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Insect Antifeedants from Tropical Plants: Structures of Dumnin and Dumsenin

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Two novel A-seco limonoids, dumnin and dumsenin, were isolated from the methanolic extract of *Croton jatrophoides* by bioassay-guided fractionation, and the structures were determined by nuclear magnetic resonance, circular dichroism, and mass spectrometry experiments. These compounds showed potent antifeedant activity ($PC_{50} \leq 2.0$ μg/mL) against the larvae of pink bollworm, *Pectinophora gossypiella*, and/or fall armyworm, *Spodoptera frugiperda*, providing results comparable to dumsin and zumsin, previously isolated from the same plant.

KEYWORDS: Limonoid; insect antifeedant; dumnin; dumsenin; *Pectinophora gossypiella*; *Spodoptera frugiperda*; *Croton jatrophoides*

INTRODUCTION

Insect antifeedants can be found among all of the classes of secondary metabolites such as alkaloids, phenolics, and terpenoids (*1*). Limonoid is classified as a tetranortriterpenoid, having attractive antifeedant potential from an agricultural point of view (*2*, *3*). Furthermore, they possess various additional biological activities including antimalarial (*4*, *5*), cell adhesion inhibition (*6*), chloroplast H^+-ATPase inhibition (*7*), and anticancer (*8*, *9*) activities. We recently reported the isolation and structural determination of two unique limonoids, dumsin (**1**) and zumsin (**2**) (**Figure 1**), from the East African medicinal plant "msinduzi" (Swahili, tentatively identified as *Croton jatrophoides* Pax.) (*10*, *11*). During our continuing study of biologically active substances from the same medicinal plant, two novel A-seco limonoids, dumnin (**3**) and dumsenin (**4**) (named from msinduzi), were isolated as potent insect antifeedants. In this study, we have established complete nuclear magnetic resonance (NMR) assignments for **1** and the structural determinations of **3** and **4** and conducted a comparative antifeedant study of **1**−**4** against the larvae of pink bollworm, *Pectinophora gossypiella*, and fall armyworm, *Spodoptera frugiperda*, as test organisms.

MATERIALS AND METHODS

General Experimental Procedures. Infrared (IR) spectra were recorded in KBr on a Shimadzu 435 spectrometer (Kyoto, Japan). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal reference on a JEOL JNM-GX-400 spectrometer (Akishima, Japan). High-resolution mass spectrometry−fast atom bombardment (HRMS-FAB) was measured in the positive ion mode on a JEOL JMS-DX 303 spectrometer. The samples were homogeneously mixed with 3-nitrobenzyl alcohol and bombarded with 10 kV of xenon-based atoms. Circular dichroism (CD) spectra were recorded in MeOH on a JASCO J-40 spectropolarimeter (Easton, MD). Preparative high-performance liquid chromatography (HPLC) was performed by a gradient mode with an EYELA LPG-1000 with an EYELA UV7000 detector (Tokyo Rikakikai Co. Ltd., Tokyo, Japan) and a 10

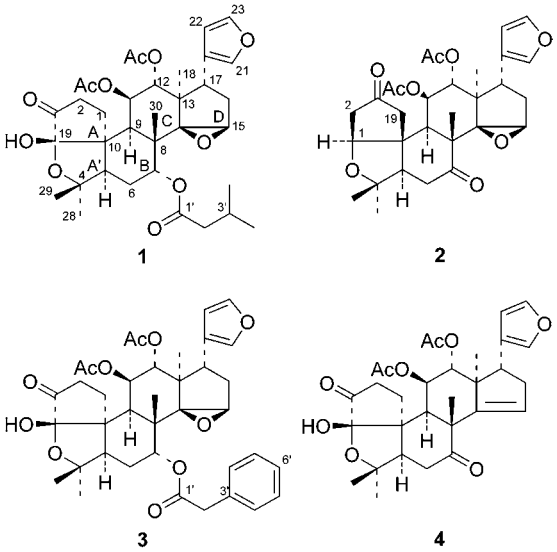

Figure 1. Structures of compounds **1**–**4**.

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Table 1. ^{1}H and ^{13}C NMR Assignments for **1**, **3**, and **4** in $CDCl_3$

	1[a]		**3**		**4**	
position no.	δ_H (mult. *J* in Hz)	δ_C (mult.)	δ_H (mult. *J* in Hz)	δ_C (mult.)	δ_H (mult. *J* in Hz)	δ_C (mult.)
1	1.88 (m)	35.7 (t)	1.66 (ddd, 1.6, 9.5, 13.9)	36.0 (t)	2.07 (m)	35.6 (t)
	2.35 (m)		2.12 (ddd, 8.8, 9.5, 13.9)		2.25 (m)	
2	2.38 (m)	30.6 (t)	2.27 (td, 9.5, 19.8)	31.1 (t)	2.30 (m)	31.5 (t)
	2.57 (ddd, 3.0, 9.0, 11.0)		2.50 (ddd, 1.6, 8.8, 19.8)		2.60 (m)	
3		208.2 (s)		208.9 (s)		209.4 (s)
4		84.6 (s)		84.5 (s)		86.6 (s)
5	2.37 (dd, 6.0, 11.0)	49.9 (d)	1.85 (dd, 6.0, 15.0)	49.7 (d)	2.67 (t, 7.4)	58.7 (d)
6	1.81 (ddd, 2.0, 6.0, 14.0)	25.3 (t)	1.70 (ddd, 4.0, 6.0, 15.0)	26.2 (t)	2.54 (dd, 7.4, 13.4)	38.3 (t)
	2.12 (ddd, 4.0, 11.0, 14.0)		2.01 (dt, 2.7, 15.0)		2.93 (dd, 7.4, 13.4)	
7	4.74 (dd, 2.0, 4.0)	74.0 (d)	4.65 (dd, 2.7, 4.0)	75.2 (d)		206.9 (s)
8		43.3 (s)		39.4 (s)		50.5 (s)
9	3.38 (d, 4.5)	45.0 (d)	3.22 (d, 4.4)	45.4 (d)	3.01 (d, 4.6)	48.5 (d)
10		55.6 (s)		56.0 (s)		56.0 (s)
11	5.17 (dd, 4.0, 4.5)	73.8 (d)	5.08 (dd, 3.6, 4.4)	74.5 (d)	5.08 (t, 4.6)	73.9 (d)
12	5.41 (d, 4.0)	79.8 (d)	5.34 (d, 3.6)	79.8 (d)	5.33 (d, 4.6)	82.9 (d)
13		44.2 (s)		44.6 (s)		50.8 (s)
14		71.9 (s)		72.3 (s)		147.9 (s)
15	3.54 (bs)	57.4 (d)	3.43 (bs)	58.0 (d)	5.84 (d, 1.8, 3.2)	127.4 (d)
16	1.61 (dd, 11.0, 14.0)	33.6 (t)	1.26 (dd, 11.0, 15.0)	33.9 (t)	2.47 (ddd, 3.2, 8.0, 16.0)	37.3 (t)
	2.11 (dd, 6.0, 14.0)		1.94 (dd, 5.9, 15.0)		2.51 (ddd, 1.8, 11.0, 16.0)	
17	2.87 (dd, 6.0, 11.0)	37.5 (d)	2.78 (dd, 5.9, 11.0)	37.9 (d)	3.05 (dd, 8.0, 11.0)	51.4 (d)
18	1.20 (s)	15.0 (q)	1.07 (s)	15.7 (q)	1.10 (s)	17.0 (q)
19		104.7 (s)		104.6 (s)		105.1 (s)
20		122.6 (s)		122.7 (s)		124.1 (s)
21	7.01 (m)	140.2 (d)	7.00 (m)	140.7 (d)	7.16 (m)	140.4 (d)
22	6.01 (m)	111.3 (d)	6.02 (m)	111.9 (d)	6.23 (m)	111.8 (d)
23	7.32 (m)	141.7 (d)	7.32 (m)	142.2 (d)	7.33 (m)	142.3 (d)
28	1.34 (s)	27.4 (q)	1.23 (s)	27.9 (q)	1.37 (s)	27.3 (q)
29	1.42 (s)	31.7 (q)	1.24 (s)	32.3 (q)	1.42 (s)	31.3 (q)
30	1.42 (s)	20.8 (q)	1.34 (s)	21.3 (q)	1.75 (s)	28.7 (q)
OH	3.65 (bs)		3.57 (bs)		3.70 (bs)	
OAc[b]	1.92 (s)	20.7 (q)	1.80 (s)	21.2 (q)	1.82 (s)	21.5 (q)
		170.6 (s)		170.2 (s)		170.8 (s)
OAc[b]	2.10 (s)	20.9 (q)	1.99 (s)	21.4 (q)	1.94 (s)	21.6 (q)
		171.3 (s)		170.6 (s)		171.9 (s)
1′		171.9 (q)		171.0 (q)		
2′	1.25 (s)	39.1 (t)	3.69 (s)	42.5 (t)		
3′	2.22 (m)	26.0 (d)		134.0 (s)		
4′	1.04 (d, 6.0)	21.8 (q)	7.34 (m)	129.0 (d)		
5′	1.04 (d, 6.0)	21.9 (q)	7.34 (m)	129.0 (d)		
6′			7.34 (m)	126.7 (d)		
7′			7.34 (m)	129.0 (d)		
8′			7.34 (m)	129.0 (d)		

[a] The ^{1}H NMR assignments for **1** have been reported previously (*10*). [b] Assignment may be reversed.

mm × 250 mm i.d., 10 μm, Alltech Econosil C-18 column (Deerfield, IL). Initially, 40% MeCN/H_2O was used as the HPLC solvent. The gradient elution was started at 5 min, and the solvent composition was changed to 80% MeCN/H_2O in 30 min. The flow rate and detected wavelength were adjusted at 5 mL/min and 210 nm, respectively. Preparative thin-layer chromatography (TLC) plates were purchased from Analtech, Inc. (Newark, DE). All solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Dumsin (**1**) was available from our previous work (*10*).

Extraction and Isolation. The root bark of the East African medicinal plant locally known as msinduzi was collected near Mombasa, Kenya, and the plant was tentatively identified as *C. jatrophoides* (Euphorbiaceae) (*12*). The plant specimen was deposited in the Department of Botany Herbarium at the University of Nairobi. The root bark was peeled off at the collection site. The air-dried root bark (500 g) was cut into small pieces and extracted with MeOH (500 mL × 3) at ambient temperature for 2 weeks. The solvent was evaporated in vacuo, and then, the resulting residue (40 g) was partitioned between water (800 mL) and *n*-hexane (200 mL × 3), $CHCl_3$ (200 mL × 3), and EtOAc (200 mL × 3), respectively. A leaf disk assay against second-instar larvae of *P. gossypiella* identified the $CHCl_3$ fraction (4.5 g) as containing the antifeedant activity. This fraction was further divided into six fractions (I, 0.2 g; II, 0.7 g; III, 0.8 g; IV, 0.4 g; V, 1.1 g; and VI, 0.5 g) using chromatography on 70−230 mesh, 250 g silica gel eluted with 1−20% MeOH/$CHCl_3$. Subsequent bioassays showed strong activity in the 10% MeOH/$CHCl_3$ eluted fraction (IV). This fraction was subjected to preparative TLC with 10% MeOH/$CHCl_3$, and then, further purification by preparative HPLC gave 23 mg of **2** (t_R = 23.5 min), 10 mg of **3** (t_R = 31.5 min), and 18 mg of **4** (t_R = 24.5 min) as amorphous solids.

Dumnin (3). HRMS-FAB, *m*/*z*: $[M + Na]^+$ calcd for $C_{38}H_{44}O_{11}$-Na, 699.2782; found, 699.2780. IR (KBr): 1758, 1738, 1244, 1221, 786 cm^{-1}. CD (MeOH): 305 nm ($\epsilon = -1.78$ degree/M/cm). ^{1}H and ^{13}C NMR assignments are shown in **Table 1**.

Dumsenin (4). HRMS-FAB, *m*/*z*: $[M + Na]^+$ calcd for $C_{30}H_{36}O_9$-Na, 563.2257; found, 563.2238. IR (KBr): 1758, 1738, 1242, 1222 cm^{-1}. CD (MeOH): 295 nm ($\epsilon = +1.21$ degree/M/cm). ^{1}H and ^{13}C NMR assignments are shown in **Table 1**.

Bioassay. Second-instar larvae of *P. gossypiella* and *S. frugiperda* were used as the test organisms, and a leaf disk assay was performed by the method as previously reported (*13*). Briefly, leaf disks (1 cm^2) were punched out from a glandless cotton cultivar, randomized, and arranged (12 disks/dish) concentrically on moistened filter paper within polyethylene foam grids inside glass Petri dishes (100 mm × 15 mm). Alternate disks were treated on their upper surface with either 25 μL of acetone or with 0−100 μg of the sample dissolved in 25 μL of acetone applied with a microliter syringe. Three larvae were then placed in the dishes at 22 °C in a dark incubator. After 48 h, the larvae were removed and disks were examined visually at percent area of the leaf disk consumed vs control. PC_{50} and PC_{95} values are the concentrations

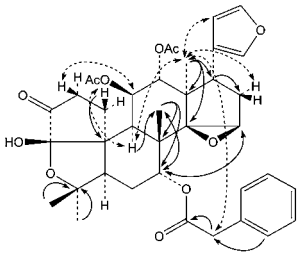

Figure 2. Key NOE and COLOC correlations in **3**. The dashed and solid lines with the double-headed arrow expresses NOE on α-face and β-face, respectively. The single-headed arrow represents COLOC correlation.

at which the test compounds afforded ca. 50 and 95% protection of the host plant substrate, respectively. The assays were performed in triplicate on separate occasions, and their range of error was within 0.5 μg/mL.

RESULTS AND DISCUSSION

The MeOH extract of the bitter-tasting root bark of *C. jatrophoides* showed antifeedant activity against second-instar larvae of *P. gossypiella*. By further fractionation between water and several organic solvents, it was found that the $CHCl_3$ fraction retained a strong antifeedant activity. To identify the active principles, this fraction was evaporated in vacuo and the resultant residue was subjected to silica gel chromatography and preparative TLC, followed by preparative HPLC to yield two compounds, **3** and **4** (**Figure 1**).

Compound **3** was isolated as an amorphous solid, and the molecular formula was established as $C_{38}H_{44}O_{11}$ by HRMS-FAB. A strong absorption from carbonyl moieties was observed at 1758 cm^{-1} in the IR spectrum. Compound **3** was identified as a tetranortriterpene of the limonoid type because the presence of a β-furan ring was established by observing signals at 6.02, 7.00, and 7.32 ppm in the ^1H NMR spectra and 111.9, 122.7, 140.7, and 142.2 ppm in the ^{13}C NMR spectra. Two acetyl (δ_H 1.80, 1.99; δ_C 21.2, 21.4, 170.2, 170.6) and four methyl (δ_H 1.07, 1.23, 1.24, 1.34; δ_C 15.7, 21.3, 27.9, 32.2) resonances as well as the number of similarities with ^1H and ^{13}C NMR data for **1** indicated that **3** possessed a dumsin-like structure (**Table 1**). However, it should be mentioned that instead of the isopentanoyl group of **1**, resonances suggesting a phenylacetyl group (δ_H 3.65, 7.34; δ_C 42.5, 126.7, 129.0, 134.0, 171.0) were found in the ^1H and ^{13}C NMR spectra.

A proton signal at 3.43 ppm and carbon signals at 58.0 and 72.3 ppm were assigned to H-15 and C-14 in a trisubstituted epoxy moiety by $^1H-^{13}C$ correlation spectroscopy (COSY) experiments, respectively. This methine proton was correlated to the β-furan attached methine at 2.78 ppm (H-17) via methylene protons at 1.26 and 1.94 ppm (H-16). In addition, observation of COLOC correlations between H-18 and C-13, C-14, and C-17 allowed this sequence to be placed in the D ring (**Figure 2**). A doublet oxymethine proton at 5.34 ppm (H-12) possessed a cross-peak with a double-doublet oxymethine at 5.08 ppm (H-11) in the $^1H-^1H$ COSY spectra. This oxymethine was further coupled to a methine at 3.22 ppm (H-9), indicating that two acyloxy moieties were located in the C ring. A remaining oxymethine proton at 4.65 ppm (H-7) was correlated to diastereotopic methylene protons at 1.70 and 2.01 ppm (H-6) that were coupled to a methine proton at 1.85 ppm (H-5). This proton sequence was assigned to the B ring fragment of **3** according to the comparison with the ^1H and ^{13}C NMR assignments for **1** and several COLOC correlations observed on the C-30 methyl (**Figure 2**). Four methylene protons (δ_H 1.66, 2.12, 2.27, 2.50), correlated with each other in the $^1H-^1H$ COSY spectra, suggested the A ring structure of **3**. The dumsin type A−A′ ring closure was deduced from the presence of an acetal carbon at 104.6 ppm (C-19). The position of phenylacetyl and acetyl groups as shown in **Figure 1** could be elucidated from the number of similarities between ^1H and ^{13}C NMR data for **1** and **3**, although cross-peaks between the ester moieties and the limonoidal skeleton of **3** could not be found in the COLOC spectra.

The stereochemistry of **3** was determined by nuclear Overhauser enhancement spectroscopy experiments and the inspection of coupling constants in the ^1H NMR spectra (**Figure 2**). Three different coupling constants (5.9, 11.0, and 15.0 Hz) at H-16 were similar to those of **1** and **2**. Accordingly, the orientation of the epoxy ring should be β (*10*, *11*). A nuclear Overhauser effect (NOE) correlation observed between two protons at positions H-9 and H-18, as well as small coupling constants (3.6 and 4.4 Hz) at H-11, proved the C ring conformation to be the boat form and the vicinal acyloxy moieties thus trans. The chair form of the B ring was expected by coupling constants at H-5 (6.0 and 15.0 Hz) and H-7 (2.7 and 4.0 Hz) and two NOE correlations between H-5 and H-15 or H-30. In addition to this stereochemical observation, NOE correlations between benzyl protons (H′-2) in the phenylacetyl group and α-orientated methyl protons (H-18) supported the β-orientation of the oxymethine proton (H-7) in the B ring. Finally, the A′−B cis-fused structure of **3** was ascertained by two NOE correlations between H-9 and H-1β and H-11 and H-2β.

Compound **4** was isolated as an amorphous solid, and the molecular formula was established as $C_{30}H_{36}O_9$ by HRMS-FAB. A strong absorption at 1769 cm^{-1} in the IR spectrum indicated the presence of carbonyl moieties in this structure. A proton signal at 7.33 ppm (H-23) was correlated to a signal at 6.23 ppm (H-22) in the $^1H-^1H$ COSY spectra, whereas a signal at 7.16 ppm (H-21) was isolated. In addition, the observations of three methine carbon signals at 111.8, 140.4, and 142.3 ppm and a quaternary carbon at 124.1 ppm suggested the presence of a β-furan ring in the structure of **4**. The signals of two acetate groups (δ_H 1.82, 1.94; δ_C 21.5, 21.6, 170.8, 171.9) and four methyl groups (δ_H 1.10, 1.42, 1.37, 1.75; δ_C 17.0, 27.3, 31.3, 28.7) were found in ^1H and ^{13}C NMR spectra so that **4** would represent a structure similar to **2** as previously reported (*11*).

However, it should be noted that the signals of a trisubstituted olefin (δ_H 5.84; δ_C 127.4, 147.9) were observed instead of the trisubstituted epoxy resonances of **2**. The olefinic methine proton (H-15) was correlated to a β-furan attached methine at 3.05 ppm (H-17) through methylenes at 2.47 and 2.51 ppm (H-16) in $^1H-^1H$ COSY spectra. Therefore, the olefin was located in the D ring. A triplet oxymethine at 5.08 ppm (H-11) possessed two cross-peaks between a doublet oxymethine at 5.33 ppm (H-12) and a doublet methine at 3.01 ppm (H-9). This sequence established the skeleton of the C ring in the same way as **2**. Two small coupling constants (4.6 Hz) at H-11 were consistent with a trans alignment of two acyloxy moieties and a boat form for the C ring.

The resonances at 2.54, 2.67, and 2.93 ppm were assigned to H-5 and H-6 in the B ring because their cross-peaks were shown in the $^1H-^1H$ COSY spectrum. A vicinal coupling constant (7.4 Hz) at H-5 in the ^1H NMR spectra was somewhat smaller than that of **2** as shown in the ^1H NMR assignments for a limonoid, sudachinoid A (*11*, *14*). This might be governed by the conformational difference of the A, A′, and B rings between **2** and **4**. The remaining resonances should come from the nuclei of the A and A′ rings. A signal from a quaternary carbon at 105.1 ppm was identified as the acetal carbon at H-19 by ^{13}C NMR and DEPT experiments. This highly oxygenated carbon center was observed in the structures of **1** and **3** so that

Table 2. Insect Antifeedant Activities of **1**–**4**[a]

compounds tested	*P. gossypiella*		*S. frugiperda*	
	PC_{50} (μg/mL)	PC_{95} (μg/mL)	PC_{50} (μg/mL)	PC_{95} (μg/mL)
1	1.0	8.0	*b*	*b*
2	1.0[c]	8.0[c]	2.0[c]	16.0[c]
3	1.0	16.0	*b*	*b*
4	2.0	8.0	1.0	4.0

[a] All values are expressed as the mean of three separate experiments, and the range of error was found within 0.5 μg/mL. [b] Not tested due to limited amount. [c] These data have been reported previously (*11*).

compound **4** did not possessed the zumsin type but a dumsin type linkage at the A and A′ rings. Consequently, signals at 2.07, 2.25, 2.30, and 2.60 ppm coupled to each other were placed in the A ring as H-1 and H-2. The ^{1}H and ^{13}C NMR assignments for **4** are shown in **Table 1**.

Compound **3** showed a negative Cotton effect at 305 nm ($n \rightarrow \pi^*$ of a ketone group) that represented the same sign as **1**. Therefore, the stereochemistry of **3** should be similar to that of **1**. In contrast, a positive Cotton effect at 295 nm ($n \rightarrow \pi^*$ of a ketone group) for **4** suggested that the structure surrounding the two ketones differed from **2**. This result did not contradict the stereochemical observations by NMR experiments.

The occurrence of the phenylacetate in natural products would be an unique case, although a minute amount of the corresponding acid was found in aged red wine (*15*). However, it has been reported that dephnane and tigliane type diterpenes from Euphorbiaceae (*16*, *17*), pyrrolizidine alkaloids from Convolvulaceae (*18*), and coumarins from Rutaceae (*19*) contain phenylacetate in their structures. Compound **3** is the first example of a limonoid possessing a phenylacetyl group, whereas other substitutions with aromatic chromophores such as cinnamate and benzoate have been observed previously (*20*).

Recently, structure−activity relations of insect antifeedant activity with limonoids from Rutaceae and Meliaceae were reported in detail based on the results from bioassays using a number of semisynthetic and naturally occurring compounds and investigations by molecular modeling (*2*, *21*). Accordingly, the insect antifeedant activity of the four unique limonoids from *C. jatrophoides* was also examined by a conventional leaf disk bioassay method (*13*). Each limonoid showed potent activity against lepidopteran larvae of *P. gossypiella* with a PC_{50} of 2.0 μg/mL (**Table 2**). Among the dumsin and zumsin type limonoids obtained, the A′−B ring linkage, the alternative to an olefin or epoxide in the D ring, and modification at C-7 may not be important for insect antifeedant potency. Similar results were obtained in antifeedant experiments using the larvae of *S. frugiperda*, although complete data could not be achieved due to the limited amount of **1** and **3**.

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