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Neolignans from *Piper aequale*

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Abstract

Two new benzofuran type neolignans were isolated from the aerial parts of *Piper aequale*. Their structures were elucidated on the basis of spectroscopic evidence as (2*R*,3*R*)-2,3-dihydro-2-(4-hydroxyphenyl)-5-methoxy-3-methyl-7–propenylbenzofuran and 2-hydroxy-4,4′-bis[3-methyl-5-(*E*)-propenyl)benzofuran-2-yl] diphenylether, a dineolignan.

Keywords: Piper aequale; Piperaceae; Neolignans; Dineolignan

1. Introduction

In our continuing studies on the chemistry of *Piper* species in Trinidad (Maxwell & Rampersad, 1988, 1989a,b,c, 1991), we have investigated *Piper aequale* C.DC., a tall shrub found in moist, shady locations. To the best of our knowledge, no phytochemical studies have been done on this plant nor are there any reports of its use in folk medicine. From the acetone extract of the aerial parts of *P. aequale*, we isolated ten benzofuranoid neolignans, three (**4**, **8** and **10**) of which are new natural products.

2. Results and discussion

The ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** showed the characteristic features of the *trans*-2-aryl-3-methyl-2,3-dihydrofuran system and the mass spectral data supported the structures shown. Compound **2** was previously isolated from *Krameria cystisoides* and its spectral data closely matched those reported (Achenbach, Groß, Dominguez, Cano, Verde Star, Brussolo et al., 1987). The spectral data for **1** were virtually identical to those reported for conocarpan (Hayashi & Thomson, 1975; Achenbach et al., 1987). Achenbach, Groß, Dominguez, Cano, Verde Star, Brussolo et al. (1987) used the positive Cotton effect observed at 260 nm to assign the 2*R*,3*R* configuration to conocarpan, which exhibited a positive $[\alpha]_D$. The negative sign of the $[\alpha]_D$ we obtained for **1** suggests the 2*S*,3*S* configuration in **1**.

Compound **3** gave ^{1}H and ^{13}C NMR data very similar to those of **1** except for the absence of signals for the *trans* propenyl moiety and the presence of signals (δ_H 9.87, δ_C 190.8) indicating an aldehydic moiety. The data indicated that **3** was identical to decurrenal (Chauret et al., 1996).

Comparison of the 500 MHz ^{1}H NMR spectra of **1** and **4** showed that they differed in the benzene ring of the benzofuran moiety. The three proton ABX system was replaced by signals for two *meta* protons (δ 6.61, *br s* and δ 6.63, *br s*) and a methoxy group was indicated (3H, s, δ 3.87). Further, a 2H doublet at δ 3.35 ($J = 8.8$ Hz) and vinyl protons at δ 5.10 (*m*) and δ 5.97 (*m*) suggested a 2-propenyl instead of a 1-propenyl side chain as in **1**. The location of the –OMe and 2-propenyl groups was confirmed by HMBC. Thus, both the H-4 (δ 6.61) and H-6 (δ 6.63) signals showed correlations to C-7a (δ 145.6) while the benzylic protons at C-8 gave a cross peak only to C-6 (δ 111.7). A NOE difference experiment established the *trans* relative stereochemistry at C-2 and C-3. Irradiation of the methyl signal at δ 1.35 resulted in enhancement (4.4%) of the signal for H-2. The ^{13}C NMR and HREIMS ($[M]^+$ *m/z* 296.1418, $C_{19}H_{20}O_3$ requires 296.1412)

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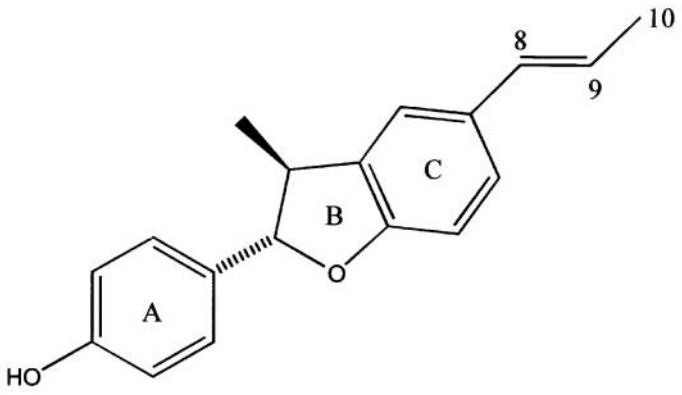

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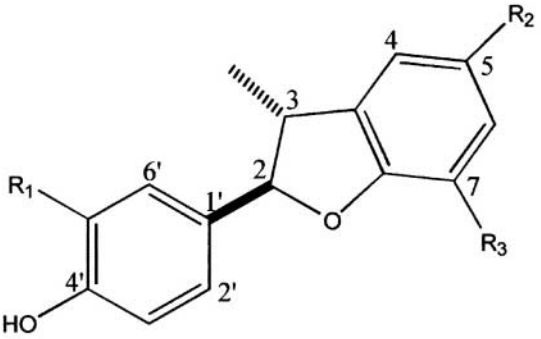
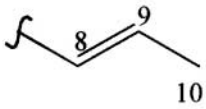
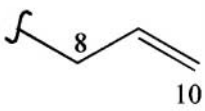


2 R_1 = -OMe R_2 =  R_3 = H

3 R_1 = H R_2 = -CHO R_3 = H

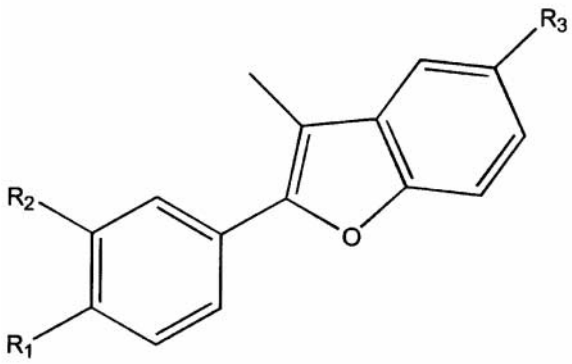
4 R_1 = H R_2 = -OMe R_3 = 

data further confirm the structure assigned to compound **4**, which is here reported for the first time.

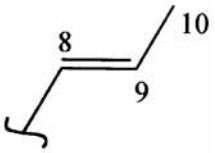
The features of the ^{1}H NMR spectrum of compounds **5**–**7** indicated the presence of the benzofuran ring. A methyl singlet appeared at about δ 2.40 in these compounds while the doublet at δ 5.07 and multiplet at δ 3.39 in the spectrum of **1** were absent. Comparison of the ^{13}C NMR data of **1** with those of compounds **5**–**7** showed the absence of the signals at δ 93.3) (C-2) and δ 45.6 (C-3) and the appearance of signals at δ 150.9 and δ 110.1. Further, the C-3 methyl signal was shifted upfield from δ 17.6 for **1** to about δ 9.40 (Agrawal & Thakur, 1985) for **5**–**7**.

Compound **5** was previously isolated from *Krameria triandra* (Stahl & Ittel, 1981) and was named eupomatenoid 6 (Bowden, Ritchie, & Taylor, 1972). The ^{1}H and ^{13}C NMR and mass spectral data of **5** closely matched those reported (Bowden et al., 1972; Stahl & Ittel, 1981).

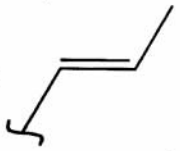
The ^{1}H NMR, ^{13}C NMR and mass spectral data allowed the identification of **6** as eupomatenoid 5, which was previously isolated from *Eupomatia laurina* (Bowden et al., 1972) while the ^{1}H and ^{13}C NMR data of **7** indicated its identity with eupomatenoid 3, which has also been isolated from the same plant (Bowden et al., 1972). We report here for the first time the ^{13}C NMR and mass spectral data of **7**.



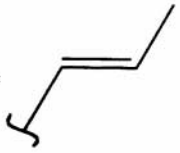
5 R_1 = OH R_2 = H R_3 =



6 R_1 = OH R_2 = -OMe R_3 =

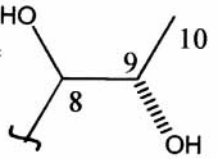


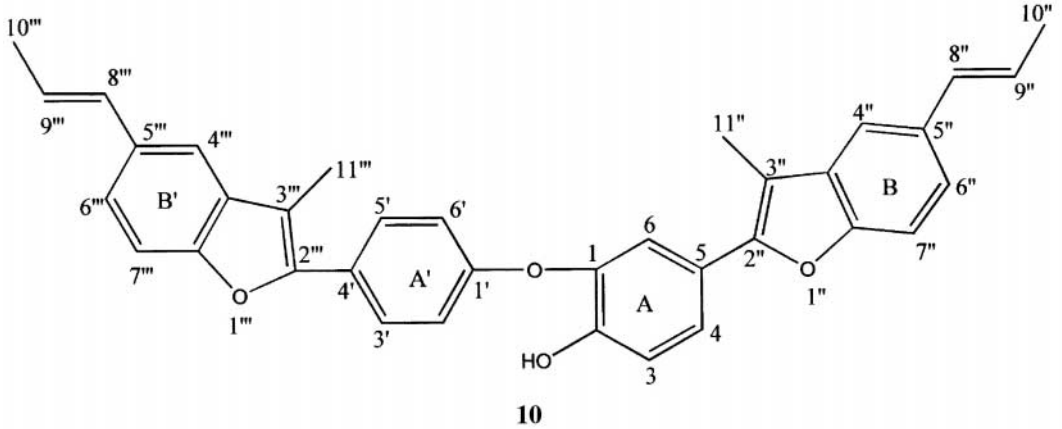
7 R_1,R_2 = $-OCH_2O-$ R_3 =



8 R_1,R_2 = $-OCH_2O-$ R_3 = $-CH_2\overset{8}{C}\overset{O}{\overset{\|}{}}\overset{10}{C}H_3$

9 R_1,R_2 = $-OCH_2O-$ R_3 =





10

While compounds **5** and **6** were previously reported from *Piper decurrens*, this is the first report of the occurrence of eupomatenoid 3 (Hayashi & Thomson, 1975) in the Piperaceae.

The 2-oxopropyl side chain ($-CH_2COCH_3$) in **8** was indicated by the presence of a 3H singlet at δ 2.18, a 2H singlet at δ 3.80 in its ^{1}H NMR spectrum and a signal at δ 207.2 for the carbonyl carbon in its ^{13}C

Table 1
NMR data for compound **10** (500 MHz, $CDCl_3$)

C	δ_H	δ_C	^1H–^1H COSY δ_H	HMBC δ_C
1	–	143.1	–	
2	–	147.3	–	
3	7.18	116.5	7.52	147.25, 143.06, 124.53
4	7.52	123.7	7.18	150.31, 147.25
5	–	124.5	–	
6	7.41	117.5	–	150.31, 147.25, 143.06, 123.7
1′	–	156.3	–	
2′,6′	7.20	118.0	7.80	156.22, 127.11, 117.99
3′,5′	7.80	128.3	7.20	156.22, 150.39
4′	–	127.1	–	
2″	–	150.3	–	
3″	–	110.3	–	
3″a	–	131.3	–	
4″	7.45	116.3	–	152.99, 131.11, 122.53, 110.35
5″	–	132.7	–	
6″	7.30	122.5	7.38	152.99, 131.1, 116.25
7″	7.38	110.8	7.30	132.71, 131
7″a	–	153.0	–	
8″	6.51	131.1	6.25, 1.91	122.35, 116.11, 18.55
9″	6.25	124.4	6.51, 1.91	132.62, 18.55
10″	1.91	18.6	6.25, 6.51	131.11, 124.29
11″	2.37	09.5	–	150.39, 131.33, 110.89
2‴	–	150.4	–	
3‴	–	110.9	–	
3‴a	–	131.3	–	
4‴	7.41	116.1	–	152.8, 113.1, 122.4
5‴	–	132.6		
6‴	7.25	122.4	7.32	152.8, 132.6, 131.1, 116.1
7‴	7.32	110.7	7.25	132.6
7‴a	–	152.4	–	
8‴	6.49	131.1	6.21, 1.89	122.4, 116.1, 18.6
9‴	6.21	124.3	6.49, 1.89	132.6, 18.6
10‴	1.89	18.6	6.21, 6.49	131.1, 124.3
11‴	2.45	09.4	–	150.4, 131.3, 110.9

NMR spectrum. HREIMS gave a $[M]^+$ at m/z 308.1052 (calcd for $C_{19}H_{16}O_4$, 308.1048) in agreement with the molecular formula. Compound **8** was previously synthesised from eupomatenoid 11 (Picker, Ritchie, & Taylor, 1973) but this is the first report of its occurrence as a natural product.

The IR spectrum indicated the presence of hydroxyl group(s) in the side chain of **9**. The HREIMS gave a $[M]^+$ at m/z 326.1158 indicating a molecular formula $C_{19}H_{18}O_5$ (calcd 326.1154) which suggested a 1,2-dihydroxypropyl side chain. The ^1H and ^{13}C NMR data corroborated this indication. Compound **9** was previously isolated from *Caryodaphnosis tonkinensis* (Ripperger, Anh, Himmelreich, Sung & Adam, 1995) by Ripperger et al., who established the relative stereochemistry of the side chain as *erythro*.

The structure of the novel natural product **10** was determined utilizing data from 1D and 2D NMR experiments (Table 1) as well as mass spectral data. The EIMS data of **10** gave a $[M]^+$ at m/z 526 (100%) and fragment ions at m/z 264 (32.8%) and 263 (27.6%). The HREIMS gave the formula $C_{36}H_{30}O_4$ ($[M]^+$ at m/z 526.2144). These data suggested that **10** was a dimer of **5**.

The ^1H and ^{13}C NMR spectra also indicated that **10** was a benzofuranoid dimer. The former showed signals for 30 protons and the latter gave 31 signals for the 36 carbons.

The HMQC, ^1H–^1H COSY and HMBC data enabled assignment of all the proton and carbon signals of the right benzofuran half of the molecule. Significantly, the data clearly indicated that ring A, which gives rise to an ABX system of proton signals at δ 7.18 (*d*, $J = 8.1$ Hz), δ 7.52 (*dd*, $J = 8.1$, 1.6 Hz) and δ 7.41 (*d*, $J = 1.6$ Hz), has two adjacent oxygen bearing carbons at C-1 (δ_C 143.1) and C-2 (δ_C 147.3). In the HMBC spectrum the proton at δ 7.18 gave cross peaks to both oxygenated carbons (δ_C 147.3 and 143.1) while the proton at δ 7.52 gave a cross peak with only one oxygenated—that at δ_C 147.3. This established this carbon as the C-2 carbon.

The structure of the left hand half of the dimer and the assignment of its proton and carbon signals followed from analysis of the HMQC, ^1H–^1H COSY and HMBC data. The aromatic ring A′ contained an AA′BB′ system of protons (δ 7.80, 2H, *d*, $J = 8.6$ Hz and δ 7.20, *d*, $J = 8.6$ Hz) and an oxygenated carbon (δ_C 156.2) at C-1′. The structure **10** for the dimer was thus indicated. To the best of our knowledge this is the first report of a dineolignan as a natural product.

3. Experimental

3.1. General

Mps: uncorr.; TLC and prep. TLC: silica gel 60 PF254 and 366, 0.25 and 1 mm layers, respectively; CC: silica gel 60, 70–230 mesh; EIMS (probe): 70 eV; NMR: ^1H, ^{13}C, ^1H–^1H COSY, HMQC ($^1J_{H-C} = 140$ Hz), HMBC ($^{2/3}J = 8$ Hz) and NOE spectra in $CDCl_3$ with TMS as int. standard on a Varian Unity-500 instrument.

3.2. Plant material

Aerial parts of *P. aequale* were collected at Maracas Waterfall, St. Joseph, Trinidad in May 1993. The plant material was identified by W. Johnson of the National Herbarium of Trinidad and Tobago at the U.W.I. where a voucher specimen (#32607) is on deposit.

3.3. Extraction and isolation

The air dried, milled plant material (2.2 kg) was exhaustively extracted with Me_2CO (15 l). Evaporation of the solvent under reduced pressure gave 142 g crude extract. Silica gel CC of a portion of the extract (10 g) eluting with petrol–Me_2CO mixtures of increasing polarity led to the five combined fractions. Fraction I was further separated by PLC on silica gel (petrol–Me_2CO, 49:1) to yield **7**. Fractions II–IV were combined and resubjected to silica gel CC using CH_2Cl_2–$CHCl_3$ mixtures. The combined fractions thus obtained were purified by silica gel prep. TLC using the solvent systems shown to yield **2** and **8** (petrol–$CHCl_3$, 3:2, ×3), **10** ($PhCH_3$–$CHCl_3$, 9:1), **1**, **5**, and **6** (CH_2Cl_2) and **3** and **4** (CH_2Cl_2–EtOAc, 20:1). Fraction V was rechromatographed (silica gel CC, $CHCl_3$–EtOAc mixtures). The crude compound isolated was purified by silica gel prep. TLC ($CHCl_3$–EtOAc, 3:2) to yield **9**.

3.3.1. (2S,3S)-2,3-dihydro-2-(4-hydroxyphenyl)-3-methyl-5-(E)-propenylbenzofuran (*1*)

Colourless crystals (440.7 mg), mp 128–130°C (lit. (Achenbach et al., 1987) mp 133–135°C for conocarpan), $[\alpha]_D^{25} = -103^\circ$ (MeOH; *c* 3.18) (lit. (Achenbach et al., 1987) $[\alpha]_D^{21} = +122^\circ$ (MeOH; *c* 1.03) for conocarpan).

3.3.2. (2R,3R)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran (*2*)

Colourless oil (17.2 mg), $[\alpha]_D^{25} = +84^\circ$ (MeOH; *c* 0.50) (lit. (Achenbach et al., 1987) $[\alpha]_D^{21} = +94^\circ$ (MeOH; *c* 1.10)).

3.3.3. Decurrenal (*3*)

Colourless viscous oil (5 mg), $[\alpha]_D^{25} = +32^\circ$ (MeOH; *c* 0.25); UV λ_{max} (MeOH) nm (log ε): 230 (3.38), 290 (3.20), 292 (3.20); +NaOH: 214 (4.58), 290 (4.34), 298 (4.33); IR ν_{max} (film) cm^{-1}: 3380, 1670, 1610.

3.3.4. (2R,3R)-2,3-dihydro-2-(4-hydroxyphenyl)-5-methoxy-3-methyl-7–propenylbenzofuran (*4*)

Colourless oil (53.3 mg), $[\alpha]_D^{25}$ +35° (MeOH, *c* 1.91); UV λ_{max} (MeOH) nm (log ε) = 210 (5.08), 228 (4.78), 282 (4.19); +NaOH: 212 (6.14), 238 (5.97), 246 (5.96); IR ν_{max} (film) cm^{-1}: 3420, 1610, 1510(sh), 1210, 960, 830; ^{1}H NMR: δ 1.35 (3H, *d*, *J* = 6.3 Hz, Me-3), 3.35 (2H, *d*, *J* = 8.8 Hz, H-8), 3.44 (1H, *m*, H-3), 3.87 (3H, *s*, –OMe), 5.10 (3H, *m*, H-2, H2-10), 5.54 (1H, *s*, –OH), 5.97 (1H, *m*, H-9), 6.61 (1H, *s*, H-4), 6.63 (1H, *s*, H-6), 6.78 (2H, *d*, AA′BB′ system, *J* = 7.5 Hz, H-3′, H-5′), 7.26 (2H, *d*, AA′BB′ system, *J* = 7.5 Hz, H-2′, H-6′); ^{13}C NMR: δ 17.6 (Me-3), 40.2 (C-8), 45.6 (C-3), 55.9 (–OMe), 93.3 (C-2), 111.7 (C-6), 115.4 (C-3′, C-5′), 115.6 (C-10), 115.7 (C4), 128.1 (C-2′, C-6′), 132.2 (C-3a), 133.1 (C-1), 133.4 (C-7), 137.9 (C-9), 143.8 (C-5), 145.6 (C-7a), 155.7 (C-4′); EIMS *m*/*z* (rel. int.): 296 $[M]^+$ (100.0), 295 (7.2), 281 (16.4), 267 (6.0), 255 (15.2), 253 (5.7), 240 (22.4), 239 (5.7), 238 (5.9), 189 (13.1), 107 (21.4), 77 (12.4); HREIMS *m*/*z*: 296.1418 $[M]^+$ ($C_{19}H_{20}O_3$ requires 296.1412).

3.3.5. 2-(4-hydroxyphenyl)-3-methyl-5-(E)-propenylbenzofuran (eupomatenoid 6) (*5*)

White crystals (96 mg), mp 156–157°C (lit. (Achenbach et al., 1987) mp 148–151°C).

3.3.6. 2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran (eupomatenoid 5) (*6*)

White crystals (32.5 mg), mp 113–115°C (lit. (Bowden et al., 1972) mp 114–115°C).

3.3.7. 2-(3,4-methylenedioxyphenyl)-3-methyl-5-(E)-propenylbenzofuran (eupomatenoid 3) (*7*)

Colourless needles (19.0 mg), mp 110.8–111.4°C (lit. (Bowden et al., 1972) mp 110°C); UV λ_{max} (MeOH) run (log ε): 214 (4.26), 216 (4.26), 240 (4.44), 256 (4.38), 300 (4.31), 304 (4.32), 320 (4.38); IR ν_{max} (Nujol) cm^{-1}: 1500, 1450, 1240, 1045, 960, 875; ^{1}H NMR: δ 1.95 (3H, *dd*, *J* = 7, 1.7 Hz, H-10), 2.42 (3H, *s*, Me-3), 6.02 (2H, *s*, –O–CH_2–O–), 6.22 (1H, *dq*, *J* = 155, 6.7 Hz, H-9), 6.52 (1H, *dq*, *J* = 15.5, 1.7 Hz, H-8), 6.91 (1H, *d*, *J* = 8.8 Hz, H-5′), 7.27 (1H, *dd*, *J* = 8.6, 1.7 Hz, H-6), 7.27 (1H, *s*, H-2′), 7.28 (1H, *dd*, *J* = 8.8, 1.0 Hz, H-6′), 7.35 (1H, *d*, *J* = 8.6 Hz, H-7), 7.42 (1H, *d*, *J* = 1.7 Hz, H-4); ^{13}C NMR: δ 9.5 (Me-3), 18.5 (C-10), 101.2 (–O–CH_2–O–), 107.1 (C-2′), 108.5 (C-5′), 110.1 (C-3), 110.6 (C-7), 116.1 (C-4), 120.9 (C-6′), 122.3 (C-6), 124.2 (C-9), 125.5 (C-1′), 131.2 (C-8), 131.4 (C-3a), 132.7 (C-5), 147.3 (C-4′), 147.9 (C-3′), 150.9 (C-2), 152.8 (C-7a); EIMS *m*/*z* (rel. int.): 292 $[M]^+$ (100), 278 (1.0), 264 (<1.0), 234 (3.5), 219 (4.0), 191 (3.0), 165 (6.0), 149 (5.6).

3.3.8. 2-(3,4-methylenedioxyphenyl)-3-methyl-5-(2-oxopropyl)benzofuran (*8*)

Colourless viscous oil (16 mg); UV λ_{max} (MeOH) mn (log ε): 216 (4.25), 316 (4.18); IR ν_{max} (fllm) cm^{-1}: 1710, 1610, 1500, 1240, 1040, 935; ^{1}H NMR: δ 2.18 (3H, *s*, –CO–CH_3), 2.41 (3H, *s*, Me-3), 3.80 (2H, *s*, –CH_2–CO), 6.03 (2H, *s*, –O–CH_2–O–), 6.93 (1H, *br, d*, *J* = 6.7 Hz, H-5′), 7.10 (1H, *dd*, *J* = 7.5, 1.5 Hz, H-6), 7.28 (1H, *br, s*, H-2′), 7.29 (1H, *dd*, *J* = 6.7, 1.5 Hz, H-6′), 7.33 (1H, *d*, *J* = 1.5 Hz, H-4), 7.41 (1H, *d*, *J* = 7.5 Hz, H-7); ^{13}C NMR: δ 9.5 (Me-3), 29.2 (C-10), 51.1 (C-8), 101.3 (–O–CH_2–O–), 107.2 (C-2′), 108.6 (C-5′), 110.0 (C-3), 111.0 (C-7), 119.8 (C-4), 121.0 (C-6′), 125.3 (C-1′), 125.4 (C-6), 128.3 (C-5), 131.7 (C-3a), 147.4 (C-4′), 147.9 (C-3′), 151.2 (C-2), 152.7 (C-7a), 207.2 (C-9); EIMS *m*/*z* (rel. int.): 308 $[M]^+$ (66.4), 265 (100.0), 251 (7.1), 235 (4.0), 207 (8.6), 178 (15.9), 149

(10.5), 57 (5.6); HREIMS m/z: 308.1052 $[M]^+$ ($C_{19}H_{16}O_4$ requires 308.1048).

*3.3.9. 2-(3,4-methylenedioxyphenyl)-5-(1,2-dihydroxypropyl)-3-methylbenzofuran (**9**)*

Amorphous solid (30.0 mg); $[\alpha]_D^{25} = +16^\circ$ ($CHCl_3$, c 1.50) (lit. (Ripperger et al., 1995) $[\alpha]_D^{25} = +12.0^\circ$ ($CHCl_3$; c 0.73)).

*3.3.10. Compound (**10**)*

Yellow viscous oil (16.1 mg); UV λ_{max} (MeOH) nm (log ε): 242 (5.06), 312 (4.76); IR ν_{max} (film) cm^{-1}: 3540, 1610, 1595, 1505, 1465, 965; ^1H NMR: Table 1; ^{13}C NMR: Table 1; EIMS m/z (rel. int.): 526 $[M]^+$ (100), 525 (5.4), 264 (32.8), 263 (27.6), 249 (10.5), 248 (21.9), 247 (7.2), 23 7 (11.8), 23 5 (7.1), 221 (7.8), 219 (7.4), 165 (6.6), 143 (5.3), 142 (6.7), 71 (6.6), 69 (10.7), 60 (5.3) 57 (11.9), 55 (9.7); HREIMS m/z: 526.2121 $[M]^+$ ($C_{36}H_{30}O_4$ requires 526.2144).

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