

1,3-DIARYL-PROPANES AND PROPAN-2-OLS FROM *VIOLA* SPECIES*

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Key Word Index—*Viola elongata*; *V. minutiflora*; Myristicaceae; 1,3-diarylpropane; 1-aryl-3-cyclohexenonepropane; (2R)-1,3-diarylpropan-2-ols; virolane; virolaflorine; virolanol.

Abstract—The trunk woods of two Amazonian Myristicaceae, *Viola minutiflora* and *V. elongata*, contain respectively 1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane (virolane) besides 1-(1,5-dihydroxy-4-methoxycyclohex-3-en-2-one)-3-(3,4-methylenedioxyphenyl)-propane (virolaflorine) and three 2-hydroxy-1,3-diarylpropanes substituted in the aromatic rings by 2-OH-4-OMe/3,4-O₂CH₂ (virolanol), 2,4-diOH/3-OMe-4-OH (virolanol B), 2-OH-4-OMe/3-OMe-4-OH (virolanol C) besides (2R,3S)-7,3',4'-trihydroxyflavan-3-ol (fisetinidol).

INTRODUCTION

Schultes' writings [2] on the widespread hallucinogenic and other use in South America of myristicaceous trees sparked interest in their chemical constitution [3]. As a result, among other new natural compounds, two novel flavonoid types, the 1,3-diarylpropanes and the 1,3-diarylpropan-2-ols were discovered. Virolane (1), the first 1,3-diarylpropane to be described [4], has so far been located in ten *Viola* spp., while eight other representatives of this type including the oxidative derivative spiroelliptin [5], have been located in six *Iryanthera* species. Interestingly enough, virolane proper has not yet been isolated from any *Iryanthera*. In *Viola* it is commonly accompanied by virolanol, the first and so far only 1,3-diarylpropan-2-ol described [4].

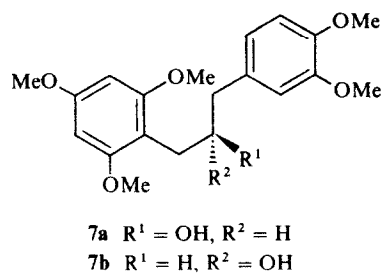
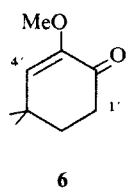
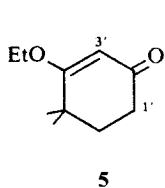
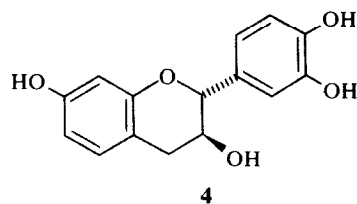
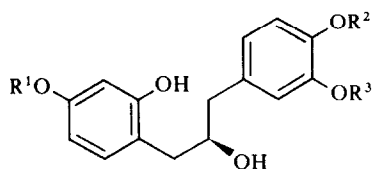
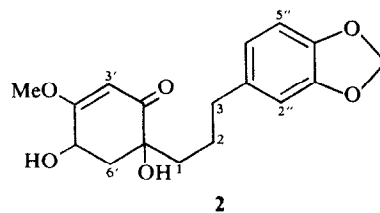
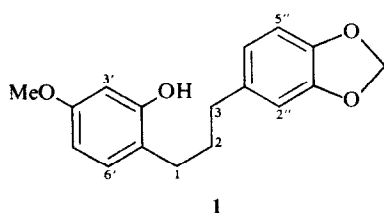
This paper reports the isolation from the trunk wood of *Viola minutiflora* of virolane (1) and of a novel oxidative derivative, virolaflorine (2). The species is not mentioned in Schultes' papers and no previous chemical analyses have been published. In opposition, *V. elongata*, *V. cuspidata*, *V. rufula* and *V. theiodora* received extensive, separate treatment by Schultes [6]. Rodrigues, the botanist who classified the specimens used in the present work, negates the existence of any significant morphological differences and considers the three latter binomials synonyms of *V. elongata* [7]. We herewith report the presence in its trunk wood of virolanol (3a) and of two novel 1,3-diarylpropan-2-ols, virolanol B (3b) and virolanol C (3c). (–)-Fisetinidol (4), a further constituent of the wood, was isolated previously from *Acacia molissima* [8].

RESULTS

Virolaflorine, C₁₅H₁₃O(OH)₂OMe.O₂CH₂, such as the co-occurring virolane (1), possesses a piperonyl group linked to a trimethylene chain (2). This fact, suggested by ¹H and ¹³C NMR signals (Table 1), was confirmed by irradiation of the C-1 and C-2 protons (δ 1.5–1.7), whereupon the 2 H-3 triplet collapsed into a singlet. This triplet was assigned to the benzylic methylene protons, since upon irradiation at its frequency (δ 2.51) the aromatic H-2'' and H-6'' signals became sharper. In this experiment double resonance involved additionally another methylene proton (H-6') represented by a double doublet at δ 2.55. This H-6' is coupled not only to its methylene partner (*J* = 13 Hz, δ 1.96), but also to the vicinal H-5' (*J* = 5.5 Hz) whose chemical shift (δ 4.46) indicates its carbinolic and allylic nature. Indeed, double irradiation at δ 4.46 simplified not only the two H-6' double doublets into doublets (*J* = 13 Hz), but also the HO-5' and olefinic H-3' (δ 5.34) doublets into singlets.

Additional clues to the particular allylic relationship of H-5' and H-3' (*J* = 1 Hz) resulted from two types of evidence. On the one hand, ¹³C NMR comparisons with the model compounds 5 [9] and 6 [10] (Table 2) indicated that the α,β-unsaturated ketone group (ν_{max} 1680 cm^{−1}) is indeed β-substituted by an oxy-group. On the other hand, irradiation at the frequency of the olefinic proton (δ 5.34) transformed the *ddd* (in presence of D₂O) of H-5' into a *dd*. The fact that addition of D₂O simplifies the signal of the proton at C-5' (*dddd* to *ddd*) is already proof for the substitution of this carbon atom by a free hydroxyl. Further evidence stems from the 1.15 ppm downfield shift of the H-5' signal upon acetylation. Only a monoacetate is obtained in this reaction. The second hydroxyl thus should be tertiary and linked to the sole fully substituted sp³-carbon (C-1', δ 75.2, *s*) of the molecule. The remaining three positions of C-1' can only be occupied by the piperonyltrimethylene group and the

*Part XV in the series "The Chemistry of Brazilian Myristicaceae". For Part XIV see ref. [1]. Based on part of the Doctorate thesis presented by A. K. to Universidade de São Paulo (1980).

Table 1. ^{13}C NMR (22.6 MHz, CDCl_3 -MeOH) and ^1H NMR (270 MHz, CDCl_3) data for virolaflorine (**2**)

Position	^{13}C	^1H		Irradiation at *			D_2O	
	δ <i>m</i>	δ <i>m</i>	<i>J</i> (Hz)	<i>m J</i>	<i>m m J</i>	<i>m</i>	<i>m</i>	<i>J</i>
1	37.3 <i>t</i>	1.5–1.7 <i>m</i>		*		altered		
2	25.0 <i>t</i>							
3	35.6 <i>t</i>	2.51 <i>t</i>			<i>s</i>	*		
1'	75.2 <i>s</i>	—						
2'	201.3 <i>s</i>	—						
3'	98.5 <i>d</i>	5.34 <i>d</i>	1	<i>s</i>			*	
4'	177.5 <i>s</i>	—						
5'	66.0 <i>d</i>	4.46 <i>dddd</i>	1, 3, 5.5, 10	*	<i>ddd</i> 1, 3, 10		<i>dd</i> 5.5, 10	
6'	41.1 <i>dd</i>	1.96 <i>dd</i>	10, 13	<i>d</i> 13	altered			
		2.55 <i>dd</i>	5.5, 13	<i>d</i> 13	*			
1''	135.8 <i>s</i>	—						
2''	108.9 <i>d</i>	6.64 <i>d</i>	2					
3''	147.7 <i>s</i>	—						
4''	145.7 <i>s</i>	—						
5''	108.2 <i>d</i>	6.70 <i>d</i>	8					
6''	121.2 <i>d</i>	6.58 <i>dd</i>	2, 8					
MeO-4'	56.7 <i>q</i>	3.78 <i>s</i>						
CH ₂ O ₂ -3'', 4''	100.8 <i>t</i>	5.91 <i>s</i>						
HO-1'	—	3.70 <i>s</i>						
HO-5'	—	2.88 <i>d</i>	3	<i>s</i>				

Table 2. NMR data (δ) for the enone systems of virolaflorine (2) and model compounds 5 and 6

	2	5	6
C-2'	201.3	198.9	193.0
C-3'	98.5	101.2	150.4
C-4'	177.5	175.6	116.7
H-3'	5.34	5.36	—
H-4'	—	—	5.60

terminals of the $-\text{CH}_2\text{CHOH.COMe}=\text{CH.CO}-$ chain. Indeed it must be the methoxyl which occupies the position on the double bond. A retro-Diels-Alder type cleavage of the cyclohexenone ring produced a mass spectral fragment m/z 114 (88), due presumably to $[\text{CHOH}=\text{COMe}-\text{CH}=\text{C}=\text{O}]^+$.

Comparison, by ^1H NMR, of the known virolanol (3a) [4], $\text{C}_{15}\text{H}_{11}(\text{OH})_2\text{OMe.O}_2\text{CH}_2$, with virolanol B (3b), $\text{C}_{15}\text{H}_{11}(\text{OH})_4\text{OMe}$, and virolanol C (3c), $\text{C}_{15}\text{H}_{11}(\text{OH})_3(\text{OMe})_2$ including consideration of the derived acetates, made the constitutional elucidation of the new compounds a trivial matter. The assignment of their 2*R*-configuration was based on the fact that the ORD curves of all three compounds, as well as of the model 7a, show troughs in the 300 nm region, while the analogous curve of the enantiomeric 7b shows a peak at 300 nm. Both 7a and 7b were prepared by Na/NH_3 reduction of the corresponding catechin ethers and *O*-methylation [11].

DISCUSSION

Hydrogenolysis of catechins has been evoked for the rationalization of the biosynthesis of 1,3-diarylpropan-2-ols [12], a postulate which receives support through the co-occurrence in *V. elongata* of the virolanols (3a, 3b, 3c) with (–)-fisetinidol (4) of identical stereochemistry at the carbinolic carbon. Analogously hydrogenolysis of flavans, which are also well represented in Myristicaceae but have curiously so far been found only in *Iryanthera* species [3], may rationalize the biosynthesis of 1,3-diarylpropanes such as virolanol (1) and its oxidation product virolaflorine (2).

EXPERIMENTAL

Isolation of constituents from *V. minutiflora* Ducke. Plant material was collected on non-inundable terrain (terra firme), at km 127 of the Santarém-Cuiabá road, on the right margin of Igarapé do Muju (Tapajoz Basin), Itaituba District, Pará State. Air dried trunk wood was reduced to powder (20 kg) and percolated with C_6H_6 . The extract (16 g) was chromatographed on Si gel (350 g). Elution (300 ml fractions) was performed with: $\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$, 1:1 (fractions 1–5); C_6H_6 (6–9); $\text{C}_6\text{H}_6-\text{EtOAc}$, 4:1 (10–29); and 3:2 (30–37). Evaporation of fractions 1–5 and 20–29 gave oily aliphatic material (4 and 3 g respectively) which was not examined further. Evaporation of the other fractions gave solids which were recrystallized from the indicated solvents: fractions 6–9 (MeOH) gave sitosterol (920 mg); 10–21 ($\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$) gave 1 (840 mg); 30–37 ($\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$) gave 2 (500 mg).

Isolation of constituents from *V. elongata* (Spr. ex Benth.) Warb. Plant material was collected on the right margin of Rio Madeira at km 6 of the Transamazonian Road, linking Humaitá (Amazonas State) to Itaituba. Air dried trunk wood was reduced

to powder (2.5 kg) and percolated successively with C_6H_6 and EtOAc. The C_6H_6 extract (5 g) was chromatographed on Si gel (100 g). Elution, with mixtures of $\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$ of increasing polarity, gave first oily aliphatic material (3 g) and then a solid which upon recrystallization from MeOH gave sitosterol (1 g). The EtOAc extract (10 g) was chromatographed on Si gel (250 g). Elution (300 ml fractions) was performed with CHCl_3 (fractions 1–7, 1st group); $\text{CHCl}_3-\text{EtOAc}$, 9:1 (8–21, 2nd group) and 4:1 (22–27, 3rd group). The 3 groups were evaporated. The residue of the 1st group (3 g) was rechromatographed on Si gel (100 g). Elution (300 ml fractions) was performed with $\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$, 1:1 (fractions 1–9), 3:7 (10–13) and 1:4 (14–18). Fractions 1–3 gave aliphatic material and 4–9 gave sitosterol (380 mg). The solid residue of fractions 10–13 was recrystallized from $\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$ to 3a (190 mg). The residue of fractions 14–18 was purified by prep. TLC (Si gel, $\text{C}_6\text{H}_6-\text{EtOAc}$, 7:3) to 3c (100 mg). The residue of the 2nd group of fractions (1.3 g) was separated by prep. TLC (Si gel, $\text{C}_6\text{H}_6-\text{EtOAc}$, 1:1) into 3b (825 mg) and 1 (715 mg). The residue of the 3rd group was purified in the same way to 4 (800 mg).

1-(2-Hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)propane (virolane, 1), identified by comparison with an authentic sample [4].

1-(1,5-Dihydroxy-4-methoxycyclohex-3-en-2-one)-3-(3,4-methylenedioxyphenyl)propane (virolaflorine, 2), mp 152–3° ($\text{C}_6\text{H}_{14}-\text{C}_6\text{H}_6$) [M found 320.1320; $\text{C}_{17}\text{H}_{20}\text{O}_6$ requires: 320.1260]. $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3475, 1680, 1640, 1510, 1475, 1390, 1200, 1170. $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 243, 283 (ϵ 19 150, 5150). MS (m/z): 321 (18%) $M + 1$, 320 (95) M^+ , 191 (25), 163 (10), 149 (12), 135 (100), 114 (88), 86 (93), 77 (32), 56 (62). Monoacetate, prepared by treatment of 1 with Ac_2O -pyridine at room temp., mp 137–8° (purified by TLC). $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3442, 1739, 1667, 1613, 1493, 1439, 1370, 1258, 1124, 985, 926. ^1H NMR (60 MHz, CDCl_3 , δ): 1.5–1.9 (*m*, 2H-1, 2H-2), ca 2.0 (*m*, H-6'), 2.25–2.65 (*m*, H-6', 2H-3), 3.7 (*s*, MeO-4'), 5.37 (*d*, $J = 1$ Hz, H-3'), 5.5–5.85 (*m*, H-5'), 5.86 (*s*, O_2CH_2), 6.55–6.7 (*m*, H-2", H-5", H-6"). MS (m/z): 343 (5%) $M + 1$, 342 (24), M^+ , 320 (45), 302 (22), 284 (23), 191 (17), 149 (32), 135 (51), 114 (47), 111 (51), 43 (100).

(2*R*)-2-Hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)propane (virolanol, 3a), identified by comparison with an authentic sample [4]. $[\alpha]_{\text{D}}^{25}$ (MeOH, $c = 0.4$) -1° . ORD (MeOH): $[\phi]_{350} - 1250$, $[\phi]_{330} - 1550$, $[\phi]_{320} - 1400$, $[\phi]_{295}^{\text{r}} - 2300$, $[\phi]_{285}^{\text{r}} 0$.

(2*R*)-2-Hydroxy-1-(2,4-dihydroxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane (virolanol B, 3b), mp 62–3° (purified by TLC [M found: 290.1130; $\text{C}_{16}\text{H}_{18}\text{O}_5$ requires: 290.1154]. $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3333, 3125, 1600, 1505, 1449, 1031, 970. $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 220, 279 (ϵ 13250, 7600); no AlCl_3 and $\text{H}_3\text{BO}_3 + \text{NaOAc}$ shifts; $\lambda_{\text{max}}^{\text{MeOH} + \text{NaOH}}$ nm: 283 (ϵ 7250). Gibbs test [13]: positive. ^1H NMR [60 MHz, $(\text{CD}_3)_2\text{CO}$, δ): 2.65–2.85 (*m*, 2H-1, 2H-3), 3.83 (*s*, MeO-3"), 3.9–4.4 (*m*, H-2), 6.34 (*dd*, $J = 2$ and 8 Hz, H-6'), 6.43 (*d*, $J = 2$ Hz, H-3'), 6.7–7.0 (*m*, H-6', H-2", H-5", H-6"), MS (m/z): 290 (40%) M^+ , 167 (20), 166 (20), 153 (27), 138 (100), 137 (60), 124 (23), 123 (53), 107 (30), $[\alpha]_{\text{D}}^{25}$ (MeOH, $c = 0.57$) -1° . ORD (MeOH): $[\phi]_{350} 0$, $[\phi]_{290}^{\text{r}} - 550$, $[\phi]_{285} 0$. Tetraacetate, oil [M found: 458.1502; $\text{C}_{24}\text{H}_{26}\text{O}_9$ requires: 458.1569]. $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1770, 1730, 1613, 1504, 1429, 1370, 1250–1200, 909, 757. ^1H NMR (270 MHz, CDCl_3 , δ): 1.94 (*s*, AcO-2), 2.15, 2.25, 2.28 (3*s*, 3 AcO-Ar), 2.74 (*dd*, $J = 6$ and 14 Hz, H-3), 2.75 (*dd*, $J = 6$ and 14 Hz, H-1), 2.84 (*dd*, $J = 7$ and 14 Hz, H-3), 2.86 (*dd*, $J = 7$ and 14 Hz, H-1), 3.8 (*s*, MeO-3'), 5.18 (*tt*, $J = 6$ and 7 Hz, H-2), 6.76 (*dd*, $J = 2$ and 8 Hz, H-6'), 6.79 (*d*, $J = 2$ Hz, H-2"), 6.89 (*d*, $J = 2.5$ Hz, H-3'), 6.91 (*d*, $J = 8$ Hz, H-5'), 6.95 ($J = 2.5$ and 8.5 Hz, H-5'), 7.23 (*d*, $J = 8.5$ Hz, H-6'). MS (m/z): 458 (3%) M^+ , 416 (8), 398 (3), 356 (45), 314 (20), 272 (20), 137 (45), 123 (35), 52 (48), 43 (100).

(2R)-2-Hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)-propane (virolanol C, **3c**), oil, $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}): 3390, 1613, 1575, 1504, 1449, 1429, 1361, 1266, 1196, 1156, 1117, 1039. $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 220, 279 (ϵ 21 700, 7600); no AlCl_3 or H_3BO_3 + NaOAc shifts; $\lambda_{\text{max}}^{\text{MeOH} + \text{NaOH}}$ nm: 242, 291 (ϵ 18 500, 8350). Gibbs test [13]: positive. $^1\text{H NMR}$ (60 MHz, CDCl_3 , δ): 2.7–2.95 (*m*, 2H-1, 2H-3), 3.8 and 3.9 (2*s*, 2MeO), 4.0–4.3 (*m*, H-2), 5.6 (*br. s*, OH), 6.42 (*dd*, $J = 2$ and 8 Hz, H-5'), 6.51 (*d*, $J = 2$ Hz, H-3'), 6.7–6.8 (*m*, H-2'', H-5'', H-6''), 6.97 (*d*, $J = 8$ Hz, H-6'). MS (m/z): 304 (4%) M^+ , 256 (6), 218 (4), 213 (6), 187 (4), 167 (7), 143 (25), 137 (45), 95 (32), 74 (63), 60 (58), 43 (100). $[\alpha]_{\text{D}}^{25}$ (MeOH, $c = 0.3$) -1° . ORD (MeOH): $[\phi]_{350} - 2000$, $[\phi]_{290} - 2350$, $[\phi]_{280} - 2050$. Triacetate, mp 123–4° (purified by TLC). $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}): 1770, 1730, 1610, 1510, 1470, 1215, 1160, 955, 905. $^1\text{H NMR}$ (60 MHz, CDCl_3 , δ): 1.97 (*s*, AcO-2), 2.17 and 2.3 (2*s*, 2AcO-Ar), 2.65–2.95 (*m*, 2H-1, 2H-3), 3.77 and 3.8 (2*s*, 2MeO), 5.17 (*quintet*, $J = 7$ Hz, H-2), 6.6 (*d*, $J = 2$ Hz, H-3'), 6.66 (*dd*, $J = 2$ and 8 Hz, H-5'), 6.78 (*m*, H-2'', H-6''), 6.9 (*d*, $J = 8$ Hz, H-5''), 7.1 (*d*, $J = 8$ Hz, H-6'). MS (m/z): 431 (2%) $\text{M}^+ + 1$, 430 (6) M^+ , 370 (15), 329 (10), 328 (80), 286 (36), 285 (25), 150 (15), 137 (100), 43 (45).

(2R,3S)-7,3',4'-Trihydroxyflavan-3-ol [(–)-fisetinidol, **4**], mp 210–2° (C_6H_6 – Me_2CO), $[\alpha]_{\text{D}}$ (Me_2CO – H_2O , 1:1, $c = 0.3$) -10° . Lit. [8] gives mp 211–4°, $[\alpha]_{\text{D}}$ (same solvent) -9° , but no spectral data. $\nu_{\text{max}}^{\text{KBr}}$ (cm^{-1}): 3333–3226, 1600, 1504, 1443, 1414, 1220, 1163, 1111, 1064, 1008. $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 281 (ϵ 11 500), $\lambda_{\text{max}}^{\text{MeOH} + \text{NaOH}}$ nm: 285 (ϵ 11 350), $\lambda_{\text{max}}^{\text{MeOH} + \text{AlCl}_3}$ nm: 288 (ϵ 12 050). Gibbs test [13]: positive. $^1\text{H NMR}$ [60 MHz, $(\text{CD}_3)_2\text{CO}$, δ]: 2.7–3.0 (*m*, 2H-4), 4.20 (*ca dq*, $J = 2$ and 7 Hz, H-3), 4.7 (*d*, $J = 7$ Hz, H-2), 6.43 (*d*, $J = 2$ Hz, H-8), 6.46 (*dd*, $J = 2$ and 8 Hz, H-6), 6.83 (*br. s*, H-2', H-5', H-6'), 6.93 (*d*, $J = 8$ Hz, H-5). MS (m/z): 274 (32%) M^+ , 256 (20), 152 (52), 123 (100). ORD (MeOH): $[\phi]_{350} - 1100$, $[\phi]_{295} - 2750$, $[\phi]_{290} 0$, $[\phi]_{280} + 1100$, $[\phi]_{263} + 530$, $[\phi]_{250}^{\text{pk}} + 2000$. Tetraacetate, $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}): 1770, 1740, 1626, 1504, 1429, 1370, 1250, 901, 789. $^1\text{H NMR}$ (60 MHz, CCl_4 , δ): 1.93 (*s*, AcO-3), 2.20 (*s*, AcO-Ar), 2.23 (*s*, 2AcO-Ar), 2.8–3.05 (*m*, H-4), 5–5.3 (*m*, H-2, H-3), 6.5 (*dd*, $J = 2$ and 8 Hz, H-6), 6.57 (*d*,

$J = 2$ Hz, H-8), 6.75–7.2 (*m*, H-5, H-2', H-5', H-6'). MS (m/z): 442 (1%) M^+ , 400 (1), 382 (8), 340 (12), 298 (12), 256 (12), 157 (15), 149 (55), 83 (85), 43 (100).

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