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THREE MEXICANOLIDES FROM THE ROOT BARK OF *ENTANDROPHRAGMA ANGOLENSE*

Nsiam Tienabe Kipassa,^a Hiroaki Okamura,^a Matsumi Doe,^b Yoshiki Morimoto,^b Tetsuo Iwagawa,^a and Munehiro Nakatani^{a,*}

^a Department of Chemistry and Bioscience, Faculty of Science, Kagoshima University, 1-21-35 Korimoto, Kagoshima 890-0065, Japan

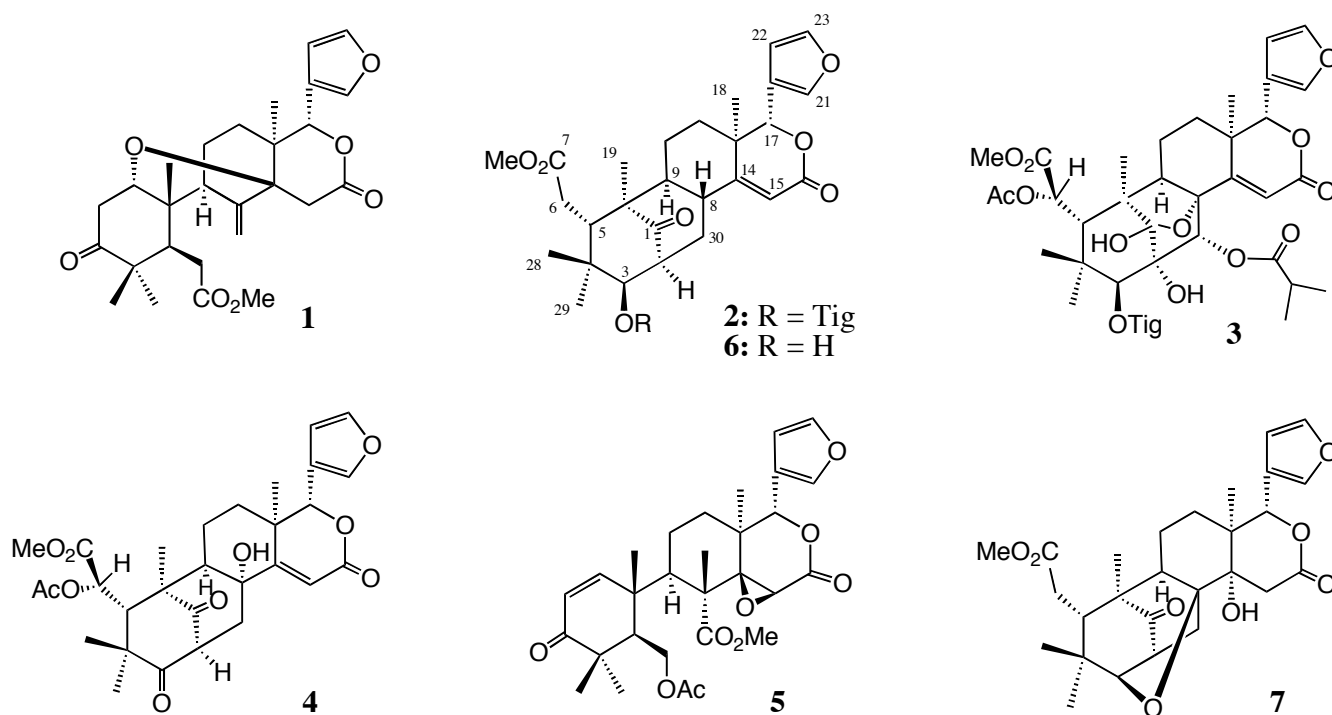
^b Analytical Division, Graduate School of Science, Osaka City University, 3-3-7 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

Abstract—Three new mexicanolide-type rings B,D-*seco* limonoids were isolated together with four known rings B,D-*seco* compounds, methyl angolensate, secomahoganin, 3 β -hydroxy-3-deoxycarapin, and xylocensin K from the root bark of a meliaceous plant *Entandrophragma angolense*. The structure of these new compounds was elucidated by spectroscopic means. The antifeedant property of the isolated compounds is also briefly described.

Entandrophragma is a genus of eleven mahogany in the family Meliaceae restricted to tropical Africa. The plants of this genus are used in folk medicine to treat various diseases and *E. angolense* is widely employed in ethnomedical treatment of various gastrointestinal disorders including peptic ulcer in human and as an antimalarial.¹ Methyl angolensate (**1**), a well known rings B,D-*seco* limonoid, have been isolated for the first time from *E. angolense*,² but the limonoids reported from this plant were only two with gedunin.² Methyl angolensate (**1**) has been reported to possess a spasmolytic activity^{3,4} and gedunin having an antimalarial activity *in vitro* has been expected as a possible leading compound for new drugs.⁵

Limonoids have been classified on the basis of which the four rings, designated as A, B, C and D in the intact triterpene nucleus, have been oxidized. Rings B,D-*seco* compounds are commonly found in the mahogany group, and they are divided into sub-groups depending on whether further transformations have occurred. In subgroup (I) rings B and D are opened (Ia: andirobins and Ib: secomahoganins), and in subgroup (II) a new ring has been formed between C-2 and C-30 in Ia (mexicanolides).

During our continuing research of limonoid antifeedants from Meliaceae plants,⁶⁻⁸ the extract of the root bark of *E. angolense* collected at DR Congo showed considerable antifeedant activity against *Spodoptera* insects. The limonoid constituents of the methanol extract were studied and three new mexicanolide-type limonoids, named angolensins A (**2**)-C (**4**), were isolated together with four known rings B,D-*seco* compounds, methyl angolensate (**1**), secomahoganin (**5**),⁹ 3 β -hydroxy-3-deoxycarapin



(6),¹⁰ and xylocensin K (7).¹¹ The isolation and structural elucidation of the new compounds are described herein. Antifeedant activity of the isolated compounds against the third-instar larvae of *Spodoptera littoralis* (Boisduval) is also briefly discussed.

Vacuum chromatography of the methylene chloride soluble part (4.8 g) of the extract on silica, followed by a combination of column chromatographic separation and reversed phase HPLC purification, gave three new mexicanolide-type limonoids, **2** (5 mg), **3** (2.6 mg), and **4** (2.2 mg), together with four known limonoids, **1** (74 mg), **5** (10 mg), **6** (11 mg), and **7** (5 mg). The structures of the known compounds were identified by comparison of their NMR data with those reported and their stereochemistry was also confirmed by NOE studies.

Angolensin A (**2**) was isolated as amorphous powder and it was shown to have the molecular formula $C_{32}H_{40}O_8$ by a pseudomolecular ion $[M+1]^+$ at m/z : 553.2794 (Δ -0.8 mmu) in the HRFAB-MS and from the analysis of ^{13}C NMR spectroscopic data. The IR spectrum revealed a complex absorption band at $1740\text{--}1710\text{ cm}^{-1}$ for many carbonyl groups. The UV spectrum indicated the presence of conjugated system at 213 nm. From the 1H and ^{13}C NMR spectra, it was clear that eight of the thirteen elements of unsaturation were present as double bonds: four carbon-carbon (one furan ring) and four CO (one ketone and three esters). Therefore, the molecule is pentacyclic. The NMR spectroscopic data (Table 1 and 2) also revealed that compound **2** contained 7 CH_3 (five tertiary, one secondary and one methoxy), 4 CH_2 , 11 CH (five olefinic), and 10 quaternary carbons (three olefinic). From the NMR data, the presence of a β -furyl group (δ_H 6.43, 7.42 and 7.49; each 1H) and a tigloyl moiety (δ_H 1.85: d and 1.90: br s; each 3H, and δ_H 6.96: br q; 1H) was also recognized.

All of the protons directly bonded to carbon atoms were assigned by analysis of its HMQC spectrum. The data from the subsequent 2D NMR studies using 1H - 1H COSY, HMBC, and NOESY spectra,

strongly suggested that **2** was a mexicanolide-type limonoid.^{12,13} Thus, the 6-methylene protons at δ 2.41 (dd, $J = 8.9$ and 17.2 Hz) and 2.50 (br d, $J = 17.2$ Hz) attached to a carbon at δ 33.6 (t) adjacent to an ester carbonyl (δ 174.4), were coupled with the H-5 broad doublet proton at δ 3.37, and the presence of this moiety and a characteristic low-field H-17 singlet at δ 5.01 showing significant HMBC correlations with furanyl carbons at δ 109.9 (C-23), 120.0 (C-20) and 141.2 (C-21), revealed that **2** was a rings B,D-seco limonoid. In addition to this knowledge, the absence of signal due to the one tertiary methyl at 8β (C-30) in the basic limonoid skeleton and olefinic signals to be assigned to exo-methylene protons suggested that **2** was a mexicanolide-type compound having the dicyclo[3,3,1]-ring system, instead of angolensate derivatives.

In the HMBC spectrum of **2**, the observed long-range C-H correlations of the H-5 signal with the ^{13}C signals at δ 17.8 (q), 20.3 (q), 24.1 (q), 38.2 (s), 48.7 (d), 51.3 (s), and 78.4 (d) led to their assignments as C-19, C-28, C-29, C-4, C-9, C-10 and C-3, respectively. A complex signal due to one methylene proton at δ 2.25 assigned to H-30 β showed significant HMBC correlations with a carbonyl carbon at δ 218.6 (C-1), two methine carbons at δ 34.4 (d) and 46.6 (d) to be assigned to C-8 and C-2, and the methine carbons of C-3 and C-9. The presence of a tigloyl group at C-3 was also confirmed by the correlation of the H-3 doublet at δ 5.71 attached to C-3 with a tigloyl carbonyl carbon at δ 167.1. These findings clearly characterized the first molecular fragment, the left-hand dicyclo[3,3,1]nonane ring system.

An olefinic proton at δ 5.71 (s, H-15) attached to a carbon at δ 112.7 adjacent to a lactone carbonyl carbon at δ 164.5 (C-16), showed correlations with another olefinic carbon at δ 170.4 (C-14), a quaternary carbon at δ 38.3 (C-13), and the 8-methine carbon. The carbon signal due to C-13 was correlated to the signals of the 17-methine proton, the methylene protons at δ 1.71-1.77 and δ 1.44 and 1.62 assigned to H₂-11 and H₂-12, and the methyl protons at δ 1.03 (Me-18). Finally, the 11-methylene signals attached to the carbon at δ 18.8 showed correlations with the C-8–C-10 and C-12 signals together with the C-13 signal. These correlations characterized the second fragment of the molecule, C-8, C-9 and C-11–C-17 of the C and D rings, including 13-Me (Me-18) and a furan ring.

The structure of **2**, including the stereochemistry, was fully explained from the NMR data by consideration of the NOE correlations shown in Figure 1 using a molecular model. Strong cross-peaks of the broad signal at δ 3.30 with the signals at δ 1.62 (H-12 β) and 2.25 (H-30 β) and the H-5 signal, and of the H-12 β signal with the H-17 signal indicated the β orientation for these protons. On the other hand, the large coupling of $J = 10$ Hz and strong NOE correlation between the H-3 signal and the H-2 signal at δ 3.14, revealed the α orientation of H-3. Finally, NOE correlations observed between the H-9 signal at δ 1.74 and the Me-18 and Me-19 proton signals at δ 1.03 and 1.10 established the structure of **2** with certainty, because the absolute chemistry of the dicyclo[3.3.1]nonane ring system in the mexicanolide, including the configuration of Me-19 and 5-ester side chain,

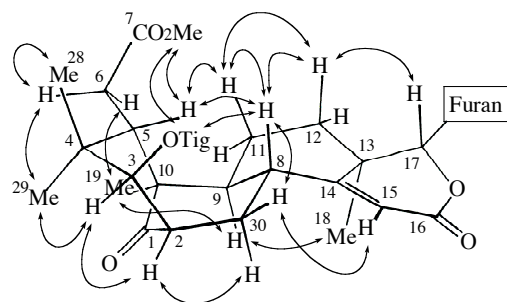


Figure 1. NOE correlations in **2**.

has been clarified.¹⁴ The differences in the chemical shifts, coupling constants with H-5, and NOE correlations of the protons (H_a and H_b) at C-6 in **2** showed that the C-5 side chain was preferentially present in a conformer, and the NOE correlations of the 7-carboxymethyl signal with the 5-H, 4 β -Me and tigloyl 2'- and 3'-Me resonances implied that the 7-CO₂Me group was oriented to the same β -side as H-5 and 3-tigloyl group of the molecule. This compound was consequently identified as the 3-*O*-tiglate of 3 β -hydroxy-3-deoxycarapin (**6**).¹⁰

Angolensin B (**3**) was obtained as a white amorphous powder. The molecular formula (C₃₈H₄₈O₁₄, 15 unsaturations) was determined by HRFAB-MS (m/z : 729.3102 [M+1]⁺, Δ +0.2 mmu) and NMR spectra. The IR spectrum showed different absorptions for hydroxyl (3600–3200 cm⁻¹) and carbonyl (1736–1720 cm⁻¹) groups as broad bands from those of **2**, but the UV spectrum indicated the presence of a similar conjugated system at 216 nm. The NMR spectrum showed the change of several functional groups in **3** from **2**, which included the presence of additional hydroxyl, acetyl and 2-methylpropanoyl groups in **3**. The most significant difference was the absence of the keto carbonyl group in **2**, and the presence of an acetal carbon at δ_C 108.1 (s) in **3**. Since an acetal linkage of C-1 to C-8 has been observed in some mexicanolides,^{12,13} the presence of a similar partial structure in **3** was predicted and it was supported by the HMBC correlations of the 1-OH signal at δ 4.52 with three quarternary carbons at δ 108.1 (C-1), 81.1 (C-2) and 43.1 (C-10). A mexicanolide-type structure of **3** having the C-1–C-8 acetal linkage and the C-14–C15 double bond, was confirmed by the ¹H and ¹³C NMR data as presented in Tables 1, and by the NOE correlations (Figure 2).

The location of three ester groups was elucidated by the HMBC correlations of the methine protons at δ 4.67 (H-3), 5.25 (H-6), and 5.46 (H-30) with tigloyl, acetyl, and 2-methylpropanoyl carbonyl carbons at δ 168.2, 169.7 and 175.4, respectively. The configuration of H-30, not coupling with any protons, was assigned to be β from the NOE observation with the H-5 β signal at δ 2.97, which also showed NOE correlations with H-6, H-11 β (δ 2.43) and H-30 signals and the 4 β -Me (28) proton signal at δ 0.94 to identify the stereochemistry of the dicyclo[3.3.1]nonane ring. On the other hand, the significant NOE observations between the H-12 β (δ 2.05) and H-17 (δ 4.85) signals and the H-12 β and H-30 signals

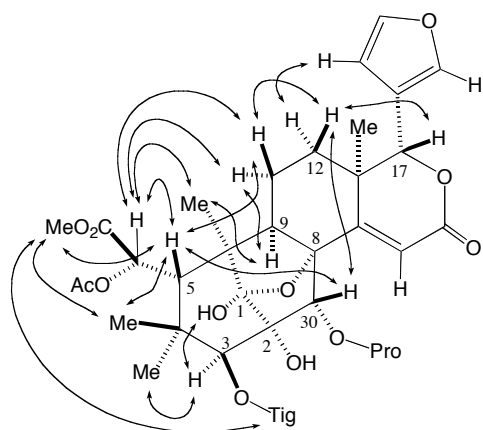


Figure 2. NOE correlations in **3**.

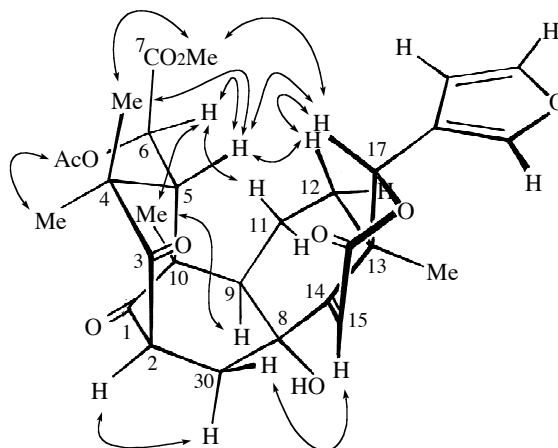


Figure 3. Significant NOE correlations in **4**.

Table 1. ^1H - and ^{13}C -NMR spectral data of angolensins A (**2**), B (**3**) and C (**4**)

no	2		3		4	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1		218.6		108.1		212.2
2	3.14 ddd (10.0, 3.5, 2.5)	46.6		81.1	3.36 dd (8.4, 3.6)	56.3
3	5.10 d (10.0)	78.4	4.67 s	85.2		208.4
4		38.2		39.2		50.0
5	3.37 dd (8.9, 1.4)	40.5	2.97 br s	43.8	3.14 br s	42.6
6a	2.50 br d (17.2)	33.6	5.25 br s	71.6	5.59 br s	72.5
b	2.41 dd (17.2, 8.9)					
7		174.4		171.0		170.5
8	3.30 br m	34.4		80.0		72.2
9	1.74 m	48.7	2.30 dd (11.3, 9.6)	51.5	2.18 m	60.2
10		51.3		43.1		50.7
11 α	1.71-1.77	18.8	2.09 m	15.3	2.09 m	19.3
β			2.43 m		1.71 m	
12 α	1.44 dd (13.3, 6.9)	26.9	1.42 dd (13.5, 8.8)	25.0	1.50 ddd (15.4, 9.6, 4.1)	29.7
β	1.62 m		2.05 m		1.94 ddd (15.4, 9.5, 4.5)	
13		38.3		38.8		39.0
14		170.4		158.2		165.4
15	5.71 d (1.8)	112.7	6.03 s	118.4	6.05 s	116.6
16		164.5		163.0		164.5
17	5.01 s	81.4	4.85 s	81.3	5.57 s	79.7
18	1.03 s	18.0	1.22 s	19.7	1.29 s	21.4
19	1.10 s	17.8	1.19 s	20.5	1.28 s	18.7
20		120.0		119.9		119.7
21	7.49 br s	141.2	7.49 br s	141.2	7.56 br s	141.9
22	6.43 br s	109.9	6.42 br s	109.9	6.50 br s	110.4
23	7.42 br s	143.0	7.42 br s	143.0	7.44 br s	143.0
28	0.83 s	20.3	0.94 s	24.2	1.09 s	21.9
29	0.84 s	24.1	1.61 s	24.6	1.13 s	21.9
30 α	1.59 m	34.8	5.46 s	74.8	2.57 dd (15.1, 8.4)	41.9
β	2.25 ddd (13.7, 4.3, 3.2)				3.17 dd (15.1, 3.6)	
OMe	3.72 s		3.77 s	52.9	3.75 s	53.3
OH			4.52 br s (1-OH)		1.93 br	
			4.30 br (2-OH)			
OAc			2.18 s	21.0	2.18 s	20.9
				169.7		169.5
Tigloyl						
1'		167.1		168.2		
2'		127.7		127.5		
3'	6.96 br q (7.1)	139.0	6.86 br q (6.6)	139.8		
4'	1.85 d (7.1)	14.7	1.86 br d (6.6)	14.6		
4'-Me	1.90 br s	12.2	1.81 br s	11.9		
2-methylpropanoyl						
1''				175.4		
2''			2.48 hept (6.9)	34.1		
3''			1.05 d (6.9)	6.9		
2''-Me			1.06 d (6.9)	6.9		

Measured in CDCl_3 .Chemical shift values are in ppm from TMS, and J values (in Hz) are presented in parentheses.

clarified the stereochemistry at C-8, C-9 and C-13. From the NOE correlations with the 4 α -Me (29) and 1-OH proton signals at δ 1.61 and 4.52, the configuration of H-3 was assigned to be α . Finally, the *R* configuration at C-6 inferred from that of some known mexicanolids,^{15,16} was also supported by the very small coupling between the H-5 and H-6 signals referring to the dihedral angle of H-5/H-6 to be ca 90° and the NOE correlations observed between the H-6 signal and the H-5, H₂-11 and Me-19 resonances, and the 7-carboxymethyl signal and the 5-H, 4 β -Me and tigloyl 2'- and 3'-Me resonances. These data strongly suggested that the 5-ester moiety was preferentially present in a conformer such as shown in Figure 2. A significant low-field shift of the 4 α -Me signal to δ 1.61 by the influence of the neighboring 1-hydroxyl and 6-acetate groups also accounted well for the stereochemistry of **3**.

The molecular formula of angolensin C (**4**) was determined as C₂₉H₃₄O₁₀ by HRFAB-MS (m/z : 543.2223 [M+H]⁺, Δ -0.7 mmu). Compound **4** was also predicted by the NMR spectra to be a mexicanolide from the presence of the signals due to four quarternary methyls and the 6-CO₂Me group. This compound, having the signals due to 14–15 double bond at δ_C 165.4 (s) and 116.6 (d) and one acetyl methyl signal at δ_H 2.18, however, was significantly different from **2** and **3** in the presence of two keto carbonyl groups at δ_C 208.4 and 212.2 and one hydroxyl group at δ 1.93, and the lack of tigloyl group.

These ketone groups were located at C-1 and C-3, because both carbonyl carbons were correlated in the HMBC spectrum to the 30-methylene protons at δ 2.57 and 3.17 attached to a carbon at δ 41.9 (C-30), each carbonyl carbon to the methyl protons at δ 1.28 (Me-19) and to another two methyl protons at δ 1.08 (Me-28) and 1.13 (Me-29), respectively. The proton signal due to the 2-methine group lying between two carbonyl groups, consequently, was observed at the low field of δ 3.36. The structure of **4**, including its stereochemistry, was fully explained from the NMR data by the consideration of NOE correlations (Figure 3) using a molecular model. Strong cross-peaks of the H-5 broad singlet at δ 3.14 with a signal at δ 1.94 (H-12 β) and the characteristic H-17 signal at δ 5.57 indicated the same β -orientation for these protons and the folded conformation of **4** as shown in Figure 3. The latter also accounted for the stereochemistry at C-8. An NOE correlation observed between the H-30 β and H-15 resonances also accounted well for the stereochemistry of the ring system of **4**. Finally, the configuration at C-6 was assumed to be the same *R* as that of **3** in a similar manner as above.

Antifeedant activity of the isolated compounds was tested by a conventional leaf disk method against the third instar larvae of Japanese insect pest *Spodoptera littoralis* (Boisduval).¹⁷ All of the compounds showed the activity at 1000 ppm, with 50 ppm corresponding to a concentration of ca. 1 μ g/leaf-cm², but their activity was not so potent. Although compounds **2** and **3** were active at 500 ppm, the activity was much weaker than that of well-known ring C-seco antifeedants of azadirachtins¹⁸ and meliacarpinins.¹⁹

EXPERIMENTAL

¹H and ¹³C NMR spectra were measured at 500 and 125 MHz in CDCl₃ on a JEOL FX-600 spectrometer. IR (Film) and UV (MeOH) spectra were recorded on JASCO FT/IR 5300 and Shimadzu UV-210A spectrophotometers. Specific rotation was measured in MeOH at 22°C using a JASCO DIP-370s spectropolarimeter. HPLC was performed on Waters μ Bondapak C₁₈ column by using a gradient of 30-60% H₂O/MeOH as eluent.

Plant material. The root bark was collected at Jardin Botanique de Kisantu in Bas Congo, DR Congo.

Extraction and isolation. The dried root bark (1 kg) was extracted successive, each 3L of hexane, Et₂O, acetone and MeOH at 20° C for 1 week to yield 17, 28, 53 and 112 g of materials, respectively. The MeOH extract was suspended in H₂O and extracted with CH₂Cl₂ to give the extract (4.8 g), which was fractionated by vacuum column chromatography on silica gel using a CH₂Cl₂–MeOH solvent system. A limonoid fraction (1.6 g) eluted with CH₂Cl₂ was separated to four fractions by middle pressure chromatography with successive, 50% hexane–CH₂Cl₂, CH₂Cl₂, 2% MeOH–CH₂Cl₂, and 5% MeOH–CH₂Cl₂. From the fractions (0.9 g) eluted with 50% hexane–CH₂Cl₂ and CH₂Cl₂, three rings B,D-*seco* compounds of **1** (74 mg), **2** (5 mg) and **5** (10 mg) were separated by HPLC with 25-40% H₂O–MeOH, followed by HPLC purification with 45-55% H₂O–MeCN. The third limonoid fraction (1.9 g) eluted with 2% MeOH–CH₂Cl₂ was further fractionated on SiO₂ by column chromatography with a CH₂Cl₂–MeOH solvent system to give three fractions (fr 1: 400 mg, fr 2: 430 mg and fr 3: 735 mg). Fraction 1 was separated to three fractions by HPLC with 25-35% H₂O–MeOH, one of which was further purified with 40% H₂O–MeCN to give **3** (2.6 mg). Fraction 2 was also separated by HPLC with 30-40% H₂O–MeOH and purified with 45% H₂O–MeCN to give **4** (2.2 mg), **6** (11 mg) and **7** (5 mg).

Angolensin A (2). A white amorphous powder, C₃₂H₄₀O₈; HRFABMS m/z: 553.2794 [M+1]⁺, Δ -0.8 mmu; [α]_D -2° (c 0.27); IR ν_{max} cm⁻¹: 1740-1710, 1651, 874 cm⁻¹; UV λ_{max} nm (ε): 213 (11000).

Angolensin B (3). Colorless amorphous solid, C₃₈H₄₈O₁₄; HRFABMS m/z: 729.3102 [M+1]⁺, Δ +0.2; [α]_D +2° (c 0.13); IR ν_{max} cm⁻¹: 3600–3200, 1736–1720, 1635, 875 cm⁻¹; UV λ_{max} nm (ε): 216 (8000).

Angolensin C (4). Colorless amorphous solid; C₂₉H₃₄O₁₀; HRFABMS m/z: 543.2223 [M+1]⁺; Δ -0.7 mmu, [α]_D -22° (c 0.35); IR ν_{max} cm⁻¹: 3450-3200, 1735, 1730, 1701, 1649, 875 cm⁻¹; UV λ_{max} nm (ε): 213 (9000).

Antifeedant test. The antifeedant potential of the isolated compounds was assessed by presenting them on leaf disks of a Chinese cabbage to the third instar larvae of *Spodoptera littoralis* (Boisduval), and visually comparing the treated and untreated disks eaten by the larvae.¹² Ten larvae were placed in a Petri dish with the five leaf disks treated with sample and the five untreated disks as control. The feeding assay terminated after the larvae had eaten approximately 50% of one of the disks. This choice test was done at the concentrations of 500 and 1000 ppm.

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