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Anti-inflammatory Constituents of Topically Applied Crude Drugs. III.[1] Constituents and Anti-inflammatory Effect of Paraguayan Crude Drug "Tamandá cuná" (*Catasetum barbatum* LINDLE)[2]

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The 70% EtOH extract of the aerial parts of *Catasetum barbatum* LINDLE showed inhibitory effects on carrageenin-induced paw edema when topically applied to rats and on histamine-induced contraction in guinea pig ileum.

Four compounds including a new phenanthrene, 2,7-dihydroxy-3,4,8-trimethoxyphenanthrene (**2**), were isolated from the active fraction. 2,7-Dihydroxy-3,4-dimethoxyphenanthrene (**1**) showed inhibitory effects in both biological assays.

Keywords——anti-inflammatory effect; *Catasetum barbatum*; Orchidaceae; 2,7-dihydroxy-3,4-dimethoxyphenanthrene; 2,7-dihydroxy-3,4,8-trimethoxyphenanthrene; carrageenin edema; H_1-receptor

In the course of a search for biologically active substances from Paraguayan medicinal plants, the 70% EtOH extract of the aerial parts of *Catasetum barbatum* LINDLE (Orchidaceae), "Tamandá cuná" in Paraguay, was found to have anti-inflammatory activity when topically applied. Tamandá cuná is a folk medicine used for the treatment of asthma, lumbago, *etc.* in Paraguay, and little is known about the chemical constituents.

In this paper, we report the separation and identification of some chemical constituents of the active fraction along with their anti-inflammatory activity in the carrageenin-induced paw edema (CPE) test and inhibitory effect on histamine-induced contraction in guinea pig ileum (HCI).

The 70% EtOH extract (fr. A) was suspended in water and extracted with Et_2O under acidic conditions (pH 3) to give the Et_2O-soluble fraction (fr. B) and H_2O-soluble fraction (fr. C). The active fr. B was further fractionated as shown in Chart 1 to afford acidic (fr. D), weakly acidic (fr. E) and neutral fractions (fr. F).

In the CPE test with topical application[1] of frs. A—F, frs. A, B and E showed inhibitory activity at an early time after carrageenin injection (Table I).

Thus, we examined the inhibitory effect on the contraction in guinea pig ileum induced by histamine (considered to be a chemical mediator at the early stage of acute inflammation), and the result (shown in Table II) corresponded well with that of the CPE test.

Active fr. E was subjected to column chromatography on silica gel with a solvent system of $CHCl_3$–MeOH (gradient), with monitoring by thin layer chromatography (TLC), to give four fractions (frs. 1—4). Fractions 1 and 2 showed inhibitory effects on HCI and were further

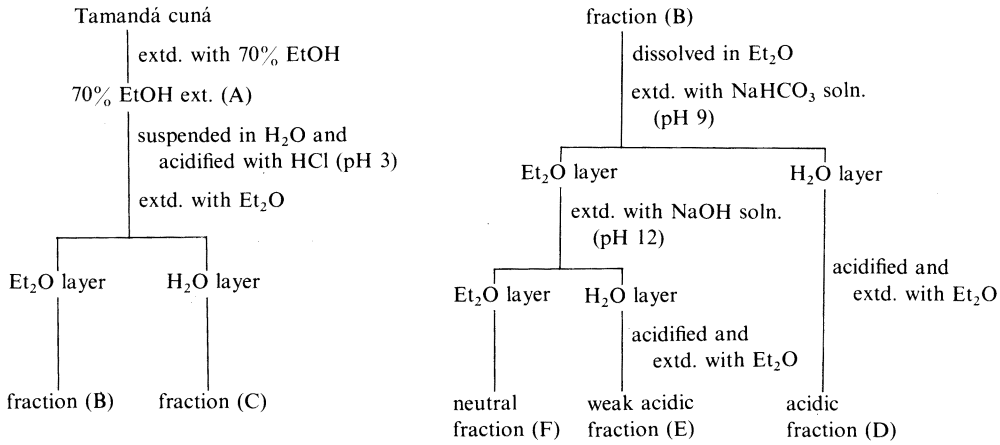


Chart 1. Extraction and Fractionation of Aerial Parts of Tamandá cuná

TABLE I. Inhibitory Effects of Frs. A—F and Compound **1** on Carrageenin Paw Edema in Rats[a]

Fraction and compound	Dose (mg/site × 4)	Inhibition of swelling (%)			
		1 h	2 h	3 h	4 h[b]
A	5	30.7[d]	22.8[d]	17.4	—
B	5	57.9[e]	20.3	24.1[d]	17.1
C	5	—[c]	—	—	—
D	5	—	—	14.3	18.6
E	5	43.5[d]	21.8[d]	29.7[d]	32.5[d]
F	5	—	17.2	14.2	18.6
Indomethacin	0.5	—	15.8	37.3[d]	33.3[d]
1	4	34.6[d]	33.4[d]	31.1[d]	36.8[e]

a) $n=4$ or 5. *b*) Time after carrageenin injection. *c*) No effect (less than 10%). *d*) $p<0.05$. *e*) $p<0.01$.

TABLE II. Inhibitory Effects of Frs. A—F and Compounds **1**—**4** on Histamine (10^{-7} g/ml)-Induced Contraction in Guinea Pig Ileum

Fraction	IC_{50} (g/ml)	Compound	IC_{50} (g/ml)
A	4.8×10^{-5}	**1**	5.4×10^{-6}
B	3.0×10^{-5}	**2**	9.0×10^{-6}
C	$>10^{-4}$	**3**	1.5×10^{-5}
D	$>10^{-4}$	**4**	2.0×10^{-5}
E	1.1×10^{-5}	Diphenhydramine·HCl	1.2×10^{-8}
F	$>10^{-4}$		

separated and purified by repeated column chromatography to yield compounds **1**—**4**.

Compound **1**, colorless needles, mp 157—158 °C, $C_{16}H_{14}O_4$, showed a positive reaction with the ferric chloride reagent. It showed a typical ultraviolet (UV) spectrum[3] of phenanthrene (see the experimental section), and gave a diacetate (**1a**) with acetic anhydride and pyridine. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, **1** showed the presence of two phenolic methoxyl groups and six aromatic protons. The positions of the substituents were presumed to be C-2, 3, 4 and 7 from the chemical shifts and splitting patterns of aromatic protons (1H singlet, 3H ABX-type and 2H singlet) in the ^{1}H-NMR spectrum.

On the basis of the spectroscopic evidence, compound **1** was finally determined to be 2,7-dihydroxy-3,4-dimethoxyphenanthrene by comparisons of the ^{1}H-NMR and UV spectra of **1** and **1a** with those of an authentic sample.[4] This is the first isolation of this compound from the genus Catasetum.

Compound **2**, colorless needles, mp 197—199 °C, showed a positive ferric chloride reaction and its molecular formula was determined to be $C_{17}H_{16}O_5$ from the high-resolution mass spectrum (MS). The UV spectrum showed very similar absorption bands to those of **1**, indicative of a phenanthrene derivative. Compound **2** gave a diacetate (**2a**) and the ^{1}H-NMR

spectrum showed the presence of three phenolic methoxyl and five aromatic protons, giving two pairs of AB-type signals and a singlet signal, respectively (Table III). One pair of signals (δ 9.10 and 7.25) was assigned to H-5 and H-6, and the other pair (δ 7.90 and 7.58) to H-9 and H-10. Comparing the signals due to H-6 in **1** and **2**, the latter was observed as a doublet owing to only *ortho* coupling in **2**, indicating the absence of H-8 (the former was a doublet of doublets). In addition, the signals due to H-9 and H-10 in **2** each appeared as a doublet, observed only in the case of 1- or 8-substituted phenanthrene,[4] suggesting the presence of a substituent at the 8 position. A 2H singlet was seen in the case of **1** which has no substituent at the 1 or 8 position. Therefore, the positions of substituents should be C-2, C-3, C-4, C-7 and C-8. The locations of hydroxyl groups were concluded to be C-2 and C-7 from the acetylation shifts of H-1 and H-6 (Δ 0.36 and 0.17 ppm) compared with those of **1** (Δ 0.36 and 0.14 ppm) and 8-hydroxy-2,3,4,7-tetramethoxyphenanthrene (5)[5] (Δ 0.2 and 0.04 ppm) (Table III).

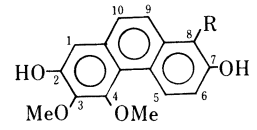
On the basis of these findings, compound **2** was determined to be 2,7-dihydroxy-3,4,8-trimethoxyphenanthrene, which is a previously unknown phenanthrene.

Compound **3**, colorless columns, showed the molecular formula $C_{16}H_{16}O_4$, having one mol of hydrogen more than **1**. The UV spectrum showed the absorption maximum at 281 nm. **3** gave a diacetate (**3a**) and the ^{1}H-NMR spectrum indicated the presence of two phenolic methoxyl and four aromatic protons as ABX-type signals and a singlet signal, besides a four-proton singlet at δ 2.63, typical of a 9,10-dihydrophenanthrene. From these findings, **3** was

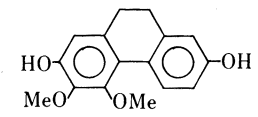
TABLE III. ^{1}H-NMR Spectral Data for **1**, **1a**, **2**, **2a**, **5** and **5a**, δ (ppm) from TMS (J=Hz)

Proton	**1**[a]	**1a**[a]	**2**[a]	**2a**[a]	**5**[b]	**5a**[b]
1	7.16 (s)	7.52 (s)	7.17 (s)	7.53 (s)	7.00 (s)	7.20 (s)
5	9.35 (d, J=9.2)	9.60 (d, J=9.2)	9.10 (d, J=9.7)	9.37 (d, J=9.7)	8.98 (d, J=9)	9.40 (d, J=10)
6	7.31 (dd, J=9.2, 2.4)	7.45 (dd, J=9.2, 2.4)	7.25 (d, J=9.7)	7.42 (d, J=9.7)	7.29 (d, J=9)	7.33 (d, J=10)
8	7.17 (d, J=2.4)	7.69 (d, J=2.4)	—	—	—	—
9	7.51 (2H, s)	7.75 (2H, s)	7.90 (d, J=9.2)	8.08 (d, J=9.2)	8.00 (d, J=9)	7.60 (2H, s)
10			7.58 (d, J=9.2)	7.77 (d, J=9.2)	7.84 (d, J=9)	
OMe	4.01 (s)	4.01 (s)	4.00 (s)	4.02 (6H, s)	3.99 (6H, s)	4.00 (s)
	3.97 (s)	3.99 (s)	3.96 (s)	3.97 (s)	3.98 (6H, s)	3.97 (s)
			3.93 (s)			3.95 (6H, s)
OH/OAc	8.44 (2H, br s)	2.37 (s)	8.30 (2H, br s)	2.39 (s)	5.98 (br)	2.45 (s)
		2.34 (s)		2.37 (s)		

a) In acetone-d_6. *b*) In $CDCl_3$. Compound **5**, 8-hydroxy-2,3,4,7-tetramethoxyphenanthrene; **5a**, monoacetate of **5**, values in literature.



1 : R=H
2 : R=OMe



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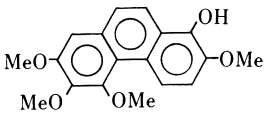

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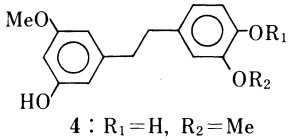

4 : R_1=H, R_2=Me
6 : R_1=Me, R_2=H

Chart 2

considered to be the 9,10-dihydrogenated derivative of **1**.

To confirm the structure, **3a** was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as described in the experimental section, to give the corresponding derivative, which was found to be identical with **1a** in terms of the ^{1}H-NMR spectrum. Compound **3** was thus concluded to be 2,7-dihydroxy-3,4-dimethoxy-9,10-dihydrophenanthrene, which has recently been isolated from *Eria carinata* and *E. stricta*.[6]

Compound **4**, a colorless oil, $C_{16}H_{18}O_4$, gave the signals of six aromatic, two phenolic methoxyl, two hydroxyl (disappeared on D_2O treatment), and four equivalent benzylic protons in the ^{1}H-NMR spectrum. The MS of **4** showed a molecular ion peak at *m/z* 274 and a base peak at *m/z* 137, arising from the tropilium ion formed by benzylic cleavage of the biphenylethane containing one hydroxyl and one methoxyl group in both aromatic rings. The structure of **4** was thus considered to be 3,4′-dihydroxy-5,5′-dimethoxydihydrostilbene (**4**) or 3,5′-dihydroxy-5,4′-dimethoxydihydrostilbene (**6**) from the splitting pattern of the aromatic protons in the ^{1}H-NMR spectrum (3H, each *meta*-coupled, and 3H, ABX-type). Crombie and Jamieson[7] reported **4** as an oil and **6** as colorless needles (mp 132—133 °C); the spectral data of the former were in agreement with those of **4** isolated by us (oil).

Finally, compound **4** was identified as 3,4′-dihydroxy-5,5′-dimethoxydihydrostilbene by comparison of the ^{1}H- and ^{13}C-NMR spectra with those of an authentic sample, and was confirmed to be different from **6**, kindly provided by Dr. Crombie, in terms of physical and spectral data.

Recently, Juneja *et al.*[8] reported the isolation of gigantol as crystals (mp 94—95 °C) from *Cymbidium giganteum* and proposed the structure **4**, but the physical and spectral data are different from those of **4** isolated by us and synthesized by Crombie and Jamieson. 'Gigantol' is rather similar to **6**, but the structure is still in question.

Biological Activities of Compounds 1—4

Compounds **1**—**4** isolated from *C. barbatum* LINDLE in the present study were tested for inhibitory effect on HCI. Among these four compounds, **1** showed the strongest activity and the other compounds also showed activity as strong as that of fr. E (Table II). We also examined the mode of action of compound **1** against H_1-receptor. As shown in Fig. 1, the histamine-induced contraction did not reach the control level when compound **1** was used at 3×10^{-6} g/ml, and the tendency increased with increasing concentration of compound **1**. From these results, compound **1** was considered to be a specific non-competitive inhibitor of H_1-receptor.

Further, compound **1** showed activity in the CPE test on topical application throughout the test period, being significantly different from the control (Table I). The other three

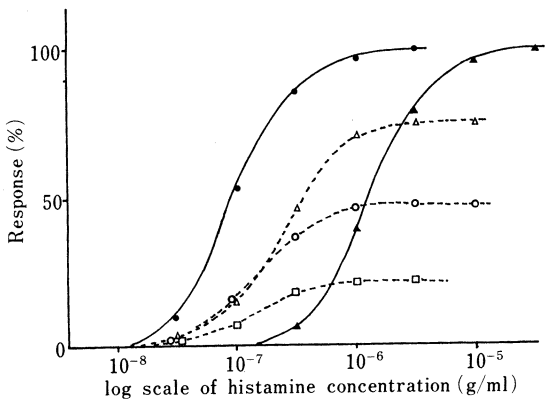

Fig. 1. Dose–Response Curve for Compound **1** on Histamine-Induced Contraction in Guinea Pig Ileum

●—●, control; ▲—▲, diphenhydramine 3×10^{-8} g/ml; △---△, compound **1** 3×10^{-6} g/ml; ○---○, compound **1** 6×10^{-6} g/ml; □---□, compound **1** 1×10^{-5} g/ml.

compounds could not be examined with this test owing to limited sample availability, but might show anti-inflammatory activity in view of the resemblance in chemical structure. In addition, it is of interest that **4** was isolated from the anti-inflammatory active fraction, considering that Goda *et al.* reported that a dihydrostilbene derivative was an inhibitor of prostaglandin and thromboxane synthetase.[9]

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: infrared (IR) spectra with a Hitachi 260-0611 spectrophotometer; UV spectra with a Hitachi 270 S spectrophotometer; MS with a JEOL JMS-D 200 spectrometer; ^{1}H-NMR spectra with a JEOL FX 90Q (90 MHz) spectrometer; ^{13}C-NMR spectra with a JEOL FX 90Q (22.5 MHz) spectrometer. Chemical shifts are given in δ (ppm) values referred to internal tetramethylsilane (TMS). TLC was carried out on precoated Kieselgel 60 F_{254} plates (Merck). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad.

Plant Materials——Aerial parts of *Catasetum barbatum* LINDLE were collected at Departomento Presidente Hayes in Chaco, Paraguay, in July 1985 and 1986. Voucher speciments are on deposit in the institute of Asuncion University.

Bioassay——Anti-inflammatory activity by topical application toward CPE and inhibitory effect on HCl were assessed as described in a previous report.[10]

Extraction and Fractionation——Fresh aerial parts of *Catasetum barbatum* LINDLE (6.8 kg) were extracted with hot 70% EtOH to give the extract (78 g) (fr. A). Fr. A was suspended in water and extracted with Et_2O under acidic conditions (pH 3) to afford the Et_2O-soluble fraction (fr. B, 14.2 g) and H_2O-soluble fraction (fr. C, 62.0 g).

Fr. B (active in the CPE test) was dissolved in Et_2O and extracted first with $NaHCO_3$ solution (pH 9) and next with NaOH solution (pH 12), followed by extraction with Et_2O again after neutralization of each alkaline solution to afford acidic (fr. D, 1.2 g) and weakly acidic fractions (fr. E, 3.6 g), and the neutral fraction (fr. F, 9.2 g) from the alkali insoluble Et_2O layer.

Constituents of the Active Fraction (Fr. E)——Fr. E (3.1 g), showing activity in the CPE test and an inhibitory effect on HCl, was chromatographed on silica gel to give fr. 1 (0.50 g), fr. 2 (0.52 g), fr. 3 (1.1 g) and fr. 4 (0.98 g) from the eluates with a $CHCl_3$–MeOH gradient system.

Fr. 1 and fr. 2 showing an inhibitory effect in the HCl test were repeatedly chromatographed together on silica gel with *n*-hexane–AcOEt (5:1—3:1) to give **1** (155 mg), **2** (73 mg), **3** (41 mg) and **4** (21 mg).

2,7-Dihydroxy-3,4-dimethoxyphenanthrene (1)——Colorless needles, mp 157—158 °C ($CHCl_3$–MeOH). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.68; H, 5.19. UV λ_{max}^{MeOH} nm (log ε): 364 (3.18), 346 (3.14), 303 (3.82), 292 (4.08), 283 (4.15), 258 (4.85), 229 (4.13). MS *m/z*: 270.0926 (M^+, Calcd for $C_{16}H_{14}O_4$: 270.0891), 255, 212. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1610, 1575 (phenyl nucleus). ^{1}H-NMR (in acetone-d_6): Table III.

2,7-Diacetoxy-3,4-dimethoxyphenanthrene (1a)——**1** was acetylated with acetic anhydride and pyridine at room temperature overnight and the mixture was added dropwise to iced water to yield **1a**, colorless needles, mp 157—160 °C (*n*-hexane–AcOEt). MS *m/z*: 354 (M^+), 312 ($M^+ - CH_2CO$), 270 ($M^+ - 2CH_2CO$, base peak), 255, 212. IR ν_{max}^{KBr} cm^{-1}: 1760, 1620, 1560. ^{1}H-NMR (in acetone-d_6): Table III.

2,7-Dihydroxy-3,4,8-trimethoxyphenanthrene (2)——Colorless needles, mp 197—199 °C ($CHCl_3$–AcOEt). UV λ_{max}^{MeOH} nm (log ε): 367 (3.36), 349 (3.31), 331 (3.12), 307 (4.15), 295 (4.27), 286 (4.39), 263 (4.91), 230 (4.49). MS *m/z*: 300.0982 (M^+, Calcd for $C_{17}H_{16}O_5$: 300.0997), 285, 253, 242, 227. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1615, 1605, 1575 (phenyl nucleus). ^{1}H-NMR (in acetone-d_6): Table III.

2,7-Diacetoxy-3,4,8-trimethoxyphenanthrene (2a)——**2** was acetylated by the method described above to yield **2a**, colorless needles, mp 159—161 °C. MS *m/z*: 384 (M^+), 342 ($M^+ - CH_2CO$), 300 ($M^+ - 2CH_2CO$, base peak), 285, 253, 242, 227. IR ν_{max}^{KBr} cm^{-1}: 1760, 1615, 1600, 1570. ^{1}H-NMR (in acetone-d_6): Table III.

2,7-Dihydroxy-3,4-dimethoxy-9,10-dihydrophenanthrene (3)——Colorless columns, mp 132—134 °C ($CHCl_3$). UV λ_{max}^{MeOH} nm (log ε): 281 (4.27), 216 (4.36). MS *m/z*: 272.1072 (M^+, Calcd for $C_{16}H_{16}O_4$: 272.1048), 257, 225, 214. IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1615, 1590 (phenyl nucleus). ^{1}H-NMR (in acetone-d_6) δ: 2.63 (4H, s, H_2-9, 10), 3.71, 3.85 (each 3H, s, OMe), 6.56 (1H, s, H-1), 6.68—6.79 (2H, m, H-6, 8), 8.08 (1H, d, J=9.2 Hz, H-5), 7.56, 8.21 (each 1H, br s, OH). ^{13}C-NMR (in acetone-d_6) δ: 61.0, 61.2 (each q, OMe), 118.8 (d, C-1), 114.1* (d, C-8), 115.3* (d, C-6), 120.6 (s, C-12), 125.4 (s, C-11), 129.1 (d, C-13), 129.1 (s, C-5), 135.1 (s, C-14), 140.1 (s, C-3), 149.6 (s, C-2), 152.1 (s, C-4), 156.6 (s, C-7). * Assignments may be interchanged.

2,7-Diacetoxy-3,4-dimethoxy-9,10-dihydrophenanthrene (3a)——**3** was acetylated by the method described above to yield **3a**, colorless columns, mp 128—130 °C. MS *m/z*: 356 (M^+), 314 ($M^+ - CH_2CO$, base peak), 272 ($M^+ - 2CH_2CO$), 257, 225. IR ν_{max}^{KBr} cm^{-1}: 1765, 1610, 1590. ^{1}H-NMR (in $CDCl_3$) δ: 2.31, 2.34 (each 3H, s, OAc), 2.75 (4H, s, H_2-9, 10), 3.74, 3.90 (each 3H, s, OMe), 6.73 (1H, s, H-1), 6.96—7.02 (2H, m, H-6, 8), 8.32 (1H, d, J=9.2 Hz, H-5).

Dehydrogenation of 3a——DDQ (8.5 mg) was added to **3a** (5 mg) in dry benzene (5 ml) and the mixture was refluxed for 12 h. The benzene solution was washed with saturated $NaHCO_3$ solution, dried and evaporated under reduced pressure, yielding the phenanthrene (3.5 mg), which was identical with **1a** in terms of the ^{1}H-NMR spectrum.

3,4′-Dihydroxy-5,5′-dimethoxydihydrostilbene (4)——Colorless oil. UV λ_{max}^{MeOH} nm ($\log\varepsilon$): 281 (3.61), 226 (4.07). MS *m/z*: 274.1188 (M^+, Calcd for $C_{16}H_{18}O_4$: 274.1204), 137 (base peak), 85, 83. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1610, 1595 (phenyl nucleus). ^{1}H-NMR (in $CDCl_3$) δ: 2.80 (4H, s, bridge methylene), 3.74, 3.83 (each 3H, s, OMe), 5.18, 5.52 (each 1H, br s, OH), 6.24 (2H, d, J=1.8 Hz, H-2, 6), 6.30 (1H, d, J=1.8 Hz, H-4), 6.61 (1H, d, J=1.8 Hz, H-6′), 6.65 (1H, d, J=7.3 Hz, H-3′), 6.83 (1H, dd, J=7.3, 1.8 Hz, H-2′). ^{13}C-NMR (in $CDCl_3$) δ: 37.2, 38.2 (each t, bridge methylene), 55.2, 56.0 (each q, OMe), 99.1 (d, C-4), 106.7 (d, C-6), 108.3 (d, C-2), 111.3 (d, C-6′), 114.3 (d, C-3′), 121.0 (d, C-2′), 133.7 (s, C-1′), 143.8 (s, C-1), 144.5* (s, C-4′), 146.3* (s, C-5′), 156.9 (s, C-3), 160.8 (s, C-5). * Assignments may be interchanged.

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