

Notes

Bioactive Iridoids and a New Lignan from *Allamanda cathartica* and *Himatanthus fallax* from the Suriname Rainforest¹

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Received May 16, 1997[®]

Bioassay-guided fractionation of the EtOAc extract of both *Allamanda cathartica* and *Himatanthus fallax* (Apocynaceae) using the Sc-7 yeast strain resulted in the isolation of the weakly cytotoxic isoplumericin and plumericin. In addition, the new lignan 7(*R*)-methoxy-8-*epi*-matairesinol and three known compounds, plumieride, matairesinol, and pinoresinol, were isolated from *H. fallax*.

As previously described,² we have embarked on a program to discover and develop potential therapeutic agents from the Surinamese rainforest and, in the process, to provide economic arguments for the preservation of this valuable resource. Plant collections under this program are being made independently by Conservation International, Suriname, and by the Missouri Botanical Garden, with the former collecting on an ethnobotanical basis and the latter on a phytochemical basis. Plant extracts are prepared at *Bedrijf Geneesmiddelen Voorziening Suriname* (BGVS). Work at Virginia Polytechnic Institute and State University (VPI&SU) is centered around the discovery of potential anticancer agents, and the Sc-7 strain of *Saccharomyces cerevisiae* (yeast) is used as a primary assay tool in this work. This strain shows growth inhibition by cytotoxic agents,³ and activities are expressed as IC₁₂ values, which are the dosages needed to produce an inhibition zone of 12 mm under defined conditions.²

As a part of our collaborative work, the plants *Allamanda cathartica* L. and *Himatanthus fallax* (Muell. Arg.) Plumel (Apocynaceae) were collected from the central region of Suriname as part of the phytochemical collection strategy by Missouri Botanical Garden. An EtOAc extract of *A. cathartica* had an IC₁₂ value of 690 µg/mL, and a similar extract of *H. fallax* had an IC₁₂ value of about 3320 µg/mL against the Sc-7 yeast strain, and fractionation studies were initiated.

Previous work on *A. cathartica* has included the isolation of the iridoid lactones plumericin and isoplumericin⁴ and of plumieride coumarate and plumieride coumarate glucoside.⁵ Plumericin and isoplumericin have also been isolated from *Allamanda doniana*,⁶ while the occurrence of iridoids in various *Allamanda* sp. has been surveyed.⁷ Studies on *Himatanthus* sp. have included the isolation of plumericin and isoplumericin, from *H. phagedaenica*,⁸ and *H. obovatus*.⁶

Table 1. ¹³C-NMR Data (δ values) for Compounds **1** and **2**^a

carbon	compound 1	compound 2
1	101.7	102.3
3	152.6	152.7
4	108.9	109.4
5	38.2	38.4
6	141.1	141.1
7	126.1	126.4
8	104.9	104.6
9	53.7	53.7
10	83.8	80.3
11	125.7	127.4
12	167.4 ^b	168.2 ^b
13	148.2	145.3
14	14.8	16.1
COOCH ₃	166.7 ^b	166.7 ^b
COOCH ₃	51.6	51.7

^a Obtained in CDCl₃. Assignments made by a combination of DEPT and HETCOR data and comparison with the spectrum of plumenoside.¹⁰ ^b The signals in each column may be interchanged.

Fractionation of *A. cathartica* involved liquid–liquid partition, in which the bioactivity went successively into the aqueous MeOH phase of a hexane–80% aqueous MeOH partition and into the CHCl₃ phase of a CHCl₃–60% aqueous MeOH partition. Purification on a Sephadex LH-20 column yielded the active material in a CH₂Cl₂–hexane (4:1) fraction, and final purification by vacuum liquid chromatography (VLC) over Si gel with Me₂CO–hexane as eluent, by column chromatography over Si gel, and by preparative TLC gave the two active products **1** (7 mg) and **2** (60 mg), with IC₁₂ values of 42 and 74 µg/mL, respectively.

The structures of the two compounds were elucidated as isoplumericin (**1**) and plumericin (**2**) on the basis of their spectroscopic data, and specifically by comparison of their ¹H-NMR data with those in the literature.⁹ Complete assignments for the ¹³C-NMR spectra of both compounds (Table 1) were made for the first time, utilizing DEPT and HETCOR experiments as well as comparison with the ¹³C-NMR data of plumenoside.¹⁰ As noted above, both compounds have previously been isolated from *A. cathartica*.⁴

Fractionation of *H. fallax* followed lines similar to that

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[®] Abstract published in *Advance ACS Abstracts*, November 15, 1997.

Table 2. ^1H - and ^{13}C -NMR Data (δ values) for Compound **6**^a

position	δ_{H}^b	δ_{C}^c
1		133.4 (0) ^d
2	6.85 (m)	108.3 (1)
3		145.2 (0) ^e
4		146.5 (0) ^f
5	6.85 (m)	114.4 (1)
6	6.85 (m)	118.7 (1)
7	5.23 (d, $J = 7.2$)	82.3 (1)
8	3.08 (dd, $J = 7.2, 8.7$)	55.9 (1)
9		172.5 (0)
1'		131.3 (0) ^d
2'	6.66 (m)	111.2 (1)
3'		144.1 (0) ^e
4'		146.4 (0) ^f
5'	6.85 (m)	114.3 (1)
6'	6.67 (m)	121.2 (1)
7'	2.55 (dd, $J = 10.6, 13.7, \beta$)	34.5 (2)
	2.76 (dd, $J = 5.3, 13.7, \alpha$)	
8'	2.91 (m)	44.2 (1)
9'	3.79 (dd, $J = 6.7, 8.7, \beta$)	72.9 (2)
	4.08 (dd, $J = 6.4, 8.7, \alpha$)	
7 OCH ₃	3.67	51.8 (3)
3,3' OCH ₃	3.87, 3.88	55.8 (3), 55.9 (3)
4,4' OH	5.52, 5.60	

^a Obtained in CDCl_3 . ^b J in Hz. ^c Carbon type as determined by DEPT spectra: 0 = quaternary, 1 = methine, 2 = methylene, 3 = methyl. ^{d,e,f} Signals for carbons with similar shifts may be interchanged.

of *A. cathartica*, and yielded six products. Two were identified again as the compounds **1** and **2**, and three inactive known compounds were identified as plumeride (**3**), pinoresinol (**4**), and matairesinol (**5**) based on comparison of their mps, $[\alpha]_{\text{D}}$, UV, and ^1H - and ^{13}C -NMR spectra with those in the literature.^{10–13} The last compound was identified as the new lignan **6**, 7(R)-methoxy-8-*epi*-matairesinol, on the basis of the evidence outlined below.

The HREIMS of **6** showed an M^+ at m/z 388.152, consistent with the molecular formula $\text{C}_{21}\text{H}_{24}\text{O}_7$. Its ^{13}C -NMR spectrum (Table 2) indicated the presence of three OMe groups, a lactone carbonyl (δ_{C} 172.5 ppm), and 12 aromatic carbon resonances, six of which were fully substituted. The remaining carbons (1 CH_2 , 1 CH_2O , 2 CH , and 1 OCH) supported the assignment of **6** as a diaryl butyrolactone-type lignan.¹³ The ^1H - and

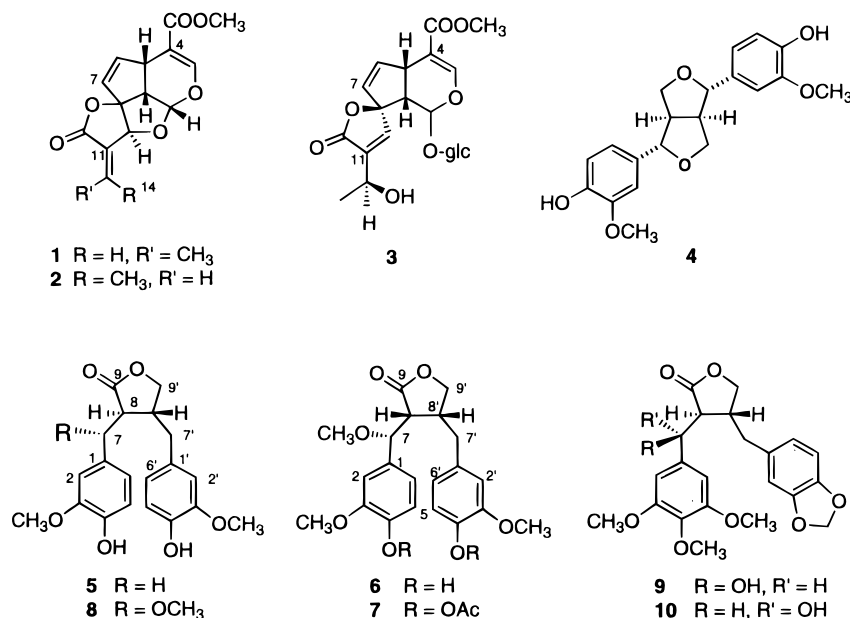
^{13}C -NMR assignments (Table 2) were made on the basis of ^1H – ^1H decoupling in different solvents, TOCSY, DEPT, and HETCOR experiments. The oxygenated CH group (δ_{H} 5.23 ppm, δ_{C} 82.3 ppm) was assigned to position 7 based on the coupling of its proton with H-8 (3.08 ppm, dd, $J = 7.2, 8.7$ Hz) rather than with H-8' (2.91 ppm, m). The C-7 substituent was assigned as a methoxyl group (δ_{H} 3.67, δ_{C} 51.8) rather than a hydroxyl group, based on the fact that the chemical shift of H-7 was essentially unchanged after acetylation of **6** to form its diacetate **7**. This assignment was further supported by correlations of the C-7 OMe group with the two H-7' protons and with H-8' in a NOESY experiment. The chemical shifts of the aryl carbons supported a 4,4'-dihydroxy-3,3'-dimethoxy substitution.¹⁴ The NOE correlations of the two resolved aryl protons at δ 6.66 and 6.67 with H-7' β and H-7' α assign them to the 2' and 6' positions, respectively.

The CD spectrum of **6** was similar to those of the rare cis-fused-type lignans.¹⁵ To determine the stereochemistry at position 7 compound **6** was allowed to epimerize in 3% methanolic KOH solution.¹⁶ The resulting epimer **8** had a CD spectrum similar to those of the more common trans-fused lignans, particularly those with the 7-position oxygenated as in podorhizol (**9**).^{16,17} The C-7 methoxyl group was assigned the α -configuration based on comparison of the $J_{7,8}$ value of **8** (7.9 Hz) with those of epipodorhizol (**10**) with a 7 α -OH group (7.7–7.9 Hz) and its 7 β -OH isomer podorhizol (**9**) (1.6–2.9 Hz) (Chart 1).^{18–20}

Isoplumericin and plumericin are known to have antifungal, algicidal, and barnicidal activities,^{5,6,21} and, in addition, plumericin possesses antimicrobial activity.²² In a cytotoxicity assay with the Madison lung carcinoma (M109) cell line, compounds **1** and **2** showed IC_{50} values of 25 and 100 $\mu\text{g/mL}$, respectively, suggesting that these compounds are not potent enough to be considered as development candidates.

The group of rare spiro lactone-containing iridoids exemplified by plumericin and isoplumericin seems to be restricted in its occurrence to the family Apocynaceae, and mainly to the two genera *Allamanda* and

Chart 1



Plumeria,⁷ although plumericin has also been reported from *Nerium indicum*.²³ Although lignans are known to occur in the Apocynaceae,²⁴ this is the first isolation of lignan derivatives from a *Himatanthus* species.

Experimental Section

General Experimental Procedures. The CD spectrum was recorded on a JASCO J720 spectropolarimeter. NMR spectra were recorded in CDCl₃ on a Varian Unity 400 NMR instrument at 399.951 MHz for ¹H and 100.578 MHz for ¹³C, using standard Varian pulse sequence programs. LRMS were taken on a VG 7070 E-HF at VPI&SU, and exact mass measurements were obtained at the Nebraska Center for Mass Spectrometry. Other conditions were as previously described.²⁵

Yeast Bioassay. The bioassay was carried out as previously described.²

Plant Collection and Extraction of *A. cathartica* and *H. fallax*. Leaves of *A. cathartica* and stems of *H. fallax* were collected in July 1994, near Asindopo Village, Suriname, and were assigned collection numbers EV1887 and EV1874, respectively. Voucher specimens are preserved at the National Herbarium of Suriname and at the herbarium of the Missouri Botanical Garden. Extraction of ca. 500 g of dried EV1887 at BGVS yielded 27.4 g of EtOAc extract as BGVS E-940241, and extraction of ca. 500 g of dried EV1874 at BGVS yielded 16.5 g of EtOAc extract as BGVS E-940200.

Isolation of Plumericin (1) and Isoplumericin (2) from *A. cathartica*. The bioactive EtOAc extract (IC₁₂ 690 µg/mL, 27.4 g) was dissolved in 250 mL of 80% aqueous MeOH and defatted with hexane (150 mL × 4). The aqueous MeOH fraction was diluted with H₂O until a 60% aqueous MeOH mixture was produced, and this was then partitioned with CHCl₃ (150 mL × 4) to afford 6.0 g of the bioactive CHCl₃-soluble extract. This fraction was purified by chromatography on Sephadex LH-20 (5 × 50 cm) using the solvents hexane–CH₂Cl₂ (1:4, 1 L), CH₂Cl₂–Me₂CO (3:2, 1 L), CH₂Cl₂–Me₂CO (1:4, 1 L), and MeOH (2 L). The active fraction (0.5 g) eluted with hexane–CH₂Cl₂ (1:4) was separated on a Si gel column (25 g) eluted with 1% Me₂CO in CHCl₃, then with 2% Me₂CO in CHCl₃, and finally with MeOH. Fractions 6 and 7, eluted with 1% Me₂CO in CHCl₃ (43 mg), were separated by preparative TLC (Si gel, 10% Me₂CO in CHCl₃) to obtain isoplumericin (**1**, 7 mg). Fractions 8–12 (2% Me₂CO in CHCl₃, 75 mg) were crystallized from CH₂Cl₂–MeOH to afford plumericin (**2**, 60 mg).

Isolation of Plumericin (1), Isoplumericin (2), Plumieride (3), Pinoresinol (4), Matairesinol (5), and 7(R)-Methoxy-8-*epi*-matairesinol (6) from *H. fallax*. The bioactive EtOAc extract was treated as above, and the active fraction, eluted with hexane–CH₂Cl₂ (1:4; 1.2 g) from the Sephadex LH-20 chromatography (5 × 50 cm column), was crystallized from CH₂Cl₂–MeOH to afford 0.4 g of inactive crystals. The bioactive supernatant (0.8 g) (IC₁₂ 890 µg/mL) was fractionated by VLC (3.5 cm × 4.5 cm, 30 g Si gel) eluted with hexane–Me₂CO mixtures. The bioactive fraction eluted with 20% Me₂CO in hexane (161 mg) was further purified using a Si gel (15 g) flash column eluted with 5% Me₂CO in CHCl₃. The active fractions (32 mg) were separated by preparative TLC (Si gel, 10% Me₂CO in

CHCl₃) to obtain isoplumericin (**1**, 1.2 mg) and plumericin (**2**, 2.6 mg).

Fractions eluted with 50% Me₂CO in hexane (110 mg) were subjected to preparative TLC (Si gel, 20% Me₂CO in CHCl₃) to afford **6** (12 mg, *R*_f 0.65). The more polar band (15 mg, *R*_f 0.5) provided pinoresinol (**4**, 6 mg) and matairesinol (**5**, 5 mg) after HPLC separation (C₁₈ Si gel, MeOH–H₂O, 1: 1).

Fractions eluted from Sephadex LH-20 with CH₂Cl₂–Me₂CO, 3:2 (0.5 g), were chromatographed by VLC (Si gel, hexane–Me₂CO–MeOH mixtures), and fractions eluted with Me₂CO (250 mg) were further purified by preparative TLC (Si gel, CHCl₃–MeOH 85:15) to afford plumieride (**3**, 150 mg).

Isoplumericin (1): colorless needles, mp 199–200 °C (CH₂Cl₂–MeOH) (lit.⁹ mp 200.5–201.5 °C); [α]_D²⁶ +189° (c 0.61, CHCl₃) (lit.⁹ [α]_D²⁹ +216.4°); ¹³C-NMR data, see Table 1.

Plumericin (2): colorless needles, mp 205–206 °C (CH₂Cl₂–MeOH) (lit.⁹ mp 211.5–212.5 °C); [α]_D²⁶ +173° (c 1.10, CHCl₃) (lit.⁹ [α]_D²⁶ +197.3°); ¹³C-NMR data, see Table 1.

Plumieride (3): colorless crystals; mp 225–226 °C (MeOH) (lit.²⁶ mp 224–225 °C); [α]_D²⁶ –68° (c 0.90, MeOH) (lit.²⁶ [α]_D²⁶ –114°(H₂O)).

Pinoresinol (4): yellowish gum; [α]_D²⁶ +70° (c 0.60, MeOH) (lit.²⁷ [α]_D²⁶ +64°).

Matairesinol (5): yellowish gum; [α]_D²⁶ –45° (c 1.0, MeOH) (lit.¹³ [α]_D²⁶ –50°).

(7R)-Methoxy-8-*epi*-matairesinol (6): white crystals, mp 160–162 °C (C₆H₆); [α]_D²⁶ +29.57° (c 0.71, MeOH); UV (MeOH) λ_{max} (ε) 214 (11 600), 225 (4900), 280 (4400) nm; (NaOMe) λ_{max} (ε) 214 (1200), 245 (6000), 294 (4200) nm; CD (MeOH, c 0.1) λ_{max} (Δε) 218 (–2.6), 240 (+2.4), 253 (–1.2), 279 (+3.8) nm; ¹H and ¹³C NMR in CDCl₃, see Table 2; ¹H NMR (C₆D₆) δ 6.39 (1H, d, *J* = 1.9 Hz, H-2') 6.48 (1H, dd *J* = 1.9, 8 Hz, H-6'), 6.93 (1H, d, *J* = 8 Hz, H-5'), 6.94 (1H, m, H-2), 6.97 (1H, dd *J* = 1.9, 8 Hz, H-6), 7.01 (1H, d *J* = 8 Hz, H-5); EIMS *m/z* 388 (M⁺, 58), 249 (12), 191(20), 180 (74), 151 (C₈H₇O₃, 57), 137 (C₈H₉O₂, 75), 122 (C₇H₆O₂, 9), 99 (C₅H₇O₂, 100), 77 (6); HREIMS *m/z* 388.152 (M⁺), calcd for C₂₁H₂₄O₇, 388.152.

7(R)-Methoxy-8-*epi*-matairesinol Diacetate (7). Compound **6** (2.0 mg) in pyridine (2.0 mL) was treated with Ac₂O (0.2 mL) for 24 h at room temperature. Evaporation of the resulting solution under a stream of argon yielded chromatographically homogeneous **7** (2.0 mg): ¹H NMR (CDCl₃) δ 1.86 (3H, s, COCH₃), 2.55 (1H, dd, *J* = 10.4, 13.5 Hz, H-7'β), 2.65 (1H, m, H-8'), 2.76 (1H, dd, *J* = 5.3, 13.5 Hz, H-7'α), 3.05 (1H, dd, *J* = 7.2, 8.7 Hz, H-8), 3.28 (3H, s, OCH₃-7), 3.30 (6H, s, 2 × OCH₃), 3.84 (1H, dd, *J* = 6.4, 8.8 Hz, H-9'β), 3.94 (1H, dd, *J* = 6.7, 8.8 Hz, H-9'α), 5.59 (1H, d, *J* = 7.2 Hz, H-7β), 6.13 (1H, d, *J* = 1.9 Hz, H-2'), 6.49 (2H, m, H-6, H-6'), 6.90 (1H, d, *J* = 8 Hz, H-5'), 7.00 (1H, br s, H-2), 7.1 (1H, d, H-5).

7(R)-Methoxymatairesinol (8). Compound **6** (4 mg) was dissolved in 3% methanolic KOH (3 mL), and the solution was allowed to stand at room temperature for 3 days. The solution was then neutralized with HOAc and extracted with CHCl₃. The CHCl₃ layer was then washed with 5% aqueous Na₂CO₃ followed by H₂O, dried, and evaporated to give a product that was homogeneous on TLC but was shown by ¹H-NMR

spectroscopy to be a mixture of two components. Separation of the mixture by HPLC (C₁₈ Si gel, MeOH–H₂O, 45:55) afforded 1.0 mg of the epimer **8** and 1.3 mg of unepimerized **6**. Compound **8** showed the following spectral characteristics: CD (MeOH, *c* 0.09) $\lambda_{\max}$ ($\Delta\epsilon$) 238 (+0.74), 247 (–7.9), 279 (+0.83); ¹H NMR (CDCl₃) δ 2.63 (1H, dd, *J* = 8.2, 13.7 Hz, H-7' β), 2.78 (1H, dd, *J* = 5.8, 13.7 Hz, H-7' α), 3.08 (2H, m, H-8, H-8'), 3.20 (3H, s, OCH₃-7), 3.62 (1H, t, *J* = 8.4 Hz, H-9' β), 3.86, 3.87 (3H each, s, 2 $\times$ OCH₃), 4.32 (1H, dd, *J* = 6.7, 8.7 Hz, H-9' α), 5.19 (1H, d, *J* = 7.9 Hz, H-7 β), 5.49, 5.54 (1H each, br s, 2 OH), 6.67 (2H, m, H-2', H-6'), 6.72 (1H, dd, *J* = 1.9, 8.2 Hz, H-5'), 6.82 (3H, m, H-2, H-5, H-6); ¹H NMR (C₆D₆) δ 2.32 (1H, dd, *J* = 8.4, 13.7 Hz, H-7' β), 2.52 (1H, dd, *J* = 6.7, 13.7 Hz, H-7' α), 3.10 (3H, s, OCH₃-7), 2.94 (1H, dd, *J* = 6.9, 8.6 Hz, H-8), 3.14, 3.20 (3H each, s, 2 $\times$ OCH₃), 3.45 (1H, dd, *J* = 10.8, 18.0 Hz, H-9' β), 4.32 (1H, t, *J* = 8.4 Hz, H-9' α), 5.06 (1H, d, *J* = 8.4 Hz, H-7 β), 5.35, 5.43 (1H each, br s, 2 OH), 6.43 (1H, d, *J* = 1.8 Hz, H-2'), 6.49 (1H, dd, *J* = 1.9, 7.9 Hz, H-6'), 6.78 (1H, dd, *J* = 1.8, 8.2 Hz, H-6), 6.96 (2H, m, H-2, H-5'), 7.10 (1H, d, *J* = 8 Hz, H-5).

Cytotoxicity Assay. The M109 cytotoxicity assays were performed as previously described.²

Acknowledgment. This work was supported by an International Collaborative Biodiversity Grant, number U01 TW/CA-00313 from the Fogarty Center, NIH. The authors thank Dr. Mamber of Bristol-Myers Squibb Pharmaceutical Research Institute for the Sc-7 yeast strain, Dr. I. Bursuker of Bristol-Myers Squibb Pharmaceutical Research Institute for the cytotoxicity assay, and Ms. Nina Baj of Virginia Polytechnic Institute and State University for technical assistance. The authors also thank Dr. M. A. Castro, Departamento de Quimica Organica, Facultad de Farmacia, Universidad de Salamanca, for a gift of a sample of podorhizol.²⁸ Mass spectra and CD spectra were obtained by Mr. Kim Harich of Virginia Polytechnic Institute and State University and the Nebraska Center for Mass Spectrometry.

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NP970253E