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Isolation of Phenolic Compounds and Spectroscopic Analysis of a New Lignan from *Trachelospermum asiaticum* var. *intermedium*

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A new lignan **1** and two phenolic compounds, scopoletin and vanillic acid, were isolated from the stems of *Trachelospermum asiaticum* NAKAI var. *intermedium* NAKAI (Apocynaceae).

The structure of **1** was elucidated as (2*R*,3*R*) 2-4″-hydroxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone by analysis of the carbon-13 nuclear magnetic resonance, mass and circular dichroism spectra.

Keywords——*Trachelospermum asiaticum* var. *intermedium*; Apocynaceae; phenolic compounds; scopoletin; vanillic acid; new lignan; (2*R*,3*R*) 2-4″-hydroxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone; ^{13}C-NMR spectra; mass spectra; CD curves

We have already reported the isolation of four lignans, arctigenin, matairesinol, trachelogenin, and nortrachelogenin, from the ether extract of the stems of *Trachelospermum asiaticum* Nakai var. *intermedium* NAKAI (Apocynaceae) and their structure determination.[1-3]

As a continuation of our investigation on the constituents in the ether extract, a new lignan **1** and two phenolic compounds, scopoletin and vanillic acid, were isolated. Scopoletin and vanillic acid were identified by comparison with authentic samples.

This paper deals with the spectroscopic analysis of the structure of **1**, based on carbon-13 nuclear magnetic resonance (^{13}C-NMR), mass (MS) and circular dichroism (CD) spectra.

The extraction was carried out as described in "Experimental." The lignan **1** was isolated as a colorless syrup, $C_{22}H_{26}O_7$, $[\alpha]_D^{18}$ −25.1° (ethanol). The infrared (IR) absorption of **1** at 1765 cm^{-1} (CO) and the appearance of signals at δ 2.33—2.70 (4H, br.s, $C_{5,6}$–H), 2.77—3.07 (2H, br, $C_{2,3}$–H) and 3.97—4.27 (2H, m, C_4–H) in the proton nuclear magnetic resonance (PMR) spectrum suggested that **1** is a 2,3-dibenzylbutyrolactone lignan.

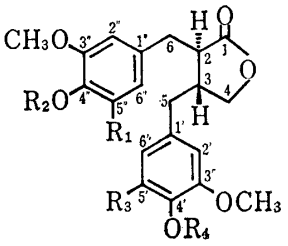
Methylation of **1** with diazomethane gave **2** as colorless needles, $C_{23}H_{28}O_7$, mp 122—123 °C, $[\alpha]_D^{18}$ −16.1° (chloroform).

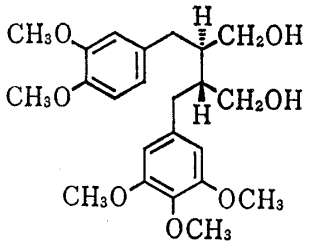
Acetylation of **1** with acetic anhydride-pyridine gave **3** as a colorless syrup, $C_{24}H_{28}O_8$, $[\alpha]_D^{20}$ −26.3° (ethanol).

The PMR spectrum of **3** showed the presence of one phenolic acetoxyl (δ 2.30), four aromatic methoxyls (δ 3.83) and five aromatic protons (δ 6.27, 6.57—7.13).

In a previous paper,[4] ^{13}C-NMR spectra were discussed with regard to the differences of chemical shifts resulting from changes in the substituents and the stereochemistry of the 2,3-dibenzylbutyrolactone skeleton.

The ^{13}C-NMR spectra of derivatives of **1** were correlated with those of known lignans, and the results were applied in the elucidation of the structure of **1**.





1: R_1=H, R_2=H, R_3=OCH_3, R_4=CH_3
2: R_1=H, R_2=CH_3, R_3=OCH_3, R_4=CH_3
3: R_1=H, R_2=Ac, R_3=OCH_3, R_4=CH_3
4: R_1=H, R_2=H, R_3=H, R_4=H
5: R_1=H, R_2=CH_3, R_3=H, R_4=CH_3
6: R_1=H, R_2=Ac, R_3=H, R_4=Ac
7: R_1=OCH_3, R_2=CH_3, R_3=H, R_4=CH_3

Chart 1

Table I presents the ^{13}C-NMR data for lignans **1**—**3** and matairesinol (**4**), methylarctigenin (**5**), matairesinol diacetate (**6**), di-O-methylthujaplicatin methyl ether (**7**) and their assignments.[4–6]

Table I. ^{13}C-NMR Chemical Shifts[a]

	1	2	3	4	5	6	7
C-1	178.7	178.7	178.5	178.1	178.5	178.2	178.1
C-2	46.5	46.6	46.4	46.1	46.7	46.2	46.4
C-3	40.9	41.1	41.1	40.7	41.3	40.8	41.0
C-4	71.2	71.2	71.2	71.1	71.2	71.0	71.1
C-5	38.8	38.9	38.9	37.7	38.4	38.1	38.1
C-6	34.4	34.6	34.6	34.2	34.8	34.4	35.0
C-1′	133.6	133.7	133.6	129.6	130.9	136.8	130.1
C-1″	129.4	130.3	136.7	129.3	130.7	136.5	133.1
C-2′	105.5	105.7	105.7	111.0	112.9	112.7	111.7
C-2″	111.6	112.5	113.4	111.6	113.3	113.3	106.2
C-3′	153.2	153.5	153.5	146.6	149.6	151.1	148.8
C-3″	146.7	149.2	151.3	146.5			152.9
C-4′	136.7	136.9	137.0	144.2	148.5	138.5	147.7
C-4″	144.6	148.1	138.8				136.8
C-5′	153.2	153.5	153.5	114.3	112.1	120.6	111.2
C-5″	114.1	111.2	121.4	114.1	112.3	121.3	152.9
C-6′	105.5	105.7	105.7	120.9	120.9	122.8	120.2
C-6″	121.9	121.4	122.7	121.7	121.7	122.6	106.2
$\underline{C}H_3CO$			20.6			20.5	
$CH_3\underline{C}O$			168.9			168.8	
CH_3O	60.7	60.9	60.9	55.5	56.2	55.7	60.7
	55.9	55.9	55.9				55.8
		56.1	56.1				56.0

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 s; number of pulses, 5000—100000; pulse flipping angle, 45°.

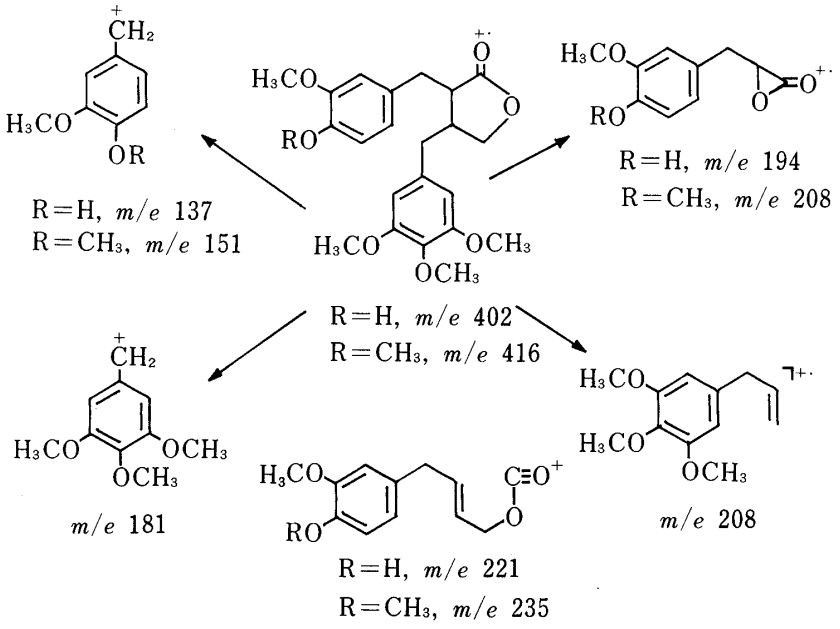


Chart 2. The Mass Fragmentation Patterns of **1** and **2**

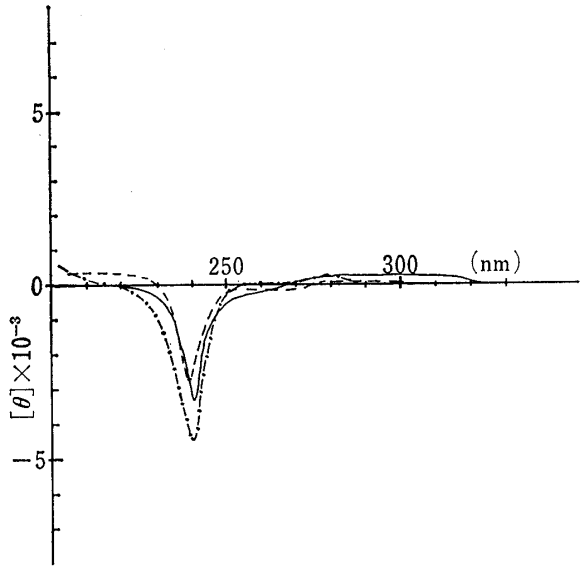


Fig. 1. Circular Dichroism Curves in Ethanol

———: 2-4″-hydroxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**1**).
—·—·—: 2-3″,4″-dimethoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**2**).
– – – – –: 2-4″-acetoxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**3**).

It was clearly confirmed that **1** contains a 4-hydroxy-3-methoxybenzyl unit at the C-2 position and a 3,4,5-trimethoxybenzyl unit at the C-3 position on a butyrolactone skeleton, and that the relative configuration of dibenzyl units is *trans*.

The mass spectral fragmentation patterns of **1** and **2** (Chart 2) are also in good agreement with the results of ^{13}C-NMR analysis.

With regard to the problem of the absolute configuration of **1**, the CD curves of **1**—**3** (Fig. 1) each showed a negative Cotton effect at around 240 nm, as in the case of **7** and related lignans reported in previous papers.[7,8] Therefore, the absolute configuration was indicated to be 2*R*, 3*R*.

Consequently, the structure of **1** has been established as (2*R*, 3*R*) 2-4-″hydroxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone.

These results were chemically supported by the fact that the absolute structure of the diol (**8**) obtained by lithium aluminum hydride reduction of **2** was identical with that of the diol obtained by the same treatment of **7**.

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, Shimadzu IR-400; PMR spectra, Jeol JNM-PMX 60 with tetramethylsilane (δ=0) as an internal reference; ^{13}C-NMR

spectra, Jeol JNM-FX 60, equipped with a JEC-980 computer; MS, Hitachi MRU-7M, Shimadzu LKB-9000 at 70 eV using a direct sample inlet into the ion source in all cases; CD curves, Jasco J-40.

Precoated thin-layer chromatography (TLC) plates, silica gel 60_{F-254} (Merck), were used for TLC and preparative TLC. The spots were detected by spraying the plates 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; m, multiplet; br, broad; br.s, broad singlet; sh, shoulder.

Isolation——The ether extract (73 g) obtained by treatment of the stems (25 kg) of *Trachelospermum asiaticum* var. *intermedium* in a previous paper[3] was subjected to column chromatography, eluting with $CHCl_3$–AcOEt (5: 1).

The fractions (100 ml each) were monitored by TLC using $CHCl_3$–AcOEt (4: 1) for development in order to isolate unidentified compounds.

The fractions showing a TLC spot at *Rf* 0.58 were concentrated, and the residue was purified by preparative TLC using $CHCl_3$–AcOEt (4: 1) to give **1** (54.7 mg).

The fractions showing a TLC spot at *Rf* 0.41 were concentrated, and the residue was recrystallized from EtOH to give scopoletin (12.3 mg). The fractions showing a TLC spot at *Rf* 0.18 were concentrated. The residue was recrystallized from EtOH to give vanillic acid (87.9 mg).

2-4″-Hydroxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**1**)——Colorless syrup. $[\alpha]_D^{18}$ $-25.1°$ ($c=0.55$ in EtOH). UV λ_{max}^{EtOH} nm (log ε): 227 (4.19) sh, 281 (3.67). UV $\lambda_{max}^{EtOH+NaOH}$ nm: 249, 297. CD ($c=4.935\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -3.33 (241) (negative maximum). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1765 (CO), 1600, 1520 (arom. C=C). MS: Calcd for $C_{22}H_{26}O_7$, 402.1733. Obsd., 402.1739. PMR (in $CDCl_3$) δ: 2.33—2.70 (4H, br.s, $C_{5,6}$–H), 2.77—3.07 (2H, br, $C_{2,3}$–H), 3.83 (12H, s, $4\times CH_3O$), 3.97—4.27 (2H, m, C_4–H), 5.53 (1H, br, OH, quenched by addition of D_2O), 6.20 (2H, s, $C_{2',6'}$–H), 6.60—6.97 (3H, m, $C_{2'',5'',6''}$–H).

2-3″,4″-Dimethoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**2**)——**1** was methylated with diazomethane in the usual way. The methylation product was recrystallized from EtOH to give colorless needles of **2**. mp 122—123°C. $[\alpha]_D^{18}$ $-16.1°$ ($c=0.81$ in $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 226 (3.99), 279 (3.31). CD ($c=3.635\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -4.45 (240) (negative maximum). IR ν_{max}^{KBr} cm^{-1}: 1760 (CO), 1581, 1502 (arom. C=C). MS: Calcd for $C_{23}H_{28}O_7$, 416.1812. Obsd., 416.1810. PMR (in $CDCl_3$) δ: 2.37—2.73 (4H, br.s, $C_{5,6}$–H), 2.83—3.13 (2H, br, $C_{2,3}$–H), 3.83, 3.87 (15H, each s, $5\times CH_3O$), 6.23 (2H, s, $C_{2',6'}$–H), 6.73 (3H, m, $C_{2'',5'',6''}$–H).

2-4″-Acetoxy-3″-methoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**3**)——**1** 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 **3** as a colorless syrup. $[\alpha]_D^{20}$ $-26.3°$ ($c=0.36$ in EtOH). UV λ_{max}^{EtOH} nm (log ε): 274 (3.49), 279 (3.45). CD ($c=6.002\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -2.79 (239) (negative maximum). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1759 (CO), 1585, 1505 (arom. C=C). MS: Calcd for $C_{24}H_{28}O_8$, 444.1184. Obsd., 444.1182. PMR (in $CDCl_3$) δ: 2.30 (3H, s, CH_3CO), 2.47—2.77 (4H, br.s, $C_{5,6}$–H), 2.83—3.13 (2H, br, $C_{2,3}$–H), 3.83 (12H, s, $4\times CH_3O$), 3.97—4.30 (2H, m, C_4–H), 6.27 (2H, s, $C_{2',6'}$–H), 6.57—7.13 (3H, m, $C_{2'',5'',6''}$–H).

$LiAlH_4$ Reduction of 2-3″,4″-Dimethoxybenzyl-3-3′,4′,5′-trimethoxybenzylbutyrolactone (**2**)——A solution of **2** in tetrahydrofuran (THF) was added dropwise to a suspension of $LiAlH_4$ in THF. The mixture was stirred for 5 h at room temperature, then added to ice-cold water, and the whole was acidified carefully with 10% H_2SO_4 soln. The product extracted with ether was purified by preparative TLC using $CHCl_3$–AcOEt (1: 1) to give the diol (**8**) as a colorless syrup.

Several attempts at crystallization were unsuccessfull. UV λ_{max}^{EtOH} nm (log ε): 227 (4.20), 278 (3.51). CD ($c=3.730\times10^{-4}$, ethanol) $[\theta]^{20}\times10^{-3}$ (nm): -3.40 (238.5) (negative maximum). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (br, OH), 1595, 1515 (arom. C=C). MS m/e: 420 (M^+), 181, 151.

The UV, CD and IR spectra of **8** were superimposable on those of the diol obtained by the $LiAlH_4$ reduction of **7**.

Scopoletin——Colorless needles, mp 210—211°C. UV λ_{max}^{EtOH} nm (log ε): 229 (4.11), 254 (3.64), 259.5 (3.62), 299 (3.67), 347.5 (4.01). IR ν_{max}^{KBr} cm^{-1}: 3325 (OH), 1690 (CO), 1620 (C=C), 1600, 1560, 1500 (arom. C=C). PMR (in $CDCl_3+CD_3OD$) δ: 3.93 (3H, s, CH_3O), 6.23 (1H, d, $J=10$ Hz, C_3–H), 6.83 (1H, s, C_8–H), 6.90 (1H, s, C_5–H), 7.63 (1H, d, $J=10$ Hz, C_4–H).

This compound was identical with authentic scopoletin.

Vanillic Acid——Colorless needles, mp 190—193°C. UV λ_{max}^{EtOH} nm (log ε): 262 (3.99), 288 (3.77). IR ν_{max}^{KBr} cm^{-1}: 3425 (OH), 1670 (CO), 1605, 1590, 1520 (arom. C=C). PMR (in CD_3OD) δ: 3.93 (3H, s, CH_3O), 6.90 (1H, d, $J=8$ Hz, C_5–H), 7.57 (1H, d,d, $J=8$ Hz, 2 Hz, C_6–H), 7.60 (1H, d, $J=2$ Hz, C_2–H).

This compound was identical with authentic vanillic acid.

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Transformation of 2,3-Dibenzylbutyrolactone Lignans containing a Secondary Hydroxyl Group to Phenyltetralin Lignans and Their Reduction Products with Lithium Aluminum Hydride

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Two 2,3-dibenzylbutyrolactone lignans containing a secondary hydroxyl group at one of the benzylic positions, 5-hydroxyarctigenin (I) and 5-hydroxytrachelogenin (XI), were transformed to phenyltetralin lignans, α-conidendrin monomethyl ether (II) and 3-hydroxy-α-conidendrin monomethyl ether (XII), respectively, by acid treatment.

The hemiacetal lignan, (1*S*,2*R*,3*S*,3a*R*) 6,7-dimethoxy-3-hydroxy-2-hydroxymethyl-1-3′,4′-dimethoxyphenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid lactol (XV), was obtained in addition to isoolivil dimethyl ether (XIV), the normal reduction product, when 3-hydroxy-α-conidendrin dimethyl ether (XIII) was treated with lithium aluminum hydride, and a mechanism is proposed for this reaction.

Keywords——lignans; 5-hydroxyarctigenin; 5-hydroxytrachelogenin; transformation to phenyltetralin lignans; reduction with $LiAlH_4$; stereospecific hemiacetal lignan; reaction mechanism

In a previous paper,[1] we reported the stereospecific introduction of an alcoholic hydroxyl group at the C-5 position of 2,3-dibenzylbutyrolactone lignans with lead tetraacetate.

This paper deals with the transformation of two 2,3-dibenzylbutyrolactone lignans containing a secondary hydroxyl group, 5-hydroxyarctigenin (I) and 5-hydroxytrachelogenin (XI),[1] to phenyltetralin lignans, α-conidendrin monomethyl ether (II) and 3-hydroxy-α-conidendrin monomethyl ether (XII), respectively, and describes an investigation of the reduction products of the methyl ethers (III and XIII) of compounds II and XII with lithium aluminum hydride.

Compound I was transformed to compound II, mp 244—247 °C, $[\alpha]_D^{23}$ −52.3 ° (chloroform), by acid treatment. This reaction is similar to the well known stereospecific acid-catalyzed conversion of hydroxymatairesinol to α-conidendrin.[2] Methylation of II with diazomethane gave compound III, mp 173—176 °C, $[\alpha]_D^{23}$ −114.2 ° (chloroform), which was identical with authentic natural α-conidendrin dimethyl ether.[3]