THE CONVERSION OF FURANOEREMOPHILANES TO
# EPIEREMOPHILENOLIDES

Keizo Naya,* Takashi Matsuura,

Masao Makiyama, and Minoru Tsumura

Department of Chemistry, Faculty of Science,

Kwansei Gakuin University, Nishinomiya 662, Japan

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 pro-
posed by us in earlier papers.

All natural eremophilenolides so far identified, such as
eremophilenolide (I),[1] 6β-hydroxyeremophilenolide (II),[2,3] 6β,8β-
dihydroxyeremophilenolide (III),[3,4] eremophil-7(11)-ene-12,8α;14β,
6α-diolide (IV),[4] and 8β-hydroxyeremophil-7(11)-ene-12,8α;14β,6α-
diolide (V),[4] contain 8β-substituents (hydrogen or hydroxyl). In
previous papers,[3,5] we reported on the photooxygenation of furano-
eremophilanes to yield pairs of 8α- and 8β-methoxy isomers. A de-
tailed comparison of the natural 8β-substituted lactones with the
synthetic 8α,β-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, 8α-nonster-oidal or 8β-steroidal A/B *cis* chair/chair configurations.[5] The present paper describes the stereoselective syntheses of nonnatu-ral-type 8α-substituted eremophilenolides, designated as epieremo-philenolides,[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, 3β(eq),6β(pseu-doeq)-dihydroxyfuranoeremophilane, based on the coupling pattern of 3α-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 quan-titative 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) (color-less needles from benzene-pentane). Both gave positive peroxide tests (KI-AcOH) and similar IR spectra. Subsequently, a mixture of VIIa,b was treated with Ac_2O-pyridine to afford quantitatively an epimeric mixture, which was separated to give 3β,6β-diacetoxy-8α-methoxyepieremophilenolide (VIIIa): mp 132.5-133° (prisms from diisopropyl ether-pentane) and 3β,6β-diacetoxy-8β-methoxyeremo-philenolide (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 8α-
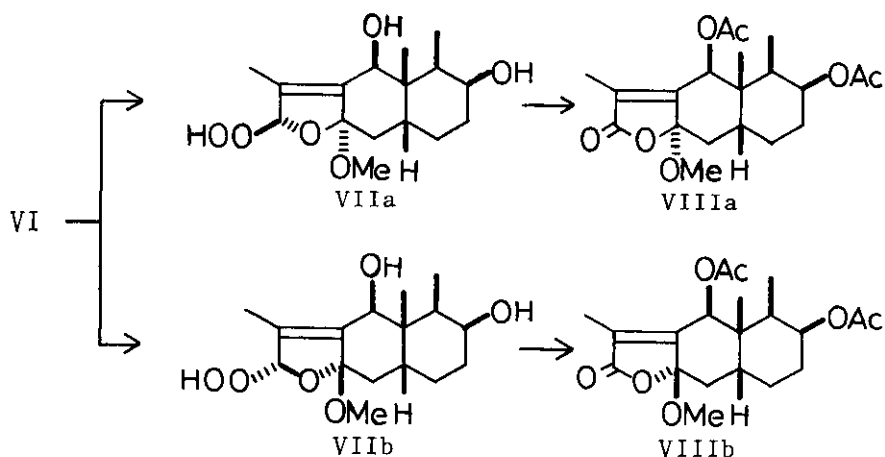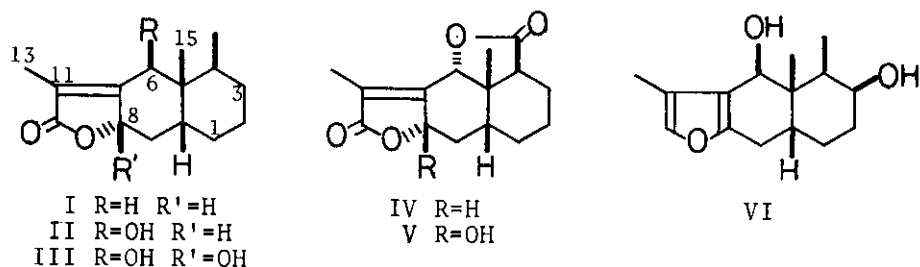
Scheme 1

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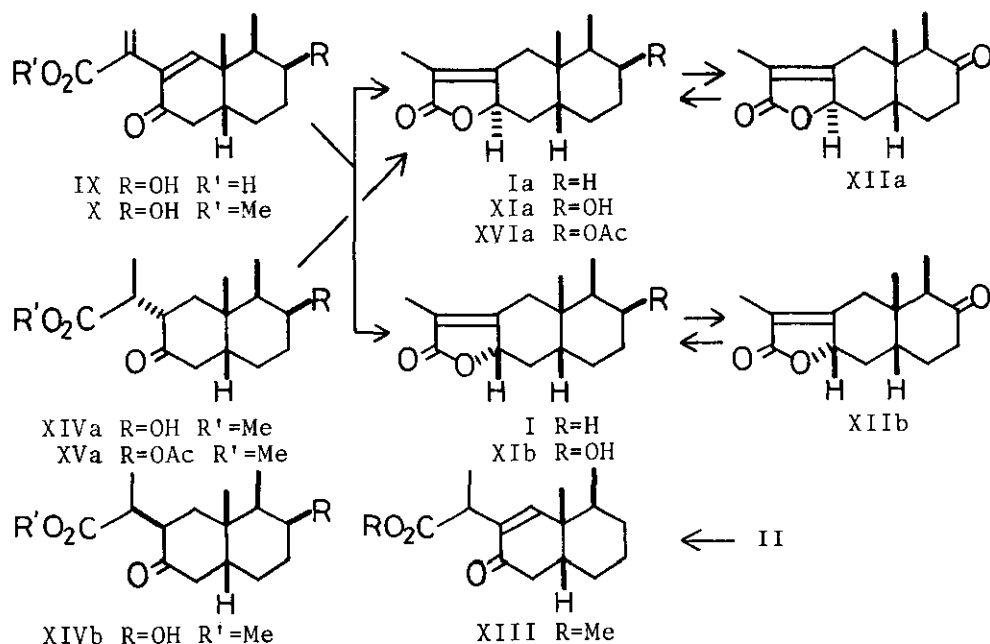and R_f values of the corresponding isomers

Compound		15-Me	14-Me	13-Me	6-H	3-H	$[\alpha]_D^\circ$	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
								2:1
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
								1:1
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 properties[8] than the *cis*-like, dextrorotatory 8β-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 8α-methoxy derivatives exhibit homoallylic couplings between 6α-H and 13-Me (J=1.8 Hz), and characteristic broad signals ($W^1/_2$=18 Hz) due to 3α(ax)-H, while the 8β-isomers show narrow signals ($W^1/_2$=7 Hz) due to 3α(eq)-H。 Furthermore, the 8α-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 8β-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° (c, 1.04, $CHCl_3$); IR($CHCl_3$): 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, 3α-H), 3.05 (br s, OH), 1.29 (s, 15-Me), 1。00 (d, J=6.3 Hz, 14-Me).

Reduction of X with $NaBH_4$ 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 3β-hydroxyepieremophilenolide (XIa), mp 167-168° (colorless needles), and 3β-hydroxyeremophilenolide (XIb), mp169-170° (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	$[\alpha]_D^\circ$	R_f
		CDCl$_3$				CHCl$_3$	C$_6$H$_6$:AcOEt
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
							2:1
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
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
							30:1
I	1.02s	0.78d J=5.5	1.73s	4.56m W^1/$_2$=16		+163	0.55

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 gen-

eral procedure mentioned above (cf. Table 2). For further compar-

ison, I was also prepared from 6β-hydroxyeremophilenolide (II) by

alkaline hydrolysis followed by esterification with CH_2N_2-etherate

and then by reduction with $NaBH_4$ 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 CH_2N_2-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 3α-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°

(c, 1.35, $CHCl_3$); IR($CHCl_3$): 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 8β-substituted eremophilenolides.[12] Therefore, the above synthetic procedures for epieremophilenolides may achieve stereoselectively because of the greater stability of the 3β(eq)-hydroxyl group in a nonsteroidal conformation compared with the 3β(ax)-hydroxyl group in a steroidal conformation, where it is involved in a 1,3-diaxial interaction with 15β-Me.

Further synthses of nonnatural-type lactones are in progress.

References and Notes

1. L. Novotný, V. Herout, and F. Šorm, Tetrahedron Lett., 697 (1961); L. Novotný, J. Jizba, V. Herout, F. Šorm, L. H. Zalkow, S. Hu, and C. Djerassi, Tetrahedron, 19, 1101 (1963).

2. L. Novotný, V. Herout, and F. Šorm, Collect. Czech. Chem. Commun., 29, 2189 (1964).

3. K. Naya, R. Kanazawa, and M. Sawada, Bull. Chem. Soc. Jpn., 48, 3220 (1975).

4. Y. Moriyama and T. Takahashi, Chem. Pharm. Bull., 24, 360 (1976).

5. K. Naya, N. Nogi, Y. Makiyama, H. Takashina, and T. Imagawa, Bull. Chem. Soc. Jpn., 50, 3002 (1977).

6. K. Naya, Y. Makiyama, T. Matsuura, N. Ii, H. Nagano, and T. Takahashi, Chem. Lett., 301 (1978).

7. K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, Tetrahedron Lett., 2961 (1971).

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 14β-Me to 14α-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.

12. E. Piers and M. B. Geraghty, Can. J. Chem., 51, 2166 (1973); I. Nagakura, S. Maeda, M. Ueno, M. Funamizu, and Y. Kitahara, Chem. Lett., 1143 (1975); Y. Kitahara, S. Maeda, M. Ueno, M. Funamizu, T. Kato, L. Novotný, V. Herout, and F. Šorm, Chem. Lett., 1031 (1977).