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Aryltetralone lignans and 7,8-seco-lignans from *Holostylis reniformis*

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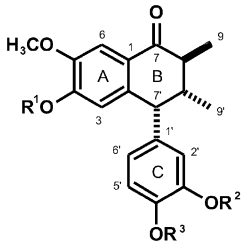
Abstract

Aryltetralone lignans and two 7,8-seco-lignans were isolated from the acetone and hexane extracts of the roots of *Holostylis reniformis*, together with (−)-galbacin. Their structures were determined by spectroscopic methods.

Keywords: *Holostylis reniformis*; Aristolochiaceae; Aryltetralone lignans; Seco-lignans; Lignans; Neolignans

1. Introduction

Holostylis reniformis Duch. (Aristolochiaceae), used in Brazilian traditional medicine to treat malaria (Hoehne, 1942), has been proposed to be included in the *Aristolochia* due to morphological similarities (González, 1997). Chemotaxonomically, nearly 60 lignoids of different structural types have been isolated from the Aristolochiaceae family (Lopes et al., 2001), of which the furanoid, tetralinic, β-aryloxyarylpropanoic and benzofuranoid types were isolated mainly from *Aristolochia* species of the American continent. This paper describes the isolation and structural elucidation of eight aryltetralone lignans (**1**–**8**), of which six are new, and two unusual 7,8-seco-lignans (**9** and **10**), together with the lignan (−)-galbacin from the roots of *H. reniformis*. The presence of compounds **1**, **2** and (−)-galbacin in *Aristolochia* species has been reported previously (Urzúa and Shamma, 1988; Watanabe and Lopes, 1995).



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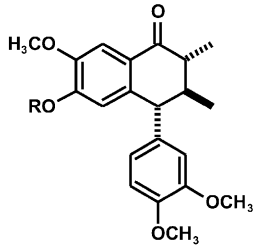
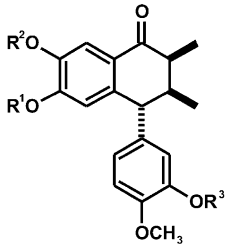
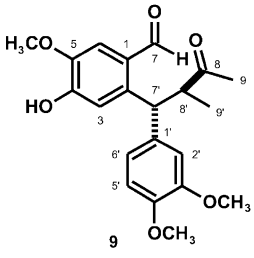
2	CH_3	CH_3	CH_3
5	H	CH_3	CH_3



	R
3	CH_3
6	H



	R^1	R^2	R^3
4	CH_3	CH_3	CH_3
7	H	CH_3	CH_3
8	CH_2		CH_3
13	CH_2		H



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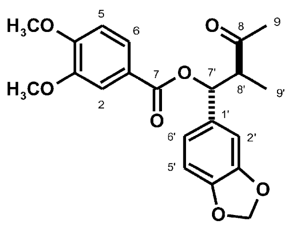

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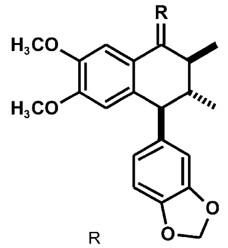
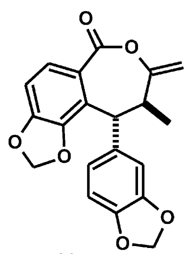


	R
11	O
12	H_2



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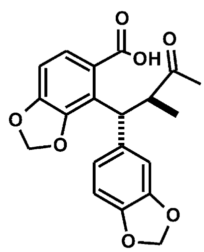

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2. Results and discussion

The hexane and acetone extracts of the roots of *H. reniformis* gave 11 lignans [**1**–**10** and (−)-galbacin] by column chromatography followed by TLC and/or semi-preparative HPLC. Lignans **1**, **2** and (−)-galbacin were identified by comparing their physical (mp, α_D) and spectroscopic (MS, IR, UV, ^{1}H and ^{13}C NMR) data to those reported in the literature for (−)-aristotetralone (Urzúa et al., 1987), (−)-aristoligone (Urzúa and Shamma, 1988), and (−)-galbacin (Agrawal and Thakur, 1985; Biftu and Stevenson, 1987), respectively.

The ESI-MS of compounds **3** and **4** displayed a *quasi*-molecular ion $[M+H]^+$ at m/z 371, and their ^{13}C NMR spectra showed a total of 22 signals, which were consistent with the molecular formula $C_{22}H_{26}O_5$. The IR spectra of these compounds showed an absorption band characteristic of an aromatic ketone at 1667 cm^{-1}. The ^{1}H, ^{13}C NMR, *g*HMQC, and *g*HMBC spectra of lignans **3** and **4** showed signals very similar to those observed for (−)-aristoligone (**2**). The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) suggested the presence of four aromatic methoxyl groups, 1,2,4,5-tetrasubstituted and 1,3,4-trisubstituted aromatic rings (A and C rings, respectively), two methyl groups, one carbonyl carbon, and three methine carbons. Analysis of ^{1}H–^{1}H COSY, *g*HMQC, and *g*HMBC data enabled the precise assignment of all hydrogens and carbons in the basic structure (Tables 1 and 2). The main differences among the spectra obtained for **2**–**4** were the observed chemical shifts for the hydrogens and carbons in the B ring and the multiplicities of these hydrogens.

^{1}H-^{1}H COSY and ^{1}H selective irradiation NMR experiments of lignan **3** showed coupling constants for *trans* di-axial H-8,8′ ($J=12.5$ Hz) and H-7′,8′ ($J=11.5$ Hz) that were characteristic of aryltetralone lignans (Lopes et al., 1982), whereas those of compounds **1** and **2** suggested only one J value characteristic of a di-axial hydrogen ($J_{H\text{-}8,8'} \cong 11.7$ Hz, $J_{H\text{-}7',8'} \cong 4.3$ Hz), and **4** did not show a J value with this characteristic magnitude ($J_{H\text{-}8,8'}=4.2$ Hz, $J_{H\text{-}7',8'}=5.4$ Hz). 1D- and 2D-NOESY experiments of these lignans showed spatial

Table 1
^{1}H NMR spectral data for compounds **3**–**5** ($CDCl_3$, 500 MHz, J in Hz)[a]

H	3		4		5	
	(δ)	*g*NOESY and nOeDS	(δ)	*g*NOESY and nOeDS	(δ)	*g*NOESY and nOeDS
3	6.13 *s*	OCH_3-4	6.36 *s*	OCH_3-4, H-7′	6.57 *s*	H-7′
6	7.48 *s*	OCH_3-5	7.49 *s*	OCH_3-5	7.53 *s*	OCH_3-5
8	2.33 *dq* (12.5, 6.5)	H-9	2.70 *dq* (4.2, 6.9)	H-9, H-8′	2.39 *dq* (11.5, 7.0)	H-9′
9	1.27 *d* (6.5)	H-9′, H-8, H-8′	1.06 *d* (6.9)	H-8	1.15 *d* (7.0)	H-9′
2′	6.53 *d* (2.0)	OCH_3-3′	6.54 *d* (1.8)	OCH_3-3′, H-7′	6.48 *d* (2.0)	OCH_3-3′, H-7′
5′	6.81 *d* (8.0)	OCH_3-4′, H-6′	6.71 *d* (8.4)	H-7′	6.68 *d* (8.0)	OCH_3-4′, H-6′
6′	6.70 *dd* (8.0, 2.0)		6.47 *dd* (8.4, 1.8)	OCH_3-4′	6.45 *dd* (8.0, 2.0)	H-5′
7′	3.65 *d* (11.5)	H-9′, H-8, H-6′	3.91 *d* (5.4)	H-9′, H-8′, H-3, H-2′	4.02 *d* (5.0)	H-3, H-2′
8′	2.03 *ddq* (12.5, 11.5, 6.0)	H-9′	2.35 *ddq* (5.4, 4.2, 6.9)	H-9′, H-8, H-7′, H-2′	2.27 *ddq* (11.5, 5.0, 7.0)	H-9′
9′	0.89 *d* (6.0)	H-9, H-8′	0.92 *d* (6.9)	H-9, H-8′, H-7′	0.90 *d* (7.0)	H-9, H-8′, H-7′
OCH_3-3′	3.76 *s*	H-2′	3.75 *s*	H-2′	3.72 *s*	H-2′
OCH_3-4′	3.86[b] *s*	H-5′	3.79 *s*	H-5′	3.77 *s*	H-5′
OCH_3-4	3.57 *s*	H-3	3.70 *s*	H-3		
OCH_3-5	3.87 [b] *s*	H-6	3.88 *s*	H-6	3.90 *s*	H-6
OH					5.94 *br s*	

[a] Multiplicities were determined with the assistance of ^{1}H–^{1}H COSY.
[b] Assignments may be interchangeable within the same column.

Table 2
^{13}C NMR spectral data for compounds **3-5** ($CDCl_3$, 126 MHz)[a]

C	**3**		**4**		**5**	
	^{13}C (δ)	*g*HMBC	^{13}C (δ)	*g*HMBC	^{13}C (δ)	*g*HMBC
1	125.7 *s*	H-3	125.6 *s*	H-6, H-3	125.2 *s*	H-7′, H-6, H-3
2	141.5 *s*	H-6	138.7 *s*	H-6, H-3	142.5 *s*	H-7′, H-6
3	111.2 *d*		111.7 *d*		114.4 *d*	H-7′
4	153.2 *s*	OCH_3-4	153.7 *s*	OCH_3-4, H-6, H-3	150.8 *s*	H-6, H-3
5	148.0 *s*	OCH_3-5, H-3	148.0 *s*	OCH_3-5, H-6, H-3	145.9 *s*	OCH_3-5, H-3
6	108.1 *d*		108.2 *d*		108.3 *d*	
7	198.8 *s*	H-9	200.0 *s*	H-9, H-8, H-8′, H-6	200.5 *s*	H-9, H-8, H-6
8	48.5 *d*	H-9, H-9′	42.7 *d*	H-9, H-9′, H-8, H-8′, H-7′	39.8 *d*	H-9, H-9′, H-8′, H-7′
9	12.6 *q*		11.9 *q*	H-8, H-8′	12.9 *q*	H-8′, H-8′
1′	136.1 *s*		136.2 *s*	H-7′, H-5′	132.1 *s*	H-7′, H-5′
2′	111.8 *d*		111.9 *d*	H-7′, H-6′	113.6 *d*	H-6′
3′	149.3 *s*	OCH_3-3′	149.1 *s*	OCH_3-3′, H-5′	148.6 *s*	OCH_3-3′
4′	147.9 *s*	OCH_3-4′, H-2′	147.9 *s*	OCH_3-4′, H-6′, H-2′	147.8 *s*	OCH_3-4′, H-6′, H-5′
5′	111.0 *d*		111.0 *d*		110.9 *d*	
6′	122.2 *d*		121.1 *d*	H-7′	122.2 *d*	H-2′
7′	53.3 *d*	H-9′	50.3 *d*	H-9′, H-8, H-8′, H-6′, H-3, H-2′	49.7 *d*	H-9′, H-8′, H-6′, H-3, H-2′
8′	43.8 *d*	H-9, H-9′	42.5 *d*	H-9, H-9′, H-8, H-7′	43.0 *d*	H-9, H-9′
9′	18.0 *q*		15.9 *q*	H-8, H-7′	18.0 *q*	H-8, H-8′, H-7′
OCH_3-3′	55.8 *q*		55.9 *q*		55.9 *q*	
OCH_3-4′	56.0 *q*		56.0 *q*		56.0 *q*	
OCH_3-4	55.9 *q*		55.8 *q*			
OCH_3-5	56.0 *q*		56.0 *q*		56.1 *q*	

[a] The ^{13}C NMR data were assigned with the assistance of DEPT, *g*HMQC and *g*HMBC experiments.

correlations between hydrogens at the B rings and the substituents of these rings, which enabled the establishment of the most stable conformations of these molecules and the relative configurations for **1**–**4** with greater certainty (Fig. 1). Therefore, two possible conformations were determined for each lignan: **Ia** and **Ib** for **1** and **2**, as previously reported (Urzúa and Shamma, 1988), **IIa** and **IIb** for **3**, and **IIIa** and **IIIb** for **4** (Fig. 1).

The ^{13}C NMR spectra of compounds **5**–**8** showed a total of 21 signals for each compound. Compounds **5**–**8** were also suggested to be aryltetralone lignans based on an analysis of their IR data (**5**–**7**: $\nu_{C=O} \cong 1664\ cm^{-1}$, **8**: $\nu_{C=O}$ 1672 cm^{-1}), ^1H and ^{13}C NMR spectra, which were similar to those of **1**–**4**, and by their MS data. Lignans **5**–**7** displayed a *quasi*-molecular ion $[M+H]^+$ at *m*/*z* 357, whereas this was at *m*/*z* 355 for **8**, which were consistent with the molecular formulas $C_{21}H_{24}O_5$ and $C_{21}H_{22}O_5$, respectively. From detailed analysis of ^1H and ^{13}C NMR, ^1H-^1H COSY, *g*HMQC, and *g*HMBC spectra (Tables 1–4), the constitutions of **5**–**8** were determined, and the positions of aromatic substituents in the A and C rings were confirmed by NOESY experiments. The main differences between **5**–**7** and **2**–**4** were due to the presence of a hydroxy group at C-4, instead of a methoxyl group, whereas lignan **8** had methylenedioxyl and dimethoxyl groups at the A and C

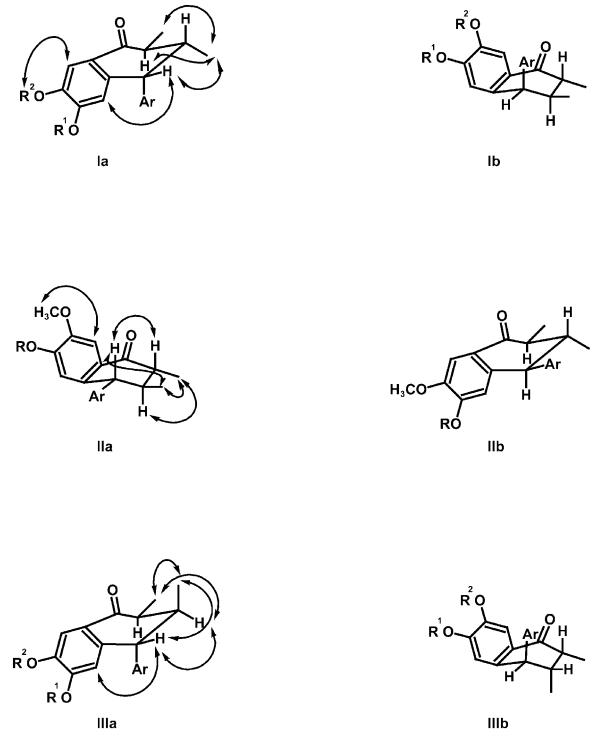

Fig. 1. Selected nOe interactions and possible conformations for lignans **1**, **2**, **5** (Ia, Ib), **3**, **6** (IIa, IIb), **4**, **7**, and **8** (IIIa, IIIb).

rings, respectively, which were interchanged compared to **1**. An analysis similar to that described for **1**–**4**, which included an evaluation of the coupling constants observed for H-8,8′ and H-7′,8′ as well as the spatial interactions between the hydrogens and the substituents at the B ring (observed by 1D- and 2D-NOESY experiments, Tables 1 and 3), allowed the most stable conformations and the relative configurations for **5**–**8** to be established (Fig. 1).

Previously, lignan **11** was transformed into (−)-isogalcatin (**12**) (Kato et al., 1990), for which the absolute configuration has been established (Klyne et al., 1966).

Table 3
^{1}H NMR spectral data for compounds **6**–**8** ($CDCl_3$, 500 MHz, *J* in Hz)[a]

H	**6**		**7**		**8**	
	(δ)	*g*NOESY and nOeDS	(δ)	*g*NOESY and nOeDS	(δ)	*g*NOESY and nOeDS
3	6.20 *s*		6.44 *s*	H-7′	6.35 *s*	OCH_3-4, H-7′
6	7.48 *s*	OCH_3-5	7.51 *s*	OCH_3-5	7.45 *s*	OCH_3-5
8	2.31 *dq* (12.0, 7.0)	H-9, H-9′, H-7′	2.71 *dq* (4.5, 7.0)	H-9, H-8′	2.71 *dq* (4.5, 7.0)	
9	1.25 *d* (7.0)	H-9′, H-8	1.07 *d* (7.0)	H-9′, H-8	1.06 *d* (7.0)	H-9′, H-8, H-8′
2′	6.50 *d* (2.0)	OCH_3-3′	6.55 *d* (2.0)	OCH_3-3′, H-7′	6.55 *d* (2.0)	
5′	6.78 *d* (8.0)	OCH_3-4′	6.72 *d* (8.0)	OCH_3-4′	6.72 *d* (8.5)	
6′	6.66 *dd* (8.0, 2.0)	H-7′	6.49 *dd* (8.0, 2.0)	H-7′	6.49 *dd* (8.5, 2.0)	H-7′
7′	3.60 *d* (10.5)	H-9′, H-8, H-6′	3.85 *d* (6.5)	H-9′, H-6′, H-3, H-2′	3.86 *d* (5.5)	H-9′, H-6′
8′	2.03 *ddq* (12.0, 10.5, 7.0)	H-9, H-9′, H-2′	2.37 *ddq* (6.5, 4.5, 7.0)	H-9′, H-8	2.35 *ddq* (5.5, 4.5, 7.0)	H-9′, H-7′
9′	0.86 *d* (7.0)	H-9, H-8′, H-8, H-7′	0.91 *d* (7.0)	H-9, H-8′	0.91 *d* (7.0)	H-9, H-8′, H-7′
OCH_3-3′	3.74 *s*	H-2′	3.75 *s*	H-2′		
OCH_3-4′	3.83 *s*	H-5′	3.80 *s*	H-5′		
OCH_3-4					3.76 *s*	H-3
OCH_3-5	3.87 *s*	H-6	3.90 *s*	H-6	3.80 *s*	H-6
OCH_2O					5.93 *d* ($w_{1/2}$ 1.5)	
OH	5.83 *br s*		5.94 *br s*			

[a] Multiplicities were determined with the assistance of ^{1}H–^{1}H COSY.

Table 4
^{13}C NMR spectral data for compounds **6**–**8** ($CDCl_3$, 126 MHz)[a]

C	**6**		**7**		**8**	
	^{13}C (δ)	*g*HMBC	^{13}C (δ)	*g*HMBC	^{13}C (δ)	*g*HMBC
1	125.5 *s*	H-3	125.2 *s*	H-6, H-3	127.0 *s*	H-3
2	142.4 *s*	H-7′, H-6	140.0 *s*	H-7′, H-6	141.0 *s*	H-7′, H-6
3	114.7 *d*	OH-4	115.4 *d*	OH-4	109.5 *d*	H-7′
4	150.3 *s*	OH-4, H-6, H-3	150.7 *s*	OH-4, H-6, H-3	152.2 *s*	OCH_2O, H-3
5	145.6 *s*	OH-4, OCH_3-5, H-3	145.8 *s*	OH-4, OCH_3-5, H-6, H-3	147.2 *s*	OCH_2O, H-3
6	108.0 *d*		108.0 *d*		105.8 *d*	
7	198.8 *s*	H-9, H-8	200.0 *s*	H-9, H-8, H-8′, H-6	199.5 *s*	H-9
8	48.6 *d*	H-9, H-9′	43.2 *d*	H-9′, H-8′, H-7′	43.0 *d*	
9	12.6 *q*	H-8	11.7 *q*	H-8, H-8′	11.7 *q*	
1′	136.0 *s*	H-7′, H-5′	136.2 *s*	H-7′, H-5′	136.0 *s*	H-7′, H-5′
2′	111.8 *d*	H-7′, H-6′	112.0 *d*	H-7′, H-6′	111.9 *d*	H-7′
3′	149.3 *s*	OCH_3-3′, H-5′	149.1 *s*	OCH_3-3′, H-5′	149.2 *s*	OCH_3-3′, H-5′
4′	148.0 *s*	OCH_3-4′, H-6′, H-2′	147.8 *s*	OCH_3-4′, H-6′, H-2′	147.9 *s*	OCH_3-4′, H-6′, H-2′
5′	111.1 *d*		115.4 *d*	H-7′	111.1 *d*	
6′	122.0 *d*	H-7′, H-2′	121.2 *d*	H-7′, H-2′	121.1 *d*	H-7′, H-2′
7′	53.1 *d*	H-9′, H-3, H-2′	49.7 *d*	H-9′, H-8, H-8′, H-3, H-2′	50.6 *d*	H-9′, H-3, H-2′,
8′	43.5 *d*	H-9, H-9′, H-8, H-7′	41.9 *d*	H-9, H-9′, H-8	42.0 *d*	H-9, H-9′, H-7′
9′	18.0 *q*	H-7′	16.0 *q*	H-8, H-8′, H-7′	15.9 *q*	H-7′
OCH_3-3′	55.9 *q*		55.9 *q*			
OCH_3-4′	56.0 *q*		56.0 *q*			
OCH_3-4					55.9 *q*	
OCH_3-5	56.1 *q*		56.1 *q*		56.0 *q*	
OCH_2O					101.6 *t*	

[a] The ^{13}C NMR data were assigned with the assistance of DEPT, *g*HMQC and *g*HMBC experiments.

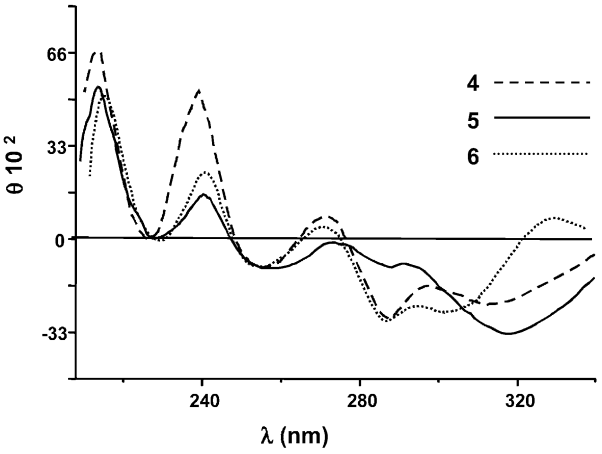

Fig. 2. CD curves for lignans **4**–**6**.

Thus, the absolute configurations of **11** and **12** should be (7′*S*,8*S*,8′*R*) and (7′*S*,8*R*,8′*S*), respectively. The CD curve of lignan **11** displayed a positive Cotton effect at $\lambda = 298$ nm and a negative effect at $\lambda = 325$ nm, which were, for 3,8-unsubstituted aryltetralone lignans, in accordance with β-aryl (C-7′) and 8*S* configurations, respectively, as shown in Fig. 2. The sign and magnitude of the Cotton effect at $\lambda \cong 320$ nm were easier to analyze than those for the effect at $\lambda \cong 298$ nm.

Lignans **3** and **6** showed very similar CD curves from 210 to 340 nm, and positive signals at $\lambda = 332$ nm, which indicated an 8*R* configuration (Fig. 2). Furthermore, these CD curves showed Cotton effects opposite to those reported for **11**. Therefore, the absolute configuration for **3** and **6** could be established as 7′*R*,8*R*,8′*S*.

Lignan **5** displayed a CD curve (Fig. 2) that could practically be superimposed on those of lignans **1** and **2**. The absolute configuration of lignan **2** has already been suggested to be 7′*R*,8*S*,8′*R* based on the sign and magnitude of the optical rotation (Urzúa and Shamma, 1988). Lignans **1**, **2** and **5** showed negative Cotton effects at $\lambda \cong 317$ nm, which were in accordance with an 8*S* configuration. Thus, their absolute configurations could be given as 7′*R*,8*S*,8′*R*. Lignans **4**, **7** and **8** showed CD curves from 240 to 320 nm (Fig. 2) that were very similar to that reported for enshicine (**13**) (Liu et al., 1984). They showed negative Cotton effects at $\lambda \cong 315$ nm, which permitted inferences to be made that their absolute configurations were 7′*R*,8*S*,8′*S*. These absolute configurations were confirmed by isomerization at the stereocenter C-8 of **4**, under basic conditions, which gave diastereomer **3**.

The APCI-MS of lignan **9** displayed a *quasi*-molecular ion $[M+Na]^+$ at *m*/*z* 395, and its ^{13}C NMR spectrum showed a total of 21 signals, consistent with the molecular formula $C_{21}H_{24}O_6$. The IR spectrum showed absorption bands characteristic of hydroxyl (ν_{OH} 3423 cm^{-1}) and carbonyl groups ($\nu_{C=O}$ 1709 cm^{-1}, broad band absorption suggesting the presence of two carbonyl groups in the molecule). The ^1H and ^{13}C NMR spectra, along with DEPT and *g*HMQC experiments (Tables 5 and 6), showed the presence of one methyl ketone group ($\delta_{C=O}$ 211.3, $\delta_{C\text{-}9}$ 28.9, $\delta_{3H\text{-}9}$ 2.02), one aromatic aldehyde ($\delta_{C=O}$ 189.9, $\delta_{H\text{-}7}$ 10.31), three aromatic methoxyl groups (δ_C 55.9, 56.0, 56.1; δ_H 3.76, 3.78, 3.84), one 1,3,4 trisubstituted and one 1,2,4,5-tetrasubstituted aromatic rings, one methyl group (δ_C 16.6,

Table 5
^1H NMR spectral data for compounds **9** and **10** ($CDCl_3$, 500 MHz, *J* in Hz)[a]

H	**9** (δ)	*g*NOESY and nOeDS	**10** (δ)	*g*NOESY and nOeDS
2			7.41 *d* (2.0)	OCH_3-3
3	6.99 *s*	H-8′		
5			6.79 *d* (8.0)	OCH_3-4, H-6
6	7.24 *s*	OCH_3-5	7.56 *dd* (8.0, 2.0)	H-5
7	10.31 *s*	H-7′, H-6		
9	2.02 *s*	H-9′, H-8′, H-7′, H-3	2.17 *s*	H-9′
2′	6.72 *d* (2.0)	OCH_3-3′, H-7′	6.83 *dd* (2.0, 1.0)	H-9′, H-7′
5′	6.72 *d* (8.5)	OCH_3-4′	6.71 *dd* (7.5, 1.0)	H-6′
6′	6.78 *dd* (8.5, 2.0)		6.84 *dd* (7.5, 2.0)	H-8′, H-5′
7′	5.08 *d* (11.5)	H-9′, H-7, H-2′	5.84 *d* (10.0)	H-9′, H-2′
8′	3.38 *dq* (11.5, 7.0)	H-9′, H-3	3.11 *dq* (10.0, 7.0)	H-9, H-9′, H-6′
9′	1.02 *d* (7.0)	H-9, H-8′, H-7′	0.91 *d* (7.0)	H-9, H-8′, H-7′, H-2′
OCH_3-3′	3.76 *s*	H-2′		
OCH_3-4′	3.78 *s*	H-5′		
OCH_3-3			3.83 *s*	H-2
OCH_3-4			3.85 *s*	H-5
OCH_3-5	3.84 *s*	H-6		
OCH_2O			5.88, 5.87 2*d* ($w_{1/2}$ 1.5)	
OH-4	6.08 *br s*			

[a] Multiplicities were determined with the assistance of ^1H–^1H COSY.

$\delta_{3H\text{-}9'}$ 1.02), and two methylenic groups ($\delta_{C\text{-}7'}$ 45.5, $\delta_{C\text{-}8'}$ 51.7; $\delta_{H\text{-}7'}$ 5.08, $\delta_{C\text{-}8'}$ 3.38). In addition, a *g*HMBC experiment showed a correlation between the aldehyde carbon and the aromatic hydrogen H-6 (δ 7.24). The substitution pattern of the aromatic rings was corroborated by ^{1}H–^{1}H COSY and *g*NOESY experiments. *g*NOESY experiments also showed correlations between the methoxyl hydrogens at δ 3.76 and 3.78 and the aromatic hydrogens at δ 6.72 (H-2′, H-5′), and between the methoxyl hydrogens at δ 3.84 and the hydrogen at δ 7.24 (H-6) (Fig. 5). The methylenic hydrogen H-7′ (δ 5.08, *d*, $J = 11.5$ Hz) was shown to be correlated by *g*HMBC to C-9′, C-8, C-6′, C-3, C-2′ and C-1 (^3J) as well as to C-8′, C-2, and C-1′ (^2J), which indicated that C-7′ was linked to both aromatic groups and to an alkyl chain. Furthermore, H-7′ showed a correlation due to coupling with H-8′ (δ 3.38 *dq*, $J = 11.5$, 7.0 Hz) in the ^{1}H–^{1}H COSY spectra, and was spatially correlated to H-7, H-2′, and 3H-9′ by *g*NOESY experiments. The remaining protons and carbons could be entirely assigned by analysis of the 2D NMR spectral data of **9**, including ^{1}H–^{1}H COSY, *g*NOESY, *g*HMQC, and *g*HMBC data (Tables 5 and 6, Fig. 3). This analysis, the magnitude of the coupling constant between H-7′ and H-8′, and the spatial correlation observed between H-8′ and H-3 (δ 6.99, *s*) and methyl hydrogens (3H-9′) allowed establishment of the structure of **9** as rel (−)-(7′*S*, 8′*R*)-4-hydroxy-3′,4′,5-trimethoxy-7,8-seco-2,7′-cyclolignan-7,8-dione (named 7,8-seco-holostylone A). Recently, obtulignolide (**14**) was isolated from *Chamaecyparis obtusa* (Cupressaceae) (Kuo et al., 2001), whose hypothetical biosynthetic intermediate (**15**) has the same carbon skeleton as that proposed for **9**.

Table 6
^{13}C NMR spectral data for compounds **9** and **10** ($CDCl_3$, 126 MHz)[a,b]

C	**9**		**10**	
	^{13}C (δ)	*g*HMBC	^{13}C (δ)	*g*HMBC
1	126.5 *s*	H-7, H-7′, H-6, H-3	122.5 *s*	H-5
2	141.8 *s*	H-7′, H-6	112.2 *d*	
3	112.9 *d*	H-7′	148.7 *s*	OCH_3-3
4	150.9 *s*	H-6, H-3	153.2 *s*	OCH_3-4, H-2
5	145.1 *s*	OCH_3-5, H-3	110.3 *d*	
6	112.6 *d*	H-7	123.5 *d*	H-2
7	189.9 *d*	H-6	165.3 *s*	H-2
8	211.3 *s*	H-9, H-9′, H-8′	209.6 *s*	H-9, H-9′
9	28.9 *q*	H-8′	28.9 *q*	
1′	134.3 *s*	H-7′, H-5′	132.1 *s*	
2′	111.8 *d*	H-7′, H-6′	107.3 *d*	
3′	148.4 *s*	OCH_3-3′, H-5′	148.0 *s*	OCH_2O
4′	147.9 *s*	OCH_3-4′, H-6′	147.9 *s*	H-6′, H-2′
5′	111.5 *d*		108.2 *d*	
6′	120.3 *d*	H-7′, H-2′	121.4 *d*	
7′	45.5 *d*	H-9′, H-8′, H-6′, H-3, H-2′	78.0 *d*	H-9′
8′	51.7 *d*	H-9, H-9′, H-7′	52.4 *d*	H-9′
9′	16.6 *q*	H-8′, H-7′	13.6 *q*	
OCH_3-3′	56.0 [b] *q*			
OCH_3-4′	55.9 [b] *q*			
OCH_3-3			56.0 *q*	
OCH_3-4			56.0 *q*	
OCH_3-5	56.1 *q*			
OCH_2O			101.2 *t*	

[a] The ^{13}C NMR data were assigned with the assistance of DEPT, *g*HMQC and *g*HMBC experiments.
[b] Assignments may be interchangeable within the same column.

The ESI-MS of lignan **10** displayed an $[M]^{+\cdot}$ at *m*/*z* 386 (100%), and its ^{1}H and ^{13}C NMR spectra showed signals to 22 hydrogens and 21 carbons, respectively, corresponding to two aromatic rings (one veratryl and one piperonyl), two carbonyl carbons, two methine carbons, and two methyl groups (Tables 5 and 6), which were in accordance with the molecular formula, $C_{21}H_{22}O_7$. The results of a *g*HMBC experiment supported the presence of methyl ketone ($\delta_{C=O}$ 209.6, $\delta_{C\text{-}9}$ 28.9) and veratryl ester ($\delta_{C=O}$ 165.3) groups (Table 6). The *g*HMBC experiment also showed that the carbonyl carbon (C-8) was correlated to both 3H-9 (δ 2.17, *s*) and 3H-9′ (δ 0.91, *d*, $J = 7.0$ Hz). Furthermore, the prominent absorption bands at 1712 cm^{-1} observed in the IR spectrum were in accordance with methyl ketone and ester groups in the molecule. A ^{1}H–^{1}H COSY experiment showed that H-7′ (δ 5.84, *d*, $J = 10.0$ Hz) was coupled to H-8′ (δ 3.11, *dq*, $J = 10.0$, 7.0 Hz) which, in turn, was also coupled to 3H-9′. Considering the magnitude of the coupling constant between H-7′ and H-8′ ($J = 10.0$ Hz) as well as the correlations observed by NOESY experiments (Fig. 4), the structure of **10** could be established as rel (−)-(7′*R*, 8′*S*)-3,4-dimethoxy-3′,4′-methylenedioxy-7,8-seco-7,7′-epoxylignan-7,8-dione. Moreover, the EI-MS spectra displayed ions at *m*/*z* 204 and 182 that arose from McLafferty rearrangement, which supported the proposed structure for lignan **10** (named 7,8-seco-holostylone B).

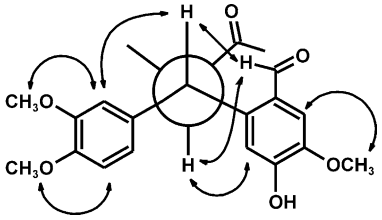

Fig. 3. Selected nOe interactions for lignan **9**.

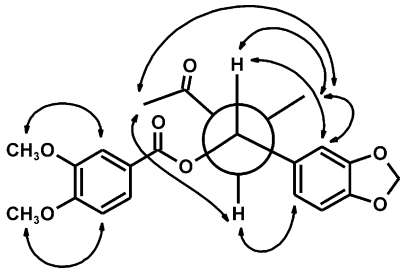

Fig. 4. Selected nOe interactions for lignan **10**.

Oxidative cleavage of C7–C8 bond of aryltetralone lignans may be involved in the biosynthesis of lignans **9** and **10**, since the presence of aryltetralone lignans in this species is quite unusual.

Indeed, aryltetralone lignans have only been isolated from one species in the Aristolochiaceae, *A. chilensis* (Urzúa and Shamma, 1988). The great structural similarities among the lignans isolated from *H. reniformis* and *A. chilensis* support the proposal of González (1997) to include *Holostylis* in the *Aristolochia* genus.

3. Experimental

3.1. General experimental procedures

NMR spectra were measured on Varian INOVA 300 and INOVA 500 spectrometers (11.7 T or 7.0 T) at 500 or 300 MHz (^{1}H) and 126 or 75 MHz (^{13}C), using the solvents as an internal standard. Mass spectra (EI-MS, APCI-MS, and ESI-MS) were obtained on a Fisons Platform II, and flow injection into the electrospray source was used for ESI-MS. IR spectra were obtained on a Nicolet-730 FT-IR spectrometer using KBr discs. UV absorptions were measured on a Hewlett-Packard 8452A diode array spectrophotometer. Optical rotations were measured on a Polamat A Carl Zeiss Jena polarimeter. Circular dichroism spectra were recorded on a JASCO J-720 spectrometer. HPLC analyses were carried out using a Shimadzu liquid chromatograph 10Avp equipped with a UV–vis detector. Columns were RP-18 (Shimadzu, C_{18}, 3.9×150 mm for analytical analysis and 250×20 mm for semi-preparative analysis), and chromatograms were acquired at 254 nm. TLC: Silica gel 60 PF_{254}. Melting points were recorded on a Fisher-Johns melting point apparatus and were uncorr.

3.2. Plant material

The plant material was collected in Ituiutaba, MG, Brazil, in January, 1998, and identified as *Holostylis reniformis* Duch. by Dr. Condorcet Aranha (Secretaria do Meio Ambiente da Prefeitura de Joinville, Joinville, SC, Brazil). A voucher specimen was deposited at the herbarium of the Instituto Agronômico de Campinas, Campinas, SP, Brazil.

3.3. Isolation

The roots (255.9 g) of *H. reniformis* were dried (~45°), ground and extracted exhaustively at room temp. with hexane, Me_2CO, and EtOH successively, and the extracts were individually concentrated.

One-third of the hexane extract (0.5 g) was fractionated by CC (silica gel, 15 g, hexane–EtOAc gradient) to give 16 fractions. Fractions 1, 7, and 8 gave (−)-galbacin (12.0 mg), **1** (4.9 mg), and **8** (25.4 mg), respectively. Fractions 10-12 were individually subjected to semi-prep. HPLC (MeOH-H_2O 3:2). Fraction 10 gave **3** (4.9 mg) and **6** (10.0 mg), fraction 11 gave **2** (4.9 mg), **4** (18.0 mg) and **10** (3.7 mg), and fraction 12 gave **7** (2.2 mg).

Half of the crude acetone extract (4.0 g) was fractionated by CC (silica gel, 120 g, hexane–EtOAc gradient) to give 75 fractions (20 ml). After analytical TLC and HPLC, some fractions were combined to give 26 fractions. Further purifications on TLC ($CHCl_3$–MeOH 98:2) fractions 4 and 9 gave (−)-galbacin (1.2 mg) and **9** (4.4 mg), respectively. Purification on semi-prep. HPLC (MeOH-H_2O 3:2) of fraction 8 yielded **1** (21.2 mg) and **8** (15.0 mg), of fraction 12 yielded **2** (30.9 mg), **3** (28.8 mg), and **4** (129.3 mg), and of fraction 13 yielded **5** (1.6 mg), **6** (2.0 mg), **7** (4.9 mg), and a mixture of **2**–**4** (19.5 mg).

To a soln. of **4** (40.0 mg, 1.08×10^{-4} mmol) in ^{t}BuOH was added a soln. of ^{t}BuOK in ^{t}BuOH (20 ml, 7.3×10^{-3} mol) at room temp. The mixture was stirred for 15 min, neutralized with a 10% HCl soln. and then extracted with CH_2Cl_2 (3×25 ml). The combined organic phases were washed with H_2O, dried (Na_2SO_4), and concentrated. Purification of the product by HPLC (MeOH–H_2O 3:2) yielded 3 (30 mg).

3.3.1. (7′R,8S,8′R)-8,8′-Dimethyl-4,5-dimethoxy-3′,4′-methylenodioxy-2,7′-cyclolignan-7-one [(−)-aristotetralone, 1]

Amorphous yellow solid. $[\alpha]_D^{25}$ −135.3° ($CHCl_3$; *c* 0.60) [lit. −164 ° ($CHCl_3$; *c* 1.54) (Urzúa et al., 1987). (Found: C, 71.3; H, 6.3. Calc. for $C_{21}H_{22}O_5$: C, 71.2; H, 6.3%.) Positive ESI-MS (probe) 70 eV, *m*/*z* (rel. int.): 355 $[M+H]^+$ (100), 233 (51), 165 (19), 149 (16). IR, UV, and ^{1}H NMR data agree with those reported in the literature (Urzúa et al., 1987). ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.6 (*s*, C-7), 153.8 (*s*, C-4), 148.4 (*s*, C-5), 147.5, 146.3 (2*s*, C-3′,4′), 140.6 (*s*, C-2), 133.2 (*s*, C-1′), 125.5 (*s*, C-1), 123.2 (*d*, C-6′), 110.7 (*d*, C-3), 110.3 (*d*, C-2′), 108.5 (*d*, C-5′), 107.8 (*d*, C-6), 101.0 (*t*, OCH_2O), 56.0 (*q*, CH_3O-4′,5), 50.1 (*d*, C-7′), 42.6 (*d*, C-8), 39.8 (*d*, C-8′), 18.1 (*q*, C-9′), 12.7 (*q*, C-9). CD (MeOH; *c* 0.1): $[\theta]_{214}$ +7458, $[\theta]_{221}$ 0, $[\theta]_{226}$ −1551, $[\theta]_{233}$ 0, $[\theta]_{240}$ +3267, $[\theta]_{249}$ 0, $[\theta]_{258}$ −1419, $[\theta]_{271}$ 0, $[\theta]_{276}$ +594, $[\theta]_{283}$ 0, $[\theta]_{295}$ −1485, $[\theta]_{317}$ −4059.

3.3.2. (7′R,8S,8′R)-8,8′-Dimethyl-3′,4′,4,5-tetramethoxy-2,7′-cyclolignan-7-one [(−)-aristoligone, 2]

Amorphous yellow solid. $[\alpha]_D^{25}$ −206.4° ($CHCl_3$; *c* 0.72) [lit. −190° ($CHCl_3$; *c* 0.78) (Urzúa and Shamma, 1988)]. (Found: C, 71.3; H, 7.1. Calc. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1%.) Positive ESI-MS (probe) 70 eV, *m*/*z* (rel. int.): 371 $[M+H]^+$ (100), 233 (38), 205 (10), 165 (19). IR, UV, and ^{1}H NMR data agree with those reported in the literature (Urzúa and Shamma, 1988). ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.8 (*s*, C-7), 153.8 (*s*, C-4), 148.5

(*s*, C-3′), 148.3 (*s*, C-5), 147.9 (*s*, C-4′), 140.7 (*s*, C-2), 132.0 (*s*, C-1′), 125.4 (*s*, C-1), 122.2 (*d*, C-6′), 113.5 (*d*, C-2′), 110.9 (*d*, C-5′), 110.7 (*d*, C-3), 108.5 (*d*, C-6), 56.0 (*q*, CH_3O-3′,5), 55.9 (*q*, CH_3O-4′), 55.8 (*q*, CH_3O-4), 50.0 (*d*, C-7′), 42.8 (*d*, C-8), 39.9 (*d*, C-8′), 18.0 (*q*, C-9′), 12.8 (*q*, C-9). CD (MeOH; *c* 0.1): $[\theta]_{212}$ +2376, $[\theta]_{221}$ 0, $[\theta]_{227}$ −462, $[\theta]_{232}$ 0, $[\theta]_{240}$ +1914, $[\theta]_{248}$ 0, $[\theta]_{258}$ −495, $[\theta]_{273}$ 0, $[\theta]_{286}$ −462, $[\theta]_{291}$ −363, $[\theta]_{317}$ −1702.

3.3.3. (7′*R*,8*R*,8′*S*)-8,8′-Dimethyl-3′,4′,4,5-tetramethoxy-2,7′-cyclolignan-7-one [(+)-8,8′-epi-aristoligone, **3**]

Yellow crystals, m.p. 146.5–149.3 °C. $[\alpha]_D^{25}$ −30.0° ($CHCl_3$; *c* 1.33). (Found: C, 71.3; H, 7.1. $C_{22}H_{26}O_5$ requires: C, 71.3; H, 7.1%.) Positive ESI-MS (probe) 70 eV, *m*/*z* (rel. int.): 371 $[M+H]^+$ (100), 233 (57), 205 (53), 165 (96). IR ν_{max}^{KBr} cm^{-1}: 3076, 2962, 2934, 1667. UV λ_{max}^{MeOH} nm (log ϵ): 232 (4.5), 212 (4.4), 274 (4.2), 308 (4.0). For ^1H and ^{13}C NMR, see Tables 1 and 2. CD (MeOH; *c* 0.1): $[\theta]_{212}$ +1716, $[\theta]_{224}$ 0, $[\theta]_{226}$ −33, $[\theta]_{227}$ 0, $[\theta]_{240}$ +1320, $[\theta]_{250}$ 0, $[\theta]_{255}$ −149, $[\theta]_{260}$ 0, $[\theta]_{270}$ +363, $[\theta]_{276}$ 0, $[\theta]_{288}$ −1155, $[\theta]_{301}$ −858, $[\theta]_{320}$ 0, $[\theta]_{332}$ +703.

3.3.4. (7′*R*,8*S*,8′*S*)-8,8′-Dimethyl-3′,4′,4,5-tetramethoxy-2,7′-cyclolignan-7-one [(−)-8′-epi-aristoligone, **4**]

Yellow crystals, m.p. 130.0–132.0 °C. $[\alpha]_D^{25}$ −64.3° ($CHCl_3$; *c* 1.04). (Found: C, 71.3; H, 7.1. $C_{22}H_{26}O_5$ requires: C, 71.3; H, 7.1%.) Positive ESI-MS (probe) 70 eV, *m*/*z* (rel. int.): 371 $[M+H]^+$ (43), 233 (100), 205 (53), 165 (96). IR ν_{max}^{KBr} cm^{-1}: 3068, 2956, 2912, 1667. UV λ_{max}^{MeOH} nm (log ϵ): 234 (4.0), 214 (3.9), 275 (3.8), 313 (3.6). For ^1H and ^{13}C NMR, see Tables 1 and 2. CD (MeOH; *c* 0.1): $[\theta]_{214}$ +6697, $[\theta]_{226}$ +333, $[\theta]_{239}$ +5445, $[\theta]_{248}$ 0, $[\theta]_{254}$ −561, $[\theta]_{263}$ 0, $[\theta]_{272}$ +1056, $[\theta]_{277}$ 0, $[\theta]_{288}$ −3201, $[\theta]_{298}$ −1518, $[\theta]_{314}$ −2368.

3.3.5. (7′*R*,8*S*,8′*R*)-8,8′-Dimethyl-4-hydroxy-3′,4′,5-trimethoxy-2,7′-cyclolignan-7-one [(−)-8,8′-epi-holostylone, **5**]

Amorphous yellow solid. $[\alpha]_D^{25}$ −171.6° ($CHCl_3$; *c* 0.32). (Found: C, 70.7; H, 6.8. $C_{21}H_{24}O_5$ requires: C, 70.8; H, 6.8%.) Positive APCI-MS (probe) 30 eV, *m*/*z* (rel. int.): 357 $[M+H]^+$ (100), 233 (16), 219 (65). IR ν_{max}^{KBr} cm^{-1}: 3423, 3072, 2968, 2847, 1663. UV λ_{max}^{MeOH} nm (log ϵ): 234 (4.3), 213 (4.3), 279 (4.1), 314 (3.8). For ^1H and ^{13}C NMR, see Tables 1 and 2. CD (MeOH; *c* 0.1): $[\theta]_{214}$ +5247, $[\theta]_{228}$ 0, $[\theta]_{241}$ +1650, $[\theta]_{247}$ 0, $[\theta]_{257}$ −1155, $[\theta]_{273}$ −33, $[\theta]_{287}$ −1023, $[\theta]_{292}$ −858, $[\theta]_{318}$ −3333.

3.3.6. (7′*R*,8*R*,8′*S*)-8,8′-Dimethyl-4-hydroxy-3′,4′,5-trimethoxy-2,7′-cyclolignan-7-one [(+)-holostylone, **6**]

Amorphous yellow solid. $[\alpha]_D^{25}$ −27.4° ($CHCl_3$; *c* 0.31). (Found: C, 70.7; H, 6.8. $C_{21}H_{24}O_5$ requires: C, 70.7; H, 6.8%.) Positive EI-MS (probe) 40 eV, *m*/*z* (rel. int.): 357 $[M+H]^+$ (11), 149 (100), 217 (90), 135 (45), (165 (41), 233 (25). IR ν_{max}^{KBr} cm^{-1}: 3433, 3074, 2924, 2855, 1666. UV λ_{max}^{MeOH} nm (log ϵ): 278 (4.0), 240 (4.0), 312 (3.9). For ^1H and ^{13}C NMR, see Tables 3 and 4. CD (MeOH; *c* 0.1): $[\theta]_{212}$ +5148, $[\theta]_{227}$ +297, $[\theta]_{240}$ 2508, $[\theta]_{247}$ 0, $[\theta]_{254}$ −726, $[\theta]_{263}$ 0, $[\theta]_{271}$ +627, $[\theta]_{272}$ 0, $[\theta]_{288}$ −2607, $[\theta]_{297}$ −2145, $[\theta]_{304}$ −2343, $[\theta]_{323}$ 0, $[\theta]_{332}$ +891.

3.3.7. (7′*R*,8*S*,8′*S*)-8,8′-Dimethyl-4-hydroxy-3′,4′,5-trimethoxy-2,7′-cyclolignan-7-one [(−)8,8′-epi-holostylone, **7**]

Yellow crystals, m.p. 169.0–172.0 °C. $[\alpha]_D^{25}$ −40.6° ($CHCl_3$; *c* 1.23). (Found: C, 70.8; H, 6.8. $C_{21}H_{24}O_5$ requires: C, 70.8; H, 6.8%.) APCI-MS (probe) 30 eV *m*/*z* (int. rel.): 357 $[M+H]^+$ (47), 219 (100). IR ν_{max}^{KBr} cm^{-1}: 3420, 3067, 2968, 2844, 1663. UV λ_{max}^{MeOH} nm (log ϵ): 235 (4.9), 210 (4.9), 278 (4.6), 314 (4.4). For ^1H and ^{13}C NMR, see Tables 3 and 4. CD (MeOH; *c* 0.1): $[\theta]_{214}$ +5247, $[\theta]_{229}$ +136, $[\theta]_{241}$ +1452, $[\theta]_{248}$ 0, $[\theta]_{254}$ −528, $[\theta]_{264}$ 0, $[\theta]_{273}$ +627, $[\theta]_{279}$ 0, $[\theta]_{288}$ −1848, $[\theta]_{300}$ −1155, $[\theta]_{311}$ −1254.

3.3.8. (7′*R*,8*S*,8′*S*)-8,8′-Dimethyl-3′,4′-dimethoxy-4,5-methylenodioxy-2,7′-cyclolignan-7-one [(−)-4′-*O*-Methylenshicine, **8**]

Amorphous yellow solid. $[\alpha]_D^{25}$ −47.1° ($CHCl_3$; *c* 1.00). (Found: C, 71.2; H, 6.2. $C_{21}H_{22}O_5$ requires: C, 71.2; H, 6.3%.) Positive ESI-MS (probe) 70 eV, *m*/*z* (rel. int.): 377 $[M+Na]^+$ (100), 355 $[M+H]^+$ (18), 217 (75), 202 (8), 189 (6). IR ν_{max}^{KBr} cm^{-1}: 3074, 2962, 2914, 1672. UV λ_{max}^{MeOH} nm (log ϵ): 233 (4.9), 213 (4.7), 275 (4.7), 311 (4.4). For ^1H and ^{13}C NMR, see Tables 3 and 4. CD (MeOH; *c* 0.1): $[\theta]_{212}$ +4158, $[\theta]_{221}$ 0, $[\theta]_{225}$ −198, $[\theta]_{228}$ 0, $[\theta]_{239}$ +5214, $[\theta]_{254}$ 0, $[\theta]_{258}$ −200, $[\theta]_{263}$ 0, $[\theta]_{271}$ +680, $[\theta]_{275}$ 0, $[\theta]_{288}$ −3168, $[\theta]_{303}$ −647, $[\theta]_{319}$ −408.

3.3.9. rel. (7′*S*,8′*R*)-4-Hydroxy-3′,4′,5-trimethoxy-7,8-seco-2,7′-cyclolignan-7,8-dione (7,8-seco-holostylone A, **9**)

Amorphous yellow solid. $[\alpha]_D^{25}$ −181.8° ($CHCl_3$; *c* 0.44). (Found: C, 67.7; H, 6.5. $C_{21}H_{24}O_6$ requires: C, 67.7; H, 6.5%.) Positive APCI-MS (probe) 30 eV *m*/*z* (int. rel.): 395 $[M+Na]^+$ (5), 284 (100), 301 (29), 355 (26). IR ν_{max}^{KBr} cm^{-1}: 3423, 3079, 2926, 2858, 1709. UV λ_{max}^{MeOH} nm (log ϵ): 211 (4.4), 235 (4.4), 279 (4.1). For ^1H and ^{13}C NMR, see Tables 5 and 6. CD (MeOH; *c* 0.1): $[\theta]_{215}$ −1339, $[\theta]_{234}$ −1815, $[\theta]_{273}$ −33, $[\theta]_{241}$ −149, $[\theta]_{285}$ 0, $[\theta]_{317}$ +856.

3.3.10. rel. (7′*R*,8′*S*)-3,4-Dimethoxy-3′,4′-methylenedioxy-7,8-seco-7,7′-epoxylignan-7,8-dione (7,8-seco-holostylone B, **10**)

Amorphous yellow solid. $[\alpha]_D^{25}$ +37.0° ($CHCl_3$; *c* 0.13). (Found: C, 65.3; H, 5.8. $C_{21}H_{22}O_7$ requires: C, 65.3; H, 5.7%.) Positive EI-MS (probe) 15 eV, *m*/*z* (rel. int.): 386 $[M]^+$ (98), 149 (95), 204 (81), 182 (74). IR ν_{max}^{KBr} cm^{-1}: 3078, 2927, 2857, 1712; UV λ_{max}^{MeOH} nm (log ϵ): 221 (3.8), 264 (3.4), 289 (3.3). For ^1H and ^{13}C NMR, see Tables 5 and 6. CD (MeOH; *c* 0.1): $[\theta]_{229}$ −1188, $[\theta]_{241}$

0, $[\theta]_{262}$ +1155, $[\theta]_{285}$ +99, $[\theta]_{297}$ +597, $[\theta]_{306}$ 0, $[\theta]_{312}$ −99, $[\theta]_{319}$ 0, $[\theta]_{344}$ −231.

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