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Two Limonoids, Khayalenoids A and B with an Unprecedented 8-Oxa-tricyclo[4.3.2.0^{2,7}]undecane Motif, from *Khaya senegalensis*

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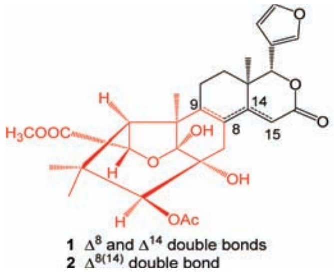
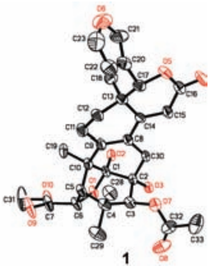
ABSTRACT



1 Δ^8 and Δ^{14} double bonds
2 $\Delta^{8(14)}$ double bond



Two limonoids, namely khayalenoids A (1) and B (2) with an unprecedented 8-oxa-tricyclo[4.3.2.0^{2,7}]undecane motif in the nortriterpenoid core, were isolated from the stems of *Khaya senegalensis*. Their structures with absolute configuration were determined by spectroscopic data, X-ray crystallography, and CD analysis.

Limonoids, a class of structurally diverse nortriterpenoids with a wide range of biological activities, have been challenging compounds for natural products and synthetic chemistry.[1] Synthetic studies of limonoids have led to the successful construction of several structurally complex molecules by Corey,[2] Ley,[3] and their co-workers. Recently, an array of limonoids with fascinating structural features has been isolated from the plant family Meliaceae by our group,[4] and some of these limonoids exhibited significant biological activities.

The genus *Khaya* is the main source of African mahogany,[5] and there are eight species of the *Khaya* genus

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(1) (a) Brandt, G. E. L.; Schmidt, M. D.; Prisinzano, T. E.; Blagg, B. S. J. *J. Med. Chem.* **2008**, *51*, 6495–6502. (b) Roy, A.; Saraf, S. *Biol. Pharm. Bull.* **2006**, *29*, 191–201. (c) Mulholland, D. A.; Parel, B.; Coombes, P. H. *Curr. Org. Chem.* **2000**, *4*, 1011–1054. (d) Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. G. E.; Towers, G. H. N. *Phytochemistry* **1992**, *31*, 377–394. (e) Akhila, A.; Rani, K. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: Vienna, Austria, 1999; Vol. 78, pp 47−149. (f) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918–919.

(2) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720–6721.

(3) (a) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629–7632. (b) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7633–7635. (c) Veitch, G. E.; Pinto, A.; Boyer, A.; Beckmann, E.; Anderson, J. C.; Ley, S. V. *Org. Lett.* **2008**, *10*, 569–572.

(4) (a) Zhang, C. R.; Fan, C. Q.; Zhang, L.; Yang, S. P.; Wu, Y.; Lu, Y.; Yue, J. M. *Org. Lett.* **2008**, *10*, 3183–3186. (b) Zhang, C. R.; Yang, S. P.; Liao, S. G.; Fan, C. Q.; Wu, Y.; Yue, J. M. *Org. Lett.* **2007**, *9*, 3383–3386. (c) Yin, S.; Wang, X. N.; Fan, C. Q.; Liao, S. G.; Yue, J. M. *Org. Lett.* **2007**, *9*, 2353–2356. (d) Yin, S.; Fan, C. Q.; Wang, X. N.; Lin, L. P.; Ding, J.; Yue, J. M. *Org. Lett.* **2006**, *8*, 4935–4938. (e) Wang, X. N.; Yin, S.; Fan, C. Q.; Wang, F. D.; Lin, L. P.; Ding, J.; Yue, J. M. *Org. Lett.* **2006**, *8*, 3845–3848.

(5) Adesida, G. A.; Adesogan, E. K.; Okorie, D. A.; Taylor, D. A. H.; Styles, B. T. *Phytochemistry* **1971**, *10*, 1845–1853.

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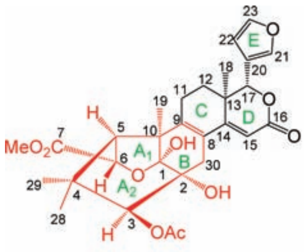
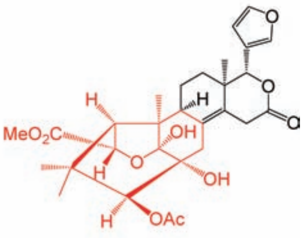
growing in the tropical zone.[6] Plants *Khaya senegalensis* (Desr.) A. Juss. (Meliaceae) have been traditionally applied in Africa for the treatment of malaria.[7] Previous chemical investigations on this plant by other research groups worldwide have afforded a series of rings B, D-*seco* limonoids.[8] As a continuation of our studies on the structurally fascinating limonoids from the family Meliaceae, khayalenoids A (**1**) and B (**2**) featuring an unprecedented 8-oxatricyclo[4.3.2.0^{2,7}]undecane motif in the limonoid core were isolated from the stems of *K. senegalensis*, which was collected from the Hainan island of China. We present herein the details of isolation and structure elucidation of these two compounds.



1



2

The air-dried powder of plant material (6.0 kg) was percolated with 95% EtOH at room temperature (3 × 10 L), and the crude extract was partitioned between H_2O and EtOAc. The EtOAc soluble fraction (220 g) was subjected to MCI gel chromatography (MeOH/H_2O, from 30/70 to 90/10, v/v) to give five fractions 1−5. Fraction 1 was extensively separated over columns of silica gel, RP-18 silica gel, and semipreparative HPLC to obtain **1** (15 mg) and **2** (30 mg).

Table 1. ^{1}H and ^{13}C NMR Data of **1−2**

	1^a		**2**^{b}	
no.	δ_H (mult, J, Hz)	δ_C	δ_H (mult, J, Hz)	δ_C
1		107.2		106.1
2		77.1		77.2
3	5.86 (s)	81.8	5.00 (s)	80.4
4		39.4		37.9
5	2.87 (s)	60.0	2.37 (s)	56.5
6	5.00 (s)	76.2	4.61 (s)	76.3
7		173.6		172.9
8		126.2		130.5
9		148.1	2.49 (br s)	40.9
10		51.0		47.9
11α	2.42 (m)	24.6	1.96 (m)	20.0
11β	2.12 (br d, 9.3)		1.57 (m)	
12α	1.46 (2H, m)	29.6	1.31 (m)	29.5
12β			1.46 (m)	
13		37.1		38.4
14		158.3		123.8
15α	6.29 (s)	110.2	3.27 (d, 19.9)	32.7
15β			3.39 (d, 19.9)	
16		165.7		170.2
17	5.12 (s)	80.4	5.11 (s)	80.2
18	0.95 (3H, s)	16.4	0.88 (3H, s)	16.1
19	1.50 (3H, s)	18.4	1.11 (3H, s)	22.8
20		121.1		120.1
21	7.68 (d, 1.1)	142.0	7.40 (br s)	140.9
22	6.60 (d, 1.1)	110.8	6.36 (br s)	109.9
23	7.56 (br s)	143.6	7.38 (t, 1.8)	142.8
28	1.20 (3H, s)	22.6	1.11 (3H, s)	23.6
29	1.25 (3H, s)	30.7	1.08 (3H, s)	30.0
30α	3.34 (d, 17.0)	33.6	2.11 (d, 16.9)	32.0
30β	2.89 (d, 17.0)		2.68 (d, 16.9)	
3-OAc		170.8		171.2
	2.18 (3H, s)	21.0	2.13 (3H, s)	20.9
7-OMe	3.68 (3H, s)	52.0	3.71 (3H, s)	52.3

[a] Data were recorded in C_5D_5N at 400 MHz (^{1}H) and 100 MHz (^{13}C).
[b] Data were recorded in $CDCl_3$ at 400 MHz (^{1}H) and 100 MHz (^{13}C).

Khayalenoid A (**1**)[9] was obtained as colorless crystals (in EtOH), and had the molecular formula of $C_{29}H_{34}O_{10}$ with 13 degrees of unsaturation as determined by HREIMS at m/z 542.2134 $[M]^+$ (calcd 542.2152). The positive mode at m/z 543.4 $[M + H]^+$ and negative mode at m/z 541.7 $[M - H]^-$ ESIMS further secured the above assignment. The IR absorptions revealed the presence of hydroxyl (3430 cm^{-1}) and carbonyl (1737, 1716, 1623 cm^{-1}) groups. The ^{1}H NMR (Table 1) showed the presence of four tertiary methyls (δ_H 0.95, 1.20, 1.25, 1.50, each 3H, s), an acetyl (δ_H 2.18, 3H, s), a methoxyl (δ_H 3.68, 3H, s), and a typical β-substituted furan ring [δ_H 7.68 (d, $J = 1.1$ Hz), 6.60 (d, $J = 1.1$ Hz), 7.56 (br s)].[8a] The ^{13}C NMR (Table 1) resolved 29 carbon resonances comprising six methyls, three methylenes, eight methines (four olefinics), and twelve quaternary carbons (three ester carbonyls, four olefinic ones) as categorized by DEPT experiments. The aforementioned spectral data and functionalities (a furan ring, two double bonds, and three ester carbonyls) suggested that **1** belongs to the limonoid category featuring a pentacyclic core.

Extensive analyses of 1D and 2D NMR data revealed that **1** shared the common C, D, and E rings with angustidienolide.[10] The key issue for the structure determination of **1** was thus focused on the construction of its unique tricyclic

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(6) Chen, S. K.; Chen, B. Y.; Li, H. *Chinese Flora (Zhongguo Zhiwu Zhi)*; Science Press: Beijing, China, 1997; Vol. 43 (3), p 46.

(7) Dalziel, J. M. *The Useful Plants of West Tropical Africa*; The Crown Agents For The Colonies: London, UK, 1937; p 325.

(8) (a) Nakatani, M.; Abdelgaleil, S. A. M.; Kassem, S. M. I.; Takezaki, K.; Okamura, H.; Iwagawa, T.; Doe, M. *J. Nat. Prod.* **2002**, *65*, 1219–1221. (b) Nakatani, M.; Abdelgaleil, S. A. M.; Kurawaki, J.; Okamura, H.; Iwagawa, T.; Doe, M. *J. Nat. Prod.* **2001**, *64*, 1261–1265. (c) Abdelgaleil, S. A. M.; Okamura, H.; Iwagawa, T.; Sato, A.; Miyahara, I.; Doe, M.; Nakatani, M. *Tetrahedron* **2001**, *57*, 119–126. (d) Nakatani, M.; Abdelgaleil, S. A. M.; Okamura, H.; Iwagawa, T.; Sato, A.; Doe, M. *Tetrahedron Lett.* **2000**, *41*, 6473–6477. (e) Khalid, S. A.; Friedrichsen, G. M.; Kharazmi, A.; Theander, T. G.; Olsen, C. E.; Christensen, S. B. *Phytochemistry* **1998**, *49*, 1769–1772. (f) Govindachari, T. R.; Krishna kumari, G. N. *Phytochemistry* **1998**, *47*, 1423–1425. (g) Olmo, L. R. V.; Silva, M. F. das G. F. da, Rodrigues Fo, E.; Fernandes, J. B.; Pinheiro, A. L.; Vilela, E. F. *Phytochemistry* **1997**, *44*, 1157–1161. (h) Olmo, L. R. V.; Silva, M. F. das G. F. da, Rodrigues Fo, E.; Vieira, P. C.; Fernandes, J. B.; Marsaioli, A. J.; Pinheiro, A. L.; Vilela, E. F. *Phytochemistry* **1996**, *42*, 831–837.

(9) **Khayalenoid A (1):** Colorless crystal (EtOH); mp 257−260°C; $[\alpha]^{20}_D$ +200 (c 0.055, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 292 (4.06) nm; IR (KBr) $\acute{\nu}_{max}$ 3430, 2923, 1737, 1716, 1623, 1249, 1029, 603 cm^{-1}; for ^{1}H NMR and ^{13}C NMR data, see Table 1; ESIMS m/z 543.4 $[M + H]^+$, 1107.6 $[2M + Na]^+$, 541.7 $[M - H]^-$, 1083.8 $[2M - H]^-$; EIMS m/z 542 $[M]^+$ (4), 524 (62), 482 (34), 446 (100), 428 (19), 326 (57), 242 (47), 157 (20), 95 (36); HREIMS m/z 542.2134 $[M]^+$ (calcd for $C_{29}H_{34}O_{10}$ 542.2152).

(10) Lavie, D.; Levy, E. C.; Rosito, C.; Zelnik, R. *Tetrahedron* **1970**, *26*, 219–226.

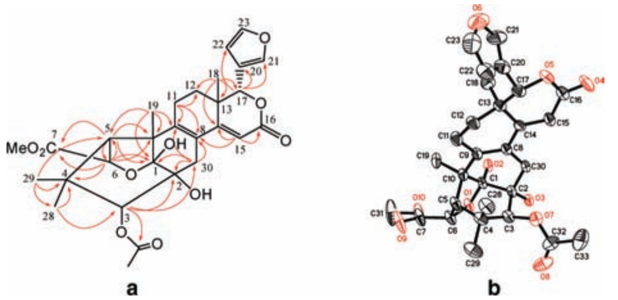

Figure 1. (a) Key HMBC correlations (H→C) of **1**. (b) Single-crystal X-ray structure of **1**.

moiety (A_1, A_2, and B rings). All the protons were readily assigned to their direct bonding carbons by a HSQC experiment. Its HMBC spectrum then enabled the establishment of an unprecedented 8-oxa-tricyclo[4.3.2.$0^{2,7}$]undecane motif in the limonoid category for **1**. In the HMBC (Figure 1a), the strong correlations from H_3-19 to C-1, C-9, and C-10, and from H_2-30 to C-1, C-2, and C-8 allowed the construction of ring B with C-19 methyl attached at C-10. The HMBC correlations of H-5/C-1, C-6, and C-10 and H-6/C-1, C-5, and C-10 indicated the presence of a tetrahydrofuran component (ring A_1), where a typical hemiketal was located at C-1 (δ_C 107.2). A methoxyformyl was linked to C-6 on the basis of HMBC correlations between H-5 and C-7 (δ_C 173.6), and between H-6 and C-7. The HMBC correlations from H_3-28 (or H_3-29) to C-3 (δ_C 81.8), C-4 (δ_C 39.4, quaternary carbon), and C-5 indicated an in-order linkage of C-3, C-4, and C-5, and also allowed the attachment of Me-28 and Me-29 to C-4. The HMBC correlations from H-3 to C-2 (δ_C 77.1) and C-30 indicated that C-2 and C-3 were connected to form the unusual ring A_2, and at C-2 a hydroxyl group was attached.

The only acetoxyl group was placed at C-3 on the basis of the HMBC correlation between H-3 and the ester carbonyl at δ_C 170.8. The planar structure of **1** with an unprecedented 8-oxa-tricyclo[4.3.2.$0^{2,7}$]undecane motif in the limonoid family was therefore assigned.

The relative configuration of **1** was established by ROESY correlations, with the only uncertainty of two hydroxyls at C-1 and C-2, but the fused-manner of 8-oxa-tricyclo[4.3.2.$0^{2,7}$]undecane motif in **1** stereospecifically required that they were α-directed (see Supporting Information S1). Fortunately, a single-crystal X-ray diffraction analysis was successfully conducted to confirm the relative configuration of **1** (Figure 1b), which was in good accordance with that of **1** in solution as established by the ROESY spectrum.

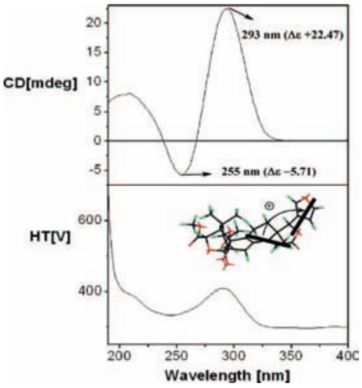

Figure 2. CD and UV spectra of **1** (in MeOH); arrows denote the electric transition dipole of two chromophores.

The absolute configuration of **1** was determined by a CD exciton chirality method.[11] The UV of **1** exhibited a strong absorption at λ_{max} 292 nm (log ε 4.06) attributable to the conjugated α,β,γ,δ-unsaturated δ-lactone (Woodward's rule gave ca. 294 nm).[12] Corresponding to this UV maximum, the CD spectrum of **1** showed a positive Cotton effect at λ_{max} 293 nm ($\Delta\varepsilon$ +22.47) and a negative Cotton effect at λ_{max} 255 nm ($\Delta\varepsilon$ −5.71) due to the transition interaction between two different chromophores of the α,β,γ,δ-unsaturated δ-lactone and the furan ring, indicating a positive chirality for **1** (Figure 2). The absolute configuration of **1** was therefore assigned.

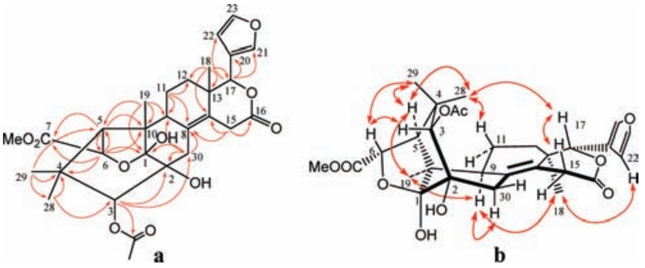

Figure 3. (a) Key HMBC correlations (H→C) of **2**. (b) Selected ROESY correlations (H↔H) of **2**.

Khayalenoid B (**2**)[13] possessed a molecular formula of $C_{29}H_{36}O_{10}$, which had two more hydrogen atoms than that of **1**. The strong IR absorptions at 3446 and 1741 cm^{-1} indicated the presence of hydroxyl and ester carbonyl groups, respectively. A combined analysis of ^{1}H, ^{13}C NMR (Table 1), HSQC, and HMBC spectra of **2** indicated that it was a closely related analogue of **1** sharing the same A_1, A_2, and the furan rings, and the only structural difference between

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[11] Berova, N.; Nakanishi, K. In *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; pp 337−382.

[12] Pretsch, E.; Bühlmann, P.; Affolter, C. In *Structure Determination of Organic Compounds: Tables of Spectral Data*, Chinese Version; Rong, G. B., Zhu, S. Z., Trans.; East China University of Science and Technology: Shanghai, China, 2002; pp 388−389.

[13] **Khayalenoid B (2):** white amorphous powder; $[\alpha]^{20}_D$ −34 (c 0.225, $CHCl_3$); IR (KBr) $\acute{\nu}_{max}$ 3446, 2950, 1741, 1238, 1027, 601 cm^{-1}; for ^{1}H NMR and ^{13}C NMR data, see Table 1; ESIMS m/z 545.3 $[M + H]^+$, 1111.6 $[2M + Na]^+$, 589.6 $[M + HCOO]^-$, 1087.6 $[2M - H]^-$; EIMS m/z 544 $[M]^+$ (15), 526 (8), 484 (10), 448 (66), 402 (100), 360 (72), 271 (96), 189 (62), 119 (73), 95 (78); HREIMS m/z 544.2301 $[M]^+$ (calcd for $C_{29}H_{36}O_{10}$ 544.2308).

the two compounds was the presence of only one $\Delta^{8(14)}$ double bond in **2** instead of the conjugated Δ^8 and Δ^{14} double bonds of **1**. This conclusion was further confirmed by the HMBC observations (Figure 3a), in which the key correlations of H_2-15/C-8 (δ_C 130.5), C-14 (δ_C 123.8), and C-16, H_3-18/C-14, and H_2-11/C-8 featured an $\Delta^{8(14)}$ double bond.

The relative configuration of **2** was verified by the ROESY experiment (Figure 3b), in which the ROESY cross-peaks of H-5/H_3-19, H-9/H_3-19, H_3-18/H-9, and H_3-18/H-22 revealed that H-5, H-9, Me-18, Me-19, and furan ring were cofacial, and were arbitrarily assigned in α-orientation. The ROESY correlations of H-6/H-3, H-6/H_3-29, H-17/H_3-28, and H-11β/H_3-28 indicated that the fused-manner of rings A_1, A_2, and B of **2** is reminiscent of **1**, suggesting that two hydroxyl groups at C-1 and C-2 were also α-configured. This was further confirmed by the fact that the ^{13}C NMR data of C-1 and C-2 (or the carbon signals around them) in both compounds **1** and **2** showed high similarity. Thus, the relative configuration and the preferred conformation in solution of **2** were established as depicted in Figure 3b.

In the CD spectrum of **2**, the Cotton effects at λ_{max} 216 nm ($\Delta\varepsilon$ +1.10) and at λ_{max} 207 nm ($\Delta\varepsilon$ −2.69) corresponding to the UV shoulder absorption at λ 201−212 nm of the furan ring,[8c] which resulted from the exciton coupling of two different chromophores (furan ring and $\Delta^{8(14)}$ double bond), showed a positive chirality of **2** (Figure 4). This allowed the assignment of the absolute configuration of **2** as depicted.

The discovery of khayalenoids A (**1**) and B (**2**) provided the first example of a limonoid containing an unprecedented 8-oxa-tricyclo[4.3.2.0^{2,7}]undecane motif in the limonoid category.

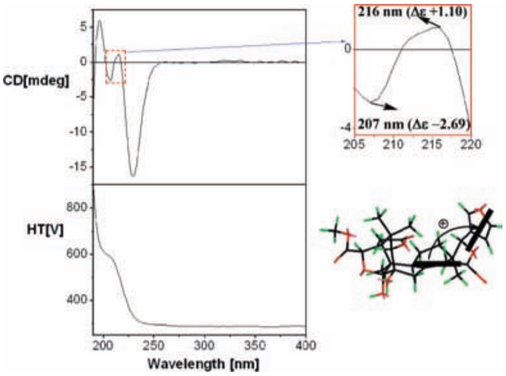

Figure 4. CD and UV spectra of **2** (in MeOH); arrows denote the electric transition dipole of two chromophores.

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Supporting Information Available: Experimental procedures; 1D and 2D NMR, EIMS, IR spectra of khayalenoids A (**1**) and B (**2**); X-ray data of khayalenoid A (**1**); and key ROESY correlations of khayalenoid A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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