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PRENYLATED LIGNANS FROM *HAPLOPHYLLUM PTILOSTYLUM*

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Key Word Index—*Haplophyllum ptilostylum*; Rutaceae; aryltetralin lignan; prenylated diarylbutyrolactone lignans; structure determination; 2D NMR.

Abstract—In addition to previously isolated coumarins and lignans, we have obtained one new aryltetralin lignan and three new prenylated diarylbutyrolactone lignans from the aerial parts of *Haplophyllum ptilostylum*. The structures of the new compounds were established by ^{1}H NMR, ^{13}C NMR (BB and DEPT), COSY, HETCOR, COLOC and selective INEPT experiments.

INTRODUCTION

In previous phytochemical investigations of the aerial parts of *Haplophyllum ptilostylum* Spach, we reported the isolation of three new coumarins, ptilostin, ptilostol [1] and ptilin [2], and four known lignans, justicin B and isodaurinol [1], and matairesinol and arctigenin [2]. Further investigation of the same extract of the plant yielded four new lignans. The first was an aryltetralin lignan with the structure and absolute configuration shown in **1**. A compound with the structure described as the enantiomer of **1** was isolated from *Heliopsis buphthalmoides* [3], but the authors reported only the ^{1}H NMR spectrum; neither the $[\alpha]_D$ nor the ^{13}C NMR spectrum was reported. For compound **1**, we have obtained the CD curve, and also present a complete set of NMR assignments determined using COSY, HETCOR, selective INEPT experiments [4–6] and molecular modelling. The other three lignans were the diarylbutyrolactones **4**–**6**, all of which possess an isoprene-derived side chain, which is rather unusual in the lignan family. There is only one other report concerning lignans with this substitution, and that is the 3-methylbutenyl ether (**7**) of pluviatilol obtained from the bark of *Zanthoxylum podocarpum* Hems. [7, 8]. According to these authors, compound **7** is of considerable biogenetic interest, since the interpolation of a mevalonate-derived substructure into a lignan has not been seen previously, although mixed biogenetic routes are common in other classes. The structures of compounds **4**–**6** were established by various ^{1}H and ^{13}C NMR spectroscopic techniques.

RESULTS AND DISCUSSION

The EI-mass spectrum of compound **1** indicated a molecular formula of $C_{20}H_{16}O_6$. The ^{13}C NMR spectrum (DEPT) revealed the presence of four methylene, eight methine and eight quaternary carbons, and the ^{1}H NMR spectrum indicated an aryltetralin structure (see ^{1}H NMR spectroscopic data in the Experimental). The vicinal J values in **1** indicated a *trans* diaxial relationship between H-1 and H-2 (J = 11 Hz) and H-2 and H-3 (J = 13.7 Hz). The ^{1}H NMR spectrum was superimposable with that reported previously [3], but the assignments of H-5 and H-8 should be interchanged. The COSY spectrum showed cross-peaks between the signal corresponding to H-4 (α and β) and the signal at δ6.56, and the signal corresponding to H-1 and that at δ6.30, inferring that the first resonance is H-5 and the second is H-8. In ref. [3], H-5 is reported at δ6.32 and H-8 at 6.58. These reassignments were confirmed by the selective INEPT experiment (Table 1), since the irradiation of H-1 (δ4.02) enhanced the signal of C-8 (δ109.9) and this signal showed a correlation with the broad singlet at δ6.30 in the HETCOR spectrum.

We have generated the structure of **1** with the molecular modelling program PCMODEL386 V 4.0 and comparison of the calculated vs the observed coupling constants involving the aliphatic protons led to the unambiguous assignment of all protons, also differentiating H-4α from H-4β, and H-3aα from H-3aβ (Table 2). The vicinal coupling constants were calculated, and the signals corresponding to those carbons bearing hydrogen were identified using the HETCOR spectrum. Considering that the chemical shifts of C-5′ (δ108.1) and C-6′ (δ123.0) are quite different, using HETCOR we could assign the A part of the AB system centred at δ6.75 to H-5′ and the B part to H-6′. The selective INEPT experiment not only led to the assignment of the signals of the quaternary carbons, but also permitted identification of the dioxymethylene moiety of each ring. The cross-peaks

Table 1. Selective INEPT experiments on compound **1** ($CDCl_3$, 90.8 MHz)

Proton irradiated	δ(ppm)	Carbons enhanced
5′, 6′	6.75	136.8 (C-1′), 146.4 (C-4′)
2′, 5	6.56	146.6 (C-6), 146.3 (C-7), 108.1 (C-5′), 109.9 (C-8),46.1 (C-1), 33.0 (C-4)
8	6.30	146.6 (C-6), 146.3 (C-7), 127.8 (C-4a), 46.1 (C-1)
$-OCH_2O-$	5.91	147.7 (C-3′), 146.4 (C-4′)
$-OCH_2O-$	5.86	146.6 (C-6), 146.3 (C-7)
3aα	4.48	175.3 (C-2a), 48.8 (C-2), 39.9 (C-3)
1	4.02	175.3 (C-2a), 136.8 (C-1′), 132.6 (C-8a), 127.8 (C-4a), 123.0 (C-6′), 109.9 (C-8), 48.8 (C-2)
3aβ	3.95	39.9 (C-3), 33.0 (C-4)
4β	2.94	132.6 (C-8a), 127.8 (C-4a), 108.4 (C-5), 39.9 (C-3)
4α	2.87	132.6 (C-8a), 127.8 (C-4a), 108.4 (C-5), 70.9 (C-3a), 39.9 (C-3)
3	2.57	70.9 (C-3a), 48.8 (C-2)
2	2.46	136.8 (C-1′), 46.1 (C-1), 33.0 (C-4)

Table 2. Observed vs calculated proton–proton *J* values for compound **1**

Proton	Obs. *J* (Hz)	Calc. *J* (Hz)
1–2	11	12.7
2–3	13.7	12.5
3–3aα	10.5	11.5
3–3aβ	6.5	7.5
3aα–3aβ	8.6	—
3–4α	11	12.2
3–4β	5.0	3.7
4α–4β	15	—
2′–5′	< 1	—
2′–6′	1.5	—
5′–6′	7.9	

Table 3. ^{13}C NMR data for lignans **1–3** ($CDCl_3$, 90.8 MHz)

C	1	2*	3*
1	46.1	43.2	44.7
2	48.8	47.2	45.9
2a	175.3	174.4	178.0
3	39.9	32.5	32.7
3a	70.9	71.9	72.6
4	33.0	33.0	31.9
4a	127.8	128.1	128.0
5	108.4	108.3	108.1
6	146.6	146.9	146.6
7	146.3	146.3	146.1
8	109.9	110.2	109.6
8a	132.6	131.0	130.6
1′	136.8	134.4	136.1
2′	109.0	111.0	108.7
3′	147.7	147.1	147.8
4′	146.4	146.7	146.6
5′	108.1	107.5	108.0
6′	123.0	124.0	120.4
$-OCH_2O-$	101.1	101.0	100.9
$-OCH_2O-$	101.0	100.8	100.8

*Data taken from ref. [12].

in the HETCOR spectrum showed the following pairs for the $-OCH_2O-$ groups, δ5.91 with 101.0 and δ5.86 with 101.1. Irradiation of the signal at δ5.86 enhanced the signals at δ146.6 and 146.3. As these two signals were also enhanced when H-8 was irradiated (δ6.30), the signals at δ5.91 and 101.0 were assigned to the $-OCH_2O-$ attached to ring A, and the signals at δ146.6 and 146.3 were assigned to C-6 and C-7, respectively. Irradiation of the other dioxymethylene protons at δ5.91 enhanced the signals at δ147.7 and 146.5, assigned to C-3′ and C-4′, respectively [9]. The other irradiations substantiated the structure of **1**.

The assignments of the aromatic carbons by ^{13}C NMR spectroscopy were in good agreement with those reported for the two isomers polygamain (**2**) [10–12] and picropolygamain (**3**) [12], and the differences between the ^{13}C NMR spectra of these three isomers are listed in Table 3. Finally, the CD curve of **1** showed a couplet of negative sign at 289 nm that, according to Hulbert *et al.* [13], is indicative of the β configuration of the aryl group at C-1. Also, the longer wavelength branch is greater than the other in this couplet, corresponding to a quasi-equatorial orientation of the aryl group at C-1 [13]. These observations were substantiated in the computer generated model.

The CIMS of the second lignan **4** indicated a molecular formula of $C_{30}H_{40}O_8$, and the ^{13}C NMR (DEPT) spectrum revealed the presence of five methyl, six methylene, 10 methine and nine quaternary carbons (Table 4). The ^1H NMR spectrum of **4** (see Experimental) indicated the presence of matairesional and 6″,7-dihydroxygeraniol moieties. The carbon chemical shifts involving C-7, C-8, C-9, C-7′, C-8′ and C-9′ were characteristic of a *trans*-fused five-membered lactone ring [14].

The structure of **4** was solved mainly on the basis of a combination of COSY, HETCOR and COLOC spectra, and a series of selective INEPT experiments.

Table 4. ^{13}C NMR data for lignans **4–6** ($CDCl_3$, 90.8 MHz)

C	4	5	6
1	130.6	131.6	130.4
2	111.9	108.7	111.9
3	149.4	147.8	149.5
4	146.8	146.3	147.1
5	113.3	113.1	113.1
6	120.4	121.5	120.5
7	38.1	38.3	38.3
8	40.9	41.1	41.2
9	71.3	71.1	71.2
1′	129.4	130.1	131.3
2′	111.5	112.4	109.5
3′	146.7	149.5	147.8
4′	144.4	147.2	146.4
5′	114.1	113.1	108.1
6′	122.0	121.2	122.2
7′	34.4	34.8	34.8
8′	46.5	46.5	46.5
9′	178.8	178.4	178.4
1″	65.8	65.8	65.8
2″	120.1	119.9	119.9
3″	140.5	137.6	137.6
4″	36.5	25.8	25.8
5″	29.3	18.2	18.2
6″	77.9	—	—
7″	73.0	—	—
8″	26.4	—	—
9″	23.2	—	—
10″	16.2		—
OMe	55.8	55.8	55.8
OMe	55.8	—	—
OCH_2O	—	101.0	101.0

A few critical details of the elucidation strategy are presented here. The AB part of the ABX system centred at δ2.90, and corresponding to H-7′, showed correlations in the COLOC spectrum with C-9′ (δ178.8), C-1′ (δ129.4), C-6′ (δ122.1) and C-2′ (δ111.5). Then, the HETCOR experiment led to the assignment of H-2′ and H-6′, and these signals showed correlations with H-5′ in the COSY spectrum, leading to the assignment of the protons and their respective carbons in this aromatic ring. We could then assign the signals corresponding to H-2, H-5 and H-6, leading to the assignment of their respective carbons through the HETCOR correlations.

The position of the side chain was determined by a selective INEPT experiment (Table 5), because irradiation of H-2, as well as irradiation of H-1″, enhanced the quaternary carbon signal at δ146.8 (C-4), thereby indicating that the 6″,7″-dihydroxy geranyloxyl moiety was attached to this carbon. The rest of the irradiations, as well as the COLOC correlations (Table 1), were straightforward and yielded the proposed structure. The proximity of the signals corresponding to H-2′, H-5′, H-6′, H-5 and H-6 in the ^1H NMR spectrum led to ambiguous enhancements in the selective INEPT experiment, but this was compensated by the long-range correlations observed in the COLOC spectrum. Finally, the negative Cotton effect observed in the CD curve at 233 nm indicated an absolute configuration as shown in **4** [15].

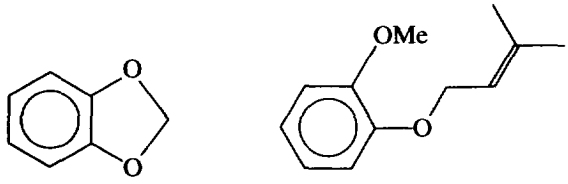
The third sample was identified as a mixture of the dibenzobutyrolactones **5** and **6**. Various methods were attempted, unsuccessfully, to separate the two isomers. The EI-mass spectrum of this sample showed a single molecular ion peak at *m/z* 424 ($C_{25}H_{28}O_6$), and the loss of isopentenyl alcohol to give a fragment at *m/z* 356. Two more important fragments were observed at *m/z* 135 and

Table 5. Selective INEPT experiments and COLOC correlations for compound **4**

Selective INEPT*			COLOC correlations†		
Proton	δ (ppm)	Carbons enhanced	Proton	δ (ppm)	Carbon
1″	4.55	146.8 (C-4)	7′	2.90	178.8 (C-9′)
		140.5 (C-3″)			129.4 (C-1′)
		120.1 (C-2″)			122.0 (C-6′)
2″	5.52	36.5 (C-4″)			111.5 (C-2″)
		16.7 (C-10″)	OMe	3.79	149.4 (C-3)
10″	1.70	140.5 (C-3″)	OMe	3.77	146.7 (C-3′)
		120.1 (C-2″)	2	6.44	120.4 (C-6)
		36.5 (C-4″)			146.8 (C-4)
8″	1.16	77.9 (C-6″)‡	2′	6.62	122.0 (C-6′)
		73.0 (C-7″)	5	6.72	149.4 (C-3)
		26.4 (C-8″)			130.6 (C-1)
		23.2 (C-9″)	5′	6.77	129.4 (C-1′)
9″	1.12	Same as 8″	6	6.48	113.3 (C-5)
			6′	6.56	144.4 (C-4′)

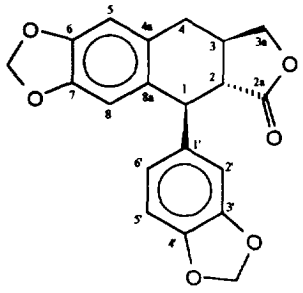
*Recorded in $CDCl_3$ at 90.8 MHz.
†Recorded in $CDCl_3$ at 75.4 MHz.
‡Irradiation of H-8″ affects H-9″ and vice versa, producing the same enhancements.

137. The ^{1}H NMR spectrum (see Experimental) showed the characteristic signals of a dibenzobutyrolactone-type lignan substituted with one dioxymethylene group, one methoxy group and an isopentenyl moiety, but all of the signals, except for those corresponding to the isopentenyl moiety, appeared split in a 2:1 ratio. In the ^{13}C NMR spectrum the splitting was more evident, and, similarly to the ^{1}H NMR spectrum, the signals corresponding to the side chain did not show splitting. The presence of two conformers was ruled out, firstly, because in the split signals the multiplicity and coupling constants are the same, and secondly, the ^{1}H NMR spectrum run at higher temperature (50°) did not produce any change in the signals. As in compound **4**, the carbon chemical shifts of C-7, C-8, C-9, C-7′, C-8′ and C-9′ (including the split signals) were in agreement with *trans*-fusion of the lactone ring [14]. Also, both the ^{13}C and ^{1}H NMR spectra of **4** were very similar to those of **5**/**6**, except for the signals of the dioxymethylene group and the side chain, indicating the presence of a mixture of two dibenzobutyrolactones that contain aromatic rings of type A and type B, as shown.

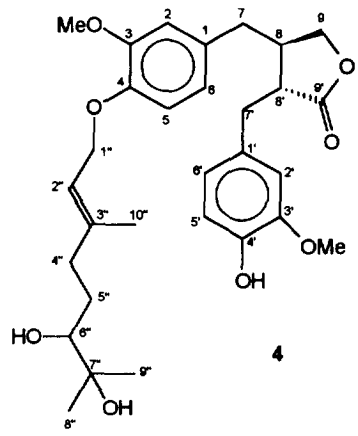


A **B**

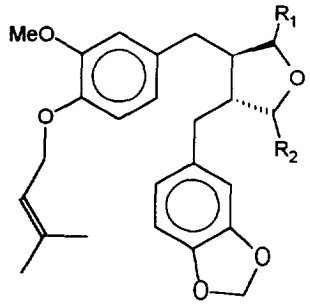
The solution to assigning the aromatic nuclei was the selective INEPT experiment. Irradiation of H-7′ (composed of a split AB part of an ABX system, giving rise to two signals with relative intensity 2:1) led to the enhancement of C-1, C-2 and C-6 of each aromatic ring type (A and B) (Table 6), as well as C-9′. The only explanation for the observed enhancement of carbons corresponding to two different aromatic rings is that in one case ring A is attached to C-7′, and in the other case ring B. This is possible because the chemical shift of the enhanced carbons is quite different for both aromatic ring types. The more intense set of enhanced signals in Table 6 is that corresponding to the ring A carbons, indicating that the major compound is the one that contains this ring attached to C-7′, i.e. structure **6**. The minor compound is **5**. The remaining carbon signals were assigned to each



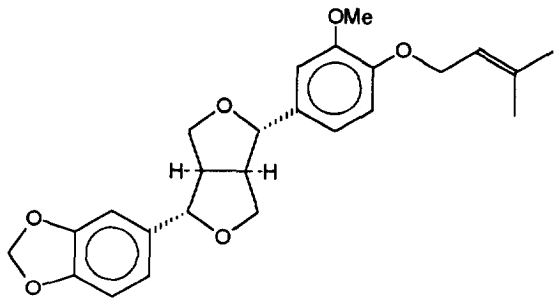
1
2. H-1β, H-2β, H-3α
3. H-1β, H-2α, H-3α



4



5. R_1 = O= ; R_2 = H
6. R_1 = H ; R_2 = O=



7

Table 6. Selective INEPT experiments on the mixture of **5** and **6** ($CDCl_3$, 90.8 MHz)

Proton irradiated	Carbons enhanced	
	5	**6**
7′*	178.4 (C-9′)	178.4 (C-9′)
	130.1 (C-1′)†	131.3 (C-1′)‡
	121.2 (C-6′)†	122.2 (C-6′)‡
	112.3 (C-2′)†	109.5 (C-2′)‡
1″	147.2 (C-4′)†	147.1 (C-4)‡
	119.9 (C-2″)	119.9 (C-2″)
	137.6 (C-3″)	137.6 (C-3″)

*Two overlapped doublets of doublets with a 2:1 intensity ratio centred at δ2.9.

†Less intense signals.

‡More intense signals.

compound in the mixture considering their relative intensities. Irradiation of H-1″ enhanced the signals at δ147.1 and 147.2 corresponding to C-4 in the type B aromatic ring, and enhancement was also observed in the side chain carbons at δ119.9 (C-2″) and 137.6 (C-3″), confirming the position of the isopentenyl group. Due to their splitting and the complexity observed in the ^{1}H NMR spectrum, the aromatic signals were not assigned.

EXPERIMENTAL

General. The ^{1}H NMR, ^{13}C NMR and DEPT spectra (200 MHz, 500 MHz, 90.8 MHz), were recorded in $CDCl_3$ with TMS as an int. standard. For the selective INEPT experiments, data sets of 16K covering a spectral width of 10 Hz were acquired. Proton pulse widths were calibrated using a sample of HOAc in 10% C_6D_6 (^1J = 6.7 Hz) in a 5-mm NMR tube [16]. The radio frequency field strength for the soft pulse was of the order of 25 Hz. For aromatic and vinylic protons $^3J_{C-H}$ = 7 Hz and for aliphatic and hydroxyl protons $^3J_{C-H}$ = 5 Hz. Computer calculations were performed using the molecular modelling program PCMODEL 386 V 4.0 from Serena Software, Bloomington, Indiana. The vicinal coupling constants were calculated using the Karplus generalized equation developed by Haasnoot *et al.* [17].

Plant material. The aerial parts of *Haplophyllum ptilostylum* were collected from southern Turkey (Ermernek) in June 1992. A voucher specimen is deposited in the Herbarium of the Faculty of Pharmacy, University of Marmara (MARE 3742).

Extraction and separation. The dried and powdered plant material (870 g) was extracted in a Soxhlet with MeOH. The extract was evapd under vacuum to yield a residue (133 g). Half the residue was CC on silica gel using a petrol–Et_2O (0 to 100%) gradients, followed by EtOH as eluent. The new lignans were obtained in the following order: **1** (25 mg, 0.0028%), **4** (30 mg, 0.034%), **5/6** (25 mg, 0.0028%). They were further purified on Sephadex LH-20 columns and on prep. TLC plates.

Compound **1**. $[\alpha]_D$ −94° ($CHCl_3$; *c* 1.2); UV λ^{MeOH} nm (log ε): 288 (3.8), 235 (4.2); IR ν^{CHCl_3} cm^{-1}: 3050, 2950, 1770, 1620, 1500, 1480, 1440, 1360, 1250, 1225, 1170, 1090, 1040, 910, 830; ^{1}H NMR ($CDCl_3$, 360 MHz): δ4.02 (1H, *br d*, *J* = 11.0 Hz, H-1), 2.46 (1H, *dd*, *J* = 11.0 and 13.7 Hz, H-2), 2.57 (1H, *m*, H-3), 3.95 (1H, *dd*, *J* = 10.5 and 8.6 Hz, H-3aα), 4.48 (1H, *dd*, *J* = 6.5 and 8.6 Hz, H-3aβ), 2.87 (1H, *br dd*, *J* = 11 and 15 Hz, H-4α), 2.94 (1H, *br dd*, *J* = 5 and 15 Hz, H-4β), 6.56 (2H, *br s*, H-5 and H-2′), 6.30 (1H, *br s*, H-8), 6.75 (AB part of ABX system, J_{AB} = 7.9, J_{AX} < 1, J_{BX} = 1.5 Hz, part A H-5′ and part B H-6′), 5.91 (2H, $-OCH_2O-$) and 5.86 (2H, $-OCH_2O-$); ^{13}C NMR: Table 3; EIMS *m/z* (rel. int.): 352 $[M]^+$ (100), 292 (5), 280 (7), 267 (10), 230 (7), 176 (5), 152 (8), 135 (10). CD $\Delta\varepsilon$ (MeCN) (nm): − 1.53 (299), 0 (288), + 0.77 (280), + 0.34 (246), − 1.40 (226).

Compound **4**. $[\alpha]_D$ − 18° ($CHCl_3$; *c* 0.4); UV λ^{MeOH} nm (log ε): 282 (4.0), 242 (4.1); IR ν^{CHCl_3} cm^{-1}: 3440, 3070, 2950, 2850, 2830, 1763, 1600, 1520, 1470, 1460, 1440, 1380, 1280, 1240, 1160, 1130, 1040, 830, 800, 760; ^{1}H NMR ($CDCl_3$, 500 MHz): δ6.44 (1H, *d*, *J* = 2 Hz, H-2), 6.72 (1H, *d*, *J* = 8 Hz, H-5), 6.48 (1H, *dd*, *J* = 8 and 2 Hz, H-6), 2.62 (1H, *dd*, *J* = 13 and 5.5 Hz, H-7a), 2.52 (1H, *dd*, *J* = 13 and 8 Hz, H-7b), 2.48 (1H, *m*, H-8), 4.13 (1H, *dd*, *J* = 9 and 7.5 Hz, H-9a), 3.87 (1H, *dd*, *J* = 9 and 7.5 Hz, H-9b), 6.62 (1H, *d*, *J* = 2 Hz, H-2′), 6.77 (1H, *d*, *J* = 8 Hz, H-5′), 6.56 (1H, *dd*, *J* = 8 and 2 Hz, H-6′), 2.90 (2H, AB part of ABX system J_{AB} = 14 Hz; J_{AX} = 5.5 Hz; J_{BX} = 6.5Hz, H_2-7′), 2.56 (1H, *ddd*, *J* = 6.5, 5.5 and 5 Hz, H-8′), 3.78 (3H, *s*, OMe), 3.76 (3H, *s*, OMe), 4.55 (2H, *d*, *J* = 6.5 Hz, H_2-1″), 5.52 (1H, *br t*, *J* = 6.5 Hz, H-2″), 2.32 (1H, *ddd*, *J* = 15, 10 and 4.5 Hz, H4″a), 2.12 (1H, *ddd*, *J* = 15, 9 and 7 Hz, H-4″b), 1.61 (1H, *m*, H-5″a), 1.44 (1H, *m*, 5b), 3.30 (1H, *dd*, *J* = 10 and 1.5 Hz, H-6″), 1.16 (3H, *s*, H_2-8″), 1.12 (3H, *s*, H_3-9″), 1.70 (3H, *br s*, H_3-10″). ^{13}C NMR: Table 4. CIMS *m/z* (rel. int.): 529 $[M + 1]^+$ (3), 359 [M − side chain + 1]$^+$ (27), 358 M − side chain]$^+$ (29), 341 (7), 153 (100). CD $\Delta\varepsilon$ (MeOH) (nm): − 0.55 (233).

Mixture of **5** *and* **6**. UV λ^{MeOH} nm (log ε): 283 (3.8), 234 (4.2); IR ν^{CHCl_3} cm^{-1}: 3040, 2950, 2840, 1770, 1610, 1590, 1520, 1485, 1440, 1420, 1380, 1240, 1190, 1160, 1040, 1020, 930. ^{1}H NMR ($CDCl_3$, 360 MHz): δ6.8–6.4 (6H, aromatic protons), 5.91 (2H, $-OCH_2O-$), 5.49 (1H, *m*, H-2″), 4.53 (2H, *br d*, *J* = 6.5 Hz, H_2-1″), 4.13 in **6** and 4.10 in **5** (1H, *dd*, *J* = 9.5 and 7.5 Hz, H-9a), 3.86 in **6** and 3.81 in **5** (1H, *dd*, *J* = 9.5 and 7.5 Hz, H-9b), 3.79 in **6** and 3.80 in **5** (3H, *s*, OMe), 2.89 in **6** and 2.91 in **5** (2H, centre of AB part of ABX system, J_{AB} = 14.5 Hz, J_{AX} = 5.5 Hz, J_{BX} = 6.8 Hz, H_2-7′), 2.4–2.6 (4H, complex *m*, H_2-7, H-8, H-8′), 1.75 (3H, *br s*, H_3-4″), 1.71 (3H, *br s*, H_3-5″). ^{13}C NMR: Table 4. EIMS *m/z* (rel. int.): 424 $[M]^+$ (21), 4.07 [M − 17]$^+$ (3), 356 [M − side chain]$^+$ (100), 339 (5), 137 (23), 135 (34).

Bioassay. Compounds **1** and **4** were inactive against the following cell lines: human lung carcinoma LU-1, hormone-dependent human prostate and hormone-dependent human breast cancer [18]. Compound **1**, when tested on HIV-1 reverse transcriptase (p66/p51) assay [19], showed moderate activity (IC_{50} = 11.7 μg ml^{-1}).

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