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Introduction of an Alcoholic Hydroxyl Group into 2,3-Dibenzylbutyrolactone Lignans with Oxidizing Agents and Carbon-13 Nuclear Magnetic Resonance Spectra of the Oxidation Products[1]

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Attempts were made to introduce an alcoholic hydroxyl group stereospecifically at the C-5 or C-6 position of 2,3-dibenzylbutyrolactone lignans with lead tetraacetate and osmic acid as oxidizing agents.

5-Acetoxyarctigenin monoacetate (III) was obtained from arctigenin monoacetate (II), 5-acetoxyisoarctigenin monoacetate (XIII) from isoarctigenin monoacetate (XII) and 5-acetoxytrachelogenin diacetate (XXIII) from trachelogenin diacetate (XXII) by oxidation with lead tetraacetate in acetic acid.

6-Hydroxyisomethyltrachelogenin (XXXII) was obtained from 3-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxybenzylidene)butyrolactone (XXXI) by oxidation with osmic acid.

The ^{13}C-NMR spectra of these oxidation products and analogs are discussed with regard to the differences of the chemical shifts resulting from changes in the substituents and the stereochemistry of the 2,3-dibenzylbutyrolactone skeleton.

Keywords——2,3-dibenzylbutyrolactone lignans; reaction with oxidizing agents; introduction of an alcoholic hydroxyl group; 5-hydroxy-2,3-dibenzylbutyrolactone lignans; 2,5-dihydroxy-2,3-dibenzylbutyrolactone lignans; 2,6-dihydroxy-2,3-dibenzylbutyrolactone lignans; ^{13}C-NMR

As an example of the introduction of an alcoholic hydroxyl group into the side chain of an aromatic compound, Dimroth and Schweizer[3] reported that benzyl acetate was obtained by treating toluene with lead tetraacetate in boiling acetic acid.

In addition, a remarkable cyclodehydrogenation of a 2,3-dibenzylbutyrolactone lignan, arctigenin methyl ether, to a phenylnaphthalide lignan by treatment with lead tetraacetate was found by Haworth and Kelly.[4]

The reaction mechanism was proposed to be as follows.[5] Presumably a carbonium ion or a radical is first formed at the benzyl position next to one of the aromatic rings. This then leads to electrophilic or radical substitution on the other aromatic nucleus, followed by dehydrogenation.

Recently we found that the benzyl position of dihydroeugenol acetate is not affected by lead tetraacetate, while on the other hand, an acetoxyl group is introduced into dihydroeugenol methyl ether.[6]

1) Presented at the 21st Symposium on the Chemistry of Natural Products, Sapporo, August 1978.
2) Location: *a) Ishikari-Tobetsu, Hokkaido, 061-02, Japan; b) Kanda-Surugadai, Chiyoda-Ku, Tokyo, 101, Japan; c) Hongo, Bunkyo-ku, Tokyo, 113, Japan; d) Kita-9, Nishi-9, Sapporo, Hokkaido, 060, Japan.*
3) O. Dimroth and R. Schweizer, *Chem. Ber.*, **56**, 1375 (1923).
4) R.D. Haworth and W. Kelly, *J. Chem. Soc.*, **1936**, 998.
5) K. B. Wiberg (ed.), "Oxidation in Organic Chemistry," Part A, Academic Press, New York, 1965, p. 319.
6) Our work on the oxidation of dihydroeugenol derivatives has hitherto been unpublished.

The resistance of dihydroeugenol acetate to oxidation with lead tetraacetate is assumed to depend on the reduced reactivity of the benzyl position due to the presence of an acetoxyl group at the *p*-position of the aromatic ring.

In these studies, the differences of reactivity were applied to the oxidation of 2,3-dibenzylbutyrolactone lignans in order to obtain lignans possessing an acetoxyl group at one of the benzyl groups without cyclodehydrogenation, as shown in Chart 1.

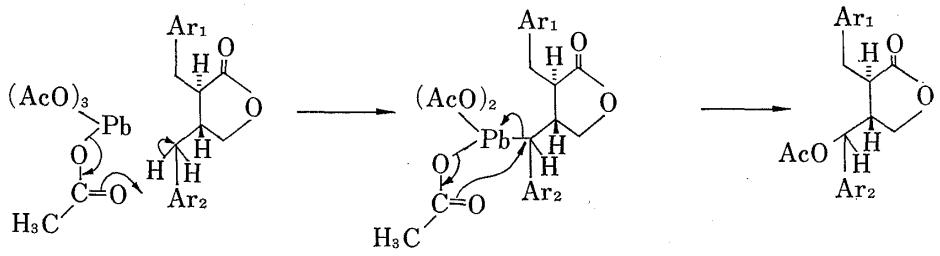


Chart 1

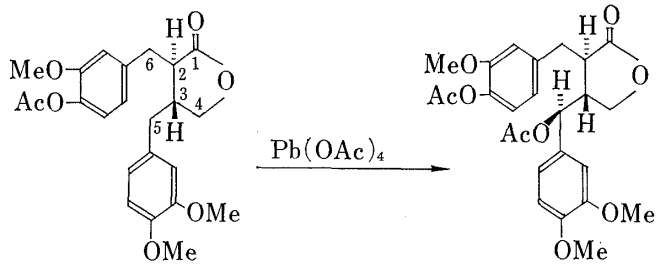
The oxidation of unsaturated 2,3-dibenzylbutyrolactone lignan with osmic acid was attempted in order to obtain a lignan possessing *cis* vicinal hydroxyl groups.

In addition, the carbon-13 nuclear magnetic resonance (^{13}C–NMR) spectra of these oxidation products are discussed in the light of the differences of the chemical shifts due to changes in the substituents and the stereochemistry of the 2,3-dibenzylbutyrolactone skeleton.

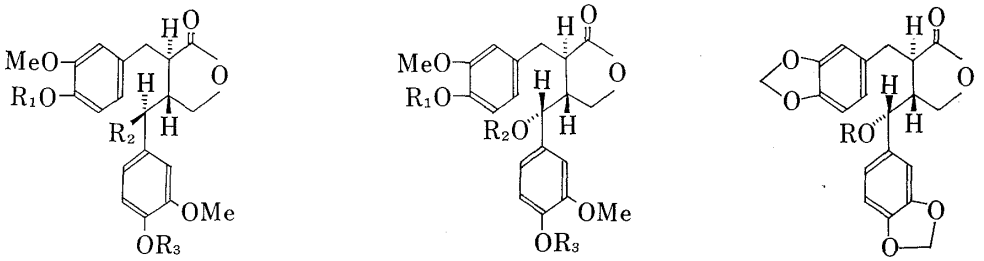
Reaction of Arctigenin Monoacetate (II) with Lead Tetraacetate

Arctigenin monoacetate (II) was treated with lead tetraacetate in acetic acid.

The purification of the oxidation product by chromatography on a silica gel column afforded compound III as a colorless syrup without cyclodehydrogenation.



II III



I: R_1=H, R_2=H, R_3=Me
IV: R_1=H, R_2=OH, R_3=Me
Va: R_1=Me, R_2=OH, R_3=Me
VIa: R_1=Me, R_2=OAc, R_3=Me
VIIa: R_1=H, R_2=OH, R_3=H

VIIb: R_1=H, R_2=H, R_3=H
Vb: R_1=Me, R_2=H, R_3=Me
VIb: R_1=Me, R_2=Ac, R_3=Me

VIIIa: R=H
VIIIb: R=Ac

Chart 2

The proton nuclear magnetic resonance (PMR) spectrum of III showed a signal at δ 5.57 (1H, d, J=8 Hz) due to the C_5-proton, indicating the introduction of an acetoxyl group at one of the benzyl positions.

The structure of III was elucidated as 5-acetoxyarctigenin monoacetate on the basis of the PMR spectral data.

The saponification of III with 4% methanolic potassium hydroxide solution afforded colorless needles of 5-hydroxyarctigenin (IV), mp 140—141°, $[\alpha]_D^{25}$ +6.32° (ethanol).

The conversion of III to a lariciresinol-type lactone, as in the case of acetylparabenzlactone (VIIIb),[7] did not occur.

At present, 5-allohydroxymatairesinol (VIIa),[8] 5-hydroxymatairesinol (VIIb)[8,9] and parabenzlactone (VIIIa)[7,10] are known as naturally occurring lignans possessing a hydroxyl group at the benzyl position.

The chemical shifts of the signal due to the C_5-proton in compounds III, IV, VIIb, 5-allohydroxymatairesinol dimethyl ether (Va), 5-alloacetoxymatairesinol dimethyl ether (VIa),

Table I. PMR Spectral Data for the C_5-Proton in Various Compounds

Compounds	III	IV	Va	VIa	VIIb	Vb	VIb	VIIIa	VIIIb
C_5–H	5.57, d	4.13, d	4.13, d	5.57, d	4.63, d	4.63, d	5.83, d	4.60, d	5.75, d
J (Hz)	8.0	8.0	8.0	8.0	6.5	6.5	6.0	6.5	6.0

Shifts are shown as ppm from TMS (δ=0).

Table II. ^{13}C-NMR Chemical Shifts of 2,3-Dibenzylbutyrolactone Lignans[a]

	I	Va	VIa	VIIb	Vb	VIb	VIIIa	VIIIb
C-1	178.7	179.1	178.0	179.4	179.2	178.2	178.7	178.0
C-2	46.5	46.2	44.0	45.2	45.2	44.0	45.1	43.9
C-3	40.9	43.5	43.6	43.6	43.9	43.4	43.7	43.5
C-4	71.3	68.2	67.9	68.6	68.4	67.9	68.4	68.0
C-5	38.1	73.9	75.4	75.2	75.4	76.1	75.4	76.3
C-6	34.6	34.7	34.3	35.1	35.0	34.8	35.1	35.1
C-1′	129.5	130.0	129.5	129.5	130.2	129.6	131.1	130.7
C-1″	130.4	134.4	130.0	133.5	134.1		135.3	131.0
C-3′	144.5	147.9		144.4	149.0	148.1	146.2	146.6
C-3″	146.6	148.9	148.0	145.5	149.1	149.1	147.5	147.8
C-4′	146.7	149.2	149.1	146.8	149.4	149.2	147.6	148.1
C-4″	147.8						148.0	
C-2′	111.2	109.0	109.7	108.3	109.1	109.7	106.1	106.6
C-2″	111.4	111.1	111.2	111.9	111.2	111.2	108.1	108.2
C-5′	111.7	112.4	112.4	114.0	112.9	112.7	108.2	109.7
C-5″	114.1	118.3	118.2	114.4	118.3	118.9	109.8	120.1
C-6′	120.5	121.4	121.4	118.8	121.8	121.7	119.3	122.6
C-6″	122.0			122.5			122.7	
CH_3O	55.9	55.8	55.9	55.8	55.9	55.9		
	55.8							
CH_3CO			169.8			169.8		169.8
			20.9			21.1		20.9
CH_2O_2							100.8	101.0
							101.6	101.4

a) The spectra were taken with a JNM-FX 60 spectrometer (15.00 MHz) in $CDCl_3$ with TMS as an internal reference, using micro cells. FT-NMR conditions: spectral width, 4 KHz; number of data points, 8192; pulse repeat time, 1.2 sec; number of pulses, 5000—100000; pulse flipping angle, 45°.

7) M. Niwa, M. Iguchi, S. Yamamura, and S. Nishibe, *Bull. Chem. Soc. Jpn.*, **49**, 3359 (1976).
8) K. Freudenberg and L. Knof, *Chem. Ber.*, **90**, 2857 (1957).
9) S. Ohmori and A. Sakakibara, *Mokuzai Gakkaishi*, **19**, 41 (1973).

5-hydroxymatairesinol dimethyl ether (Vb) and 5-acetoxymatairesinol dimethyl ether (VIb) are summarized in Table I, for comparison with those of VIIIa and VIIIb, whose configurations are established as 5*R*.[7]

The chemical shifts clearly suggest that the reaction of II with lead tetraacetate stereospecifically affords III having the 5*S* configuration. Saponification and methylation afforded Va; the dimethyl ether (Vb) of natural VIIb[9] is known to have the 5*R* configuration. Since we have shown that the stereochemistry of VIIb is 5*R*, and VIIa is known to be a diastereoisomer of VIIb at the C-5 position,[8] the synthetic Va might be identical with the dimethyl ether of natural VIIa.[11]

Table II presents the ^{13}C-NMR data for compounds I, Va, VIa, VIIb, Vb, VIb, VIIIa, and VIIIb and their assignments.

The signal of the C-5 atom of Va relative to that of I is shifted downfield by 35.8 ppm due to the introduction of a secondary hydroxyl group.

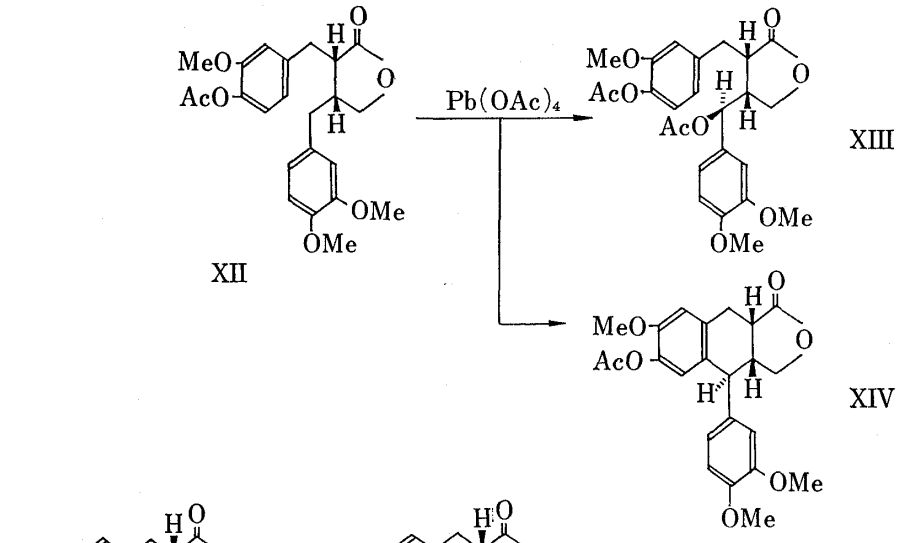
In addition, the chemical shifts of the C-5 and C-2 atoms of Va relative to those of Vb and VIIIa appear upfield by *ca* 1.5 ppm and downfield by *ca* 1 ppm, respectively, due to the difference of configuration at the C-5 position.

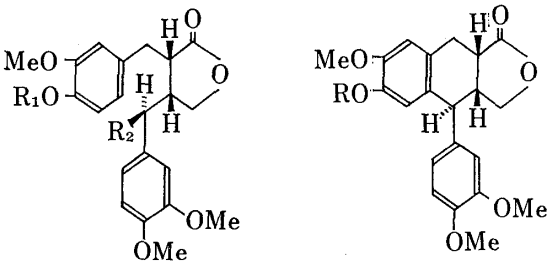
These shifts give valuable insights for ^{13}C-NMR analysis of the stereochemistry of 2,3-dibenzylbutyrolactone lignans having a secondary hydroxyl group.

Similar shifts were reported in a ^{13}C-NMR analysis of *l*-ephedrine and *d*-pseudoephedrine by Yamasaki *et al.*[12]

Reaction of Isoarctigenin Monoacetate (XII) with Lead Tetraacetate

Isoarctigenin monoacetate (XII) was treated with lead tetraacetate in acetic acid.





XI : R_1=H, R_2=H

XV : R=H
XVI : R=Me

Chart 3

10) K. Wada and K. Munakata, *Tetrahedron Lett.*, **1970**, 2017.
11) We could not carry out direct comparison, since an authentic sample was not available.
12) K. Yamasaki and K. Fujita, *Chem. Pharm. Bull.*, **27**, 43 (1979).

The oxidation products showed two spots of *Rf* 0.8 and 0.7 on thin layer chromatography (TLC) using chloroform-ethyl acetate (1: 1) as a developing solvent.

Purification by chromatography on a silica gel column afforded compound XIII, $[\alpha]_D^{21}$ +61.9° (chloroform), as a colorless syrup and compound XIV, $[\alpha]_D^{21}$ +29.4° (chloroform), as a colorless syrup in a 3: 1 ratio.

The PMR spectrum of XIII showed a signal at δ 6.12 (1H, d, J=3 Hz) due to the C_5-proton, indicating the introduction of an acetoxyl group at one of the benzyl positions.

The structure of XIII was elucidated as 5-acetoxyisoarctigenin monoacetate on the basis of the PMR spectral data.

The saponification and isomerization of XIII with 4% methanolic potassium hydroxide solution gave a compound identical with 5-hydroxyarctigenin (IV).

Therefore, the configuration of XIII at the C-5 position is 5*S*.

The PMR spectrum of XIV showed the signal of an aromatic proton at δ 6.37 (1H, s), which appears upfield relative to those of other aromatic protons, indicating the presence of a phenyltetralin skeleton in which an aromatic proton attached to one of the aromatic rings lies within the shielding zone of the other aromatic ring.[13]

The structure of XIV was assumed to be β-acetylconidendrin monomethyl ether from the PMR spectral data and this was confirmed as follows.

Compound XV, mp 217—220° as colorless needles, obtained by the saponification of XIV, was methylated with diazomethane in the usual way to afford compound XVI, mp 153—154°.

Table II. ^{13}C-NMR Chemical Shifts of 2,3-Dibenzylbutyrolactone Lignans[a]

	XII	XIII	XXI	XXII	XXIII	XXIV	XXXII	XLIIa[b]	XLIIb
C-1	177.8	177.1	178.6	174.9	174.0	178.7	177.8	—[c]	181.3
C-2	45.4	43.5	76.5	80.2	80.4	79.2	75.4	78.6	79.0
C-3	40.0	43.3	43.8	42.7	45.5	48.1	47.5	78.1	77.0
C-4	69.5	66.7	70.2	71.8	67.8	65.9	70.1	74.1	74.2
C-5	32.7	72.1	31.6	33.5	73.1	70.0	31.8	39.1	37.6
C-6	30.8	30.7	42.0	43.2	41.5	42.9	76.9	37.8	37.1
C-1′	130.9	130.1	126.2	130.3	130.4	133.9	130.1	125.5	132.9
C-1″	138.5	139.1	131.1	132.7	131.9	126.2	130.9	126.6	135.4
C-3′	147.9	137.5	145.1	148.0	149.2	145.2	147.9	148.9	148.6
C-3″	149.2	149.5	146.6	149.2	151.2	146.8	148.7	149.1	149.3
C-4′	151.3	149.8	147.9	139.5	139.5	148.6	149.2	149.1	150.2
C-4″	137.7	151.7	149.2	151.2		149.2	149.6	148.9	150.6
C-2′	111.5	109.5	111.6	111.6	109.9	109.0	110.7	111.2	111.3
C-2″	112.0	112.2	112.3	111.8	111.2	111.4	111.4	111.4	111.7
C-5′	112.8	113.6	112.8	114.9	114.5	112.9	111.7	113.4	113.6
C-5″	120.4	118.1	114.4	120.5	119.1	114.4	111.9	122.2	114.7
C-6′	120.9	120.5	120.9	122.9	122.8	117.6	120.6	122.5	122.3
C-6″	122.9	123.2	123.2			123.2			123.3
CH_3O	55.9	56.3	55.9	55.9	55.9	56.1	55.9	55.9	55.8
									55.9
CH_3CO	169.1	168.9		168.9	168.9				
		169.8		170.3	169.3				
					170.3				
	20.7	20.6		20.5	20.7				
		21.0			20.9				

a) FT-NMR conditions: see Table II.
b) This spectrum was taken with a JNM-FX 100 spectrometer (25.05 MHz) in $CDCl_3$ with TMS (δ=0) as an internal reference using 1.7 mm tubes. FT-NMR conditions: spectral width, 5 KHz; number of data points, 4095; pulse repeat time, 2.0 sec; number of pulses, 36000; pulse flipping angle, 40°.
c) This signal was not observed because of the small amount of sample used.

13) D.C. Ayres and C.K. Lim, *J. Chem. Soc. Perkin I*, **1972**, 1350.

XVI was identical with authentic β-conidendrin dimethyl ether.[14]

The ^{13}C-NMR data for XII and XIII and their assignments are summarized in Table III.

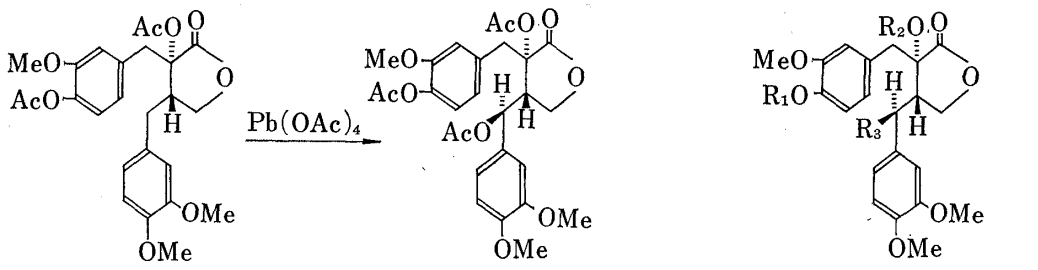
The upfield shifts of both C-5 and C-6 of XII relative to those of I are *ca.* 4—5 ppm, which are attributable to the γ-interaction between C-5 and C-6.

Thus, these shifts give valuable indications for the distinction between *cis* and *trans* configurations of benzyl groups at the C-2, 3 positions of the butyrolactone ring by ^{13}C-NMR analysis.

The downfield shift of the C-5 atom of XIII relative to that of XII is 39.4 ppm.

Reaction of Trachelogenin Diacetate (XXII) with Lead Tetraacetate

Trachelogenin diacetate (XXII) was treated with lead tetraacetate in acetic acid.



XXII XXIII XXI: R_1=H, R_2=H, R_3=H
XXIV: R_1=H, R_2=H, R_3=OH

Chart 4

Purification of the oxidation product by chromatography on a silica gel column afforded compound XXIII, $[\alpha]_D^{21}$ +10.2° (chloroform), as a colorless syrup, mass spectrum (MS) *m/e* 530 [M$^+$].

The PMR spectrum of XXIII showed a signal at δ 5.67 (1H, d, J=8 Hz) due to the C_5-proton, indicating the introduction of an acetoxyl group at one of the benzyl positions.

The structure of XXIII was elucidated as 5-acetoxytrachelogenin diacetate on the basis of the PMR spectral data.

The configuration of XXIII is assumed to be 5*S*, considering the attack of an acetoxyl radical at the C-5 position from the side less sterically hindered against a hydrogen atom attached to C-3 on the butyrolactone ring, as in the case of II.

This is also supported by the coupling constant (J=8 Hz) of the C_5-proton in the PMR spectrum of XXIII.

Table III presents the ^{13}C-NMR data for trachelogenin (XXI), XXII, XXIII and 5-hydroxytrachelogenin (XXIV), and their assignments.

The chemical shifts of the carbon atoms of the dibenzylbutyrolactone skeleton in XXI relative to those of I are downfield by 7.5 ppm at C-6 and 2.9 ppm at C-3 due to the β-effect of the tertiary hydroxyl group, and upfield by 6.5 ppm at C-5 and 1.1 ppm at C-4 due to the γ-effect of the tertiary hydroxyl group, respectively.

Further, the downfield shift of the C-5 signal of XXIV relative to that of XXI is 38.4 ppm.

Reaction of 3-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxybenzylidene) butyrolactone (XXXI) with Osmic Acid

In the previous paper,[15] S. Nishibe, one of the authors, reported that 2,3-dihydroxy-

14) W.M. Hearon, H.B. Lackey, and W.W. Moyer, *J. Am. Chem. Soc.*, **73**, 4005 (1951).
15) S. Nishibe, S. Hisada, and I. Inagaki, *Yakugaku Zasshi*, **93**, 374 (1973).

isomethylarctigenin (XLIIa), an isomer of natural di-O-methylthujastandin (XLIIb),[16] was obtained by the oxidation of 2,3-unsaturated dibenzylbutyrolactone (XLI) with osmic acid.

In this paper, an attempt was made to obtain a 2,3-dibenzylbutyrolactone lignan possessing vicinal hydroxyl groups at the C-2 and C-6 positions.

3-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxybenzylidene)butyrolactone (XXXI)[15] was treated with osmic acid in pyridine.

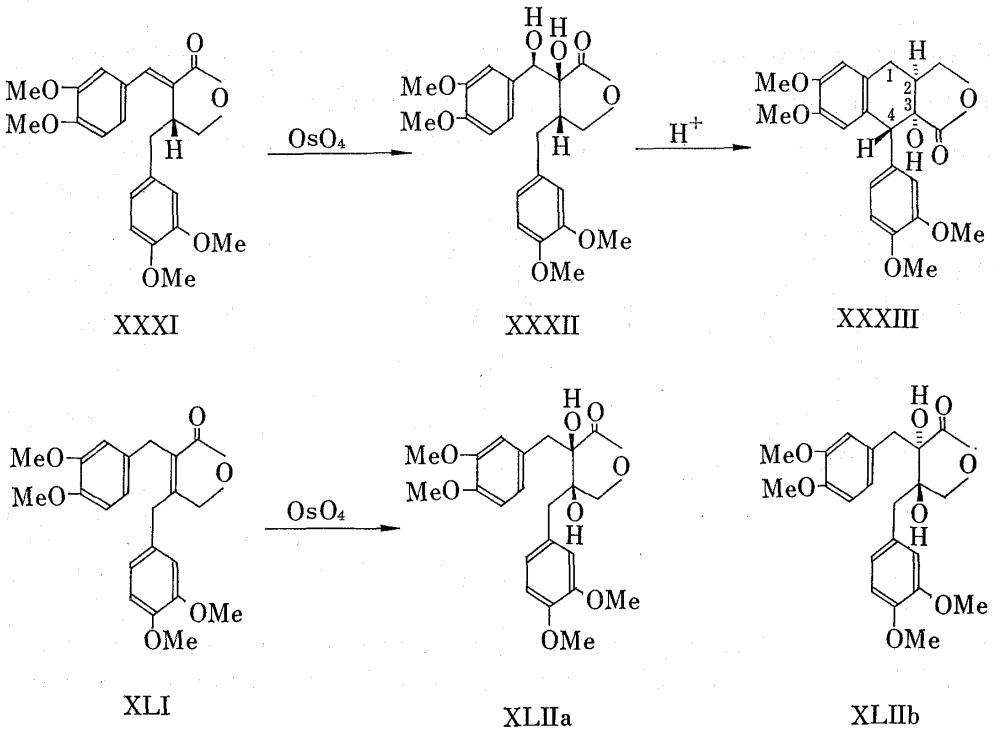


Chart 5

Purification of the reaction products by preparative TLC and recrystallization from ethanol gave compound XXXII, mp 111—114°, $[\alpha]_D^{22}$ −40.7° (ethanol), as colorless needles.

The PMR spectrum of XXXII showed a signal at δ 4.93 (1H) as a singlet due to the C_6-proton, indicating the presence of vicinal hydroxyl groups.

The structure of XXXII was elucidated as 6-hydroxyisomethyltrachelogenin, based on the PMR spectral data.

The stereochemistry of the butyrolactone skeleton was determined as follows.

It is known that the catalytic reduction of XXXI over palladium black gives isomethylarctigenin by hydrogenation from the less sterically hindered side.[15,17]

Here, it seems reasonable to assume that a similar stereospecific reaction also occurs in the case of the oxidation of XXXI with osmic acid.

Therefore, the stereochemistry of the C-2 and C-3 benzyl groups might be *cis*, as shown in Chart 5.

XXXII was transformed to 3-hydroxy-β-retroconidendrin dimethyl ether (XXXIII), mp 183—184°, $[\alpha]_D^{22}$ +31.7° (chloroform), by acid treatment.[8,18]

The circular dichroism (CD) curve of XXXIII is almost symmetrical about the Cotton effect at around 230 nm, corresponding to that of XVI whose stereostructure is established.

These results indicate the configuration of XXXII to be 2*S*, 3*S*, 6*R*.

16) K. Murakami, *Mokuzai Gakkaishi*, **13**, 265 (1967).
17) S. Nishibe, M. Chiba, and S. Hisada, *Yakugaku Zasshi*, **97**, 1366 (1977).
18) H. Kuhn and A. Von Wartburg, *Helv. Chim. Acta*, **50**, 1546 (1967).

Table III presents the ^{13}C-NMR data for XXXII, XLIIa and XLIIb and their assignments.

No distinct difference of the C-5 and C-6 chemical shifts is observed between XLIIa and XLIIb, despite the difference of stereostructure.

This can be explained by assuming that the γ-effect of a hydroxyl group for the methylene carbon atom of the benzyl group in XLIIb is almost the same as that of the benzyl group in XLIIa.

Based on the value of 30.8 ppm for the C-6 signal in XII, +7.5 ppm β-effect due to the tertiary hydroxyl group (XXI relative to I) and +38.4 ppm due to the introduction of a secondary hydroxyl group (XXIV relative to XXI), the calculated chemical shift value of C-6 in XXXII is 76.7 ppm, which is in fair agreement with the observed value, 76.9 ppm.

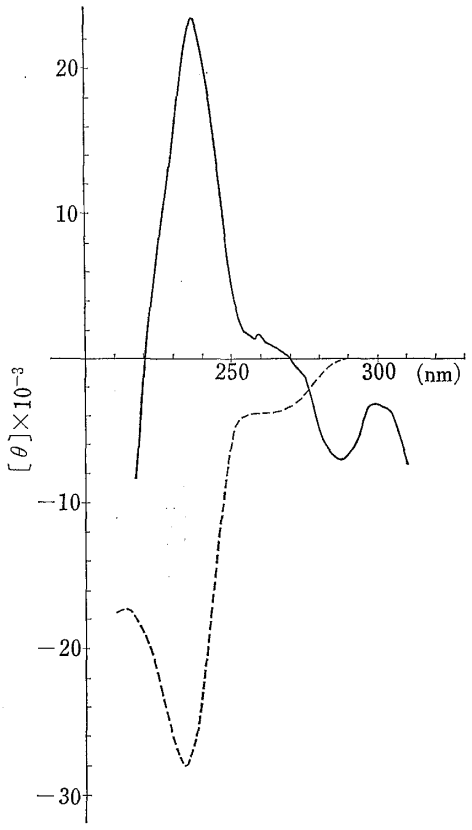


Fig. 1. Circular Dichroism Curves in Ethanol

—: XVI, —: XXXIII.

Experimental

All melting points were determined on a Yanagimoto-micro melting point apparatus and are uncorrected.

The following instruments were used: optical rotation values, Yanagimoto OR-10; UV spectra, Hitachi EPS-3T, Shimadzu UV-210; IR spectra, Jasco IRA-2, Shimadzu IR-400; PMR spectra, JEOL JNM-PMX 60 with tetramethylsilane ($\delta=0$) as an internal reference; ^{13}C-NMR spectra, JEOL JNM-FX 60, equipped with a JEC-980 computer; MS spectra, Shimadzu LKB-9000 at 70 eV using a direct sample inlet into the ion source in all cases; CD curves, Jasco J-40.

Precoated TLC plates, silica gel 60_{F-254} (Merck), were used for TLC and preparative TLC. The spots were detected by spraying with 10% H_2SO_4 soln. and heating.

Silica gel (100 mesh, Mallinckrodt) was used for column chromatography.

The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; br.s, broad singlet.

Arctigenin Monoacetate (II)——A solution of 400 mg of I in 4 ml of acetic anhydride and 4 ml of pyridine was allowed to stand overnight. The mixture was poured into ice-cold water.

The reaction product was extracted with Et_2O. The Et_2O soln. was washed with 10% HCl soln., 10% $NaHCO_3$ soln. and water successively.

Et_2O was removed *in vacuo*. The crude product was chromatographed on a silica gel column and eluted with $CHCl_3$–AcOEt (4: 1) to afford 340 mg of II as a colorless syrup. UV λ_{max}^{EtOH} nm (log ε): 224 (4.02), 281 (3.61). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (CO), 1610, 1595, 1510 (arom. C=C). *Anal.* Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.81; H, 6.47. PMR ($CDCl_3$) δ: 2.33 (3H, s, $OCOCH_3$), 2.50—2.77 (4H, br.s, $C_{5,6}$–H), 2.87—3.17 (2H, br, $C_{2,5}$–H), 3.83, 3.90, 3.93 (9H, each s, $3\times CH_3O$), 4.00—4.40 (2H, m, C_4–H), 6.57—7.27 (6H, m, arom.H).

5-Acetoxyarctigenin Monoacetate (III)——Compound II (400 mg) was dissolved in 4 ml of AcOH and treated with 400 mg of $Pb(OAc)_4$ at 70—80° for 5 hr. The mixture was poured into ice-cold water.

The reaction product was extracted with Et_2O. The Et_2O soln. was washed with 10% $NaHCO_3$ soln. and water successively.

Et_2O was removed *in vacuo*. The crude product was chromatographed on a silica gel column and eluted with $CHCl_3$–AcOEt (4: 1) to afford 285 mg of III as a colorless syrup. UV λ_{max}^{EtOH} nm (log ε): 228 (4.18), 282 (3.83). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (CO), 1610, 1595, 1510 (arom. C=C). *Anal.* Calcd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.24; H, 5.98. PMR ($CDCl_3$) δ: 2.03 (3H, s, alcoholic $OCOCH_3$), 2.27 (3H, s, phenolic $OCOCH_3$), 2.43—3.17 (4H, m, $C_{2,3,6}$–H), 3.70, 3.80, 3.87 (9H, each s, $3\times CH_3O$), 4.13 (2H, d, separation of 6 Hz, C_4–H), 5.57 (1H, d, $J=8$ Hz, C_5–H), 6.33—7.07 (6H, arom.H). MS *m/e*: 472 (M^+), 430 ($M-CH_2CO$), 388 ($M-2\times CH_2CO$), 370 ($M-2\times CH_2CO-H_2O$), 137.

5-Hydroxyarctigenin (IV)——Compound III (100 mg) was dissolved in 30 ml of 4% methanolic KOH soln. After standing overnight, the solution was neutralized with acetic acid.

The product was extracted with Et_2O. The Et_2O soln. was washed with 10% Na_2CO_3 soln. and water. After removal of the Et_2O *in vacuo*, the residue was chromatographed on a silica gel column and eluted with $CHCl_3$–AcOEt (1: 1) to obtain 53 mg of IV.

Recrystallization from EtOH afforded colorless needles of IV. mp 140—141°. $[\alpha]_D^{25}$ +6.32° (c=0.7 in EtOH). UV λ_{max}^{EtOH} nm (log ε): 232 (4.16), 281 (3.81). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525 (OH), 1760 (CO), 1600, 1510 (arom. C=C). *Anal.* Calcd for $C_{21}H_{24}O_7$: C, 64.93; H, 6.23. Found: C, 64.96; H, 6.09. PMR ($CDCl_3$) δ: 2.17 (1H, br, OH, quenched by addition of D_2O), 2.73 (4H, br.s, $C_{2,3,6}$–H), 3.77, 3.80, 3.87 (9H, each s, 3×CH_3O), 4.13 (1H, d, J=8 Hz, C_5–H), 4.23—4.53 (2H, m, C_4–H), 5.57 (1H, br, OH, quenched by addition of D_2O), 6.33—6.90 (6H, m, arom.H).

5-Allohydroxymatairesinol Dimethyl Ether (Va)——Compound IV (30 mg) was methylated with diazomethane in the usual way. The methylation product was recrystallized from EtOH to give colorless needles of Va. mp 137—138°. $[\alpha]_D^{18}$ −8.3° (c=0.47 in THF). UV λ_{max}^{EtOH} nm (log ε): 231 (4.16), 280 (3.72). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1760 (CO), 1605, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.59; H, 6.23. PMR ($CDCl_3$) δ: 2.12 (1H, br, OH, quenched by addition of D_2O), 2.77 (4H, br.s, $C_{2,3,6}$–H), 3.78, 3.83 (12H, each s, 4×CH_3O), 4.13 (1H, d, J=8 Hz, C_5–H), 4.30—4.65 (4H, m, C_4–H), 6.50—6.92 (6H, m, arom.H).

5-Alloacetoxymatairesinol Dimethyl Ether (VIa)——Compound Va (30 mg) was acetylated with acetic anhydride–pyridine in the usual way. The crude acetate was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) to give VIa as a colorless syrup. UV λ_{max}^{EtOH} nm (log ε): 234 (4.25), 282 (3.88). IR ν_{max}^{KBr} cm^{-1}: 1760 (CO), 1740 (CO), 1600, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.98; H, 6.43. PMR ($CDCl_3$) δ: 2.15 (3H, s, $OCOCH_3$), 2.50—3.00 (4H, br, $C_{2,3,5}$–H), 3.75 (12H, s, 4×CH_3O), 4.15 (2H, d, separation of 6 Hz, C_4–H), 5.57 (1H, d, J=8 Hz, C_5–H), 6.50—6.90 (6H, m, arom. H).

5-Hydroxymatairesinol Dimethyl Ether (Vb)——5-Hydroxymatairesinol (VIIb) was methylated with diazomethane in the usual way. The crude product was purified by preparative TLC using $CHCl_3$–AcOEt (1: 1) to give Vb as a colorless syrup.

Several attempts at crystallization were unsuccessfull. $[\alpha]_D^{22}$ +11.1° (c=0.5 in THF). UV λ_{max}^{EtOH} nm (log ε): 232.8 (4.24), 280 (3.80). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1750 (CO), 1600, 1580, 1500 (arom. C=C). *Anal.* Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.33; H, 6.40. PMR ($CDCl_3$) δ: 1.57 (1H, br.s, C_3–H), 2.10 (1H, br, OH, quenched by addition of D_2O), 2.50—2.80 (1H, m, C_2–H), 2.97 (2H, br.s, C_6–H), 3.80, 3.83 (12H, each s, 4×CH_3O), 3.90 (2H, d, J=7.0 Hz, C_4–H), 4.63 (1H, d, J=6.5 Hz, C_5–H), 6.50—6.90 (6H, m, arom.H).

5-Acetoxymatairesinol Dimethyl Ether (VIb)——Compound Vb was acetylated with acetic anhydride-pyridine in the usual way. The crude acetate was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) to give VIb as a colorless syrup. UV λ_{max}^{EtOH} nm (log ε): 232.8 (4.12), 280.3 (3.68). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1730 (CO), 1590, 1580, 1500 (arom. C=C). *Anal.* Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.73; H, 6.28. PMR ($CDCl_3$) δ: 2.10 (3H, s, CH_3CO), 2.43—3.10 (4H, m, $C_{2,3,6}$–H), 3.83, 3.87 (12H, each s, 4×CH_3O), 3.93—4.10 (2H, m, C_4–H), 5.83 (1H, d, J=6.0 Hz, C_5–H), 6.47—6.90 (6H, m, arom.H).

Isoarctigenin Monoacetate (XII)——Compound XI (100 mg) was acetylated with acetic anhydride-pyridine in the usual way.

The crude acetate was recrystallized from EtOH to give XII as colorless needles. mp 120—121°. $[\alpha]_D^{24}$ +58.9° (c=0.43 in EtOH). UV λ_{max}^{EtOH} nm (log ε): 225 (4.15), 282 (3.73). IR ν_{max}^{KBr} cm^{-1}: 1760 (CO), 1600, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.60; H, 6.37. PMR ($CDCl_3$) δ: 2.30 (3H, s, $OCOCH_3$), 2.40—3.60 (6H, m, $C_{2,3,5,6}$–H), 3.82 (9H, s, 3×CH_3O), 4.04 (2H, br.s, C_4–H), 6.45—7.20 (6H, m, arom.H).

Reaction of Isoarctigenin Monoacetate (XII) with $Pb(OAc)_4$——Compound XII (200 mg) was dissolved in 1 ml of AcOH and treated with 100 mg of $Pb(OAc)_4$ at 70—80° for 5 hr. The mixture was poured into ice-cold water. The reaction products were extracted with Et_2O. The Et_2O soln. was washed with 10% $NaHCO_2$ soln. and water successively. Et_2O was removed *in vacuo*. The residue showed two spots of *Rf* 0.8 and *Rf* 0.7 on TLC using $CHCl_3$–EtOAc (1: 1).

The isolation and purification of the two products were achieved by preparative TLC to give 64 mg of XIII and 22 mg of XIV.

5-Acetoxyisoarctigenin Monoacetate (XIII)——Colorless syrup. TLC *Rf* 0.7. $[\alpha]_D^{21}$ +61.9° (c=0.63 in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 228 (4.24), 282 (3.84). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (CO), 1600, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.30; H, 5.98. PMR ($CDCl_3$) δ: 2.17 (3H, s, alcoholic $OCOCH_3$), 2.30 (3H, s, phenolic $OCOCH_3$), 2.50—3.60 (4H, m, $C_{2,3,6}$–H), 3.83 (9H, s, 3×CH_3O), 4.00—4.57 (2H, m, C_4–H), 6.12 (1H, d, J=3 Hz, C_5–H), 6.43—7.17 (6H, m, arom.H).

β-Acetylconidendrin Monomethyl Ether (XIV)——Colorless syrup. TLC *Rf* 0.8. $[\alpha]_D^{21}$ +29.4° (c=0.14 in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 225 (4.20), 279 (3.73). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (CO), 1610, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.31; H, 5.67. PMR ($CDCl_3$) δ: 2.20 (3H, s, $OCOCH_3$), 2.70—3.30 (4H, br, $C_{1,2,3}$–H), 3.83, 3.90 (9H, each s, 3×CH_3O), 4.00—4.40 (3H, m, $C_{4,3\alpha}$–H), 6.37 (1H, s, arom.H), 6.57—7.00 (5H, m, arom.H).

Isomerization of Isoarctigenin Monoacetate (XII) to 5-Hydroxyarctigenin (IV)——Compound XII (30 mg) was dissolved in 10 ml of 4% methanolic KOH soln. After standing overnight, the solution was neutralized with acetic acid. The product was extracted with Et_2O. The Et_2O soln. was washed with 10% Na_2CO_3 soln. and water successively.

After removal of the Et_2O *in vacuo*, the product was purified by preparative TLC using $CHCl_3$–AcOEt (1: 1) and recrystallized from EtOH to afford colorless needles. mp 140—141°.

The IR and NMR spectra of the product were superimposable on those of 5-hydroxyarctigenin (IV).

The melting point of the product showed no depression on admixture with 5-hydroxyarctigenin (IV).

β-Conidendrin Monomethyl Ether (XV)——Compound XIV was saponified with 4% methanolic KOH soln. in the usual way.

Recrystallization from EtOH afforded colorless needles of XV. mp 217—220°. CD ($c=2.997\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): +2.27 (242.5), +2.53 (265) (positive maximum), −11.34 (285) (negative maximum). UV λ_{max}^{EtOH} nm (log ε): 230 (4.21) sh, 263 (3.74), 282 (3.85). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1770 (CO), 1600, 1520 (arom. C=C). *Anal.* Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.95; H, 5.89. PMR ($CDCl_3$) δ: 2.77—3.30 (4H, br, $C_{1,2,3}$–H), 3.80, 3.87 (9H, each s, $3\times CH_3O$), 4.00—4.50 (3H, m, $C_{4,3\alpha}$–H), 5.33—5.67 (1H, br, OH), 6.37 (1H, s, arom.H), 6.53—7.03 (5H, m, arom.H).

β-Conidendrin Dimethyl Ether (XVI)——Compound XV was methylated with diazomethane in the usual way. Recrystallization from EtOH afforded colorless needles of XVI. mp 153—154°. CD ($c=2.602\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): +23.38 (238) (positive maximum), −7.23 (287) (negative maximum). UV λ_{max}^{EtOH} nm (log ε): 231 (4.20), 282 (3.84). IR ν_{max}^{KBr} cm^{-1}: 1750 (CO), 1600, 1580, 1500 (arom. C=C). *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.01; H, 6.15. PMR ($CDCl_3$) δ: 2.70—3.45 (4H, br, $C_{1,2,3}$–H), 3.64 (3H, s, $1\times CH_3O$), 3.82, 3.85, 3.87 (9H, each s, $3\times CH_3O$), 4.00—4.60 (3H, m, $C_{4,3\alpha}$–H), 6.32 (1H, s, arom.H), 6.50—7.00 (5H, m, arom.H).

XVI was identical with authentic β-conidendrin dimethyl ether in all respects.

Trachelogenin Diacetate (XXII)——A solution of 100 mg of XXI in 1 ml of acetic anhydride and 1 ml of pyridine was heated at 100° for 1 hr and allowed to stand overnight. The reaction mixture was treated as described in II. The crude acetylation product was chromatographed on a silica gel column and eluted with $CHCl_3$–AcOEt (4: 1) to obtain 83 mg of XXII.

Recrystallization from EtOH afforded colorless needles of XXII. mp 152—153°. UV λ_{max}^{EtOH} nm (log ε): 224 (4.04), 280 (3.60). IR ν_{max}^{KBr} cm^{-1}: 1760 (CO), 1740 (CO), 1600, 1510 (arom. C=C). *Anal.* Calcd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.36; H, 5.97. PMR ($CDCl_3$) δ: 2.21, 2.27 (6H, each s, $2\times CH_3CO$), 2.53—2.94 (3H, m, $C_{3,5}$–H), 2.82—3.35 (2H, AB quartet, δ_A 2.97, δ_B 3.25, $J_{AB}=14$ Hz, C_6–H), 3.83 (9H, s, $3\times CH_3O$), 4.18 (2H, d, separation of 8 Hz, C_4–H), 6.30—7.18 (6H, m, arom.H).

5-Acetoxytrachelogenin Diacetate (XXIII)——Compound XXII (100 mg) was dissolved in 1 ml of AcOH and treated with 100 mg of $Pb(OAc)_4$ at 70—80° for 5 hr. The reaction mixture was treated as described in III. The crude product was chromatographed on a silica gel column and eluted with $CHCl_3$–AcOEt (4: 1) to afford 58 mg of XXIII as a colorless syrup. $[\alpha]_D^{21}$ +10.2° ($c=0.65$ in $CHCl_3$). MS *m/e*: 530 [M^+]. UV λ_{max}^{EtOH} nm (log ε): 228 (4.09), 276.5 (3.67), 279.5 (3.68). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (CO), 1600, 1590, 1510 (arom. C=C). PMR ($CDCl_3$) δ: 2.03, 2.20, 2.30 (9H, each s, $3\times CH_3CO$), 2.60—3.40 (2H, AB quartet, δ_A 2.77, δ_B 3.23, $J_{AB}=14$ Hz, C_6–H), 3.00—3.37 (1H, m, C_3–H), 3.77, 3.90 (9H, each s, $3\times CH_3O$), 4.00—4.60 (2H, m, C_4–H), 5.67 (1H, d, $J=8$ Hz, C_5–H), 6.43—7.10 (6H, m, arom.H).

5-Hydroxytrachelogenin (XXIV)——Compound XXIII was saponified with ammonia in methanol in the usual way. The crude deacetylated product was purified by preparative TLC using $CHCl_3$–AcOEt (1: 1) and recrystallized from EtOH to afford colorless needles. mp 80—83°. $[\alpha]_D^{20}$ −15.1° ($c=0.19$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 231 (4.13), 281 (3.75). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525 (OH), 1760 (CO), 1600, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.77; H, 5.75. PMR ($CDCl_3$) δ: 2.60 (2H, br, OH, quenched by addition of D_2O), 3.03 (2H, s, C_6–H), 3.37—3.73 (1H, m, C_3–H), 3.87 (9H, s, $3\times CH_3O$), 4.07—4.60 (2H, m, C_4–H), 5.03 (1H, d, $J=3$ Hz, C_5–H), 5.83 (1H, br, OH, quenched by addition of D_2O), 6.63—7.00 (6H, m, arom.H).

6-Hydroxyisomethyltrachelogenin (XXXII)——OsO_4 (200 mg) was added to a solution of 172.3 mg of XXXI dissolved in 2 ml of pyridine. The mixture was stirred overnight. After adding a mixture of 350 mg of $NaHSO_3$, 5 ml of water and 3 ml of pyridine, the solution was stirred for 2 hr. The reaction product was extracted with $CHCl_3$. The $CHCl_3$ soln. was washed with water and concentrated *in vacuo*.

Purification was achieved by preparative TLC using $CHCl_3$–AcOEt (1: 1). Recrystallization from EtOH afforded colorless needles of XXXII. mp 111—114°. $[\alpha]_D^{22}$ −40.7° ($c=0.8$ in EtOH). UV λ_{max}^{EtOH} nm (log ε): 231.5 (4.21), 279 (3.72). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3525 (OH), 1760 (CO), 1605, 1590, 1510 (arom. C=C). *Anal.* Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.20; H, 6.14. PMR ($CDCl_3$) δ: 2.63 (2H, br, OH, quenched by addition of D_2O), 2.70—3.40 (3H, m, $C_{3,5}$–H), 3.90 (12H, s, $4\times CH_3O$), 4.03—4.37 (2H, m, C_4–H), 4.93 (1H, s, C_6–H), 6.57—7.13 (6H, m, arom.H). MS *m/e*: 418 [M^+], 252, 166, 151.

3-Hydroxy-β-retroconidendrin Dimethyl Ether (XXXIII)——Compound XXXII was treated with hydrochloric acid in acetic acid at room temperature.

The cyclization product was purified by preparative TLC using $CHCl_3$–AcOEt (1: 1) and recrystallized from EtOH to afford colorless needles of XXXIII. mp 183—184°. $[\alpha]_D^{22}$ +31.7° ($c=0.54$ in $CHCl_3$). UV

λ_{max}^{EtOH} nm (log ε): 230 (4.19) sh, 283.5 (3.84). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1770 (CO), 1610, 1590, 1510 (arom. C=C). CD ($c=4.276\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -28.06 (234.6) (negative maximum). *Anal.* Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.30; H, 6.37. PMR ($CDCl_3$) δ: 2.57 (1H, br, OH, quenched by addition of D_2O), 2.67—3.40 (3H, m, $C_{1,2}$–H), 3.73 (3H, s, $1\times CH_3O$), 3.83, 3.90 (9H, each s, $3\times CH_3O$), 4.33 (1H, s, C_4–H), 4.17—4.77 (2H, m, $C_{2\alpha}$–H), 6.53 (1H, s, arom.H), 6.63—6.90 (4H, m, arom. H).

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