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Studies on the Constituents of Medicinal and Related Plants in Sri Lanka. III.[1] Novel Sesquilignans from *Hedyotis lawsoniae*

TOHRU KIKUCHI,* SATOKO MATSUDA, SHIGETOSHI KADOTA, and TAKAAKI TAI

Research Institute for Wakan-Yaku (Oriental Medicines), Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930–01, Japan

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Four new sesquilignans, named hedyotol-A, -B, -C, and -D, were isolated from the leaves of *Hedyotis lawsoniae*, along with four known lignans. The structures of these novel lignans were determined on the basis of spectroscopic and chemical evidence.

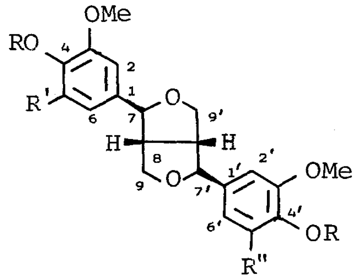
Keywords——*Hedyotis lawsoniae*; lignan; sesquilignan; hedyotol-A; hedyotol-B; hedyotol-C; hedyotol-D

In a previous paper,[2] we reported the isolation and structure elucidation of new triterpenes isolated from *Hedyotis lawsoniae* (DC.) WIGHT *et* ARN. (Rubiaceae) collected in Sri Lanka. During a further scrutiny of the constituents of this plant, we recently obtained four new lignans, named hedyotol-A (**5a**), -B (**6a**), -C (**7a**), and -D (**8a**), which are constructed from three units of coniferyl alcohol and/or sinapyl alcohol. This paper describes the structure elucidation of these novel sesquilignans.

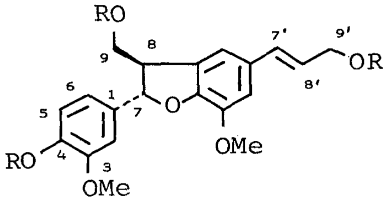
Dried leaves of *H. lawsoniae* were extracted with ether and then with hot methanol. The methanol extract was separated into the ethyl acetate-soluble part and the water-soluble part. From the former part, four new sesquilignans were isolated as the acetyl derivatives (**5b**—**8b**), along with (+)-pinoresinol (**1a**), (+)-medioresinol (**2a**), (+)-syringaresinol (**3a**), and (−)-dehydrodiconiferyl alcohol (**4a**) (see Experimental).

Hedyotol-A (**5a**) was obtained as the triacetate (**5a**), $[\alpha]_D$ +29° ($CHCl_3$), mass spectrum (MS) m/z 662 (M^+), whose composition was determined to be $C_{36}H_{38}O_{12}$ by measurement of the high-resolution MS. The infrared (IR) spectrum of **5b** showed strong absorptions at 1760 and 1740 cm^{-1} and the proton-nuclear magnetic resonance (^1H-NMR) spectrum showed the signals of three acetyl groupings at δ 2.05, 2.31, and 2.33, along with the signals due to three methoxyl groups at δ 3.82, 3.86, and 3.93 and eight aromatic protons at δ 6.81—7.06 (Table I). Furthermore, the MS exhibited strong peaks at m/z 151 ($C_8H_7O_3{}^+$, a) and 137 ($C_8H_9O_2{}^+$, c) (Chart 2), which are characteristic of pinoresinol-type lignans,[3] along with peaks at m/z 560 ($M^+-60-42$), 620 (M^+-42), and the molecular ion peak. These observations led us to suppose that **5b** might be a sesquilignan having an alcoholic and two phenolic acetoxyl groups.

The ^1H-NMR spectrum of **5b** showed a complex multiplet assignable to two methine protons at δ 3.13 (m, 8- and 8′-H), which were found to be coupled with two benzylic protons (δ 4.76, d, 7′-H and 4.85, d, 7-H), and also with two pairs of methylene protons at δ 3.74—3.99 (9α- and 9′α-H) and δ 4.23—4.37 (9β- and 9′β-H) through decoupling experiments. This signal pattern is characteristic of pinoresinol-type lignans[4] and is suggestive of the presence of a 3,7-dioxabicyclo[3.3.0]octane grouping I (Fig. 1), in which the bridge-head proton (8- and 8′-H)



1 : R'=R''=H
2 : R'=OMe, R''=H
3 : R'=R''=OMe



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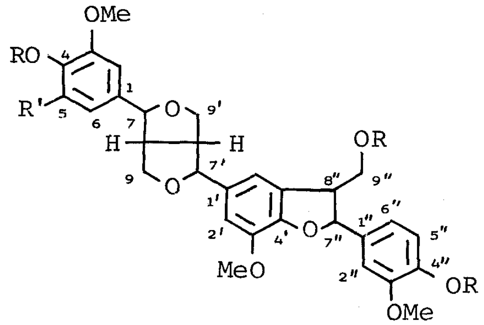
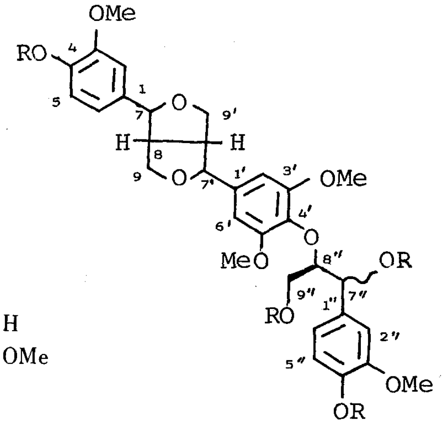


5 : R'=H
6 : R'=OMe



7 : 7''-β-OR
8 : 7''-α-OR

a : R=H **b** : R=Ac

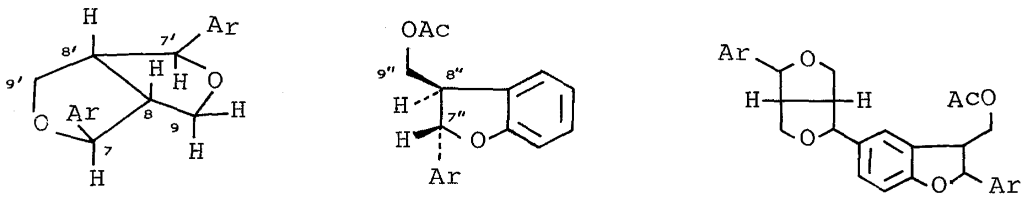
Chart 1

and the benzylic proton (7- and 7′-H) should be in a *trans* relationship in view of the coupling constant ($J_{7,8}=J_{7',8'}=5$ Hz).[4] This was substantiated by a comparison of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **5b** with those of pinoresinol diacetate (**1b**) and medioresinol diacetate (**2b**), as shown in Table II; it is clear that the chemical shifts of signals ascribable to dioxabicyclooctane carbons are essentially parallel in all three compounds. Furthermore, the chemical shifts of the C-7 and C-7′ carbons suggested the presence of aryl groups at these positions in *cis* orientation relative to the bridge-head protons.[5]

In addition, the presence of the partial structure II was presumed on the basis of the ^{1}H-NMR signals due to a methine at δ 5.58 (d, $J=7$ Hz, 7′′-H), a methylene at δ 4.48 (dd, 9′′-H) and 4.23—4.37 (9′′-H, overlapped with 9β- and 9′β-H), and a methine at δ 3.74—3.99 (8′′-H, overlapped with methoxyl signals and 9α- and 9′α-H signals), whose coupling pattern was very similar to that in dehydrodiconiferyl alcohol triacetate (**4b**). The chemical shifts of the 9′′-methylene protons suggested the *trans* relationship between the 9′′-methylene and the aryl substituent at the C-7′′ position, being comparable with the reported values of several known compounds.[6]

Thus, the basic skeleton of hedyotol-A was deduced to be III, having a pinoresinol-type and a dehydrodiconiferyl alcohol-type lignan unit. Turning to the location of the methoxyl and phenolic acetoxyl groups, a suggestion was provided by comparison of the ^{13}C-NMR spectrum with that of pinoresinol diacetate (**1b**). The chemical shifts of eighteen aromatic carbons indicated the presence of two 4-acetoxy-3-methoxy-phenyl groups and a tetra-substituted phenyl group. In view of these spectral data and on the basis of biosynthetic considerations, the structure of hedyotol-A should be represented by the formula **5a**.

Hedyotol-B (**6a**) was a minor component and was isolated as the triacetate (**6b**), $C_{37}H_{40}O_{13}$.[7] The IR and ^{1}H-NMR spectra of **6b** were very similar to those of hedyotol-A



I II III

Fig. 1

Table I. ^{1}H-NMR Spectral Data for Acetyl Derivatives of Pinoresinol and Sesquilignans from *H. lawsoniae* (in $CDCl_3$)

Proton	**1b**	**5b**	**6b**	**7b**	**8b**
7-H	4.83 (d, J=5 Hz)	4.85 (d, J=5 Hz)	4.82 (d, J=5 Hz)	4.84 (d, J=5 Hz)	4.84 (d, J=5 Hz)
8,8′-H	3.12 (m)	3.13 (m)	3.11 (m)	3.10 (m)	3.10 (m)
9,9′-H_2	3.96 (dd, J=9, 3.5 Hz), 4.31 (dd, J= 9, 7 Hz)	3.74—3.99,[b] 4.23—4.37	3.70—3.98,[b] 4.25—4.53	3.89—3.98,[b] 4.21—4.37	3.91—3.99,[b] 4.25—4.42
7′-H	4.83 (d, J=5 Hz)	4.76 (d, J=5 Hz)	4.75 (d, J=5 Hz)	4.73 (d, J=5 Hz)	4.75 (d, J=5 Hz)
7″-H		5.58 (d, J=7 Hz)	5.57 (d, J=7 Hz)	6.11 (d, J=5.0 Hz)	6.19 (d, J=6.2 Hz)
8″-H		3.74—3.99[b]	3.70—3.98[b]	4.63 (m)	4.55 (dt, J=6.2, 4.5 Hz)
9″-H_2		4.48 (dd, J=12, 5 Hz), 4.23—4.37	4.25—4.53	4.21—4.37, 4.49 (dd, J= 12, 5 Hz)	4.25—4.42
Aromatic protons	6.92 (dd, J=8, 2 Hz), 7.01 (d, J=2 Hz), 7.03 (d, J=8 Hz)	6.81—7.06 (8H)	6.60 (2H, s, 2,6-H), 6.80—7.05 (5H)	6.54 (2H, s, 2′,6′-H), 6.87—7.06 (6H)	6.54 (2H, s, 2′,6′-H), 6.90—7.12 (6H)
OCH_3	3.87[a]	3.82, 3.86, 3.93	3.82, 3.85,[a] 3.93	3.77,[a] 3.81, 3.86	3.80,[a] 3.83, 3.87
$COCH_3$	2.33[a]	2.05, 2.31, 2.33	2.06, 2.32, 2.35	1.99, 2.14, 2.29, 2.32	2.01, 2.02, 2.31, 2.33

a) Each signal contains two methoxyl or acetyl groups. *b)* The signals in this region are overlapped with methoxyl signals.

triacetate (**5b**), except that the ^{1}H-NMR spectrum of **6b** showed signals for only seven aromatic protons, and a signal for an additional methoxyl group appeared as shown in Table I. Therefore, **6b** was considered to be a monomethoxylated derivative of **5b**.

The fourth methoxyl group in **6b** should be located at the C-5 or C-5″ position, because the NMR signal due to two aromatic protons was observed at δ 6.60 as a singlet. Of these positions, the C-5 methoxyl disposition seems preferable on the basis of the decoupling experiment, which showed long-range coupling between the benzylic proton at δ 4.82 (7-H) and the aromatic protons at δ 6.60 (2H, s) and thus indicated the presence of an aromatic ring of symmetric structure at the C-7 position. Furthermore, in the MS of **5b**, strong peaks appeared at m/z 151 and 137 due to the fragment ions a and c, whereas **6b** showed peaks at m/z 181 and 167 due to the fragment ions b and d, respectively (Chart 2).[8] In view of these data, the structure of hedyotol-B was determined to be **6a**.

Hedyotol-C (**7a**) and -D (**8a**) were isolated as the tetraacetates **7b**, $[\alpha]_D$ +13° ($CHCl_3$), and **8b**, $[\alpha]_D$ +20° ($CHCl_3$), respectively, and both had the same molecular formula, $C_{39}H_{44}O_{15}$. The ^{1}H-NMR spectra closely resembled each other and both showed signals due to eight aromatic protons, four methoxyl groups, and two alcoholic and two phenolic acetoxyls. In addition, they revealed the characteristic signal pattern ascribable to the partial

Table II. ^{13}C-NMR Spectral Data for Acetyl Derivatives of Lignans and Sesquilignans (in $CDCl_3$)

Carbon	**1b**	**2b**	Carbon	**5b**	**7b**	**8b**
1	139.1 s	139.6 s	1, 1''	139.0, 139.6 s	139.4, 137.3[a] s	139.5, 136.8[a] s
2	109.8 d	102.1 d	2, 2''	109.8, 110.0[a] d	109.8, 111.4 d	109.8, 111.7 d
3	151.1 s	152.1 s	3, 3''	151.2[b] s	151.2, 150.8 s	151.1, 150.8 s
4	140.1 s	127.7 s	4, 4''	140.2, 139.6 s	140.1, 137.3 s	140.0, 138.9 s
5	122.8 d	152.1 s	5, 5''	122.8, 122.9 d	122.8, 122.4 d	122.7, 122.5 d
6	117.9 d	102.1 d	6, 6''	117.9, 118.2 d	117.9, 119.2 d	117.8, 119.6 d
7	85.5 d	85.8 d	7, 7'	85.4, 86.1 d	85.4, 86.0 d	85.4, 85.9 d
8	54.3 d	54.4 d	8, 8'	54.4[b] d	54.3[b] d	54.3[b] d
9	71.9 t	72.0 t	9, 9'	71.7, 72.0 t	71.8, 72.1 t	71.8, 72.0 t
1'		139.0 s	1'	134.9 s	134.4 s	135.6[a] s
2'		109.7 d	2'	110.5[a] d	102.7 d	102.6 d
3'		151.1 s	3'	147.6 s	153.3 s	153.1 s
4'		140.0 s	4'	144.5 s	136.2[a] s	135.8[a] s
5'		122.6 d	5'	127.1 s	153.3 s	153.1 s
6'		117.9 d	6'	114.3 d	102.7 d	102.6 d
7'		85.4 d	7''	87.9 d	80.8 d	80.7 d
8'		54.2 d	8''	50.7 d	73.9 d	75.1 d
9'		71.9 t	9''	65.4 t	62.6 t	63.3 t
OCH_3	55.9 q	55.9, 56.1[b]	OCH_3	55.9, 56.1 q	55.9,[b] 56.1[b] q	55.9[d] q
$\underline{C}OCH_3$	169.1 s	168.8, s 169.1	$\underline{C}OCH_3$	169.0, 169.2, s 170.8	168.9, 169.2, s 169.6, 171.0	168.9, 169.2, s 169.7, 170.6
$CO\underline{C}H_3$	20.7 q	20.5, 20.6 q	$CO\underline{C}H_3$	20.7,[b] 20.8 q	20.7,[b] 20.8 q 21.1	20.7,[c] 21.0 q

a) Assignments may be interchanged in each compound. *b*—*d*) Each signal contains two *b*), three *c*), or four *d*) carbons.

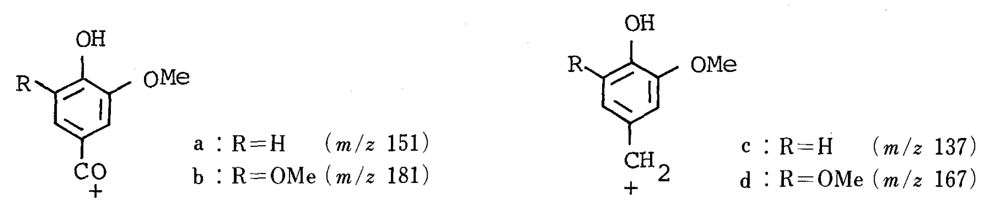
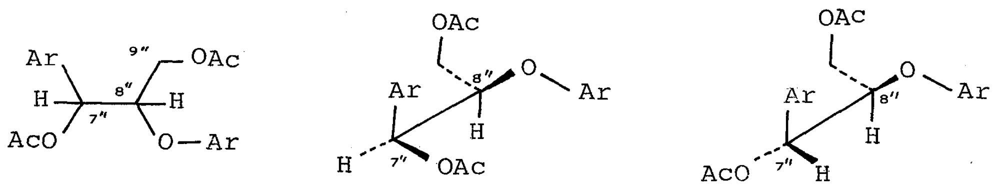


Chart 2

structure I (Table I), indicating that these compounds are also sesquilignans.

Furthermore, the ^{1}H-NMR spectrum of **7b** showed a series of signals at δ 4.49 (dd, $J=12$, 5 Hz, 9''-H), 4.21—4.37 (9''-H), 4.63 (m, 8''-H), and 6.11 (d, $J=5.0$ Hz, 7''-H), which could be analyzed as a typical AA'BX pattern on the basis of decoupling experiments and suggested the presence of a partial structure IV (Fig. 2) in **7b**. In the case of **8b**, the corresponding signal pattern was observed at δ 4.25—4.42 (9''-H_2), 4.55 (dt, $J=6.2$, 4.5 Hz, 8''-H), and 6.19 (d, $J=6.2$ Hz, 7''-H). From these findings, together with the fact that the MS of both compounds were almost identical with each other, it was deduced that **7b** and **8b** might have the same structure and might be stereoisomeric with respect to the partial structure IV.

Nakatsubo and his coworkers[9)] reported that the relative configuration of the glycerol part of triacetyl-guaiacylglycerol-β-guaiacyl ether (**9**) could be clarified on the basis of the chemical shift and the coupling constant of a benzylic proton. For instance, the signal of the benzylic proton of the *erythro* isomer of **9** appeared at δ 6.12 (d, $J=5.0$ Hz), whereas that of the *threo* isomer was shifted downfield to δ 6.17 (d, $J=6.2$ Hz). According to Nakatsubo *et al.*, **7b** and **8b** should be an *erythro* isomer (V) and a *threo* isomer (VI), respectively (Fig. 2). This

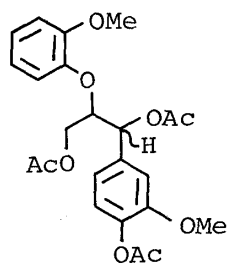


IV V VI

Fig. 2

was substantiated by the following chemical transformations.

Alkaline hydrolysis (NaOH–dioxane) of **7b** gave hedyotol-C (**7a**), along with (+)-medioresinol (**2a**) and a diol (**10**). Then treatment of **7a** with acetone in the presence of *p*-toluenesulfonic acid gave rise to the corresponding acetonide (**12**) accompanied by a small amount of **2a**. The ^{1}H-NMR spectrum of the acetonide (**12**) showed two singlets of the newly introduced *tert*-methyl groups (δ 1.48 and 1.65) and a doublet signal due to the benzylic proton at δ 4.48 ($J=10$ Hz). Furthermore, on irradiation of the methyl group at δ 1.65, a 10% nuclear Overhauser effect (NOE) increase of the benzylic proton signal intensity was observed. Therefore, the 1,2-diaxal relationship of the benzylic proton and the neighboring proton, as shown in Chart 3, was verified, confirming the *erythro* orientation of the glycerol portion in **7b**.



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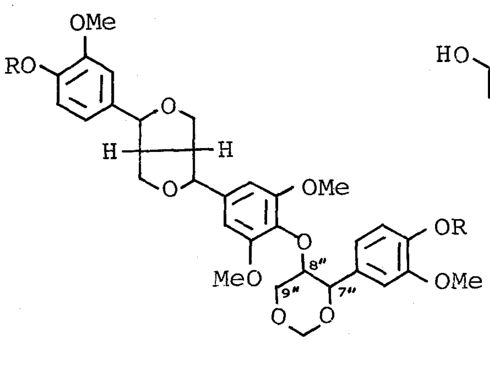
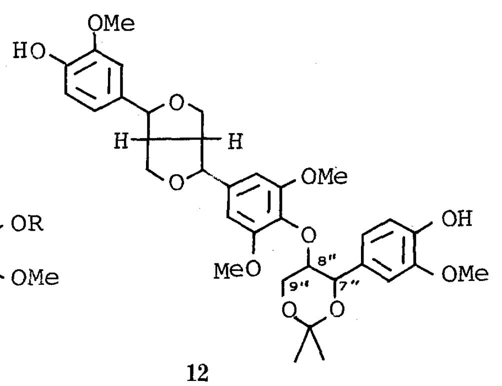


10 : R=H
11 : R=Ac



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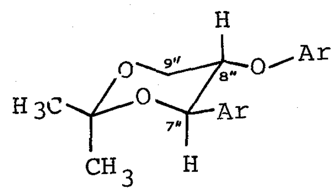

Chart 3

The structures of hedyotol-C and -D can now be represented by the combination of the partial structure IV and the medioresinol counterpart. In other words, IV is linked to medioresinol at the C-4 or C-4′ position. This was settled by inspection of the ^{13}C-NMR spectra compared with those of **1b** and **2b**. As shown in Table II, both **7b** and **8b** have two 4-acetoxy-3-methoxy-phenyl groups and a 4-alkoxy-3,5-dimethoxy-phenyl, but not a 4-acetoxy-3,5-dimethoxy-phenyl group. Furthermore, the MS of **7b** and **8b** exhibited peaks due to fragment ions e and f (Chart 4) at *m/z* 323 ($C_{16}H_{19}O_7^+$, e) and 430 ($C_{23}H_{26}O_8^+$, f), respectively, together with peaks at *m/z* 221 (e−42−60), 179 (221−42), and 388 (f−42). Thus, the structure of hedyotol-C and -D should be assigned as **7a** and **8a**, respectively.

The diol (**10**) produced during the alkaline hydrolysis of **7b** was trapped as the diacetate (**11**), $C_{36}H_{40}O_{13}$. The ^{1}H-NMR spectrum of **11** showed two singlets due to phenolic acetoxyl groups at δ 2.28 and 2.32, along with the signals due to a methine proton at δ 4.64 (d, J= 9.5 Hz, 7''-H) and methylene protons at δ 4.72 and 5.14 (each d, J=6 Hz, O–CH_2–O). In the MS of **11**, the peaks for fragment ions f and h (Chart 4) appeared at m/z 430 and 250, respectively. This diol (**10**) was probably formed by the reaction of **7a** and formaldehyde, which might be produced from the C-9'' portion of **7a** by the 1,3-diol fragmentation.

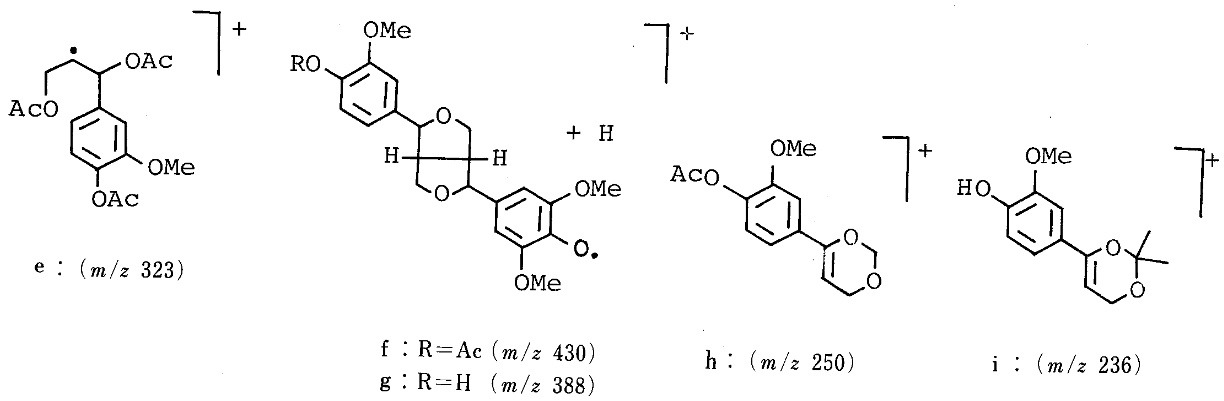

Chart 4

Up to the present, several sesquilignans and dilignans have been isolated from *Arctium lappa* L.[10a] and from *Heterotropa takaoi* M.,[10b] but hedyotol-A, -B, -C, and -D are the first examples of sesquilignans containing a 3,7-dioxabicyclo[3.3.0]octane skeleton. Several dilignans were also isolated from *Hedyotis lawsoniae* and the investigation of their structures is now in progress.

Experimental

Optical rotations were measured with a JASCO DIP-4 automatic polarimeter. MS and high-resolution MS were obtained with a JEOL JMS-D 300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a Varian Associates XL-200 spectrometer with tetramethylsilane (TMS) as an internal standard. Column chromatography was carried out using Mallinckrodt silica gel and the eluted solutions were concentrated *in vacuo*. For thin layer chromatography (TLC), Kieselgel 60 F_{254} (Merck) was used and spots were detected by spraying a $Ce(SO_4)_2$–aq. H_2SO_4 reagent or under ultraviolet (UV) light. For preparative TLC, Kieselgel 60 F_{254} (Merck) was employed and the plates were examined under UV light. Extraction of substances from the silica gel was done with MeOH–CH_2Cl_2 (1 : 9) mixture. Organic solutions were dried over anhydrous $MgSO_4$.

Isolation and Properties of Lignans and Sesquilignans from *Hedyotis lawsoniae*——Leaves (dried weight 0.98 kg) of *H. lawsoniae* collected at Horton Plains, Sri Lanka, in July, 1983, were extracted with ether at room temperature to give an ether extract (*ca.* 21 g). The plant material was then extracted with hot MeOH (8 l × 3) and the MeOH solution was concentrated *in vacuo*. The residue was diluted with water (1 l), and extracted with AcOEt (300 ml × 3). The AcOEt layer was washed with water, dried, and concentrated *in vacuo* to give a syrupy residue (*ca.* 10 g), which was chromatographed on a silica gel (250 g) column, eluting successively with acetone–$CHCl_3$ mixture (2 : 98, 1.3 l, fractions 1—13; 5 : 95, 1 l, fractions 14—23; 1 : 9, 2 l, fractions 24—41) and MeOH–$CHCl_3$ mixture (1 : 9, 1.5 l, fractions 42—55; 2 : 8, 1 l, fractions 56—65).

Fractions 14—29 (2.52 g) were combined, suspended in 5% NaOH (250 ml), and extracted with ether (100 ml × 2). The ether layer was washed with water, dried, and concentrated to afford a neutral material (460 mg). On the other hand, the aqueous layer was acidified with dil.HCl and extracted with ether (100 ml × 3). The combined ether solution was washed with water, dried, and concentrated to give a residue (2.03 g), which was rechromatographed on silica gel (100 g) and the fractions were further purified repeatedly by preparative TLC with AcOEt–hexane (1 : 1) as the eluent, giving (+)-pinoresinol (**1a**) (600 mg), oil, $[\alpha]_D^{22}$ +63° (c=1.2, $CHCl_3$), (+)-medioresinol (**2a**) (202 mg), colorless prisms (from MeOH), mp 182—185 °C, $[\alpha]_D^{22}$ +54° (c=1.0, $CHCl_3$), and (+)-syringaresinol (**3a**) (14 mg), colorless prisms (from MeOH), mp 187—190 °C, $[\alpha]_D^{22}$ +23° (c=0.7, $CHCl_3$).[11]

Fraction 51 (913 mg) was also separated into a neutral portion (220 mg) and an acidic one (560 mg) in the same manner as above, and the latter portion[12] was acetylated with Ac_2O and pyridine in the usual way to give a complex acetate mixture (590 mg), which was separated roughly into three fractions by preparative TLC with AcOEt–hexane (1 : 1) as the eluent. The least polar fraction (25 mg) was a mixture of lignans, whose separation is now under investigation. The next fraction (32 mg) was further purified by repeated preparative TLC (developed with acetone–$CHCl_3$, 5 : 95) to give hedyotol-A triacetate (**5b**) (14 mg) from the more mobile fraction and hedyotol-B triacetate (**6b**) (2 mg) from the less mobile fraction. The most polar fraction (56 mg) was also purified repeatedly by preparative TLC (developed with acetone–$CHCl_3$, 5 : 95) to afford hydyotol-C tetraacetate (**7b**) (25 mg) from the upper band and hedyotol-D tetraacetate (**8b**) (10 mg) from the lower band.

Hedyotol-A Triacetate (**5b**): Amorphous powder, $[\alpha]_D^{21}$ +29° (c=1.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740, 1600, 1510, 1240. UV λ_{max}^{EtOH} nm (log ε): 276 (3.79), 281 (3.81). MS m/z: 662 (M^+), 620 ($M^+ - 42$), 560 ($M^+ - 42 - 60$), 151 (a), 137 (c). High-resolution MS: Found 662.2389, Calcd for $C_{36}H_{38}O_{12}$ (M^+) 662.2364; Found 620.2213, Calcd for $C_{34}H_{36}O_{11}$ 620.2257; Found 560.2031, Calcd for $C_{32}H_{32}O_9$ 560.2045; Found 151.0363, Calcd for $C_8H_7O_3$ (a) 151.0394; Found 137.0625, Calcd for $C_8H_9O_2$ (c) 137.0603.

Hedyotol-B Triacetate (**6b**): Amorphous powder. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740. MS m/z: 692 (M^+), 632, 590, 181 (b), 167 (d). High-resolution MS: Found 692.2504, Calcd for $C_{37}H_{40}O_{13}$ (M^+) 692.2469.

Hedyotol-C Tetraacetate (**7b**): Amorphous powder, $[\alpha]_D^{22}$ +13° (c=1.15, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740, 1600, 1510, 1240. UV λ_{max}^{EtOH} nm (log ε): 274 (3.76), 280 (3.74). MS m/z: 752 (M^+), 710, 650, 430 (f), 388, 323 (e), 281, 263, 221, 181, 179, 167, 151, 137, 131. High-resolution MS: Found 430.1613, Calcd for $C_{23}H_{26}O_8$ (f) 430.1627; Found 323.1132, Calcd for $C_{16}H_{19}O_7$ (e) 323.1131. *Anal.* Calcd for $C_{39}H_{44}O_{15}$: C, 62.23; H, 5.89. Found: C, 61.80; H, 5.83.

Hedyotol-D Tetraacetate (**8b**): Amorphous powder, $[\alpha]_D^{22}$ +20° (c=0.70, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740, 1600, 1510, 1240. UV λ_{max}^{EtOH} nm (log ε): 274 (3.75), 279 (3.73). MS m/z: 752 (M^+), 430 (f), 388, 323 (e), 221, 181, 179, 167, 151, 137, 131. *Anal.* Calcd for $C_{39}H_{44}O_{15}$: C, 62.23; H, 5.89. Found: C, 61.91; H, 5.94.

From fractions 52—53, a syrupy residue (2.09 g) was obtained, and was separated into a neutral portion (535 mg) and an acidic one (1.10 g) in the same manner as above. The latter portion was acetylated with Ac_2O and pyridine in the usual way to give an acetate mixture (1.21 g). This mixture was subjected to centrifugal chromatography on a rotor coated with silica gel (Kieselgel 60 PF_{254}, thickness 4 mm) using a Harrison model 7924 Chromatotron, developed with AcOEt–hexane mixture (3 : 7, 200 ml; 1 : 1, 300 ml; 7 : 3, 200 ml). The AcOEt–hexane (1 : 1) eluate gave a complex mixture of lignans (270 mg), which was further purified by preparative TLC with acetone–$CHCl_3$ (5 : 95) as the eluent to give (−)-dehydrodiconiferyl alcohol triacetate (**4b**) (7 mg, impure).[13] $[\alpha]_D^{22}$ −3.8° (c=0.5, $CHCl_3$). ^{1}H-NMR δ: 2.05, 2.10, and 2.30 (each 3H, s, OAc), 3.81 and 3.92 (each 3H, s, OMe), 3.72—3.82 (1H, m, 8-H), 4.30 (1H, dd, J=12, 8 Hz, 9-H), 4.46 (1H, dd, J=12, 5.5 Hz, 9-H), 4.72 (2H, dd, J=6.5, 1 Hz, 9′-H_2), 5.55 (1H, d, J=7 Hz, 7-H), 6.16 (1H, dt, J=16, 6.5 Hz, 8′-H), 6.61 (1H, br d, J=16 Hz, 7′-H), 6.64—7.04 (5H, aromatic protons). MS m/z: 484 (M^+), 424, 382, 137.

The AcOEt–hexane (7 : 3) eluate gave a mixture (200 mg) containing dilignans, whose purification will be reported in a forthcoming paper.

Alkaline Hydrolysis of Hedyotol-C Tetraacetate (7b)——A little 1 N NaOH (2 drops) was added to a solution of **7b** (14 mg) in dioxane (2 ml) and the mixture was allowed to stand overnight at room temperature. After acidification with dil. HCl, the reaction mixture was diluted with water and extracted with AcOEt (100 ml × 3). The combined AcOEt extract was washed with sat. NaCl aq., dried, and concentrated *in vacuo*. The residue was subjected to preparative TLC with MeOH–$CHCl_3$ (5 : 95) as the eluent, and the more polar band gave hedyotol-C (**7a**) (4 mg), amorphous powder. ^{1}H-NMR δ: 3.14 (2H, m, 8- and 8′-H), 3.91 (9H, s, OMe × 3), 3.93 (3H, s, OMe), 4.07—4.18 (1H, m, 8″-H), 4.77 (1H, d, J=5 Hz, 7′-H), 4.80 (1H, d, J=5 Hz, 7-H), 5.02 (1H, m, $W_{1/2}$=7 Hz, 7″-H), 5.60 and 5.64 (each 1H, s, phenolic hydroxyl), 6.64 (2H, s, 2′- and 6′-H), 6.72—6.98 (6H, aromatic protons). MS m/z: 566 ($M^+ - H_2O$), 536 ($M^+ - 48$), 388 (g), 181, 180, 167, 151, 137. High-resolution MS: Found 566.2142, Calcd for $C_{31}H_{34}O_{10}$ ($M^+ - 18$) 566.2151; Found 388.1504, Calcd for $C_{21}H_{24}O_7$ (g) 388.1521.

On the other hand, the less polar band gave a mixture of two products, which was then acetylated in the usual way. The acetate mixture (7 mg) thereby obtained was separated by preparative TLC with acetone–$CHCl_3$ (5 : 95) as the eluent. The lower zone gave (+)-medioresinol diacetate (**2b**)[14] (1 mg) and the upper zone gave the diacetate (**11**) (3 mg), amorphous powder. ^{1}H-NMR δ: 2.28 and 2.32 (each 3H, s, OAc), 3.04 (2H, m, 8- and 8′-H), 3.64 (6H, s, OMe × 2), 3.80 and 3.86 (each 3H, s, OMe), 4.64 (1H, d, J=9.5 Hz, 7″-H), 4.68 (1H, d, J=5 Hz, 7′-H), 4.80 (1H, d, J=5 Hz, 7-H), 4.92 and 5.14 (each 1H, d, J=6 Hz, O–$\underline{CH_2}$–O), 6.42 (2H, s, 2′- and 6′-H), 6.87—7.11 (6H, aromatic protons). MS m/z: 680 (M^+), 638, 430 (f), 388, 250 (h), 208, 181, 167, 151, 137. High-resolution MS: Found 680.2504, Calcd for $C_{36}H_{40}O_{13}$ (M^+) 680.2469; Found 430.1602, Calcd for $C_{23}H_{26}O_8$ (f) 430.1627; Found 250.0808, Calcd for $C_{13}H_{14}O_5$ (h) 250.0841.

Preparation of the Acetonide (12) of Hedyotol-C (7a)——Compound **7a** (4 mg) and TsOH (1 mg) were dissolved in anhydrous acetone (1 ml) and the solution was left to stand at room temperature overnight. The reaction mixture was diluted with water and extracted with AcOEt (4 ml × 3). The combined AcOEt extract was dried and concentrated *in vacuo*. The residue was purified by preparative TLC (developed with acetone–$CHCl_3$, 5 : 95) to give an amorphous acetonide (**12**) (0.8 mg) and medioresinol (**2a**) (0.5 mg), together with the unchanged starting material (**7a**)

(2 mg). Acetonide (**12**): ^{1}H-NMR δ: 1.47 and 1.65 (each 3H, s, CH_3), 3.04 (2H, m, 8- and 8′-H), 3.66 (6H, s, OMe × 2), 3.85 (3H, s, OMe), 3.93 (3H, s, OMe), 4.65 (1H, d, J=5 Hz, 7′-H), 4.74 (1H, d, J=5 Hz, 7-H), 4.88 (1H, d, J=10 Hz, 7″-H), 5.54 and 5.61 (each 1H, br s, phenolic hydroxyl), 6.40 (2H, s, 2′- and 6′-H), 6.75—7.03 (6H, aromatic protons). MS m/z: 624 (M^+), 388 (g), 236 (i), 181, 167, 151, 137. High-resolution MS: Found 624.2559, Calcd for $C_{34}H_{40}O_{11}$ (M^+) 624.2570; Found 388.1529, Calcd for $C_{21}H_{24}O_7$ (g) 388.1522; Found 236.1016, Calcd for $C_{13}H_{16}O_4$ (i) 236.1047.

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References and Notes

1) Part II: T. Kikuchi, S. Kadota, S. Matsuda, K. Tanaka, and T. Namba, *Chem. Pharm. Bull.*, **33**, 557 (1985).
2) T. Kikuchi, S. Matsuda, S. Kadota, Y. Sakai, T. Namba, K. Watanabe, and R. B. Dissanayake, *Chem. Pharm. Bull.*, **32**, 3906 (1984).
3) A. Pelter, *J. Chem. Soc. (C)*, **1967**, 1376.
4) H. Kakisawa, T. Kusumi, H. Y. Hsū, and Y. P. Chen, *Bull. Chem. Soc. Jpn.*, **43**, 3631 (1970); C. Nishino and T. Mitsui, *Tetrahedron Lett.*, **1973**, 335.
5) In the case of *trans* orientation, the benzylic and bridgehead carbons resonate upfield at about 82 and 50 ppm, respectively. A. Pelter, R. S. Ward, E. Venkata Rao, and K. V. Sastry, *Tetrahedron*, **32**, 2783 (1976); A Pelter, R. S. Ward, and C. Nishino, *Tetrahedron Lett.*, **1977**, 4137; A. Pelter, R. S. Ward, and D. J. Watson, *ibid.*, **1978**, 1509.
6) It is known that the methyl signals in *cis*-2-aryl-3-methyl-2,3-dihydrobenzofuran are shifted towards high field by 0.4—0.6 ppm compared with those of *trans* isomers, but the C-9″ methylene signals of **5b** are parallel to the corresponding signals of dehydrodiconiferyl alcohol triacetate (**4b**), which has the *trans* configuration. M. Gregson, W. D. Ollis, B. T. Redman, and I. O. Sutherland, *Chem. Commun.*, **1968**, 1394; A. Ichihara, Y. Nakamura, H. Kawagishi, and S. Sakamura, *Tetrahedron Lett.*, **1979**, 3735.
7) The optical rotation of **6b** could not be measured because the amount available was too small.
8) Dehydrodiconiferyl alcohol triacetate (**4b**) did not show a significant peak at m/z 151. Therefore, it seems that the fragment ion at m/z 181 in the MS of **6b** mainly arises from the diaryl dioxabicyclooctane moiety.
9) F. Nakatsubo, K. Sato, and T. Higuchi, *Mokuzai Gakkaishi*, **22**, 29 (1976); F. Nakatsubo and T. Higuchi, *Holzforschung*, **29**, 193 (1975).
10) *a*) A. Ichihara, K. Oda, Y. Numata, and S. Sakamura, *Tetrahedron Lett.*, **1976**, 3961; A. Ichihara, S. Kanai, Y. Nakamura, and S. Sakamura, *ibid.*, **1978**, 3035; A. Ichihara, Y. Numata, S. Kanai, and S. Sakamura, *Agric. Biol. Chem.*, **41**, 1813 (1977); S. Yamanouchi, M. Takido, U. Sankawa, and S. Shibata, *Yakugaku Zasshi*, **96**, 1492 (1976); *b*) M. Niwa, Y. Terada, M. Nonoyama, and S. Yamamura, *Tetrahedron Lett.*, **1979**, 813; S. Yamamura, M. Niwa, Y. Terada, and M. Nonoyama, *Bull. Chem. Soc. Jpn.*, **55**, 3573 (1982).
11) S. Omori and A. Sakakibara, *Mokuzai Gakkaishi*, **18**, 577 (1972); H. Fujimoto and T. Higuchi, *ibid.*, **23**, 405 (1977).
12) The ^{1}H-NMR spectrum of this crude fraction did not show acetyl methyl signals, indicating that the new compounds, hedyotol-A, -B, -C, and -D, have no acetyl group.
13) The impurity contained in the sample of **4b** is believed to be (−)-dihydrodehydrodiconiferyl alcohol. The latter compound had been isolated from another lot of the plant material as described in the previous paper.[2] For the spectral properties, see T. Takehara and T. Sasaya, *Mokuzai Gakkaishi*, **25**, 660 (1979).
14) Further purification of this product could not be achieved because the quantity available was too small. Compound **2b** showed $[\alpha]_D$ +20° (c=0.1, $CHCl_3$).