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FLAVONOIDS FROM *ARTOCARPUS HETEROPHYLLUS*

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Key Word Index—*Artocarpus heterophyllus*; Moraceae; flavanone; prenylflavone; 5,2′-dihydroxy-7,4′-dimethoxyflavanone; 8-(γ,γ-dimethylallyl)-5,2′,4′-trihydroxy-7-methoxyflavone; artocarpanone A; artocarpetin A; heterophylol; ^{13}C NMR.

Abstract—A new flavanone, a new prenylflavone, a novel phenolic compound, heterophylol, reported in a previous paper, and nine known flavonoids have been isolated from the root of *Artocarpus heterophyllus*. The two new flavonoids have been characterized as 5,2′-dihydroxy-7,4′-dimethyoxyflavanone and 8-(γ,γ-dimethylallyl)-5,2′,4′-trihydroxy-7-methoxyflavone, respectively.

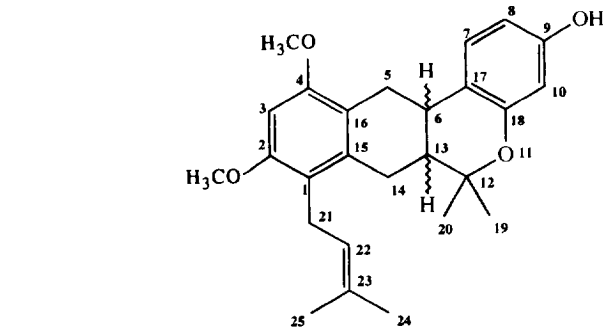
INTRODUCTION

In previous papers [1–3], we reported four new flavonoids, a new tridecyl docosanoate and a novel phenolic compound named heterophylol (**1**) [2] from the root bark of *Artocarpus heterophyllus*. In a continuing study of this plant, a new flavanone named artocapanone A (**2**), and seven known flavonoids, cycloartocarpin A [3], artocarpanone(**4**), artocarpetin(**5**), norartocarpetin(**6**), artocarpin(**7**), cyanomaclurin(**8**) and dihydromorin were isolated from the heartwood of the root, and a new prenylflavone, named artocarpetin A (**3**) and two known flavonoids, cudraflavone A and cycloheterophyllin were further obtained from the root bark. In this paper, we report the structural elucidation of the two new compounds and the ^{13}C NMR spectral assignments for some known flavonoids which have not been reported before. We also discuss in detail the novel phenolic compound, heterophylol (**1**).

RESULTS AND DISCUSSION

Compound **1**, showed unconjugated aromatic absorption maxima at 204, 228 sh and 284 nm in its UV spectrum [4, 5]. The IR spectrum of **1** showed a hydroxyl signal at 3420 cm^{-1} and aromatic C=C stretching absorptions at 1620 and 1600 cm^{-1}. In the ^{1}H NMR spectrum a set of γ,γ-dimethylallyl signals at δ 5.03 (*m*, CH=), 3.34 (*br d*, J = 6.9 Hz, $-CH_2-$), 1.80 (Me) and 1.64 (Me), two methoxyl signals at δ3.83 (*s*) and 3.84 (*s*), and a phenolic signal at δ8.15 were distinguished. The aromatic signals at δ 6.26 (*d*, J = 2.5 Hz), 6.43 (*dd*, J = 2.5, 8.5 Hz) and 7.18 (*d*, J = 8.5 Hz), and a one-proton singlet at δ 6.55 suggested the existence of a two-aromatic ring system. The other aliphatic signals in the ^{1}H NMR of **1** showed two quaternary methyl signals at δ1.43 (*s*) and 1.19 (s), two CH_2 signals at δ2.21 (1H, *dd*, J = 12, 16 Hz, axial), 2.92 (1H, *dd*, J = 5, 16 Hz, equatorial), 2.32 (1H, *dd*, J = 12, 16 Hz, axial) and 3.53 (1H, *dd*, J = 5, 16 Hz, equatorial) and two methine signals at δ1.65 (1H, *dt*, J = 5, 12 Hz) and 2.61 (1H, *dt*, J = 5, 12 Hz). These aliphatic signals suggested the existence of a $-CH_2-CH-CH-CH_2-$ system, which was supported by the ^{1}H–^{1}H COSY spectrum of **1**. The ^{13}C NMR spectrum of **1** showed four phenolic carbons at δ154.1, 155.9, 156.1 and 156.2 and a quaternary oxygenated carbon at δ 76.5. These signals combined with the information from the ^{1}H NMR and ^{1}H–^{1}HCOSY spectra, suggested that **1** contained fused tetrahydronaphthalene and chromane ring moieties. The HETCOR spectrum of **1** revealed the correlation of appropriate proton and carbon signals and the long-range HETCOR spectrum (Fig. 1) proved the substitution pattern of the aromatic system. The combined evidence established that **1** had a tetracyclic ring system. Therefore, heterophylol (**1**) was characterized as **1**. The EI-mass spectrum (Scheme 1) showed $[M]^+$ at *m/z* 408 (base peak) with significant peaks at *m/z* 409 (19), 310 $[309 + H]^+$ (5.3) and 309 $[M - OMe - 68]^+$(27) attributed to the retro-Diels–Alder-type fragmentation of the D-ring which could be interpreted by their relative intensity ratio (19/100 = 5.3/27). Significant peaks at *m/z* 285, 232, 189, 176, 175, 161 and 133 were attributed to the retro-Diels–Alder-type fragmentation of the C-ring [6,7] also supporting the structure of heterophylol as **1**.

The ^{13}C NMR chemical shifts were determined by the HETCOR and long-range HETCOR spectra. The stereochemistry of H-6 and H-13 was assigned as *trans* because of the diaxial $J_{6,13}$ = 12 Hz, but the absolute conformation was still undefined.



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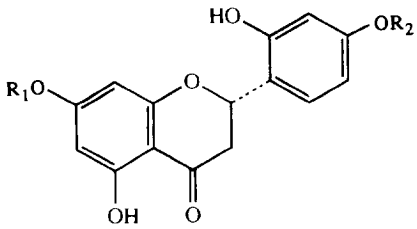

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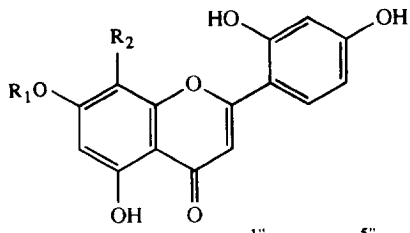
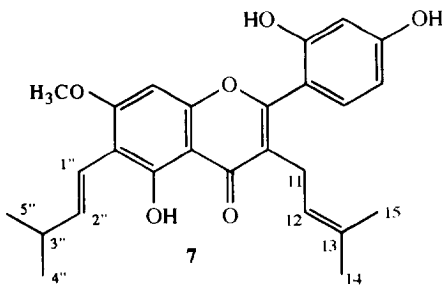
4: R_1=Me, R_2=H, R_3=H



3: R_1=Me, R_2=
5: R_1=Me, R_2=H
6: R_1=H, R_2=H



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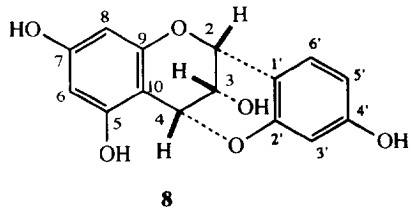

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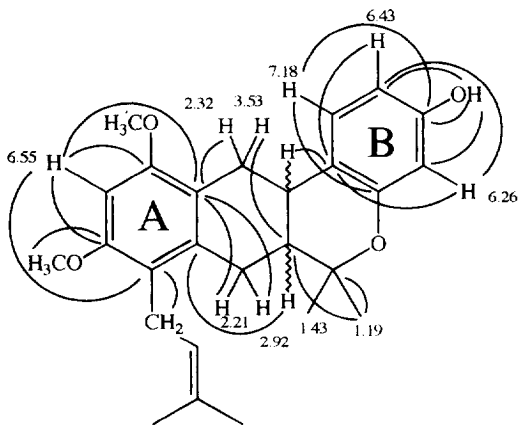
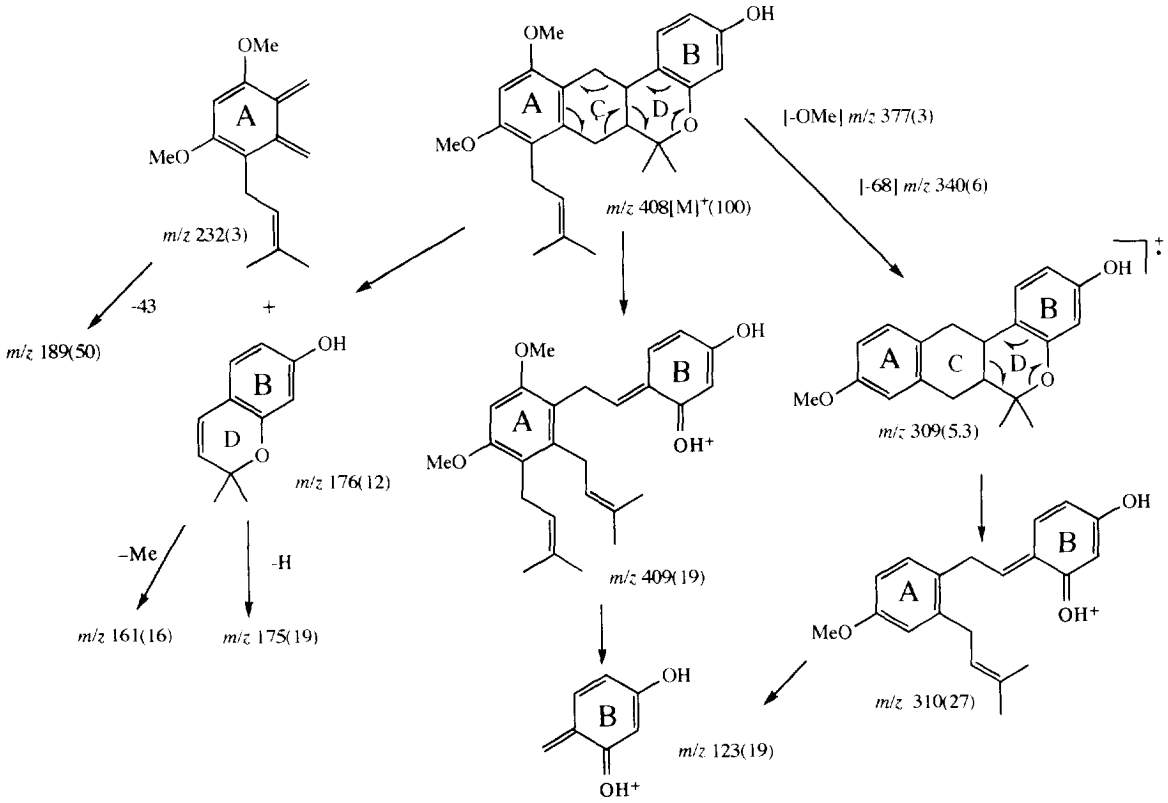


Fig. 1. Correlations in the long-range HETCOR spectrum of **1**.

Compound **2**, needles, UV spectrum showed similar absorption maxima to those of the 5,7,2,4′-tetraoxygenated flavanone, kenusanone I [8]. The $AlCl_3$-induced bathochromic shift and the absence of NaOAc- and NaOMe-induced bathochromic shifts, indicated that **2** was a 5-hydroxy-7,4′-dimethoxylated flavanone [9]. The IR spectrum of **2** gave a hydroxy signal at 3225 cm^{-1} and a chelated carbonyl signal at 1645 cm^{-1}. The ^1HNMR spectrum showed three one-proton double doublets for H-2, H-3ax and H-3eq typical of a flavanone at δ5.75 (J = 3, 13 Hz), 3.21 (J = 13, 17 Hz) and 2.76 (J = 3, 17 Hz) [8, 9], together with two methoxyl signals at δ3.77 and 3.85 and two phenolic signals at δ8.82 and 12.16 (chelated). The aromatic protons at δ6.52 (*d*, J = 2.2 Hz), 6.54 (*dd*, J = 2.2, 8 Hz) and 7.42 (*d*, J = 8 Hz) could be assigned to the H-3′, H-5′ and H-6′ of a 2′,4′-dioxygenated B ring of a flavonoid. The other aromatic signals at δ6.03 and 6.06 were assigned to the H-6 and/or H-8 of a flavanone [8]. The EI-mass spectrum of **2** showed a $[M]^+$ at m/z 316, a base peak at m/z 167 and significant peaks at m/z 151, 150, 137 and 121 attributed to the typical retro-Diels–Alder fragmentation of a flavonoid [8]. The above fragmentations supported a structure with a dioxygenated B-ring. The intense peaks at m/z 193 and 124 due to the cleavage of the



Scheme 1.

B-ring [8] also supported the presence of two methoxyl groups located on ring A and ring B of **2**, respectively. Based on the above evidence, artocarpanone A (**2**) was characterized as 5,2′-dihydroxy-7,4′-dimethoxy flavanone.

The ^{13}C NMR spectrum (Table 1) of **2** was assigned by comparison with the ^{13}C NMR spectral data for the 2′,4′-dixoygenated flavanones, kenusanone I [8] and artocarpanone (**4**), and on the basis of shifts induced by methylation [10].

Compound **3**, pale yellow needles, had similar UV absorptions to norartocarpetin (**6**) [11]. $AlCl_3$- and NaOMe-induced bathochromic shifts and the absence of a NaOAc-induced bathochromic shift suggested that **3** was a 7-substituted 5,2′,4′-trihydroxylated flavone [9]. The IR spectrum of **3** showed a hydroxyl signal at 3400 cm^{-1} and a chelated carbonyl signal at 1650 cm^{-1}. The ^1H NMR spectrum of **3** showed a methoxyl signal at δ3.79, a set of γ,γ-dimethylallyl signals at δ5.50 (*m*, CH=), 3.70 (*br d*, J = 6.9 Hz, $-CH_2-$), 1.86 (Me) and 1.66 (Me), a chelated phenolic OH at δ14.01 and two broad phenolic signals at δ12.56 and 13.09. The signals at δ6.94 (*d*, J = 2.2 Hz), 6.99 (*dd*, J = 2.2, 7 Hz) and 8.23 (*dd*, J = 7 Hz) corresponded to the H-3′, H-5′ and H-6′ of a 2′,4′-dioxygenated flavone. Two further aromatic singlets were observed at δ6.66 and 7.86. In the EI-mass spectrum of **3**, the $[M]^+$ appeared at *m/z* 368 with significant peaks at *m/z* 353 $[M-Me]^+$, 325 $[M-43]^+$, 313 $[M-55]^+$ and 300 $[M-68]^+$ indicating the existence of a γ,γ-dimethylallyl group. The intense peaks at *m/z* 233, 219, 191, 179, 167, 136, 135 and 134 due to the retro-Diels–Alder-type fragmentation of flavonoid [9] indicated that **3** had γ,γ-dimethylallyl and methoxyl groups located on the A-ring and a dihydroxylated B-ring. Based on the above evidence, and the $AlCl_3$-induced bathochromic shift, **3** was characterized as 8-(γ,γ-dimethylallyl)-5,2′,4′-trihydroxy-7-methoxyflavone [12] and the signals at δ6.66 and 7.86 in the ^1H NMR spectrum were reasonably assigned to H-6 and H-3, respectively. The structure of **3** was confirmed by the NOESY spectrum shown in Fig. 2. The ^{13}C NMR spectrum (Table 1) of **3** was assigned by comparison with those of the 2′,4′-dihydroxy flavones, kuwanone C [13] and artocarpetin (**5**). The observed signals supported the structure of **3**.

The ^{13}C NMR spectra (Table 1) of the known flavonoids, artocarpanone (**4**), artocarpetin (**5**), norartocarpetin (**6**), artocarpin (**7**) and cyanomaclurin (**8**) were assigned by comparison with corresponding literature data [10].

EXPERIMENTAL

Plant material, extraction and isolation. Root bark (1 kg) and heartwood (5 kg) of *Artocarpus heterophyllus*, collected at Ping Tung Hsieng, during July 1992, was chipped and extracted ×3 with Me_2CO at room temp. The Me_2CO extract was chromatographed on silica

Table 1. ^{13}C NMR chemical shift assignments for the flavonoids **2**, **3**, **4**, **5**, **6**, **7** and **8***

C	2†	3‡	4†	5‡	6§	7†	8†
2	74.4	162.9[a]	75.9	163.6	163.1	160.2	71.6
3	41.6	109.0	43.0	108.6	109.1	122.3	62.8
4	197.0	183.9	198.5	183.5	184.2	183.7	65.5
5	160.0	160.7	160.0	162.1	160.2	157.8[a]	159.1[a]
6	93.5	95.3	94.8	98.2	99.8	113.3	95.2
7	167.8	163.6	169.1	165.6	165.6	164.2	159.3[a]
8	94.4	107.8	95.7	92.6	94.8	90.8	94.4
9	163.6[a]	161.3	165.1[a]	162.7	163.3	162.8	154.8[a]
10	102.7	104.5	104.1	105.9	105.2	106.0	99.3
11						25.0	
12						122.9	
13						132.6	
14						26.2	
15						18.0	
1′	117.6	110.7	117.1	109.9	110.7	110.2	113.0
2′	155.2	154.8	156.7	158.3	159.4	157.6[a]	154.6[a]
3′	101.4	105.4	103.9	104.7	104.2	104.2	102.5
4′	164.0[a]	163.2[a]	165.4[a]	164.2	163.9	161.9	158.4
5′	105.0	107.8	108.3	108.0	106.4	108.5	108.4
6′	127.9	130.7	129.4	130.6	131.0	132.7	132.0
1″		22.3				117.4	
2″		123.4				142.6	
3″		131.6				34.3	
4″		25.8				23.5	
5″		18.0				23.5	
OMe	54.5,55.2	56.1	56.6	55.8		57.0	

*The number of directly attached protons to each carbons was verified with a DEPT pulse sequence.

[a]These signals may be reversed in each column.

†Detected in acetone-d_6.

‡Detected in pyridine-d_5.

§Detected in CD_3OD + acetone-d_6.

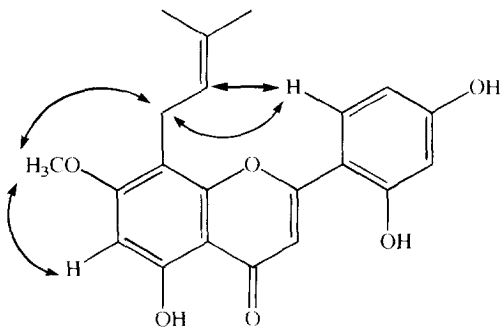


Fig. 2. NOESY spectrum of **3**.

gel. Elution of the root bark extract with $CHCl_3$–cyclohexane (1:3) yielded heteroflavanone A, B [1] and 9-hydroxytridecyl docosanoate [3]; elution with $CHCl_3$–cyclohexane (1:2, 2% Me_2CO) yielded heterophylol (**1**) [2] and cudraflavone A; elution with $CHCl_3$–cyclohexane (1:1, 2% Me_2CO) yielded cycloartocarpin A [3] and heteroflavanone C [3] and elution with $CHCl_3$–cyclohexane (3:1, 5% MeOH) yielded cycloheterophyllin and artocarpetin A (**3**). The elution of heartwood extract with $CHCl_3$–cyclohexane (1:1, 2% Me_2CO) yielded cycloartocarpin A, artocarpin (**7**), artocarpanone A (**2**); elution with $CHCl_3$–cyclohexane–MeOH (7:2:1) yielded artocarpanone (**4**), artocarpetin (**5**) and norartocarpetin (**6**) and elution with $CHCl_3$–cyclohexane (8:1:1) yielded dihydromorin and cyanomaclurin (**8**). All compounds were purified by further CC and recrystallization. The known compounds were all determined by spectral methods and compared with literature data [14].

Compound **1**. Needles ($CHCl_3$–MeOH), mp 217–218°, $[\alpha]_D^{24}$ −3° (acetone; *c* 0.1), IR ν_{max}^{KBr} cm^{-1}: 3420, 1620, 1600. UV λ_{max}^{MeOH} (log ε) nm: 204 (4.82), 228sh (4.29), 284 (3.94). ^1H NMR (acetone-d_6): δ1.19 (3H, *s*, C-12ax Me), 1.43 (3H, *s*, C-12eq Me), 1.64 (3H, *s*, C-24 Me), 1.65 (1H, *dt*, *J* = 5, 12 Hz, H-13), 1.80 (3H, *s*, C-25 Me), 2.21 (1H, *dd*, *J* = 12, 16 Hz, H-14ax), 2.32 (1H, *dd*, *J* = 12, 16 Hz, H-5ax), 2.61 (1H, *dt*, *J* = 5, 12 Hz, H-6), 2.92 (1H, *dd*, *J* = 5, 12 Hz, H-14 eq), 3.34 (2H, *br d*, *J* = 6.9 Hz, H_2-21), 3.53 (1H, *dd*, *J* = 5, 12 Hz, H-5eq), 3.83 (3H, *s*, OMe), 3.84 (3H, *s*, OMe), 5.03 (1H, *m*, H-22), 6.26 (1H, *d*, *J* = 2.5 Hz, H-10), 6.43 (1H, *dd*, *J* = 2.5, 8.5 Hz, H-8), 6.55 (1H, *s*,

H-3), 7.18 (1H, *d*, J = 8.5 Hz, H-7), 8.15 (1H, *s*, C-9 OH). ^{13}C NMR (acetone-d_6): δ17.0 (C-25), 18.4 (C-19), 23.5 (C-21), 24.9 (C-24), 25.2 (C-14), 27.0 (C-20), 31.9 (C-6), 33.6 (C-5), 43.2 (C-13), 54.6 (OMe), 55.2 (OMe), 76.5 (C-12), 93.1 (C-3), 103.4 (C-10), 107.8 (C-8), 116.0 (C-16), 116.7 (C-17), 119.2 (C-1), 123.5 (C-22), 127.4 (C-7), 129.7 (C-15), 135.6 (C-23), 154.1 (C-18), 155.9 (C-2), 156.1 (C-4), 156.7 (C-9). EIMS (direct inlet, 70 eV) *m/z* (rel. int.): 409 $[M + H]^+$ (19), 408 $[M]^+$ (100), 393 $[M - Me]^+$ (7), 377 $[M - OMe]^+$ (3), 365 $[M - 43]^+$ (4), 353 $[M - 55]^+$ (7), 352 (18), 351 (22), 340 $[M - 68]^+$ (6), 321 (5), 310 $[309 + H]^+$ (5.3), 309 $[M - OMe - 68]^+$ (27), 285 (5), 243 (4), 232 (3), 229 (8), 219 (9), 215 (8), 201 (8), 189 (50), 176 (12), 175 (19), 161 (16), 159 (14), 151 (8), 133 (3), 123 (19), 115 (9), 91 (7), 69 (21). HRMS: Calc. for $C_{26}H_{32}O_4$: 408.2301. Found: 408.2318.

Compound **2**. Needles (MeOH), mp 159 ~ 160°, $[\alpha]_D^{23}$ − 6.7° (acetone; *c* 0.06), IR ν_{max}^{KBr} cm^{-1}: 3225 (OH), 1645 (C=O), 1605. UV λ_{max}^{MeOH} (log ε) nm: 214 (4.51), 227sh (4.44), 285 (4.31), 337sh (3.63), 402 (2.81); MeOH–$AlCl_3$: 222, 308, 387, 400 sh; MeOH–NaOAc: unchanged; MeOH–NaOMe: unchanged. ^{1}H NMR (acetone-d_6): see text. ^{13}C NMR (acetone-d_6): see Table 1. EIMS (direct inlet, 70 eV) *m/z* (rel. int.): 316 $[M]^+$(14), 299 (21), 298 $[M - H_2O]^+$(91), 297 (55), 193 (7), 177 (7), 168 (10), 167 (100), 151 (10), 150 (57), 137 (26), 124 (9), 123 (6), 121 (14). HRMS: Calc. for $C_{17}H_{16}O_6$ 316.0947. Found: 316.0949.

Compound **3**. $C_{21}H_{20}O_6$, pale yellow needles ($CHCl_3$–MeOH), mp 270 ~ 271°, IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1650 (chelated C=O), 1605. UV λ_{max}^{MeOH} (log ε) nm: 207 (4.76), 252sh (4.36), 269 (4.45), 288 (4.20), 356 (4.43); MeOH–$AlCl_3$: 210, 236, 274, 298, 360, 402; MeOH–NaOAc: unchanged; MeOH–NaOMe: 208, 264, 296sh, 404. ^{1}H NMR (pyridine-d_5): see text. ^{13}C NMR (pyridine-d_5): see Table 1. EIMS (direct inlet, 70 eV), *m/z* (rel. int.): 368 $[M]^+$(79), 353 $[M - Me]^+$ (98), 313 $[M - 55]^+$ (18), 312 $[M - 56]^+$ (19), 300 $[M - 68]^+$ (57), 219 (28), 191 (13), 179 (33), 167 (13), 161 (10), 149 (16), 148 (7), 135 (35), 134 (48), 131 (10), 117 (8), 69 (100). HRMS: Calc. for $C_{30}H_{30}O_7$: 368.1260. Found: 368.1258.

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