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Insect Antifeedants from Tropical Plants II: Structure of Zumsin

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A novel A-seco limonoid was isolated from methanolic extract of *Croton jatrophoides* and designated as zumsin. This compound showed potent antifeedant activity against two lepidopteran larvae, pink bollworm, *Pectinophora gossypiella* (PC_{50} = 1 μg/cm^2, PC_{95} = 8 μg/cm^2), and fall armyworm, *Spodoptera frugiperda* (PC_{50} = 2 μg/cm^2, PC_{95} = 16 μg/cm^2). The structure of zumsin was determined as **1** using a variety of spectroscopic methods including nuclear magnetic resonance, mass spectrometry, and circular dichroism. The structure consists of an A′−B trans-fused ring while dumsin (**2**), a constituent of the same source, maintains an A′−B cis-fused ring, and suggests two unique biosynthetic processes after A ring oxidative expansion.

KEYWORDS: ***Croton jatrophoides*; Euphorbiaceae; *Pectinophora gossypiella*; pink bollworm; *Spodoptera frugiperda*; fall armyworm; insect antifeedant; limonoid; zumsin; dumsin**

INTRODUCTION

The origin of secondary metabolites in plants is a response to the pressures of natural selection during the coevolution of plants and insects. A number of deterrent chemicals occur in high concentrations in plants and, in certain cases, are believed to reduce insect predation. In particular, ecdysteroids agonists and antagonists that have been identified through several trials of insect antifeeding studies where ecdysis disruption proves to be a critical target in pest control (*1*). The efficacy of present day plant medicinals in affecting humans is rooted in the similarity of the primary metabolism of insects and higher animals. Hence, the often-documented sources of medicinal plants may also serve as sources of not only potent insecticidal agents beneficial in agriculture but also effective food additives and medicines. These propositions have prompted us to isolate a number of insect-affecting phytochemicals from medicinal plant sources (*2*).

We previously reported the isolation and structural determination of a novel limonoid, dumsin (**2**) (see **Figure 1** for structures), from the East African medicinal plant "msinduzi" (Swahili, tentatively identified as *Croton jatrophoides* Pax.) (*3*). This compound exhibits potent antifeedant activity in a leaf disk assay against lepidopteran larvae pink bollworm, *Pectinophora gossypiella*, and fall armyworm, *Spodoptera frugiperda* (*4*−*6*). Besides its effect on insects, limonoids are known to possess various biological activities including antimalarial activity (*7*, *8*), cell adhesion inhibitory activity (*9*), and chloroplast H^+-ATPase inhibitory activity (*10*). Research has recently established that dietary citrus limonoids and their glycosides display inhibitory activity against human breast cancer cell lines (*11*, *12*). These results indicate that limonoids may be useful agents for preventing a variety of human disorders and elucidating their etiology. Except for a few cases, the complex polycyclic structures have put an end to investigation by synthetic studies (*13*). In our continuing effort to explore the chemistry of naturally occurring compounds, we describe the isolation and structural determination of an additional novel limonoid, zumsin (**1**), from *C. jatrophoides*, a hypothesis of its unique biosynthetic pathway, and an evaluation of its insect antifeedant activity.

MATERIALS AND METHODS

General Experimental Procedures. All nuclear magnetic resonance (NMR) spectra were run on a Nicolet NT-300 spectrometer equipped with an Oxford superconducting magnet operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Samples were run in $CDCl_3$ unless otherwise specified. All shifts were reported using $CHCl_3$ as an internal reference (7.24 and 77.0 ppm). High and low resolution mass spectra were obtained using a JEOL JMS-HX 100 spectrometer in an electron impact mode. IR spectra were obtained on a Perkin-Elmer model 1310 spectrometer in $CHCl_3$. Circular dichroism (CD) measurements were obtained on a JASCO J-40 spectropolarimeter (c = g/100 mL). UV spectra were acquired on a Hitachi 100-80 spectrometer in ethanol. Preparative high-performance liquid chromatography (HPLC) was performed on an EYELA LPG-1000 with an EYELA UV-7000 detector and Alltech Econosil C-18 column (10 μm, 10 mm × 250 mm). Preparative thin-layer chromatography (TLC) was purchased from Analtech, Inc. (Newark, DE). All solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI).

Extraction and Isolation. The root bark of an East African medicinal plant locally known as msinduzi was collected near Mombasa, Kenya, and tentatively identified as *C. jatrophoides*. The plant specimen

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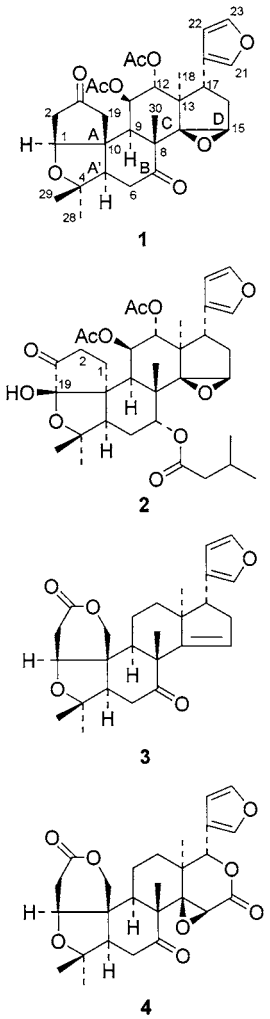

Figure 1. Structures of 1–4.

was deposited in the Department of Botany, University of Nairobi. The air-dried root bark (500 g) was extracted with MeOH at ambient temperature. The solvent was evaporated in vacuo, and then, the resulting residue was partitioned between water and organic solvents, *n*-hexane, $CHCl_3$, and AcOEt in this order. The leaf disk assay against second-instar larvae of *P. gossypiella* identified the $CHCl_3$ fraction (4.5 g) retaining the antifeedant activity (*4*−*6*). This fraction was further divided into six fractions using silica gel chromatography (70−230 mesh, 250 g, 1−20% MeOH/$CHCl_3$). The subsequent bioassay showed an activity with a 15% MeOH/$CHCl_3$ eluted fraction (0.3 g). This fraction was subjected to preparative TLC (10% MeOH/$CHCl_3$), and then, the further purification by HPLC (40−80% MeCN/H_2O) gave 23 mg of **1** as a white amorphous solid. HREIMS *m*/*z*: $[M]^+$ calcd for $C_{30}H_{36}O_9$, 540.2338; found, 540.2336. IR ($CHCl_3$): 1745, 1720, 1215 cm^{-1}. UV (EtOH): 213 nm (ϵ = 3990). CD (MeOH): 295 nm (ϵ = 5.0 degree M^{-1} cm^{-1}). ^1H 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. 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. PC_{50} and PC_{95} values are the concentrations at which the limonoids afford ca. 50 and 95% protection of the host plant substrate, respectively.

Table 1. ^1H and ^{13}C NMR Assignments of **1**[a]

carbon	δ_H (mult., *J* in Hz)	δ_C (mult.)
1	4.34 (d, 3.0)	84.0 (d)
2	2.54 (dd, 18.0, 3.0)	44.9 (t)
	2.44 (d, 18.0)	
3		215.2 (s)
4		80.4 (s)
5	2.24 (dd, 11.0, 3.5)	61.9 (d)
6	2.90 (dd, 14.0, 11.0)	37.9 (t)
	2.42 (dd, 14.0, 3.5)	
7		207.4 (s)
8		45.4 (s)
9	2.95 (d, 2.5)	46.8 (d)
10[b]		52.5 (s)
11	4.99 (dd, 2.5, 0.8)	77.1 (d)
12	5.15 (br s)	80.4 (d)
13[b]		51.1 (s)
14		67.5 (s)
15	3.78 (br s)	56.7 (d)
16	2.27 (ddd, 13.5, 6.0, 0.8)	32.8 (t)
	2.02 (dd, 13.5, 11.0)	
17	2.86 (dd, 11.0, 6.0)	41.5 (d)
18	0.95 (s)	15.3 (q)
19	2.94 (d, 19.5)	41.5 (t)
	2.71 (d, 19.5)	
20		122.2 (s)
21	7.11 (m)	140.9 (d)
22	6.11 (m)	111.6 (d)
23	7.32 (m)	142.8 (d)
28	1.30 (s)	30.8 (q)
29	1.15 (s)	23.1 (q)
30	1.33 (s)	21.9 (q)
OAc	2.10 (s)	21.0 (q)
		169.7 (s)
OAc	1.92 (s)	20.9 (q)
		169.5 (s)

[a] Chemical shifts are in δ as assigned using the solvent as an internal reference ($CDCl_3$: ^1H, 7.24 ppm; ^{13}C, 77.0 ppm). [b] Assignments may be reversed.

RESULTS AND DISCUSSION

The MeOH extract from the bitter-tasting root bark of *C. jatrophoides* showed strong antifeedant activity against *P. gossypiella* larvae in the leaf disk assay (*4*−*6*). To isolate the active principles, the extract was sequentially partitioned between water and several organic solvents. Subsequent bioassays identified the $CHCl_3$ portion as containing the antifeedant activity. Silica gel chromatography of this portion and preparative HPLC led to the isolation of the previously reported **2** and an unknown compound **1** (**Figure 1**). This novel compound was designated as zumsin based on the local name of *C. jatrophoides*.

Compound **1** was isolated as an amorphous solid. The molecular formula was established as $C_{30}H_{36}O_9$ by high-resolution electron ionization mass spectrometry (HREIMS) and was consistent with NMR data. The structure of **1** possessed limonoid-like with similarities between the NMR spectra of **2** and those of **1**. Four singlet methyl groups (δ_H 1.33, 1.30, 1.15, 0.95; δ_C 30.8, 23.1, 21.9, 15.3), two acetate groups (δ_H 2.10, 1.92; δ_C 169.7, 169.5, 21.0, 20.9), and a β-substituted furan ring (δ_H 7.32, 7.11, 6.11; δ_C 142.8, 140.9, 122.2, 111.6) were observed in the ^1H and ^{13}C NMR spectra of **1**. These spectra also suggested the presence of a cyclopentyl ketone carbonyl (δ_C 215.2) and a trisubstituted epoxide (δ_H 3.78; δ_C 67.5, 56.7). The resonances due to the isopentanoate group in **2** are replaced by those of a ketone carbonyl (δ_C 207.4). The ^{13}C shifs of a methine carbon (δ_H 4.34; δ_C 84.0) and a quaternary carbon (δ_C 80.4) indicate that they are combined with the remaining oxygen atom as an ether group. Taking into account 13 degrees of unsaturation and the functionality described thus far, compound

1 was shown to consist of the seven rings making up the basic framework of **2**.

The ^{1}H resonance of **1** was correlated to the carbon resonance from the results of a ^{1}H−^{13}C HETCOR experiment. The resonance at 3.78 ppm (H-15) appeared as a slightly broadened singlet correlated to a resonance of an epoxide at 56.7 ppm (C-15). This ^{1}H resonance was assigned as a vicinal to the methylene ^{13}C resonance (δ_C 32.8) defined as C-16 based on a comparison of ^{1}H shifts and coupling constants with **1** and **2** [**1**: δ_H 2.27 (1H, ddd, J = 13.5, 6.0, 0.8 Hz), 2.02 (1H, dd, J = 13.5, 11.0 Hz) and **2**: δ_H 2.11 (1H, dd, J = 14.0, 6.0 Hz), 1.61 (1H, dd, J = 14.0, 11.0 Hz)]. These methylene ^{1}H resonances were further coupled to a resonance at 2.86 ppm (H-17). Examination of ^{1}H shifts and couplings and the ^{13}C resonances of nilotin and several trichilin type limonoids (*14*, *15*) allowed the assignment of these resonances to the D ring of limonoids as shown in **Figure 1**.

A coupling between the methine ^{1}H at 2.95 ppm (H-9) and the methine ^{1}H at 4.99 ppm (H-11) was observed using a ^{1}H−^{1}H decoupling experiment and through inspection of a ^{1}H−^{1}H correlation spectroscopy (COSY) spectrum. The latter spectrum indicated the resonance at 4.99 ppm (H-11) to be further coupled to a broadened methine resonance at 5.15 ppm (H-12). The ^{1}H and ^{13}C NMR shifts of the two methines (δ_H 5.15, 4.99; δ_C 80.4, 77.1) suggest that their carbons are sites of oxygenation. The resonance at 2.24 ppm (H-5) was coupled to two methylene resonances at 2.90 and 2.42 ppm (H-6). Neither H-6 methylene resonances nor H-5 methine resonance was further coupled. This is consistent with being surrounded by quaternary centers. The downfield shift H-6 is consistent with being α to a carbonyl in the B ring. In model compounds such as tecleanin (**3**) and limonin (**4**), the methine at C-5 in the B ring has a shift of 60 ppm and the methine at C-9 in the C ring has a shift of 47 ppm (*16*). Hence, the methine resonance of 46.8 ppm (C-9) in **1** was placed in the C ring, and in turn, the methine shift of 61.9 ppm (C-5) was placed in the B ring as shown in **Figure 1**. Assigned ^{13}C NMR shifts of this substructure compare well to those of model compounds **3** and **4** (*16*).

The remaining nuclei are placed into the A′ and A rings including a cyclopentyl carbonyl group, an ether group, and two singlet methyl groups. The resonance at 4.34 ppm (H-1) that correlated to the resonance of an ether (δ_C 84.0) was observed in the ^{1}H−^{1}H COSY spectrum to be coupled to a ^{1}H in the 2.5 ppm region. ^{1}H−^{1}H decoupling with irradiation at 4.34 ppm (H-1) identified a vicinal ^{1}H at 2.54 ppm (H-2). No further coupling of the resonance at 4.34 ppm could be observed. A methylene resonance at 44.9 ppm (C-2) was correlated to the geminal ^{1}H resonances at 2.54 and 2.44 ppm (H-2) by ^{1}H−^{13}C HETCOR experiments. The shift of 80.4 ppm is coincided with the shift of C-4 in both **3** and **4** (*16*) and is consistent with a position at C-4 containing geminal dimethyls and an ether functionality. If the oxygen atom attached to C-4 were involved in ester functionality, it would have a shift of 85−86 ppm (*16*, *17*). These data directed the construction of partial structures of the A and A′ rings as shown in **Figure 1**. Two ^{1}H resonances at 2.71 and 2.94 ppm (H-19) were correlated to a methylene resonance at 41.5 ppm (C-19). Lack of further ^{1}H−^{1}H coupling suggests that these nuclei are isolated between two quaternary centers. Their downfield shifts are consistent as being α to a carbonyl as shown in the partial structure of the A ring in **Figure 1**. The nuclei assembled thus far can only be combined in one way in order to fulfill the requirement of two additional rings.

The stereochemistry of **1** was obtained from an analysis of their ^{1}H−^{1}H couplings, a comparison with the ^{1}H−^{1}H couplings

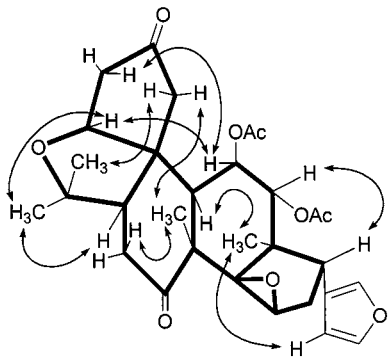

Figure 2. Significant NOE correlations in **1**.

observed for compound **2**, and differential nuclear Overhauser effect (NOE) experiments (**Figure 2**). The small 2.5 Hz coupling between H-9 and H-11 is consistent with a β-acetate at C-11. Assuming that the C ring is in a boat conformation, as it is in the case of most limonoids, including compound **2**, the small 0.8 Hz coupling between H-11 and H-12 placed the C-12 acetate in an α configuration. A much larger shift would have occurred if H-11 and H-12 were cis relative to each other. This stereochemistry is also supported by the NOE correlation between H-9 and H-18 that are the flagpoles on a boat form. The large 11.0 Hz coupling between H-5 and H-6$_\beta$ and a NOE between H-30 and H-6$_\beta$ confirm that H-5 has an α configuration. Consequently, the B ring conformation is defined in the chair form.

A long-range coupling between two geminal dimethyls (δ_H 1.30, 1.15; δ_C 30.8, 23.1) was observed in the ^{1}H−^{1}H COSY spectrum. A shielded geminal methyl ^{1}H at 1.15 ppm (H-29) possesses a NOE correlation with a vicinal ^{1}H at 2.71 ppm (H-19) on the A ring. On the other hand, two NOEs were observed on the other unshielded geminal methyl (δ_H 1.30) to a methine (δ_H 4.34) on the A ring and a methine (δ_H 2.24) on the B ring. In addition, the observation of several NOE correlations on the A ring supports that their stereochemistry is similar to those of **3** and **4**. The possible stereoisomers of **1** are limited to the single structure as shown in **Figure 1**.

The CD spectrum of **1** exhibited an extinction coefficient five times larger than that of compound **2** [**1**: CD in CH_3OH 295 nm (ϵ = 5.0 degree M^{-1} cm^{-1}) and **2**: CD in CH_3OH 295 nm (ϵ = 0.97 degree M^{-1} cm^{-1})]. This is consistent with the presence of a ketone carbonyl in a six-membered ring. Structure **1** should exhibit a Cotton effect about five times the magnitude of carbonyl groups in a five-membered ring (*18*). The negative sign of the Cotton effect of **1** suggests that the absolute stereochemistry of **1**, which is consistent with other limonoids, such as obacunone (*19*, *20*), possesses a ketone at C-7.

Both limonoids **1** and **2** represent new structures and are examples where an A ring opens before the D ring. A cis fusion of the A′ and B rings of **2** is less common, although it is found in limonoids such as jangomolide and cycloepiatalantin (*21*, *22*). The biosynthetic pathway of A′−B trans-fused limonoids, especially in the case of **4**, has been shown to be an oxyacid as the key intermediate (*23*). Limonoid **1** may be biosynthesized via the same route (path A in **Figure 3**). This route, however, does not fit the case of limonoid **2** where the A′ and B rings are cis-fused. Limonoid **2** might be biosynthesized via several unique steps. One possibility is oxidation at C-19 vs hydroxylation at C-1 (path B in **Figure 3**). We believe that *C. jatrophoides* is a rich source of varied compounds due to unique biosynthetic pathways and is a rare example of limonoids from the family Euphorbiaceae. Some may consider the isolation of

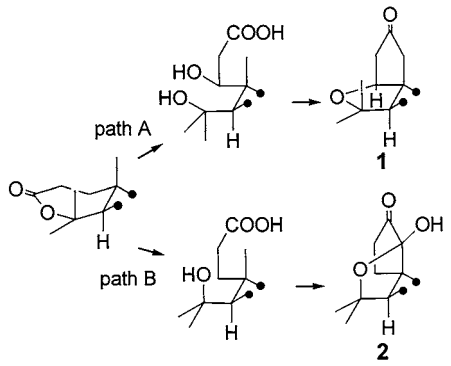

Figure 3. Proposed A–A′ ring formation of **1** and **2**.

1 and **2** to create doubts about the identification of the plant material. Limonoids are commonly found in the Rutaceae and Meliaceae families (*24*). However, there have been recent reports of limonoids with unusual structures from the Cneoraceae, Flacourtiaceae, Ptaeroxylaceae, and Simaroubaceae families (*21*, *25*, *26*). It can very well be that limonoids are more widespread and biodiverse than were previously thought.

Limonoids are currently receiving attention due to their insect antifeedant activity. Compound **1** exhibits this potent activity against both *P. gossypiella* ($PC_{50} = 1$ $\mu g/cm^2$, $PC_{95} = 8$ $\mu g/cm^2$) and *S. frugiperda* ($PC_{50} = 2$ $\mu g/cm^2$, $PC_{95} = 16$ $\mu g/cm^2$). According to the recent research, furan and epoxide groups on the C and D rings may be primary structures responsible for the antifeedant activity observed (*27*). Limonoids **1** and **2** exhibit some of these features and might have some additional biological activities on insects due to their unique A′−B fused structures. The prolonged use of these compounds in folk medicine suggests that they do not exhibit a strong toxicity in humans. In addition, some compounds containing a furan ring act as cancer-blocking agents by increasing the activity of detoxifying enzymes, such as glutathione *S*-transferase (*28*). Limonoids **1** and **2** might also inhibit carcinogenesis by preventing carcinogenic agents from reaching critical target sites in human tissue (*29*).

Large and complex molecules, from neem and related trees, such as azadirachtin and toosendanin, have been commercialized as insecticidal agents in the U.S.A. and China and could be a potential source of novel antifeedants and medicines (*13*, *30*). We are using the same plant source to look for other compounds of biological significance and practical use.

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