

Acylperoxylated and *seco*-Mexicanolides from Stems of *Khaya anthotheca*

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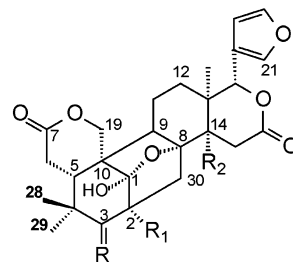
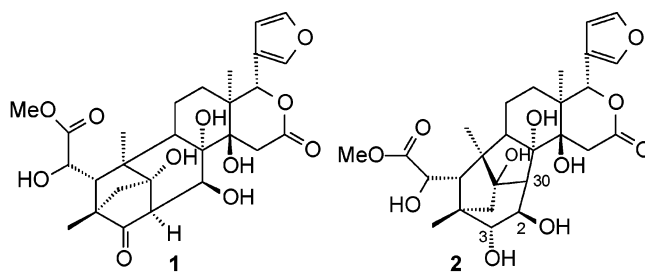
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The stems of *Khaya anthotheca* yielded two new limonoids, which were identified on the basis of spectroscopic analysis as 1 α ,8 α -oxido-3 β -acetoxy-2 α -acylperoxy-1 α ,14 α -dihydroxy-[3.3.1^{10,2}]-bicyclomeliac-7,19-olide (**3**) and 3-acetoxy-8,14-dien-8,30-*seco*-khalactone (**4**). Methyl 1 α ,2 β ,3 α ,6,8 α ,14 β -hexahydroxy-[4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate, scopoletin, and 3-*O*- β -D-glucopyranosylsitosterol were also isolated. The limonoids were of little value to clarify the basis of the nonresistance against *Hypsipyla grandella*.

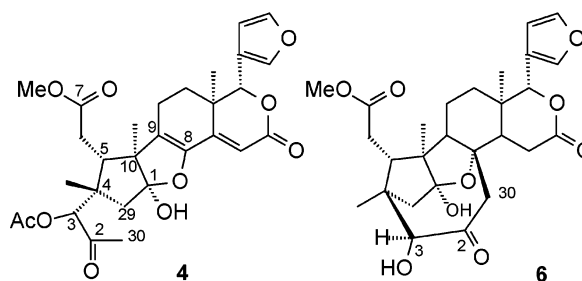
Khaya senegalensis (Desr.) A. Juss. (Meliaceae) occurs in the sub-Saharan savannah area from Senegal to Uganda.¹ However, this was introduced in Brazil and showed excellent growth and an absence of attacks by the shoot borer *Hypsipyla grandella*, in contrast to the native *K. anthotheca*.^{2,3} To determine the phytochemical basis of this resistance, we examined the exotic *K. senegalensis* and we isolated five limonoids, e.g., methyl 1 α ,6,8 α ,14 β ,30 β -pentahydroxy-3-oxo-[3.3.1^{10,2}.1^{1,4}]-tricyclomeliac-7-oate (**1**) and methyl 1 α ,2 β ,3 α ,6,8 α ,14 β -hexahydroxy-[4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate (**2**).^{2,3} The latter represented a new group of methyl tricyclomeliac-7-oates. Thus, the resistance of exotic *K. senegalensis* to native *H. grandella* may well be due to the presence of the methyl [4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate limonoids. However, it would not be surprising if these limonoids had remained undiscovered in the *K. anthotheca* because of their low concentrations or due to seasonal variations in the chemical composition of its species. Therefore, it was premature to draw any conclusions about the role of tricyclo-[4.2.1^{10,30}.1^{1,4}]-decane limonoids in a possible coevolutionary relationship between Meliaceae and *H. grandella*, until the native *K. anthotheca* could be re-evaluated for the presence of these limonoids. To establish this, we have now undertaken a further investigation of stems of *K. anthotheca*.

A dichloromethane-soluble fraction of the MeOH extract of the stems of *K. anthotheca* was purified by repeated column chromatography on silica gel and preparative TLC to give **2**,³ scopoletin, sitosterol, stigmasterol, campesterol, 3-*O*- β -D-glucopyranosylsitosterol, and two new limonoids (**3**, **4**). The limonoid **3** was identified on the basis of the following data. The ¹H NMR spectrum (Table 1) indicated the presence of three tertiary methyl groups (δ 0.92, 0.99, 1.48), three downfield shifted signals attributed to a 3-substituted furan ring (δ 7.47, 7.46, 6.40), four signals characteristic of protons attached to a carbon adjacent to an oxygen atom (δ 4.20 d, J = 12.0 Hz; 4.40 d, J = 12.0 Hz; 5.27 s; 5.59 s), and two AB-type methylenes (δ 2.86 d, J = 19 Hz; 3.04 d, J = 19 Hz; and 1.89 d, J = 14 Hz; 2.69 d, J = 14 Hz). From the HMBC experiments (Table 1) the observed correlation between the ¹H signal at δ 5.27, assigned to H-17, and the C signal at δ 140.8 (C-21) determined the position of the furan ring at C-17. The



3: R = H, β OAc; R₁ = OOAc; R₂ = OH

5: R = O; R₁ = R₂ = H



signal for H-17 showed a one-bond correlation with the C signal at δ 77.2. The methyl proton at δ 0.99 showed long-range correlations with the C-17 signal (δ 77.2) and the C signals at δ 30.4 (CH₂, by HSQC and DEPT 135°), 40.3 (quaternary), and 71.9 (quaternary), thus indicating the hydroxyl group to be located at C-14 and leading to their assignments as H₃-18, C-12, C-13, and C-14, respectively. The C-12 signal at δ 30.4 showed a one-bond correlation with the protons at δ 1.54 and 1.84, which were coupled to each other and to the hydrogens at δ 1.39 and 1.63, and both latter signals also showed cross-peaks with the C at δ 20.6 in the HSQC experiments. These signals were then assigned to H₂-12, H₂-11, and C-11, respectively. The large

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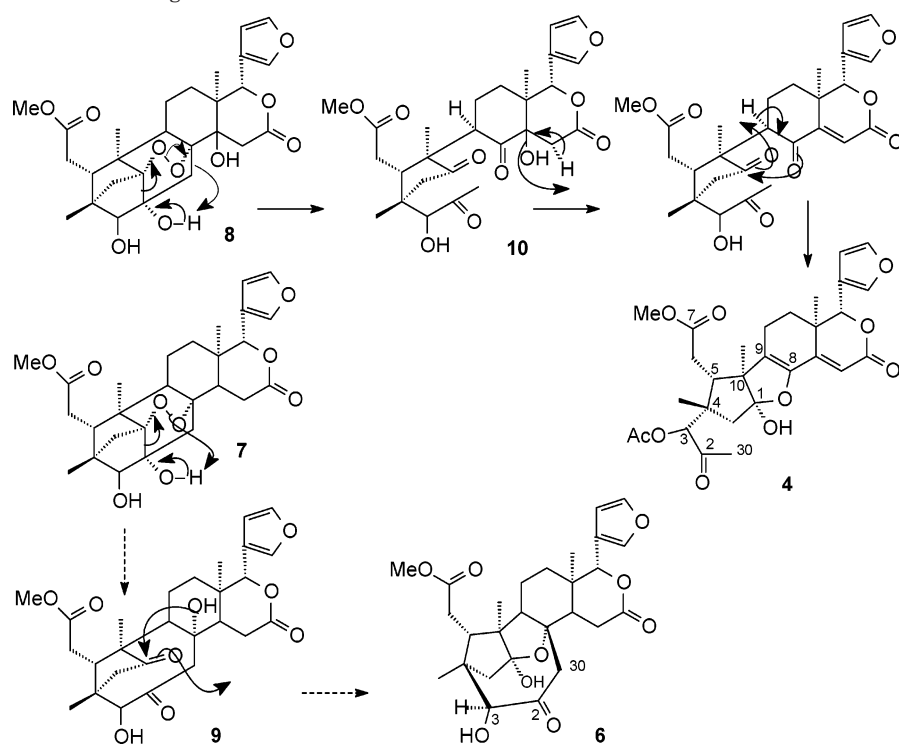
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Table 1. NMR Data for Compounds **3** and **4**

compound 3						compound 4					
position	δ ¹ H	mult., J/Hz	NOESY/NOEDIF	δ ¹³ C	HMBC (C)	position	δ ¹ H	mult., J/Hz	NOESY	δ ¹³ C	HMBC (C)
1				107.6		1				117.2	
2				93.6		2				205.6	
3	5.59	s	3-OAc, 28, 29	75.6	2, 3-OAc, 4, 5, 28, 30	3	4.63	s	6, 19, 29 α	80.4	2, 3-OAc, 4, 5, 28
4				38.8		4				44.3	
5	2.25	m	28, 11 β	37.7	10	5	2.74	t, 4.2	28	46.8	3, 4, 6, 7, 9, 10, 19, 28
6	2.54	m	5, 28, 29, 3-OAc	29.8	4, 5, 7, 10	6	2.39	dd, 4.2, 7.3; 2H	19	31.8	4, 5, 7, 10
7				173.2		7				173.4	
8				81.2		8				141.9	
9	2.55	m	11 α , 12 α	52.5	5, 10	9				130.6	
10				47.5		10				57.6	
11 β	1.39	m		20.6		11a	2.14	m		16.8	
11 α	1.63	m				11b	2.18	m			
12 β	1.54	m		30.4		12 β	1.57	m		31.8	9, 14
12 α	1.84	m	18			12 α	2.18	m			
13				40.3		13				38.0	
14				71.9		14				150.8	
15 β	3.04	d, 19	15 α , 30 α	37.4	8, 13, 14, 16	15	6.02	s		108.6	8, 13, 16
15 α	2.86	d, 19	15 β , 18		8, 13, 14, 16	16				165.8	
16				169.0		17	5.18	s	12 β	80.7	12, 18, 20, 22
17	5.27	s	30 β , 30 α , 11 β	77.2	21	18	1.02	s		16.3	12, 13, 14, 17
18	0.99	s	/14-OH, 22	15.3	12, 13, 14, 17	19	1.13	s		15.8	1, 5, 9, 10
19 β	4.40	d, 12	9	73.3	1, 5, 7, 9, 10	20				120.1	
19 α	4.20	d, 12	29, 6		1, 5, 7, 9, 10	21	7.49	m	17	141.1	20, 22, 23
20				120.4		22	6.44	m	17, 18	109.9	20, 21, 23
21	7.47	m	17	140.8	20, 22, 23	23	7.43	m	22	143.1	20, 21, 22
22	6.40	m	17, 18, 12 β	109.9	20, 21, 23	28	1.12	s		18.5	3, 4, 29
23	7.46	m	22	143.2	20, 21, 22	29 β	1.97	d, 14		46.9	1, 5, 10, 28
28	0.92	s		24.6	3, 4, 5	29 α	2.50	d, 14	29 β		1, 3, 4, 28
29	1.48	s		22.5	3, 4, 5, 28	30	2.19	s		28.7	2
30 β	1.89	d, 14	5, 30 α , 11 β	39.9	2, 8, 9	7-OMe	3.84	s		52.0	7
30 α	2.69	d, 14			2, 8, 9	3-OAc	2.15	s	28	20.6	
1-OH	7.64	s	3, 29/3, 29		1, 2, 10	3-OAc				170.4	
14-OH	2.82	s	9/15 α , 18		13						
2-OAc	2.15	s	/3	20.6							
3-OAc	2.14	s	30 α , 28, 29/3	20.9							
2-OAc				175.2							
3-OAc				170.0							

geminal coupling constant of the C-15 methylene protons was consistent with their position α to a carbonyl group with C-14 fully substituted. This was supported by the long-range correlations of the H₂-15 signals at δ 2.86 and 3.04 to the C-16 signal at δ 169.0, indicating a D-ring δ -lactone system. Moreover, the existence of correlation between the H₂-15 signals and the carbon at δ 81.2 indicated a tertiary hydroxyl substituent at C-8 or cyclic ether. The AB-type methylene protons at δ 2.69 and 1.89 (d, J = 14.0 Hz) were attributed to H₂-30 by their correlation with the C-8 and suggested the presence of a mexicanolide limonoid. Two methyl groups at δ 0.92 and 1.48 showed cross-peaks with the C signal at δ 75.6, which showed a one-bond correlation with the proton at δ 5.59, and this in turn had a long-range correlation to the C signal at δ 170.0, thus indicating an acetoxy substituent at C-3 and establishing their assignments as H₃-28, H₃-29, C-3, and H-3, respectively. The chemical shifts of C-4 and C-5 were established as δ 38.8 (quaternary) and 37.7 (CH), respectively, via correlations of H₃-28 and H₃-29 and the carbon signals. The oxymethylene protons at δ 4.20 and 4.40 were coupled only to each other and showed a one-bond correlation with the carbon at δ 73.3 (CH₂) and long-range correlations with C-5 and the carbon at δ 173.2, suggesting the presence of a 19–7 lactone ring, since it was the only location left in the nucleus. The H₂-6 chemical shift was established as δ _H 2.54 m (δ 29.8, by HSQC) via correlation with C-7 (δ 173.2). Similarly, C-10 and C-9 were assigned via correlation of H₂-19 signals and the carbons

at δ 47.5 (quaternary) and 52.5 (CH), respectively. Two oxygen atoms must also be connected at C-1 due to the observed correlations between H₂-19 and the carbon at δ 107.6. The deshielded carbon resonance required the presence of a hemiketal involving a tertiary hydroxyl at C-1 and a cyclic ether formed by joining C-1 to O-8, which agreed closely with published data for seneganolide (**5**, δ 107.7, C-1).⁴ The relationship of the hydroxylic proton at δ 7.64 to C-1 and C-10, as well as of a second hydroxylic proton at δ 2.82 to C-13, led to their assignments as OH-1 and OH-14, respectively. Moreover, the OH-1 also showed a long-range correlation with the carbon at δ 93.6, which was attributed to C-2. The deshielded resonance observed here (δ 93.6) is not typical of a 2-acetoxymexicanolide, when compared with procerin (a 2-acetoxytricyclo-[3.3.1^{10,2}.1^{1,4}]-decane system, δ 83.1, C-2).⁵ The ¹³C NMR showed the presence of a second *O*-acetyl group (δ 175.2, Table 1). The HR-mass spectrum and ESI-MS indicated the molecular formula to be C₃₀H₃₆O₁₃ (m/z 604.21559), and the fragments at m/z 611 (M + K – O₂, 35%)⁶ suggested the presence of an acylperoxy group at C-2, whose spectroscopic properties are in accord with the above data. Several limonoids with peroxide substituents have been isolated;⁷ however, the presence of an acylperoxy functionality is reported here for the first time. Various stable peroxy esters have been synthesized, 1-(acylperoxy)adamantanes⁸ and 1-acetoperoxy-2-oxabicyclo-[4.3.0]-nonane, 1-acetoperoxy-2-oxabicyclo-[4.4.0]-decane, and 1-acetoperoxy-2-oxabicyclo-[4.10.0]-hexadecane.⁹

Scheme 1. Possible Route for the Biogenesis of **4** and **6**

The configuration suggested for **3** was based on the biosynthesis of limonoids;¹⁰ however, these were supported by the NOESY and NOEDIFF experiments (Table 1). The NOEs between the hydroxyl proton at δ 2.82 and H₃-18 and H-15 α allowed the assignment of this signal to 14-OH, also showing that the hydroxyl group at C-14 is thus in the α -orientation. In the same way, the NOEs between the hydroxyl proton at δ 7.64 and H₃-29 α and H-3 show that this signal can be attributed to the 1 α -OH and that H-3 is on the α -side of the molecule. The new natural product is, therefore, 1 α ,8 α -oxido-3 β -acetoxy-2 α -acylperoxy-1 α ,14 α -dihydroxy-[3.3.1^{10,2}]-bicyclomeliac-7,19-olide (**3**). The structural assignment was also supported by comparison of the ¹³C NMR spectrum with that of seneganolide (**5**).⁴

Limonoid **4** also showed the spectroscopic characteristics of a furan ring at C-17 and a D-ring δ -lactone system. However, instead of signals for a 14-hydroxy δ -lactone, it showed a signal for one olefinic proton (δ 6.02, s), which was attributed to H-15 by its HMBC correlation with C-16 (δ 165.8). Moreover, the existence of a correlation between H-15 and the carbon at δ 141.9 indicated a double bond between C-8 and C-9 or C-8 and C-30. A mexicanolide limonoid with a double bond between C-8 and C-30 would show a signal for an olefinic proton at ca. δ 5.40 in the ¹H NMR spectrum.⁵ Thus, placement of the double bond between C-8 and C-9 was confirmed by the absence of a second olefinic proton. The chemical shift of C-12 was established as δ 31.8, via correlations between H-17 (δ 5.18, s) and C-12. C-12 showed one-bond correlations with the protons at δ 2.18 and 1.57, and the latter signal also showed cross-peaks with the carbon at δ 130.6, which was attributed to C-9, confirming the presence of a double bond between C-8 and C-9. In the same way, C-14 emerged from the correlation between H₃-18 (δ 1.02) and the carbon at δ 150.8. The resonances observed for C-8 (δ 141.9) and C-9 (δ 130.6) are not typical of an 8,14-dien-mexicanolide, when compared with methyl 1,3-dioxo-8,14-dien-[3.3.1^{10,2}]-bicyclomeliac-7-olide (C-8, δ 124.6; C-9, δ 150.9).⁵ The above data indicated that compound **4** was not a normal mexicanolide limonoid. The ¹H NMR spectrum (Table 1) indi-

cated the presence of an *O*-methyl singlet (δ 3.84, s), showing a cross-peak with the carbon at δ 173.4 in the HMBC experiments (Table 1), hence indicating a carbomethoxy group at C-7. H₂-6 resonated at δ 2.39 dd, J = 4.2 and 7.3 Hz (δ 31.8, by HSQC), as established by its correlation with C-7 (δ 173.4). C-4, C-5, and C-10 were assigned via the correlations of H₂-6 and the carbons at δ 44.3 (quaternary), 46.8 (CH), and 57.6 (quaternary), respectively. The methyl proton at δ 1.13 showed long-range correlations with C-5 and C-10 and the carbon at δ 117.2 (quaternary), leading to its assignments as H₃-19 and indicating a hydroxyl group to be located at C-1. The AB-type methylene protons at δ 2.50 and 1.97 (d, J = 14.0 Hz) were attributed to H₂-29 by their correlation with C-1, C-4, C-5, and C-10. Moreover, H₂-29 also showed cross-peaks with the carbons at δ 80.4 (CH by DEPT 135°) and 18.5 (CH₃), confirming their assignments as C-3 and C-28, respectively. The carbon at δ 80.4 showed a one-bond correlation with the proton at δ 4.63 and this long-range correlation to the carbons at δ 170.4 and 205.6, thus indicating an acetoxy substituent at C-3 and a carbonyl at C-2 (or C-30), if we would be dealing with a normal 1,29-cyclomeliacate skeleton. The deshielded resonance for C-1 (δ 117.2) is typical of seneganolide (**5**, δ 107.7, C-1),⁴ requiring the presence of a hemiketal involving a tertiary hydroxyl at C-1 and a cyclic ether formed by joining C-1 to O-8. Oxygenated C-8 may have caused an upfield shift for C-9 (δ 130.6) and a downfield shift for C-8 (δ 141.9), when compared with 1,3-dioxo-8,14-dien-[3.3.1^{10,2}]-bicyclomeliac-7-olide (C-8, δ 124.6; C-9, δ 150.9).⁵ The ¹H and ¹³C NMR showed an additional methyl group (δ 2.19, s; δ 28.7; Table 1). From HMBC experiments these methyl protons showed a correlation with the carbon at δ 205.6. It is interesting to note that a similar structure, khayalactone (**6**), has been isolated from *Khaya grandifoliola*.¹¹ In principle cleavage of C-8 and C-30 and formation of double bonds between C-8/C-9 and C-14/C-15 may have occurred, resulting in 8,14-dien-8,30-*seco*-khayalactone, whose spectroscopic properties correspond with the above data. The protons at δ 2.19, δ 28.7 and 205.6 were then assigned

to H₃-30, C-30, and C-2, respectively, and suggested the presence of an isolated structural unit, -CH(OAc)COCH₃ (C3-C2-C30), connected at C-4. The NOESY experiments (Table 1) showed correlations between H-3 and H₂-6, H₃-19, and H-29 α (δ 2.50). This implies that the unit -CH(OAc)COCH₃ (C3-C2-C30) is on the α -side of the molecule. In the NOESY 1D experiment measured in DMSO-*d*₆, irradiation of the 1-OH signal did not influence any group with a spatial proximity such as Me-19. However, the hydroxylic proton was detected as a weak resonance at δ 8.30. Thus, this experiment did not facilitate elucidation of the relative configuration of C-1. Molecules containing an unusual *trans*-fused cyclopentane ring system have been synthesized; nevertheless, they are thermodynamically less favorable.¹² This observation suggests that in **4** both 1-OH and Me-19 occupy the α -face of the molecule. The HR-mass spectrum confirmed the molecular formula as C₂₉H₃₄O₁₀ (*m/z* 542.2152), and the largest fragment observed in the ESI-MS/MS was *m/z* 469 for [M + H - OAc - Me]⁺. Thus, the structure of the new limonoid was characterized as 3-acetoxy-8,14-dien-8,30-*seco*-khayalactone (**4**). The structural assignment was also supported by comparison of the ¹³C NMR spectrum with those of khayalactone (**6**).¹¹

As reported in previous paper, the resistance of exotic *K. senegalensis* to native *H. grandella* may well be owing to the presence of the methyl [4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate limonoids as **2**.^{2,3} However, their action is now debatable, since unresistant *K. anthotheca* afforded limonoid **2**. Limonoids with a tricyclo-[3.3.1^{10,2}.1^{1,4}]-decane system (**1**) were found in *K. senegalensis*, but not in *K. anthotheca*; however they might be the biosynthetic intermediates to limonoids **2** and **4**. Thus, the limonoids were of little value to clarify the basis of the resistance in *K. senegalensis* against *Hypsipyla grandella*.

A possible pathway leading to the formation of khayalactone (**6**) and limonoid **4** can be proposed by comparison with the route reported for tricyclo-[4.2.1^{10,30}.1^{1,4}]-decane limonoids.^{2,3} A pinacol-pinacolone rearrangement of 2,3-dihydroxy-1,8-peroxy-1,29-cyclomeliacate (**7**) and 2,3,14-trihydroxy-1,8-peroxy-1,29-cyclomeliacate (**8**) precursors may have occurred, resulting in the intermediates **9** and **10**, respectively. Subsequent addition of a hydroxyl group at C-8 to C-1 in **9** may lead to khayalactone (**6**). Elimination of H₂O at C-14/C-15, the loss of H-9 with formation of an enolate at C-8, subsequent addition of a hydroxyl group at C-8 to C-1, and acetylation of 3-OH may have occurred in **10**, resulting in **4** (Scheme 1).

Experimental Section

General Experimental Procedures. NMR spectra (¹H and ¹³C NMR; DEPT; HMBC; HSQC; COSY; NOESY-TPPI; and NOEDIF) were obtained on a Bruker DRX 400, with TMS as internal standard and the solvent CDCl₃; ESI-MSMS low resolution spectra were performed on a triple quadrupole Micromass Quattro LC instrument, equipped with a "Z-spray" ion source; HRMS were obtained on a Fisons VG Autospec; IR spectra were recorded on a Bomen-Ft/IR; [α]_D was measured with a Perkin-Elmer 241 instrument.

Plant Material. *Khaya anthotheca* was collected in Viçosa, MG, Brazil, and identified by J. R. Pirani (Universidade de São Paulo). A voucher (4863) is deposited in the Herbarium of Instituto de Biociências, USP, São Paulo.

Extraction and Isolation. Grounds stems (1000 g) were extracted with hexane, then EtOAc and finally with MeOH. The concentrated MeOH extract was partitioned into CH₂Cl₂-EtOAc- and *n*-BuOH-soluble fractions. The concentrated CH₂Cl₂ extract was subjected to CC over silica gel. Elution with a CH₂Cl₂-EtOAc-MeOH gradient afforded eight fractions and 3-*O*- β -D-glucopyranosylsitosterol (20 mg). Fraction 5 was repeatedly chromatographed on silica gel (hexane-CH₂Cl₂-MeOH gradient, 2:10:1), yielding scopoletin, sitosterol, stigmasterol, campesterol, and a mixture of limonoids, which after final purification by TLC (hexane-CH₂Cl₂-MeOH, 2:8:1) afforded compounds **2** (4 mg), **3** (5 mg), and **4** (6 mg).

1 α ,8 α -Oxido-3 β -acetoxy-2 α -acylperoxy-1 α ,14 α -dihydroxy-[3.3.1^{10,2}]-bicyclomeliac-7,19-olide (3**):** gum; [α]_D -69° (CHCl₃, *c* 0.003); IR ν_{\max} (CHCl₃) cm⁻¹ 3438, 1732, 1638, 1368, 1240, 1019, 866, 748; NMR data, Table 1; ESI-MSMS, *m/z* (rel int) 643 [M + K]⁺ (32), 611 [M + K - O₂]⁺ (35), 583 (100), 523 (10); HR-MS *m/z* 604.2123 (calcd for C₃₀H₃₆O₁₃, 604.2155).

3-Acetoxy-8,14-dien-8,30-*seco*-khayalactone (4**):** gum; [α]_D +68° (CHCl₃, *c* 0.005); IR ν_{\max} (CHCl₃) cm⁻¹ 3422, 3020, 1730, 1646, 1209, 758, 669; NMR data, Table 1; ESI-MSMS, *m/z* (rel int) 543 [M + H]⁺ (20), 469 [M + H - OAc - CH₃]⁺ (100), 301 (70), 177 (75); HR-MS *m/z* 542.2133 (calcd for C₂₉H₃₄O₁₀, 542.2152).

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