

## SYNTHESIS OF BIOLOGICALLY ACTIVE TETRAHYDRO-FUROFURANLIGNAN-(SYRINGIN, PINORESINOL)- MONO- AND BIS-GLUCOSIDES

BARBARA VERMES, OTTO SELIGMANN\* and HILDEBERT WAGNER\*

Research Group for Alkaloid Chemistry, Hungarian Academy of Sciences, P.O.B. 91.H-1521 Budapest, Hungary; \*Institute of Pharmaceutical Biology, University of München, Karlstraße 29, D-8000 München, Germany

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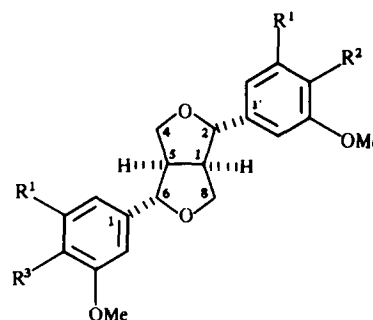
**Key Word Index**—Lignan-glucosides; synthesis; syringaresinol and pinoresinol glucosides.

**Abstract**—The naturally occurring tetrahydrofurofuran-lignan-(syringaresinol, pinoresinol)-mono- and bis-glucosides were synthesized and their structures thereby confirmed.

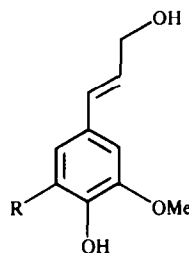
### INTRODUCTION

The observation that glucosides of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes exhibit various biological activities (e.g. cAMP phosphodiesterase inhibition and alleviation of stress [1]) and the lack of detailed pharmacological investigations has prompted us to synthesize the mono- (3) and bis-glucosides (4) of syringaresinol and pinoresinol monoglucoside (5), thereby confirming their structures. The isolation of these compounds has been reported from several sources. Dickey [2] was the first, isolating the 4',4'-bis-glucoside of the 2,6-bis(4'-hydroxy-3',5'-dimethoxy-phenyl)-3,7-dioxabicyclo[3.3.0]octane from *Liriodendron tulipifera*, but he could not establish which of the three possible diastereomers of the aglucone in the *exo-exo* (12), *exo-endo* (11) or *endo-endo* (13) form was present. Later, Briggs [3] and Pelter [4] investigated the stereochemical aspects of furanofuran-lignans and found a reliable NMR spectroscopic method to distinguish between the above diastereomers on the basis of chemical shifts and coupling constants of the hydrogens attached to the furan rings.

Later Cole *et al.* [5] reported on the reisolation of the diglucoside 4 from *Penstemon deustus* Dougl. ex Lindl. and found on the basis of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, mass and molecular rotation evidences that the aglycone possessed an *exo-exo* (diequatorial) stereostructure (syringaresinol) (1) and was identical with the aglycone of liriodendrin-B described by Dickey [2]. Meanwhile compound 4 was isolated from *Acanthopanax senticosus* Rupprecht et Maxim., Harms, (*Eleutherococcus senticosus* Maxim.) [6–8] and named eleutheroside E. The same eleutheroside E, together with syringaresinol-4'-*O*- $\beta$ -D-monoglucoside (3), syringenin-4-*O*- $\beta$ -D-glucoside and syringenin-4-*O*-apiosyl-1 $\rightarrow$ 2-glucoside was recently identified as a constituent of mistletoe (*Viscum album*) [9]. (+)-Pinoresinol-4'-*O*- $\beta$ -D-glucoside (5) was isolated by Nikaido *et al.* [10] and identified as a cAMP phosphodiesterase inhibiting constituent of *Forsythia suspensa*. ( $\pm$ )-Pinoresinol-4',4'-*O*- $\beta$ -D-bis-glucoside was isolated and synthesized earlier by Sih *et al.* [11].



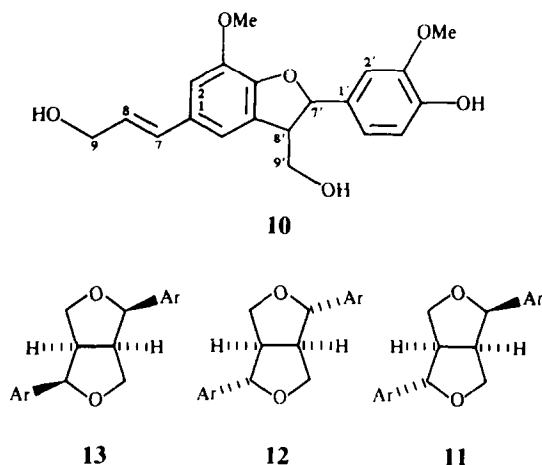
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
1	OMe	OH	OH
2	H	OH	OH
3	OMe	OH	OGlc
4	OMe	OGlc	OGlc
5	H	OH	OGlc
6	OMe	OH	OGlc (Ac) <sub>4</sub>
7	OMe	OAc	OGlc (Ac) <sub>4</sub>
8	OMe	OGlc (Ac) <sub>4</sub>	OGlc (Ac) <sub>4</sub>
9	H	OAc	OGlc (Ac) <sub>4</sub>



R  
 H Coniferyl alcohol  
 OMe Sinapyl alcohol

### RESULTS AND DISCUSSION

In preceding publications interesting enzymatic and chemical syntheses [12–18] providing the furofuran lignans have been developed, including an enantiocontrolled route [19]. For synthesis of syringaresinol (1) and



pinoresinol (2) we looked for a more simple method. For this purpose we modified Freudenberg's method [20] which consists of an oxidative dimerization of sinapyl and coniferyl alcohols [21] in the presence of oxygen and light. The reaction was catalysed by cupric sulphate. In this way syringaresinol was obtained in 90% yield, pinoresinol only in 12% yield. The reason for this is the lack of a 5-methoxy group on the aromatic ring of coniferyl alcohol. In this case, presumably, apart from the radical leading to pinoresinol another way was also followed, which together with other radicals resulted in various by-products. One of them, dehydrodiconiferyl alcohol (10) was isolated in 29% yield.

In both furanofurans, the  $^1\text{H}$  NMR signals for benzylic protons appeared between  $\delta$  3.75 and 4.7 as predicted according to Pelter *et al.* [4] for the *exo-exo* (diequatorial) diastereomers. The  $^{13}\text{C}$  NMR data also agreed with the literature [22]. Compounds 1 and 2 are racemates, which up to now could not be separated by HPLC, even using chiral columns. Coupling of 1 with  $\alpha$ -acetobromoglucose in pyridine, or chinoline using silver salts, gave negligible yields because the aglucone was destroyed by these reagents. Glucosidation in aqueous acetone-potassium hydroxide systems, however, gave not only higher yields, but also permitted the recovery of unreacted aglucone. In the course of the synthesis and purification, acidic and strong basic conditions have to be avoided. With suitable variation of reaction conditions (see Experimental: excess  $\alpha$ -acetobromoglucose added in several portions over a relative long period of time) both the 4'-*O*-mono- (3) and 4',4'-*O*-bis-glucoside (4) of syringaresinol were obtained in satisfactory yield. For the synthesis of pinoresinol-4'-*O*-glucoside (5) we followed the route worked out for the syringaresinol monoglucoside. In this case the formation of a 4',4'-*O*-bis-glucoside was not observed.

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data of our compounds showed clearly that during glucosylation the two oxolane five-membered rings did not change their *exo-exo* position. The  $\beta$ -configuration of the glycosidic linkages followed from the method of glucosylation. The correspondence in mps and spectra proved the identity of the natural and synthetic products.

#### EXPERIMENTAL

Mps: uncorr. UV: in MeOH. IR: as KBr pellets. NMR: at 80 or 360 MHz for  $^1\text{H}$  and 75.47 or 90.55 MHz for  $^{13}\text{C}$ ; chemical shifts

are given in  $\delta$  (ppm) relative to TMS and solvents, respectively. MS: NIFAB, 8 kV Xe gun, glycerol as matrix; CI, 120 eV,  $\text{NH}_3$  as reactant gas. CC: on silica gel or neutral  $\text{Al}_2\text{O}_3$ . TLC: on silica gel plates, solvent systems: (A) toluene-EtOAc (2:1), (B) toluene-EtOH (9:2), (D)  $\text{CHCl}_3$ -MeOH (20:1), (E)  $\text{CHCl}_3$ -MeOH (50:1) and (F) EtOAc-MeOH- $\text{H}_2\text{O}$  (200:33:27).

( $\pm$ ) 2,6-Bis(4'-hydroxy-3',5'-dimethoxy-phenyl)-3,7-dioxabicyclo [3.3.0] octane; racemic; syringaresinol (1). A soln of sinapyl alcohol [21] (1.05 g, 5 mmol) 200 ml  $\text{H}_2\text{O}$  and 0.8 g  $\text{CuSO}_4$  was vigorously stirred at 25° in the presence of light and air. After 48 hr the reaction mixt. was extd with  $\text{CH}_2\text{Cl}_2$ , dried, and evapd yielding 950 mg (91%) of an oily product which was purified by flash chromatography (solvent A) and recrystallized from EtOH- $\text{CHCl}_3$  (9:1). Needles (680 mg 67%). Mp 171–176° (lit. [2] 172–174°, lit. [20] 169.5–174°, lit. [13] 175–176°).  $\text{C}_{22}\text{H}_{26}\text{O}_8$  (418.43) found 63.30 C, 6.41 H; calc. 63.15 C, 6.26% H. IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 1605, 1510, 1460, 1420, 1380, 1230, 1110, 905, 850.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.10 (2H, m, H-1, 5), 3.78 (12H, s, OMe), 3.90 (2H, dd,  $J=9, 4$  Hz, H-4, H-8<sub>ax</sub>), 4.31 (2H, dd,  $J=9, 7$  Hz, H-4, H-8<sub>eq</sub>), 4.75 (2H, d,  $J=7$  Hz, H-2, H-6), 5.56 (2H, m, OH), 6.60 (4H, s, H-2', H-4').  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 54.3 (d, C-1, C-5), 56.4 (q, OMe), 71.8 (t, C-4, C-8), 86.0 (d, C-2, C-6), 102.7 (d, C-2', C-6'), 132.1 (s, C-1'), 134.3 (s, C-4'), 147.2 (s, C-3', C-5'). Diacetate: acetylation of 1 with  $\text{Ac}_2\text{O}$  in pyridine gave after usual work-up, needles, mp 182–183° (from EtOH) (lit. [23] 181–182°).

Syringaresinol-4'-*O*- $\beta$ -D-monoglucoside (3). To a soln of syringaresinol (1) (250 mg, 0.6 mmol) in  $\text{Me}_2\text{CO}$  (10 ml), 1.6 ml 2.5% KOH soln (0.7 mmol) and a soln of 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide (300 mg 0.7 mmol) in  $\text{Me}_2\text{CO}$  (10 ml) were added concurrently at 0°. Meanwhile the pH remained at 8–9. After stirring for 1.5 hr at 0° and standing overnight at 5° the soln was adjusted to pH 7. After evapn, diln with  $\text{H}_2\text{O}$  (10 ml), extn with EtOAc and repeated evapn, the residue was chromatographed on a neutral  $\text{Al}_2\text{O}_3$  column (solvent B). After eluates containing traces of unreacted aglucone (1), syringaresinol-4'-glucoside-tetraacetate (6) was collected (220 mg, 51%). Compound 6 was acetylated with  $\text{Ac}_2\text{O}$  in pyridine and worked-up as usual to yield the pentaacetate (7), as amorphous powder, mp 90°. Compound 7 (148 mg 0.2 mmol) was dissolved in MeOH (50 ml) and the soln adjusted to pH 10 with 1M NaOMe and left standing overnight. After neutralization with Dowex 50 W  $\times$  8 cation exchange resin, filtration and evapn, needles were obtained (100 mg, 87%) from EtOH, mp 174–177°.  $\text{C}_{28}\text{H}_{36}\text{O}_{13}$  (580.57) found: 58, 30 C, 6.42 H; calc. 58.06 C 6.25% H. UV  $\lambda_{\text{max}}$  nm: 209, 245 sh, 270 (lit. [9] 206, 271). IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 1590, 1500, 1460, 1420, 1370, 1225, 1112, 810.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ): 3.12 (2H, m, H-1, 5), 3.24–3.69 (7H, m, sugar H), 3.81, 3.82 (12H, each s, OMe), 3.86 (2H, m, H-4, H-8<sub>ax</sub>), 4.24 (2H, m, H-4, H-8<sub>eq</sub>), 4.68 (2H, d,  $J=4$  Hz, H-2, H-6), 4.90 (1H, br d, H-1'), 6.27, 6.71 (4H, each s, H-2', H-4').  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ): 53.6 (d, C-1, C-5), 56.1 (q, OMe), 60.9 (t, C-6'), 69.9 (d, C-4'), 71.2 (t, C-4, C-8), 74.1 (d, C-2'), 76.5 (d, C-3'), 85.1 (d, C-2, C-6), 102.6 (d, C-1'), 103.9 (d, C-2', C-6'), 131.3 (s, C-4' OH), 134.8 (s, C-1'), 137.2 (s, C-4' gl), 147.8 (s, C-3', C-5'), 152.6 (s, C-3', C-5, Agl). MS-NIFAB  $m/z$ : 579 [M-H] $^-$ , 417 [Agl-H] $^-$ .

Syringaresinol-4',4'-*O*-bis- $\beta$ -D-glucoside (4). To a soln of syringaresinol (1) (250 mg, 0.6 mmol) in  $\text{Me}_2\text{CO}$  (10 ml), 9.1 ml 2.5% KOH soln (4.08 mmol) and a soln of 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl bromide (2.05 g, 4.08 mmol) in  $\text{Me}_2\text{CO}$  (10 ml) were added concurrently at 0°. After stirring for 3 hr and remaining overnight at 5° a half amount of KOH soln and bromo-sugar was added. After 48 hr the mixt. was worked-up as described for 3. The crude octaacetate (8) was saponified in MeOH (75 ml) with 1 N NaOMe (pH 10) without previous CC. After careful neutralization with Dowex 50 W  $\times$  8 cation exchange resin, the MeOH soln was decanted, evapd to half of its vol. and cooled. From the ppt., needles (205 mg, 47%), mp

263–266°, were obtained from pyridine (lit. [2] 269–270°, [5] 265–266°).  $[\alpha]_D^{25} - 18.5$  (H<sub>2</sub>O–EtOH (3:1)  $c$  0.542), (lit. [5]  $[\alpha]_D^{25} - 12.1$  (pyridine;  $c$  0.596)). C<sub>34</sub>H<sub>46</sub>O<sub>18</sub> (742.71), found 54.55 C, 6, 12 H; calc. 54.98 C, 6.24% H. UV  $\lambda_{\max}$  nm 206, 238 sh, 271 (lit. [9] 206, 238 sh, 271). IR  $\nu_{\max}$  cm<sup>-1</sup>: 1595, 1510, 1460, 1420, 1365, 1235, 1130, 895, 815. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 3.09 (2H, *m*, H-1, 5), 3.17–3.39 (14H, *m*, sugar-H, –OH), 3.75 (12H, *s*, OMe), 4.20 (2H, *m*, H-4, H-8<sub>ax</sub>), 4.30 (2H, *d*, H-4, H-8<sub>eq</sub>), 4.68 (2H, *d*, *J* = 4 Hz, H-2, H-6), 4.92 (4H, *m*, sugar-OH), 4.99 (2H, *m*, H-1', 5'), 6.65 (4H, *s*, H-2', H-4'). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): 53.7 (*d*, C-1, C-5), 56.6 (*q*, OMe), 61.1 (*t*, C-6'), 70.2 (*d*, C-4'), 71.4 (*t*, C-4, C-8), 74.3 (*d*, C-2'), 76.7 (*d*, C-3'), 77.2 (*d*, C-5'), 85.1 (*d*, C-2, C-6), 102.9 (*d*, C-1'), 104.5 (*d*, C-2', C-6'), 134.1 (*s*, C-1'), 137.2 (*s*, C-4'), 152.6 (*s*, C-3', C-5'). MS-NIFAB *m/z*: 741 [M – H]<sup>–</sup>, 579 [M – Glc – H]<sup>–</sup>, 417 [AgI – H]<sup>–</sup>. Octaacetate (8). Compound 4 was acetylated with Ac<sub>2</sub>O in pyridine and worked-up as usual to yield 8 as plates, mp 119–122° from EtOH (lit. [5] 121–124°), C<sub>50</sub>H<sub>62</sub>O<sub>26</sub> (1079.00) found 55.30 C, 6.00 H; calc. 55.65 C, 5.79% H. IR  $\nu_{\max}$  cm<sup>-1</sup>: 1740, 1590, 1460, 1420, 1370, 1230, 1120, 1030, 905, 815. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.01, 2.02, 2.03, 2.04 (24H, each *s*, OAc), 3.07 (2H, *m*, H-1, H-5), 3.68 (2H, *m*, H-5'), 3.83 (12H, *s*, OMe), 3.92, 3.94 (2H, *dd*, *J* = 9, 4 Hz, H-4, H-8<sub>ax</sub>), 4.18 (4H, *dd*, *J* = 12, 6 Hz, H-6'), 4.25 (2H, *d*, *J* = 8 Hz, H-4, H-8<sub>eq</sub>), 4.74 (2H, *d*, *J* = 4 Hz, H-2, H-6), 5.04 (2H, *m*, H-1'), 5.28 (6H, *m*, H-2', H-3', H-4'), 6.55 (4H, *s*, H-2', H-6'). CI-MS *m/z*: 1096 [M + NH<sub>4</sub>]<sup>+</sup>, 1036, 994, 748 [M – GlcAc<sub>4</sub>]<sup>+</sup>, 747, 418 [AgI]<sup>+</sup>, 331 [GlcAc<sub>4</sub>]<sup>+</sup>, 169, 109.

(±)2,6-Bis(4'-hydroxy-3'-methoxy-phenyl)-3,7-dioxabicyclo [3.3.0]octane; racemate; pinoresinol (2). A soln of coniferyl alcohol [16] (1.8 g, 1.0 mmol), 10 ml MeOH, 200 ml H<sub>2</sub>O and 0.8 g CuSO<sub>4</sub> was vigorously stirred at 25° in the presence of light and air. After 20 hr the reaction mixt. was extd with CH<sub>2</sub>Cl<sub>2</sub>, dried and evapd yielding 1.8 g oily product. It was purified by flash CC (solvent D) giving 216 mg (12%) pinoresinol (2) 525 mg (29%) dehydro-diconiferylalcohol (10) and 350 mg (19.5%) unreacted coniferyl alcohol. Repeated purification by CC (solvent E) and evapn with EtOH resulted in amorphous pinoresinol, mp 115–118° (lit. [14] 111°, [24] 120–121°, [11] 158–159°. C<sub>20</sub>H<sub>22</sub>O<sub>6</sub> (358.4) found 67.02 C, 6.19 H, calc. 67.18 C, 6.22% H. IR  $\nu_{\max}$  cm<sup>-1</sup>: 1608, 1520, 1450, 1420, 1380, 1100, 900, 840. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.10 (2H, *m*, H-1, 5), 3.87 (2H, *dd*, *J* = 9, 4 Hz, H-4, H-8<sub>ax</sub>), 3.92 (6H, *s*, OMe), 4.30 (2H, *dd*, *J* = 9, 7 Hz, H-4, H-8<sub>eq</sub>), 4.75 (2H, *d*, *J* = 5 Hz, H-2, H-6), 5.63 (2H, *s*, OH), 6.82 (6H, *m*, H-2', H-5', H-6'). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 54.2 (*d*, C-1, C-5), 56.0 (*q*, OMe), 71.7 (*t*, C-4, C-8), 85.9 (*d*, C-2, C-6), 108.7 (*d*, C-2'), 114.3 (*d*, C-5'), 118.9 (*d*, C-6'), 132.9 (*s*, C-1'), 145.3 (*s*, C-4'), 146.7 (*s*, C-3').

Diacetate. Acetylation of 2 with Ac<sub>2</sub>O in pyridine gave after usual work-up needles, mp 160–163° (from EtOH) (lit. [14] 162–164°).

Dehydro-diconiferylalcohol (10). Mp 163–165° from 50% EtOH (lit. [21] 155–156°, [11] 160–161°). C<sub>20</sub>H<sub>22</sub>O<sub>6</sub> (358.4) found 66.90 C, 6.22 H; calc. 67.02 C, 6.19% H. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 3.5 (3H, *m*, H-8', H-9', H-9'), 3.73, 3.78 (6H, *ss*, OMe), 4.08 (2H, *t*, *J* = 5 Hz, H-9, H-9'), 4.75 (1H, *t*, *J* = 5 Hz, 9-OH), 5.00 (1H, *t*, *J* = 5 Hz, 9'-OH), 5.45 (1H, *d*, *J* = 10 Hz, H-7'), 6.15 (1H, *dt*, *J* = 15, 5 Hz, H-7), 6.48 (1H, *d*, *J* = 15 Hz, H-7), 6.75, 6.93 (5H, *ss*, Ar-H), 9.02 (1H, *s*, OH-4').

Pinoresinol-4'-O-β-D-monoglucoside (5). To a soln of 2 (178 mg, 0.5 mmol) in Me<sub>2</sub>CO (12 ml) 1.36 ml 2.5% KOH soln (0.6 mmol) and a soln of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (255 mg, 0.6 mmol) in Me<sub>2</sub>CO (8 ml) were added together at 0°. After stirring for 1.5 hr at 0° and standing overnight at 5°, evapn, diln with H<sub>2</sub>O (10 ml), extn with EtOAc and repeated evapn, the residue was dissolved in MeOH (40 ml) and the soln adjusted to pH 10 with 1 M NaOMe and left standing overnight at room temp. After neutralization with Amberlite IR-120 cation exchange resin, filtration and evapn, the

residue was chromatographed on a neutral Al<sub>2</sub>O<sub>3</sub> column (solvent F). After some unreacted aglucone (56 mg, 31.5%) 5, was collected, the eluate was evapd to give a clear oil which slowly solidified as an amorphous product (85 mg, 33%). C<sub>26</sub>H<sub>32</sub>O<sub>11</sub> (520.52), found 60.20 C, 6.05 H; calc. 59.99 C, 6.20% H. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 3.08 (2H, *m*, H-1, H-5), 3.18–3.56 (7H, *m*, sugar-H, –OH), 3.72 (2H, *m*, H-4, H-8<sub>ax</sub>), 3.77–3.79 (6H, *ss*, OMe), 4.18 (2H, *m*, H-4, H-8<sub>eq</sub>), 4.69 (2H, *d*, *J* = 4 Hz, H-2, H-6), 4.91 (1H, *m*, H-1'), 5.03–5.30 (3H, *m*, sugar-OH), 6.7–7.1 (6H, *m*, H-2', H-5', H-6'), 8.93 (1H, *s*, Ar-OH). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): 54.1, 54.2 (*d*, C-1, C-5), 56.4 (*q*, OMe), 61.3 (*t*, C-6'), 70.3 (*d*, C-4'), 71.7 (*t*, C-4, C-8), 73.7 (*d*, C-2'), 76.8, 77.2 (*d*, C-3', C-5'), 85.6, 85.9 (*d*, C-2, C-6), 100.8 (*d*, C-1'), 111.1, 111.2 (*d*, C-2'), 115.8, 116.0 (*d*, C-5'), 119.2, 119.5 (*d*, C-6'), 133.1 (*s*, C-1'), 136.1 (*s*, C-1'), 146.2 (*s*, C-3'), 148.2 (*s*, C-4'), 149.5 (*s*, C-4'). Pentaacetate (9). Acetylation of 5 with Ac<sub>2</sub>O in pyridine gave after usual work-up an amorphous acetate from EtOH–CHCl<sub>3</sub>. C<sub>36</sub>H<sub>42</sub>O<sub>16</sub> (730.70). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.02, 2.08 (12H, *ss*, sugar-OAc), 2.32 (3H, *s*, Ar-OAc), 3.12 (2H, *m*, H-1, H-5), 3.76 (1H, *m*, H-5'), 3.82, 3.85 (6H, *ss*, Ar-OMe), 3.92 (2H, *m*, H-4, H-8<sub>ax</sub>), 4.18 (2H, *d*, *J* = 12 Hz, H-6'), 4.28 (2H, *m*, H-4, H-8<sub>eq</sub>), 4.80, 4.76 (2H, *d*, *J* = 4 Hz, H-2, H-6), 4.95 (1H, *m*, H-1'), 5.23 (3H, *m*, H-2', H-3', H-4'), 6.80–7.12 (6H, *m*, H-2', H-5', H-6'). CI-MS *m/z*: 748 [M + NH<sub>4</sub>]<sup>+</sup>, 706, 331 [GlcAc<sub>4</sub>]<sup>+</sup>, 271, 169, 109, 108, 69.

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