reduction of Ester 22: Into a solution of ester **22** (231 mg) in MeOH (4 ml) was added a solution of $NaBH_4$ (91 mg) in MeOH (3.5 ml) and left at room temperature overnight. Working up as mentioned above furnished quantitatively crude crystals (202 mg). Recrystallization from light petroleum gave eremophilenolide (**13b**), mp 123.5—124.0 °C. This compound was identical with the natural and synthetic samples in all respects.

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