

THE CONVERSION OF FURANOEREMOPHILANES TO
EPIEREMOPHILENOLIDES

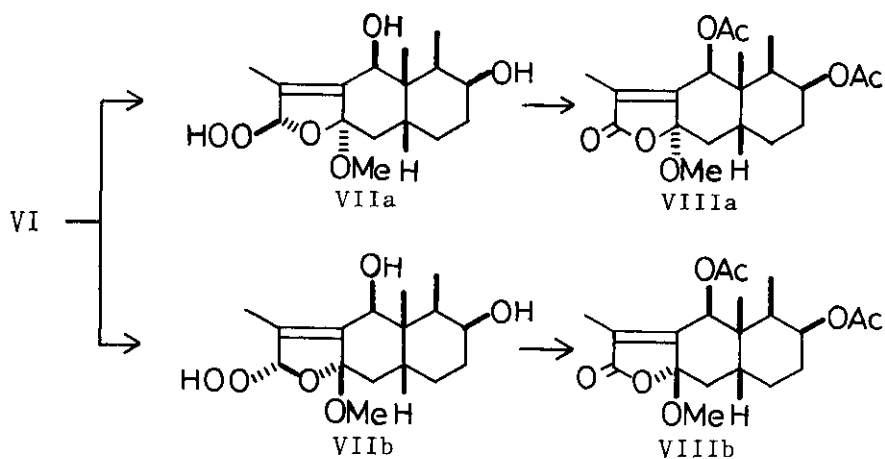
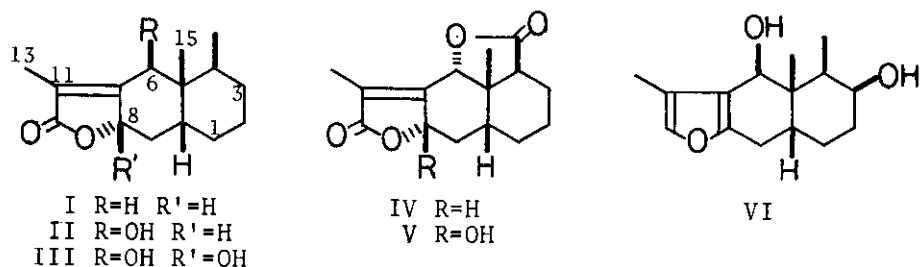
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Various nonnatural eremophilane-type lactones (epi-eremophilenolides) were synthesized stereoselectively from furanofukinol (VI) by a photosensitized oxygenation procedure, and also by lactone cleavage and reformation. Their physical properties showed excellent agreement with those expected from a classification procedure proposed by us in earlier papers.

All natural eremophilenolides so far identified, such as eremophilenolide (I),¹ 6 β -hydroxyeremophilenolide (II),^{2,3} 6 β ,8 β -dihydroxyeremophilenolide (III),^{3,4} eremophil-7(11)-ene-12,8 α ;14 β ,6 α -diolide (IV),⁴ and 8 β -hydroxyeremophil-7(11)-ene-12,8 α ;14 β ,6 α -diolide (V),⁴ contain 8 β -substituents (hydrogen or hydroxyl). In previous papers,^{3,5} we reported on the photooxygenation of furanoeremophilanes to yield pairs of 8 α - and 8 β -methoxy isomers. A detailed comparison of the natural 8 β -substituted lactones with the synthetic 8 α ,8-epimeric lactones led us to propose a procedure to distinguish the configuration at C-8 and accordingly the stereo-

chemistry of the A/B *cis* fused ring system, that is, 8 α -nonsteroidal or 8 β -steroidal A/B *cis* chair/chair configurations.⁵ The present paper describes the stereoselective syntheses of nonnatural-type 8 α -substituted eremophilanolides, designated as epieremophilanolides,³ by the photosensitized oxygenation of furanofukinol (VI)⁶ followed by dehydration, and also by cleavage of the lactone ring and recyclization. The stereochemistry of VI, isolated from *Petasites japonicus* Maxim. rhizomes,⁷ has been established by a combination of spectroscopic and chemical methods, and can be well explained in terms of a nonsteroidal conformation, 3 β (eq),6 β (pseudoeq)-dihydroxyfuranoteremophilane, based on the coupling pattern of 3 α -H in the PMR spectrum.

A mixture of VI and Rose Bengal in methanol was irradiated with a circular fluorescent lamp (30 watt) while bubbling air through the solution; a crystalline product was obtained in quantitative yield. The product showed two spots on TLC (R_f , 0.06 and 0.35; benzene-AcOEt, 2:1), and the compounds were separated on the basis of their differential solubilities in benzene to afford two isomeric hydroperoxides, a slightly soluble, polar isomer (VIIa): mp 165-165.5° (dec) (colorless prisms from acetone-MeOH) and a readily soluble, less polar isomer (VIIb): mp 94-96° (dec) (colorless needles from benzene-pentane). Both gave positive peroxide tests (KI-ACOH) and similar IR spectra. Subsequently, a mixture of VIIa,b was treated with Ac₂O-pyridine to afford quantitatively an epimeric mixture, which was separated to give 3 β ,6 β -diacetoxy-8 α -methoxyepieremophilanolide (VIIIa): mp 132.5-133° (prisms from diisopropyl ether-pentane) and 3 β ,6 β -diacetoxy-8 β -methoxyeremophilanolide (VIIIb): mp 139-140° in a ratio of 3:1. The assigned stereochemistries were readily deduced on the basis of a procedure outlined previously.^{3,5} Thus the *trans*-like, levorotatory 8 α -



Scheme 1

 Table 1. Comparison of chemical shifts (δ), specific rotations, and R_f values of the corresponding isomers

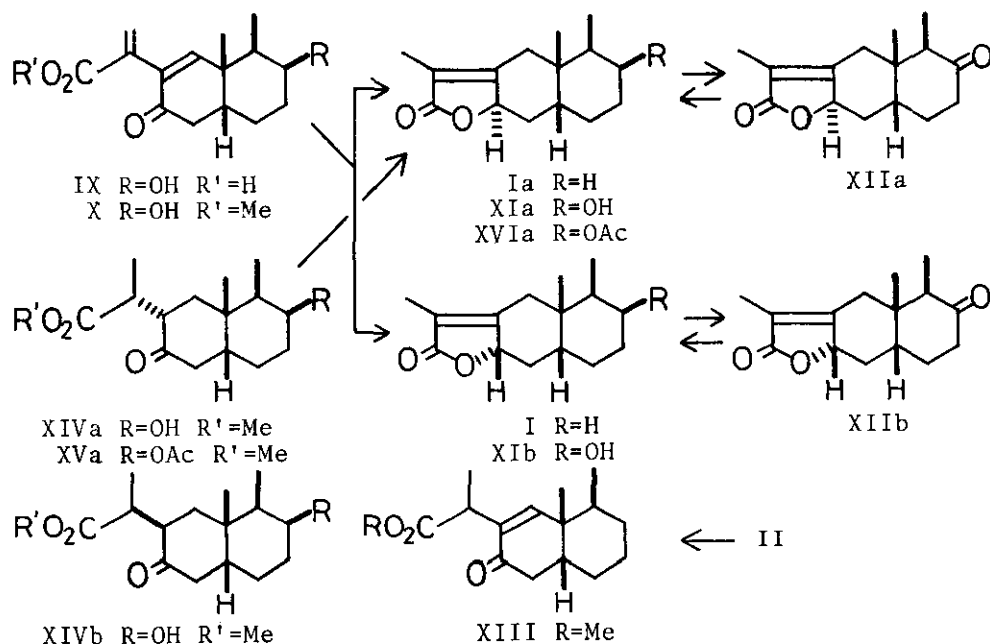
Compound		15-Me	14-Me	13-Me	6-H	3-H	$[\alpha]_D^{20}$	R_f , C_6H_6 :AcOEt
		Solvent: A=pyridine- d_5 , B=CDCl $_3$						CHCl $_3$
VIIa	A	1.11s	1.23d J=7	2.33d J=1.8	5.12q J=1.8	4.47m $W^{1/2}=18$	-24 ^{a)}	0.06
VIIb	B	1.31s	0.95d J=6	1.81s	4.27 ^{c)}	3.79m $W^{1/2}=7$	+43 ^{b)}	0.35
VIIIa	B	0.92s	0.93d J=6.9	1.87d J=1.8	5.98q J=1.8	4.85m $W^{1/2}=18$	-198	0.60
VIIIb	B	1.24s	0.92d J=7	2.01s	5.65s	4.99m $W^{1/2}=7$	+180	0.51

a): pyridine. b): MeOH. c): overlapped with a signal due to OH.

lactones generally have higher melting points, lower solubilities, and lower adsorptive properties⁸ than the *cis*-like, dextrorotatory 8 β -isomers, as expected on the basis of Dreiding models and the "von Auwers-Skita rule"⁹ (cf. Table 1). In addition, in the PMR spectra of VIIa,b and VIIIa,b, only the 8 α -methoxy derivatives exhibit homoallylic couplings between 6 α -H and 13-Me ($J=1.8$ Hz), and characteristic broad signals ($W^{1/2}=18$ Hz) due to 3 α (ax)-H, while the 8 β -isomers show narrow signals ($W^{1/2}=7$ Hz) due to 3 α (eq)-H. Furthermore, the 8 α -methoxy derivatives show chemical shifts due to 14-methyls at lower field than those due to 15-methyls, whereas this relation is reversed in the 8 β -series.

A mixture of VIIIa and VIIIb was subjected to alkaline hydrolysis to give a dienoic acid (IX), mp 163.5-164°, as a sole product in 85% yield. Treatment of the Na salt of IX with MeI in methanol gave an ester (X) in 83% yield; mp 114.5-115.5° (colorless needles from AcOEt-diisopropyl ether), $[\alpha]_D -40^\circ$ (c, 1.04, CHCl₃); IR(CHCl₃): 3420 (OH), 1715 (ester), 1670 (unsaturated ketone), 1610 and 942 cm⁻¹ (conjugated end-methylene); δ^{CDCl_3} : 6.67 (d, $J=1.5$ Hz, 6-H), 6.20 and 5.67 (each d, $J=1.5$ Hz, 13-end-methylene), 3.73 (overlapping signals of s, 12-COOMe and br m, $W^{1/2}=15$ Hz, 3 α -H), 3.05 (brs, OH), 1.29 (s, 15-Me), 1.00 (d, $J=6.3$ Hz, 14-Me).

Reduction of X with NaBH₄ in methanol for 1.5 h at 60° gave an oily mixture, which was then separated by chromatography on silica gel followed by recrystallization from AcOEt-diisopropyl ether to afford 3 β -hydroxyepieremophilanolide (XIa), mp 167-168° (colorless needles), and 3 β -hydroxyeremophilanolide (XIb), mp 169-170° (colorless needles), in a ratio of 1:1. Jones' oxidation of XIa and XIb gave quantitatively the 3-oxo derivatives, (XIIa)¹⁰ mp



Scheme 2

 Table 2. Comparison of chemical shifts (δ), specific rotations, and R_f values of the corresponding isomers

Compound	15-Me	14-Me	13-Me	8-H	3-H	$[\alpha]_D^{20}$ CHCl ₃	R_f C ₆ H ₆ :AcOEt
	CDCl ₃						
XIa	0.86s	0.97d J=6.5	1.80t J=1.2	4.80m W ^{1/2} =18	4.10ddd J=5,6,12.5 W ^{1/2} =18	-157	0.32
XIb	1.29s	1.29d J=6.5	1.80t J=1.2	4.72m W ^{1/2} =18	3.80sex J=6,6,7 W ^{1/2} =8	+196	0.65 2:1
XIIa	0.91s	1.20d J=6.5	1.80d J=1.2	4.83m W ^{1/2} =18		-157	0.70 2:1
XIIb	0.99s	0.95d J=6.5	1.82t J=1.2	4.83m W ^{1/2} =18		+154	0.75
Ia	0.89s	1.30d J=6.5	1.81d J=1.2	4.82m W ^{1/2} =18		-127	0.57
I	1.02s	0.78d J=5.5	1.73s	4.56m W ^{1/2} =16		+163	0.55 30:1

131.5-132.5° (colorless needles from AcOEt-diisopropyl ether) and (XIIb) mp 154-156° (colorless needles from AcOEt-diisopropyl ether), respectively. Thioketalization and subsequent desulfurization of XIIa and XIIb furnished epieremophilenolide (Ia) as an oil in 67% yield and eremophilenolide (I), mp 119-122° (colorless needles from diisopropyl ether), in 68% yield, respectively.

The configurational assignments to the stereostructures, XIa,b, XIIa,b, and Ia can also be determined by means of the general procedure mentioned above (cf. Table 2). For further comparison, I was also prepared from 6 β -hydroxyeremophilenolide (II) by alkaline hydrolysis followed by esterification with CH₂N₂-etherate and then by reduction with NaBH₄ via an enoic ester (XIII),¹¹ bp 116-118°/0.3 mmHg, in 86% overall yield.

Another approach to the syntheses of epieremophilenolides was examined as follows. Hydrogenation of IX in KOH-aq MeOH with Pd-C followed by refluxing in KOH-MeOH to cause isomerization, and then esterification with CH₂N₂-etherate gave a stereoisomeric mixture in 78% yield, which was separated by chromatography on silica gel (benzene-AcOEt, 20:1) to afford XIVa as an oil and XIVb, mp 71.2-72.2°, in a yield ratio of 3:1. XIVa and XIVb have already been concluded to adopt a nonsteroidal and a steroidal conformation,¹¹ respectively, on the basis of the signals due to 3 α -H (δ^{CDCl_3} : 4.01, br m, $W^{1/2}$ =19 Hz and 3.87, m, $W^{1/2}$ =7.2 Hz).⁶ XIVa or its acetate (XVa) was refluxed in the presence of *p*-toluenesulfonic acid in benzene or toluene to afford stereoselectively XIa or XVIa alone in low yield (average 15%); XVIa: an oil, $[\alpha]_D -115^\circ$ (c, 1.35, CHCl₃); IR(CHCl₃): 1740, 1735, 1680, 1255 cm⁻¹; δ^{CDCl_3} : 5.15 (br m, $W^{1/2}$ =18 Hz, 8-H), 4.90 (br m, $W^{1/2}$ =18 Hz, 3-H), 2.07 (s, AcO), 1.80 (d, J=1.5 Hz, 13-Me), 0.96 (d, J=6.5 Hz, 14-Me),

0.85 (s, 15-Me).

Attempts to synthesize eremophilane-type lactones so far have always given exclusively 8 β -substituted eremophilanolides.¹² Therefore, the above synthetic procedures for epieremophilanolides may achieve stereoselectively because of the greater stability of the 3 β (eq)-hydroxyl group in a nonsteroidal conformation compared with the 3 β (ax)-hydroxyl group in a steroidal conformation, where it is involved in a 1,3-diaxial interaction with 15 β -Me.

Further syntheses of nonnatural-type lactones are in progress.

References and Notes

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8. The adsorptive activities of the pairs of isomers, VIIa,b, XIa,b, and XIIa,b were not in accord with those expected on the basis of our proposed classification procedure. This may

be accounted for based on the steric compression around the oxygenated functions at C-3.

9. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill (1962), pp 216, 326.
10. The oxidation product of XIa showed isomerization of 14 β -Me to 14 α -Me in its PMR spectrum (we observed a pair of signals due to 14- and 15-methyls; 1.06 and 1.20, each d, J=6.5 Hz; 0.91 and 1.03, each s). XIIa was obtained by careful recrystallization.
11. The presence of diastereomers due to a C-11 asymmetric center could not be detected for these esters, XIII and XIVa,b.
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