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SESQUITERPENES, TRITERPENOIDS, LIMONOIDS AND FLAVONOIDS OF *CEDRELA ODORATA* GRAFT AND SPECULATIONS ON THE INDUCED RESISTANCE AGAINST *HYPSIPYLA GRANDELLA*

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Key Word Index—*Cedrela odorata*; *Toona ciliata*; Meliaceae; *Hypsipyla grandella*; graft; sesquiterpenes; cycloartanes; sterols; apotirucallanes; limonoids; flavonoids.

Abstract—From the stem of *Cedrela odorata* grafted on *Toona ciliata* var. *australis* were isolated calamenene, cycloeucalenol, sitosterol, stigmasterol, campesterol, gedunin, 7-deacetylgedunin, 7-deacetoxy-7-oxogedunin, methylangolensate, febrifugin, azadiradione, 20,21,22,23-tetrahydro-23-oxoazadirone, 3β-deacetylfissinolide and, catechin, together with the new limonoid 1α-methoxy-1,2-dihydrogedunin and the new cycloartane 3β-*O*-β-D-glucopyranosylcycloeucalenol. The limonoids were of little value to clarify the basis of the induced resistance in the graft against *Hypsipyla grandella*. The cycloartanes and catechin could have been translocated from *Toona* stock to the *Cedrela* graft. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

Efforts to establish large-scale homogeneous plantations of native Meliaceae have almost invariably failed due to larval attacks by the shoot borer *Hypsipyla* (Lepidoptera: Pyralidae). The host range of this oligophagous pantropical genus is limited principally to the Swietenioideae. Of this subfamily, important species of the genera *Khaya* and *Entandrophragma* in Africa, *Swietenia* and *Cedrela* in Latin America and *Toona* in Asia and Australia are attacked. However, *Toona ciliata* introduced to Brazil shows excellent growth and an absence of attacks by *H. grandella*, in contrast to the native *Cedrela odorata*. The latter has been grafted to stems of *T. ciliata* and the resistance has been translocated from the *Toona* stock to the *Cedrela* graft [1]. The natural products of these grafts have not been previously studied. Thus, we have now examined the stem of *C. odorata* grafted on *T. ciliata var. australis*, in order to determine if secondary metabolites present in the latter could be translocated into the former.

RESULTS AND DISCUSSION

A dichloromethane-soluble fraction of the methanol extract of the stem of *C. odorata* graft afforded the sesquiterpene calamenene [2], the cycloartane cycloeucalenol (**1**) [3], the sterols sitosterol, stigmasterol and campesterol, the limonoids gedunin (**2**) [4, 5], 7-deacetylgedunin (**3**) [6], 7-deacetoxy-7-oxogedunin (**4**) [6], methylangolensate (**5**) [6], febrifugin (**6**) [6] and azadiradione (**7**) [7], the apotirucallane 20,21,22,23-tetrahydro-23-oxoazadirone (**8**) [8], as well as the new limonoid **9**.

Compound **9** exhibited similar spectral data to **2** [4, 5]. The ^{1}H NMR spectrum (Table 1), instead of signals for a ring-A 1-en-3-one, showed a signal for one methoxyl singlet (δ 3.31) and ^{1}H resonances for an ABX system associated with 2H-2 (δ 2.86, J = 16.4, 4.0 and 2.65 Hz; J = 16.4 and 3.0 Hz) and H-1 (δ 3.34, *br t*, J = 3.2 Hz). The smaller coupling constant indicated that the methoxyl group was attached α to C-1. This was also supported by NOESY experiments, which showed correlations of the methoxyl signal with the signals of H-2α (δ 2.65) and H-9 (δ 3.09) and of the signal of H-1 with the signal of H_3-19 (δ 1.12). In addition, the signal of H-7 (δ 4.50) showed cross peaks with the signals of H-6β (δ 1.79), H-6α (δ 1.88), H-15 (δ 3.51) and H_3-30 (δ 1.12); this implies that the acetate is attached α to C-7, as in **2**.

The identification of the ring A as a 1-methoxy-3-one was also supported by comparison of the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) with those of 1α-methoxy-1,2-dihydroepoxyazadiradione (**10**) [9].

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Table 1. ^{1}H NMR chemical shifts for compounds **2** and **8**–**10**

H	**9**	**2**	**10**	**8**
1	3.34 *br t* (3.2)	7.07 *d* (10.2)	3.39 *t* (3.7)	7.14 *d* (12)
2β	2.86 *dd* (16.4, 4.0)	5.84 *d* (10.2)	2.90 *dd* (16.5, 3.7)	5.86 *d* (12)
2α	2.65 *dd* (16.4, 3.0)		2.64 *dd* (16.5, 3.7)	
5	2.23 *dd* (13.0, 3.0)	2.12 *dd* (13.2, 2.3)	2.24 *m*	2.17* *m*
6β	1.79 *ddd* (15.0, 13.0, 2.4)	1.79 *t* (*ca* 12)	2.13–1.50 *m*	1.91 *m*
6α	1.88 *ddd* (15.0, 3.2, 3.0)	1.92 *d* (*ca* 12)	2.13–1.50 *m*	1.80 *m*
7	4.50 *dd* (3.2, 2.4)	4.52 *br s*	4.66 *m*	5.24 *m*
9	3.09 *m*	2.46 *dd* (12.7, 6.2)	3.24 *m*	2.25 *m*
11	1.67–1.63 *m*	2.00 *m*	2.13–1.50 *m*	1.97 *m*
11	1.57–1.49 *m*	1.81 *m*	2.13–1.50 *m*	1.78 *m*
12	1.67–1.63 *m*	1.56 *dd* (11, 12)	2.13–1.50 *m*	1.76 *m*
12	1.57–1.49 *m*	1.70 *m*	2.13–1.50 *m*	1.50 *m*
15	3.51 *s*	3.50 *s*	3.37 *s*	5.30 *m*
16				2.15 *m*
16				2.06 *m*
17	5.61 *s*	5.59 *s*	3.88 *s*	1.73 *m*
18	1.25 *s*	1.22 *s*	1.05 *s*	1.02 *s*
19	1.12 *s*	1.19 *s*	1.11 *s*	1.18 *s*
20				2.73 *m*
21	7.41 *m*	7.39 *d* (1.3)	7.53 *m*	3.93 *t* (9.0)
21				4.47 *t* (9.0)
22	6.34 *br s*	6.31 *dd* (*ca* 1.3)	6.24 *m*	2.52* *dd* (16, 8)
22				2.23 *m*
23	7.41 *m*	7.39 *d* (1.3)	7.20 *m*	
28	1.02 *s*	1.03 *s*	1.02 *s*	1.08 *s*
29	0.99 *s*	1.04 *s*	0.99 *s*	1.08 *s*
30	1.12 *s*	1.12 *s*	1.17 *s*	1.18 *s*
OCOMe	2.11 *s*	2.07 *s*	2.04 *s*	1.95 *s*
OMe	3.31 *s*		3.32 *s*	

Resonances in **2** and **8** were confirmed by ^{1}H–^{1}H and ^{13}C–^{1}H shift-correlated 2D spectra; in **8** also by TOCSY; in **9** only by ^{1}H–^{1}H COSY. Coupling constants (Hz) in parentheses.

*Data obtained in this study suggest that these resonances were previously incorrectly assigned.

Moreover, the chemical shifts of the ring B–E carbons were comparable with those reported for **2** (Table 2) [4, 5]. The new natural product was therefore identified as 1α-methoxy-1,2-dihydrogedunin.

In order to confirm that **9** is a genuine natural product and was not derived from addition of methanol to the 1-en-3-one system, a solution of **2** in methanol with a small amount of silica gel added was stirred for three weeks at room temperature. After removal of solvent, the ^{1}H NMR spectrum of the recovered material indicated that no reaction occurred. This observation, together with the fact that the stem examined did not give the two possible epimers at C-1, provided conclusive evidence that **9** is naturally occurring.

The ^{1}H–^{1}H COSY, TOCSY, HMQC and HMBC on 20,21,22,23-tetrahydro-23-oxoazadirone (**8**) permitted minor corrections to previous ^{1}H and ^{13}C NMR assignments [8]. The signals for H-5 and H-22 (Table 1) and C-4, C-9, C-10, C-16 and C-22 (Table 2) were reassigned.

An ethyl acetate-soluble fraction of the methanol extract of the stem of *C. odorata* graft afforded the limonoids **2**, 3β-deacetylfissinolide (**11**) [10], the flavonoid catechin [11] and the new cycloartane **12**.

Compound **12** showed the spectral characteristics

Table 2. ^{13}C NMR chemical shifts for compounds **1**, **2**, **8**, **9**, **10** and **12a** and selected carbons in compound **13**

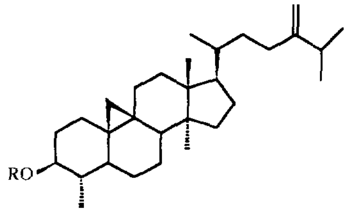
C	9	2	10	8	12a	1	13
1	82.3	157.0	82.6	157.8	30.6	30.8	
2	36.9	125.9	37.2	125.6	34.9	34.9	
3	213.9	204.0	213.8	204.5	88.0	76.6	
4	46.9	44.0	47.0	44.1*	42.5	44.6	
5	41.1	46.0	41.5	46.6	43.6	43.3	
6	23.3	23.2	24.1	23.7	24.7	24.7	
7	73.6	73.2	74.0	74.4	28.1	28.1	
8	41.9	42.6	42.9	42.7	46.9	46.9	
9	35.4	39.5	35.3	38.3*	23.5	27.3	
10	41.9	40.0	41.8	39.9*	29.2	29.5	
11	14.7	14.9	15.7	16.4	25.1	25.2	
12	25.9	25.9	28.7	33.8	32.9	35.3	
13	38.9	38.7	42.2	46.2	45.3	45.3	
14	70.0	69.7	72.9	158.7	48.9	48.9	
15	56.7	56.8	57.5	118.9	32.8	32.8	
16	167.7	167.4	208.8	34.8*	26.9	26.9	
17	78.5	78.2	50.8	58.2	52.2	52.2	
18	16.8	17.7	24.8	19.9	17.8	17.8	
19	16.1	19.7	16.3	19.0	27.3	26.9	
20	120.7	120.4	116.8	37.5	36.1	36.1	
21	142.9	143.1	141.6	72.4	18.3	18.3	
22	110.0	109.8	111.1	34.0*	35.3	34.8	
23	141.1	141.2	142.3	177.0	31.3	31.3	
24					156.9	156.9	
25					33.8	33.8	
26					21.9	21.9	
27					22.0	22.0	
28	24.8	27.1	23.6	27.0	19.1	19.1	
29	21.1	21.2	20.9	21.1	14.1	14.4	
30	18.4	18.3	19.4	27.4			
31					105.9	105.9	
O$\underline{\mathrm{C}}$OMe	170.2	169.9	170.0	170.0	169.3		
O$\underline{\mathrm{C}}$OMe					169.4		
O$\underline{\mathrm{C}}$OMe					170.4		
O$\underline{\mathrm{C}}$OMe					170.7		
OCO$\underline{\mathrm{C}}$H$_3$	21.2	21.0	21.3	21.3	20.6		
OCO$\underline{\mathrm{C}}$H$_3$					20.6		
OCO$\underline{\mathrm{C}}$H$_3$					20.7		
OCO$\underline{\mathrm{C}}$H$_3$					20.8		
OMe	56.8		56.8				
1′					102.1		102.8
2′					71.5		71.4
3′					72.9		72.8
4′					68.6		68.7
5′					71.6		71.6
6′					62.2		62.1

Assignments based on ^{1}H–^{13}C COSY/^{1}H–^{13}C LRCOSY for **2**, HMQC and HMBC for **8**, PENDANT for **1** and DEPT 135 for **9** and **12a**.

*Data obtained in this study suggest that these resonances were previously incorrectly assigned.

of a triterpene glycoside. Acetylation of **12** with acetic anhydride in pyridine gave a tetra-acetate (**12a**). The ^{1}H and ^{13}C NMR spectra of **12a** and cycloeucalenol (**1**) [3] were very similar. The presence of a 2,3,4,6-tetra-*O*-acetyl-β-glucopyranose linked at C-3β was indicated by the proton signal at δ 3.12 (*dt*, $J = 10.5$ and 4.8 Hz, H-3α) and the ^{13}C signal at δ 88.0 (Table 2). The configuration of the anomeric position of the glucose moiety was assigned to be β from the coupling constant of the anomeric proton (δ 4.58 *d*, $J = 8.0$ Hz). The nature of the sugar was confirmed by a comparative analysis of the ^{13}C NMR data for **12a** with those of quinovic acid 3β-*O*-β-D-glucopyranoside peracetyl dimethyl ester (**13**, a dimethyl urs-12-en-14,17-dioate) [12]. Thus, compound **12** was concluded to be 3β-*O*-β-D-glucopyranosylcycloeucalenol.

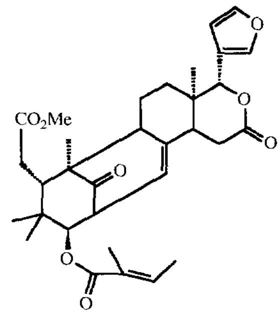
As reported previously [13], limonoid biosynthesis in *Cedrela* proceeds along only one route, which leads



1 R = H

12 R = β-D-glucopyranosyl

12a R = β-D-glucopyranosyl (OAc)



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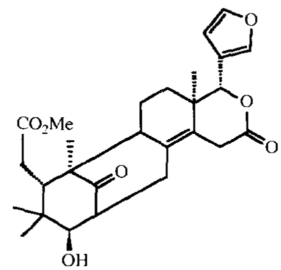

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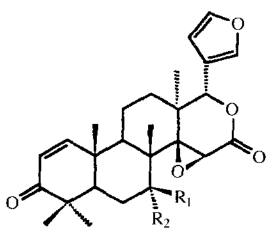
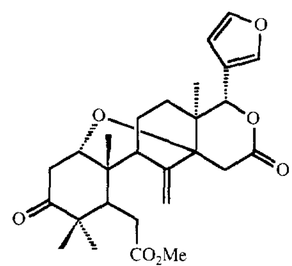


2 $R_1 = H, R_2 = OAc$

3 $R_1 = H, R_2 = OH$

4 $R_1 = R_2 = O$



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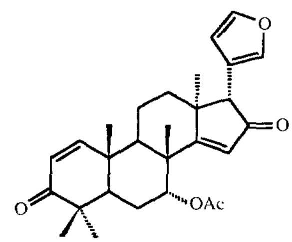

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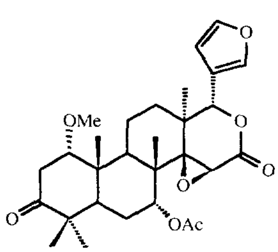

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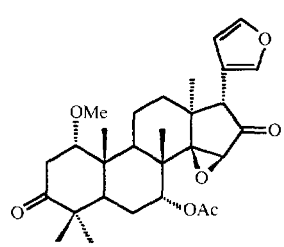

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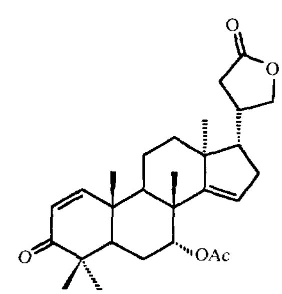

8

to the ring-D lactone derivatives (**2–5** and **9**) and then to the mexicanolide group (**6** and **11**). Thus, *C. odorata* graft produces a considerable number of limonoids which are common in *Cedrela*, but **3**, **7**, **11** and the apotirucallane **8** were not previously found from the latter. Compounds **7** and **8** are typical of the *Toona* [13], but they might be the biosynthetic intermediates to *Cedrela* limonoids.

Studies of the structure/anti-insect activity relationships for several limonoids have established that aside from the C-*seco*-limonoids, the most active compounds appear to be intact apo-euphol limonoids with a 14,15-epoxide and a 3-oxo-1-ene A ring. Absence of the 14, 15β-epoxide results in reduced activity, as with **7** [14]. Thus, the finding of both limonoids **7** and **8** is of little value to clarify the basis of induced resistance in the graft.

Stigmasterol and campesterol do not appear to have been recorded previously from *C. odorata* and *T. ciliata*. However, they are of widespread distribution and thus possibly of little chemotaxanomic interest. Representatives of the cadinene series of sesquiterpenes have been reported from the stems of *C. odorata* and *T. ciliata* [2, 15], but calamenene is known only from the former. Flavonols and 3-glycoside derivatives were found in leaves of *C. sinensis* [16], but not so far in any other *Cedrela*. Proanthocyanidins have otherwise been reported from only a single *Toona* species (stem of *T. ciliata*) [17].

The genus *Cedrela* has been widely investigated, but, to date, there are no records of cycloartanes. Our own investigations of the stem and leaves of *T. ciliata* revealed the presence of cycloeucalenol (**1**) and **12** (unpublished results). Since the latter types and proanthocyanidins have not been found in *C. odorata*, the occurrence of both cycloartanes (**1** and **12**) and catechin (in great amounts) in the graft suggests that these constituents could have been translocated from the *Toona* stock to the *Cedrela* graft. However, both species should be re-examined for condensed tannins and their precursors (as catechin), and *C. odorata* for cycloartanes.

EXPERIMENTAL

NMR: Bruker ARX 400, with TMS as int. standard; GC-MS: low resolution on a HP-2576 instrument; EIMS and DCIMS: 70 eV, low resolution on a VG Plataform II (Fisons) instrument; R-HPLC (recycling HPLC): model Shimadzu LC-6AD; the column used was a Shim-pack Prep-Sil (H), 250×20 mm, 5 μm particle size, 100 Å pore diameter; eluent: CH_2Cl_2–MeOH (49:1); flow rate: 2.5 ml min^{-1}; detection (Shimadzu SPD-6AV): UV λ 240 and 215 nm.

Plant material. Cedrela odorata grafted on *T. ciliata* var. *australis* was collected in Viçosa, MG, Brazil, and a voucher is deposited in the Herbarium of the Departamento de Engenharia Florestal, Universidade Federal de Viçosa, Viçosa, MG.

Isolation of compounds. Ground stems (3 kg, 5-year-old tree and stems worked with a diameter of 30 cm) were extracted with hexane, then CH_2Cl_2 and finally with MeOH. The concd MeOH extract was partitioned into CH_2Cl_2, EtOAc and *n*-BuOH soluble frs. The concd CH_2Cl_2-soluble fr. was subjected to CC over silica gel. Elution with a CH_2Cl_2–MeOH gradient afforded 20 frs. Fr. 1 was purified by prep. TLC (silica gel; hexane) to yield calamenene (9 mg). Frs 3–5 were flash chromatographed on silica gel, eluting with hexane–EtOAc–MeOH (94:5:1) affording **2** (490 mg) and 20 new frs. Frs 3/15–16 were recrystallized in MeOH yielding **1** (19 mg). Frs 7–8 were flash chromatographed on silica gel, eluting with hexane–EtOAc–MeOH (69:30:1) affording 10 new frs. Frs 7/2–4 yielded, after crystallization in MeOH, an amorphous solid characterized by low resolution GC-MS as a mixt. (78 mg) of sitosterol, campesterol and stigmasterol. Frs 7/5–6 were flash chromatographed on silica gel, eluting with CH_2Cl_2–MeOH (49:1) affording **2** (240 mg). Fr. 7/7 was rechromatographed as above to afford **2** (260 mg) and **3** (82 mg). Frs 7/9–10 were recrystallized in MeOH yielding **4** (78 mg) and fr. 9/1, which was rechromatographed as above, to afford new frs (9/1a and 9/1b). Fr. 9/1a (20 mg) was submitted to R-HPLC (detection UV λ 215 nm) affording, **5** (3 mg), after recycling $\times 2$, **2** (1st peak, 3 mg) and **9** (2nd peak, 7 mg), after recycling $\times 3$. Fr. 9/1b (20 mg) was submitted to R-HPLC (detection UV λ 240 nm) affording **8** (2 mg), after recycling $\times 3$, **7** (6 mg), after recycling $\times 4$, and **6** (8 mg), after recycling $\times 5$.

The concd EtOAc-soluble fr. of the MeOH extract was subjected to CC over silica gel. Elution with a CH_2Cl_2–MeOH gradient afforded 20 frs. Frs 1–2 were submitted to CC over silica gel eluting with CH_2Cl_2–MeOH (99:1) affording **2** (750 mg) and 15 new frs. Frs 1/12–13 were twice flash chromatographed on silica gel (CH_2Cl_2–Me_2CO, 24:1; hexane–EtOAc–MeOH, 50:50:1) yielding **11** (13 mg). Fr. 7 was recrystallized in MeOH yielding **12** (37 mg). Fr. 11 was flash chromatographed on silica gel, eluting with hexane–CH_2Cl_2–MeOH (3:5:2) affording **12** (3 mg) and catechin (460 mg). Compound **12** was allowed to react overnight with an excess of Ac_2O in pyridine. Work-up as usual yielded 3β-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)cycloeucalenol (**12a**).

20,21,22,23-Tetrahydro-23-oxoazadirone (**8**). Amorphous solid, mp 222–226°, $[\alpha]_D$ −15° ($CHCl_3$; *c* 0.02). IR ν_{max}^{KBr} cm^{-1}: 2928, 1777, 1731, 1665, 1461, 1375, 1248. ^1H NMR (400 MHz, $CDCl_3$): Table 1; ^{13}C NMR (100 MHz, $CDCl_3$): Table 2; TOCSY (400 MHz, $CDCl_3$): H-1/H-2, H-15/H-16/H-16/H-17, H-7/H-5/H-6/H-6, 2H-21/H-20/H-22/H-22/H-17; HMBC (400/100 MHz, $CDCl_3$): H_3-18 → C-12, C-13, C-14, C-17; H_3-19 → C-1, C-9, C-10; H_3-28/29 → C-3, C-4; H_3-30 → C-7, C-8, C-9, C-14.

1α-*Methoxy*-1,2-*dihydrogedunin* (**9**). Gum, $[\alpha]_D$ −6.34° ($CHCl_3$, *c* 0.71). IR ν_{max}^{KBr} cm^{-}: 2942, 1734, 1670, 1381, 1240, 1092, 1027, 922. ^1H NMR (400 MHz, $CDCl_3$): Table 1; ^{13}C NMR (100 MHz, $CDCl_3$): Table 2; NOESY-TPPI (400 MHz, $CDCl_3$): H-7 → H-6β, H-6α, H-15, H_3-30; H-1 → H_3-19; 1-OMe → H-2α, H-9; H-9 → H-5, H_3-18; H-2β → H_3-19, H_3-28; H-5 → H_3-29. EIMS *m/z* (rel. int.): 514 $[M]^+$ (1), 331 (48), 299 (52), 213 (67), 95 (100), (similar to **2** [18]).

3β-O-β-D-*Glucopyranosylcycloeucalenol* (**12**). Amorphous solid, mp 231–234°, $[\alpha]_D$ +24.65° (MeOH; *c* 0.14). IR ν_{max}^{KBr} cm^{-1}: 3392, 2920, 1640, 1456, 1375, 1163, 1084, 1024, 886.

3β-O-(2′,3′,4′,6′-*Tetra*-O-*acetyl*-β-D-*glucopyranosyl)cycloeucalenol* (**12a**). Needles, mp 188–192°, $[\alpha]_D$ +27.71° ($CHCl_3$; *c* 0.33). ^1H NMR (400 MHz, $CDCl_3$): δ 5.21 (H-3′, *t*, $J = 9.6$ Hz), 5.06 (H-4′, *t*, $J = 9.6$ Hz), 5.01 (H-2′, *dd*, $J = 9.6$; 8.0 Hz), 4.71 (H-31, *br s*), 4.66 (H-31, *br s*), 4.58 (H-1′, *d*, $J = 8.0$ Hz), 4.25 (H-6′, *dd*, $J = 12.0$, 5.2 Hz), 4.12 (H-6′, *dd*, $J = 12.0$, 2.4 Hz), 3.70 (H-5′, *m*), 3.12 (H-3α, *dt*, $J = 10.5$, 4.8 Hz), 2.07 (*s*, Ac), 2.04 (*s*, Ac), 2.03 (*s*, Ac), 2.01 (*s*, Ac), 1.03 (*d*, $J = 6.8$ Hz, Me), 1.02 (*d*, $J = 6.8$ Hz, Me), 0.96 (*s*, Me), 0.90 (*d*, $J = 4.8$ Hz, Me), 0.89 (*s*, Me), 0.88 (*d*, $J = 6.8$ Hz, Me), 0.36 (H-19, *d*, $J = 4.0$ Hz), 0.13 (H-19, *d*, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): Table 2. DCIMS *m/z* (rel. int.): 757 $[M+H]^+$ (1), 756 (0.5), 426 $[aglycone]^+$ (0.5), 408 $[aglycone-H_2O]^+$ (5), 331 $[peracetyl\text{-}glucose]^+$ (17), 61 (100).

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