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Biogenetically related caged *ent*-kaurane diterpenoids from *Isodon eriocalyx* var. *laxiflora*

Wei-Guang Wang [a,b], Xiao-Nian Li [a], Xue Du [a], Ke Dong [a], Wei Zhao [a], Hai-Yan Wu [a], Ling-Mei Kong [a], Yan Li [a], Jian-Xin Pu [a,*], Han-Dong Sun [a,*]

[a] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, PR China
[b] Graduate University of Chinese Academy of Sciences, Beijing 100039, PR China

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ABSTRACT

Two novel caged *ent*-kauranoids, neolaxiflorins D (**1**) and E (**2**), along with three other new *ent*-kauranoids, neolaxiflorins F–H (**3**–**5**), and a known one, eriocalyxin B (**6**), were obtained from *Isodon eriocalyx* var. *laxiflora*. Neolaxiflorin D (**1**) is the first 15,16-*seco*-16,17-dinor-*ent*-kaurane diterpenoid, and neolaxiflorin E (**2**) is the first 15,16-*seco*-17-homo-*ent*-kauranoid. The absolute configurations of *ent*-kauranoids **1** and **2** were determined by single-crystal X-ray diffraction analyses. Structural analysis of intermediate compounds **3**–**5** indicated that eriocalyxin B (**6**) is a biogenetic precursor of caged *ent*-kauranoids **1** and **2** as illustrated. The cytotoxic activity of the new compounds was evaluated by an MTT assay.

Caged natural products are a special class of complex molecules with polycyclic cages and are found in iridoids,[1] sesquiterpenoids,[2] diterpenoids,[3] triterpenoids,[4] alkaloids,[5] xanthones,[6] phlorglucinol derivatives,[7] and other compounds.[8] Many of these cage-like, secondary metabolites demonstrated biological activity, exhibiting cytotoxic,[9] antibiotic,[6a] and antioxidative[10] properties, and acting as platelet-activating factor (PAF) receptor antagonists.[11] They have therefore become targets of interest for synthetic[12] and biosynthetic[13] chemists. The molecular skeletons of the known cage-like diterpenoids can be described as clerodane-type,[3a] labdane-type,[3c] hetidane-type,[3d] halogenated,[3e] ginkgolide-type,[3g] or other.[3b,f] Of the thousands of *ent*-kaurane diterpenoids previously identified, only one compound, rubescensin S (**7**),[14] has been reported to have the 15,16-*seco*-*ent*-kaurane diterpenoid caged motif.

Isodon, a genus of the Labiatae family, produces bioactive diterpenoids with diverse skeletons, including *ent*-kaurane diterpenoids.[15] The phytochemical components of *I. eriocalyx* var. *laxiflora*, a plant found in southwest China, have been investigated previously.[16] From this species, the new neolaxiflorins D–H (**1**–**5**) and the known compound eriocalyxin B (**6**)[15] (Fig. 1) were also isolated. Neolaxiflorins D–F (**1**–**3**) are the first examples of *ent*-kauranoids bearing tricyclic oxacaged motifs.

Compounds **1**–**3** exhibited the unusual 15,16-*seco*-*ent*-kaurane diterpenoid skeleton that had previously only been observed in rubescensin S (**7**).[14] Compound **1** is reported here as the first example of a 15,16-*seco*-16,17-dinor-*ent*-kaurane diterpenoid, and compound **2** is the first 15,16-*seco*-17-homo-*ent*-kaurane diterpenoid isolated from a natural resource. A possible biogenetic pathway of compounds **1** and **2** is proposed in Scheme 1. Herein, we describe the isolation, structural elucidation and absolute

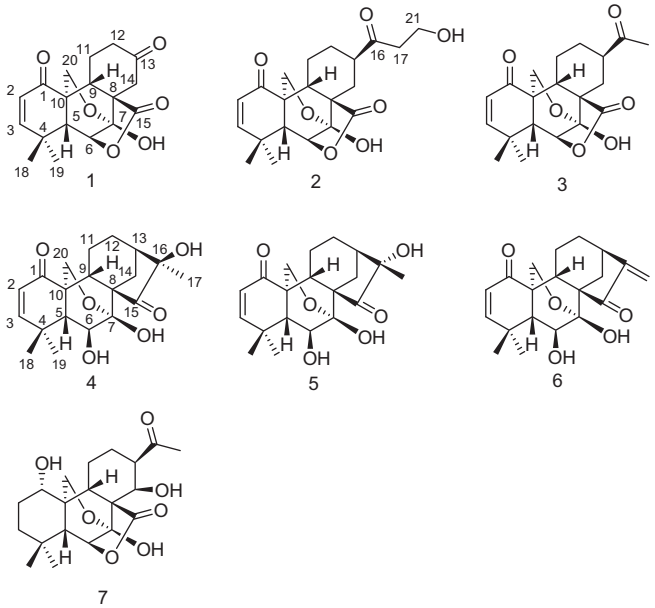

Figure 1. Structures of compounds **1**–**7**.

* Corresponding authors. Tel.: +86 871 5223251; fax: +86 871 5216343.
E-mail addresses: pujianxin@mail.kib.ac.cn (J.-X. Pu), hdsun@mail.kib.ac.cn (H.-D. Sun).

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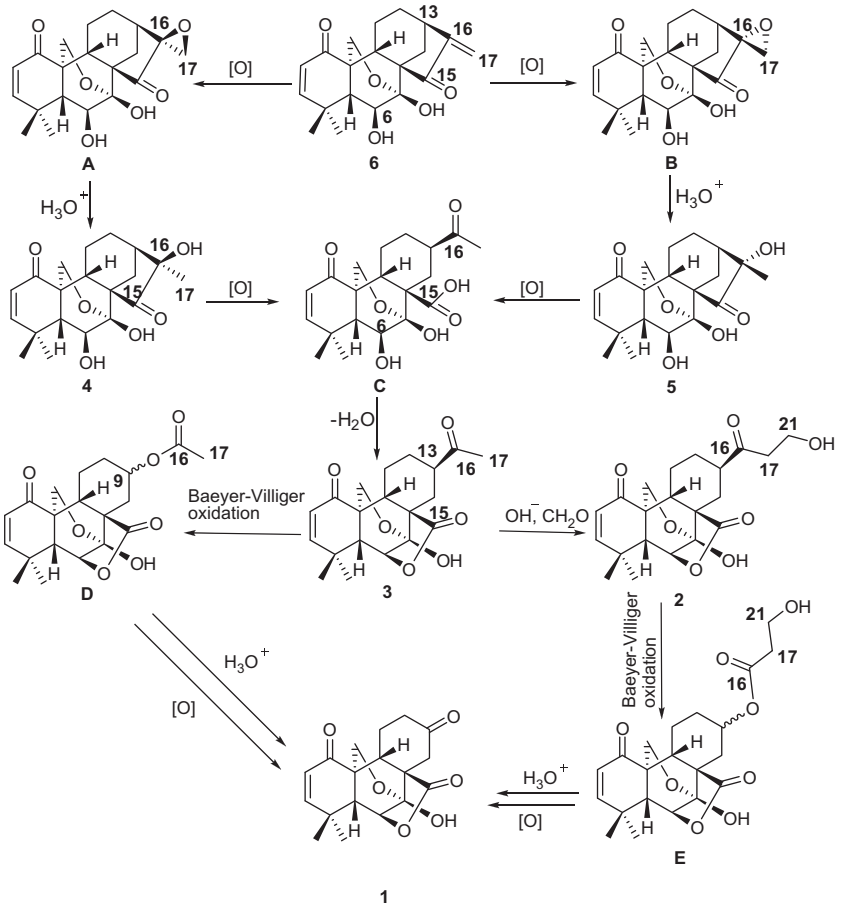

Scheme 1. Proposed biogenetic pathway of compounds **1** and **2**.

configuration, and the proposed biosynthetic pathway of compounds **1** and **2**.

Leaves from *I. eriocalyx* var. *laxiflora* were collected in Yunnan Province in September 2009. The plant material was identified by Professor Xi-Wen Li, and a voucher specimen was deposited in the Herbarium of the Kunming Institute of Botany, Chinese Academy of Sciences. The air-dried leaves (10 kg) were extracted with 7:3 aq Me_2CO (3 × 40 L, 2 d each) at room temperature. The solvent was evaporated in vacuo to afford a crude extract that was suspended in H_2O and extracted with EtOAc and then *n*-BuOH. The EtOAc-soluble mixture (600 g) was decolorized on an MCI gel with 9:1 MeOH–H_2O to yield a yellow gum (427.5 g). The gum was purified by column chromatography (CC) on SiO_2 (1:0–1:1 $CHCl_3$–Me_2CO) to yield six main fractions, A–F. Fraction B (9:1 $CHCl_3$–Me_2CO, 80 g) was resubmitted to chromatography over silica gel (30:1–1:1 petroleum ether–Me_2CO) to yield fractions B1–B4. Compound **6** (1.0 g) was crystallized from fraction B1 (30:1 petroleum ether–Me_2CO). Fraction D (7:3 $CHCl_3$–Me_2CO, 50 g) was submitted to additional CC (30:1, 20:1, and 10:1 $CHCl_3$–CH_3OH) to afford subfractions D1–D3. Subfraction D3 (10:1 $CHCl_3$–CH_3OH, 6 g) was purified by CC on RP-18 (15:85–1:0 MeOH–H_2O) to yield fractions D3/1–D3/6. Subsequently, fraction D3/3 (1.26 g) was purified by CC on SiO_2 (30:1–10:1 $CHCl_3$–isopropyl alcohol) to yield subfractions D3/3/1 (750 mg), D3/3/2 (85 mg), and D3/3/3 (120 mg). Compounds **1** (5 mg), **4** (10 mg), and **5** (5 mg) were precipitated from subfraction D3/3/1 by subsequent silica gel CC (20:1 $CHCl_3$–MeOH) and RP-18 (40:60 MeOH–H_2O). Subfraction D3/3/2 was purified by preparative HPLC (15 mL/min, detector UV λ_{max} = 208 nm, 25:75 MeCN–H_2O) to yield compound **3** (8 mg). Fraction E (6:4 $CHCl_3$–Me_2CO, 100 g) was purified using an MCI gel (3:7, 6:4, and 9:1 MeOH–H_2O) to afford fractions E1–E3. Compound **2** (8 mg) was obtained by RP-8 CC (15:85 CH_3CN–H_2O) from fraction E1 (10 g).

Table 1
^{13}C NMR data of compounds **1**–**5** (in C_5D_5N, δ in ppm, *J* in Hz)[a]

No.	1	2	3	4	5
1	198.0 (s)	198.2 (s)	198.2 (s)	197.5 (s)	197.3 (s)
2	125.6 (d)	125.8 (d)	125.8 (d)	127.5 (d)	127.4 (d)
3	156.8 (d)	156.6 (d)	156.6 (d)	160.8 (d)	160.6 (d)
4	35.3 (s)	35.3 (s)	35.2 (s)	36.2 (s)	36.1 (s)
5	53.5 (d)	53.8 (d)	53.6 (d)	58.9 (d)	59.3 (d)
6	80.3 (d)	79.7 (d)	79.7 (d)	73.7 (d)	73.6 (d)
7	98.7 (s)	99.2 (s)	99.1 (s)	96.6 (s)	96.2 (s)
8	48.1 (s)	47.5 (s)	47.5 (s)	60.5 (s)	59.9 (s)
9	43.7 (d)	43.6 (d)	43.8 (d)	49.3 (d)	49.2 (d)
10	45.8 (s)	46.2 (s)	46.0 (s)	46.4 (s)	46.4 (s)
11	21.7 (t)	22.1 (t)	21.9 (t)	19.2 (t)	19.2 (t)
12	38.7 (t)	22.7 (t)	22.8 (t)	22.5 (t)	19.2 (t)
13	208.7 (s)	44.0 (d)	43.8 (d)	40.0 (d)	39.2 (d)
14	35.9 (t)	20.4 (t)	20.3 (t)	25.2 (t)	24.0 (t)
15	178.7 (s)	179.4 (s)	179.3 (s)	222.4 (s)	225.9 (s)
16	—	210.8 (s)	209.0 (s)	79.3 (s)	79.2 (s)
17	—	43.8 (q)	27.6 (q)	20.5 (q)	25.2 (q)
18	30.3 (q)	30.4 (q)	30.3 (q)	30.1 (q)	30.0 (q)
19	22.5 (q)	22.7 (q)	22.6 (q)	24.3 (q)	24.2 (q)
20	65.1 (t)	65.3 (t)	65.2 (t)	65.6 (t)	65.6 (t)
21	—	58.2 (t)	—	—	

[a] NMR data of compounds **1**, **2**, and **5** were recorded at 125 MHz; data for compounds **3** and **4** were recorded at 100 MHz. Assignments were made based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

Neolaxiflorin D (**1**) was obtained as colorless needles. This compound was determined to have nine degrees of unsaturation

Table 2
^{1}H NMR spectroscopic data (in C_5D_5N, δ in ppm, J in Hz) of compounds **1**–**5**[a]

No.	1	2	3	4	5
2	5.90 (d, 10.2)	5.85 (d, 10.2)	5.86 (d, 10.2)	6.00 (d, 10.1)	5.93 (d, 10.1)
3	6.53 (d, 10.2)	6.48 (d, 10.2)	6.48 (d, 10.2)	6.69 (d, 10.1)	6.66 (d, 10.1)
5	2.58 (br s)	2.43 (br s)	2.41 (br s)	2.28 (d, 7.8)	2.22 (d, 7.8)
6	4.91 (br s)	4.79 (br s)	4.79 (br s)	4.34 (dd, 11.5, 7.8)	4.28 (dd, 11.6, 7.8)
9	2.49 (br d, 12.0)	2.28 (m)	2.28 (m)	2.00 (dd, 12.5, 4.5)	2.15 (dd, 12.6, 5.2)
11a	3.14 (m)	2.77 (m)	2.79 (m)	2.29 (m)	2.34 (m)
11b	2.34 (m)	1.98 (m)	1.98 (m)	1.53 (m)	1.55 (m)
12a	2.63 (m)	2.06 (m)	2.05 (m)	2.00 (m)	2.49 (m)
12b	2.38 (dd, 13.4, 3.0)	2.01 (m)	2.01 (m)	1.50 (m)	1.82 (m)
13	—	2.91 (qd, 8.9, 4.8)	2.75 (m)	2.48 (dd, 10.4, 4.4)	2.33 (dd, 10.4, 4.0)
14a	3.12 (d,16.4)	2.84 (dd,15.1, 4.5)	2.78 (d,14.0)	3.39 (d,12.2, 4.4)	2.60 (dd,13.1, 4.0)
14b	3.05 (d,16.4)	2.47 (dd,15.1, 8.9)	2.43 (d,14.0)	2.45 (d,12.2)	2.51 (d, 13.1)
17	—	3.05 (d, 6.2)	2.21 (s)	1.57 (s)	1.53 (s)
18	1.13 (s)	1.09 (s, 3H)	1.08 (s)	1.38 (s)	1.34 (s)
19	1.20 (s)	1.17 (s, 3H)	1.17 (s)	1.09 (s)	1.06 (s)
20a	4.47 (dd, 9.9, 1.4)	4.39 (d, 9.8)	4.39 (d, 9.8)	4.58 (d, 9.7)	4.58 (d, 9.9)
20b	4.34 (dd, 9.9, 2.3)	4.29 (d, 9.8)	4.27 (d, 9.8)	4.16 (dd, 9.7, 1.2)	4.13 (dd, 9.9, 1.2)
21a	—	4.27 (m)	—	—	—
21b	—	4.21 (m)	—	—	—

[a] NMR data of compounds **1** and **3** were recorded at 400 MHz; data for compounds **2**, **4**, and **5** were recorded at 500 MHz. Assignments were made based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

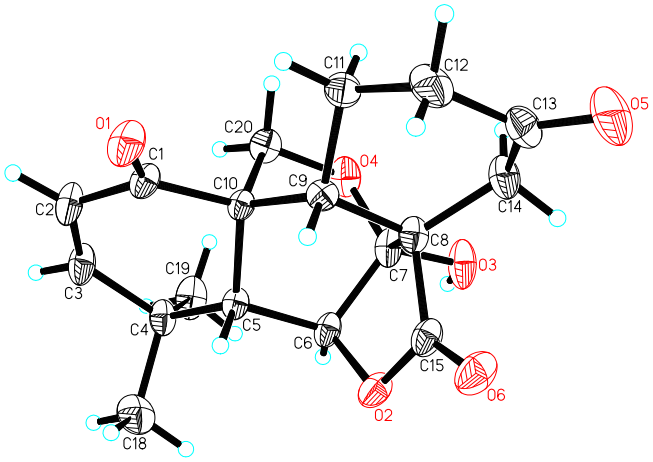

Figure 2. X-ray crystallographic structure of compound **1**.

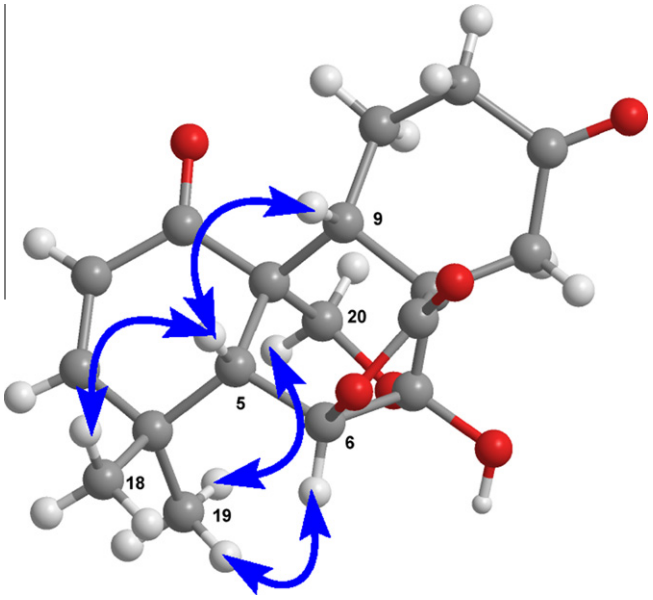

Figure 3. Key ROESY correlations of compound **1**.

corresponding to its molecular formula, $C_{18}H_{20}O_6$, as established by HRESIMS ([M+Na]$^+$ 355.1154, calcd 355.1157) and NMR spectroscopy (Tables 1 and 2). On the basis of careful analyses of 1D NMR, 2D NMR, and single-crystal X-ray diffraction using anomalous scattering of CuK$_\alpha$ radiation (CCDC 861510)[17] data (Fig. 2), the absolute configuration of compound **1** was assigned and can be described according to the following nomenclature: (5*R*,6*S*,7*S*, 8*S*,9*S*,10*S*)-7,20-epoxy-7-hydroxy-1,13-dioxo-15,16-*seco*-16,17-dinor-*ent*-kauran-2-en-6,15-olide. This compound is the first 15,16-*seco*-16,17-dinor-*ent*-kaurane diterpenoid isolated from a natural resource.

The ^{13}C NMR and DEPT spectra of compound **1** displayed 18 carbon signals corresponding to two methyls (δ_C 30.3, 22.5), four methylenes (including one oxygenated carbon (δ_C 65.1)), five methines (including one oxygenated methine (δ_C 80.3)), two olefinic carbons (δ_C 125.6, 156.8), and seven quaternary carbons (including two keto carbonyl groups (δ_C 198.0, 208.7), one ester carbonyl (δ_C 178.7), and one hemiacetal carbon (δ_C 98.7)) (Table 1).

Comparison of the NMR data for compound **1** (Table 1) with that of rubescensin S (**7**)[14] revealed many structural similarities and the following three differences. The first difference was absence of an acetyl group in **7** where there is a keto carbonyl group in **1** at C-13, which was supported by the HMBC correlations between H-11a (δ_H 3.14, m), H-11b (δ_H 2.34, m), H-12a (δ_H 2.63, m), H-12b (δ_H 2.38, dd, 13.4, 3.0), H-14a (δ_H 3.12, d,16.4), and H-14b (δ_H 3.05, d,16.4) with C-13. Second, the ring A of **7** was oxidized to an α,β-unsaturated ketone in **1**, and this was confirmed by the HMBC correlations between H-2 (δ_H 5.90, d,10.2), H-3 (δ_H 6.53, d,10.2), H-5 (δ_H 2.58, br s), H-20a (δ_H 4.47, dd, 9.9, 1.4), and H-20b (δ_H 4.34, dd, 9.9, 2.3) with C-1 and the ^{1}H–^{1}H COSY correlation between H-2 and H-3.

Finally, the oxygenated methine (δ_C 66.7) at C-14 in **7** was substituted by a methylene (δ_C 35.9) in **1**, and this was proved by HMBC correlations between H-9, H-12a, and H-12b with C-14 in **1**. In the ROESY spectrum (Fig. 3) of compound **1**, the correlations between H-5 and Me-18 and between H-5 and H-9 suggested that H-5, H-9, and Me-18 all have β configurations. The correlations between H-6 and Me-19 and between Me-19 and H_2-20 indicated that H-6, Me-19, and C-20 have α configurations. Therefore, compound **1** can be described using the following nomenclature:

7α,20-epoxy-7β-hydroxy-1,13-dioxo-15,16-*seco*-16,17-dinor-*ent*-kauran-2-en-6β,15β-olide.

The molecular formula of neolaxiflorin E (**2**) was found to be $C_{21}H_{26}O_7$ as determined by positive ion HRESIMS (*m*/*z* 413.1569 ([M+Na]$^+$ (calcd for $C_{21}H_{26}O_7Na$ [M+Na]$^+$, 413.1576). Comparison of its corresponding ^{1}H and ^{13}C NMR data (Tables 1 and 2) with that of compound **1** indicates that these two compounds are closely related. The only structural difference between the two was found at C-13; compound **1** has a keto carbonyl group at this position, and compound **2** has a 3-hydroxy-propionyl group. The planar structure of compound **2** was discovered by analyzing HMBC correlations (between H_2-17 (δ_H 3.05, d, 6.2) and H_2-21 (δ_H 4.27, m, 4.21, m) with C-16 and between H_2-17 with C-13) and ^{1}H–^{1}H COSY correlations (for the observed proton spin system, H-9/H_2-11/H_2-12/H-13/H_2-14). The relative configurations of the stereogenic centers in compound **2** were determined to be the same as those in compound **1**, based on detailed analyzes of ROESY data. Because the correlation from H-9 to H-13 was not observed in the ROESY spectrum, the relative configuration of H-13 was assumed to be α-oriented.

Following these analyses, the structure of compound **2** was elucidated and described according to the following nomenclature: 7α,20-epoxy-7β,21-dihydroxy-1,16-dioxo-15,16-*seco*-17-homo-*ent*-kauran-2-en-6β,15β-olide. Single-crystal X-ray diffraction using anomalous scattering of CuK$_\alpha$ radiation (CCDC 861511)[17] indicated the absolute stereochemistry of compound **2** to be 5*R*, 6*S*, 7*S*, 8*S*, 9*S*, 10*S*, 13*R* (Fig. 4). Previous to this example, no reported *ent*-kaurane diterpenoid had been identified as a 15,16-*seco*-17-homo-*ent*-kaurane diterpenoid.

Using HRESIMS (*m*/*z* 383.1474 for [M+Na]$^+$, calcd 383.1470), the molecular formula of neolaxiflorin F (**3**) was determined to be $C_{20}H_{24}O_6$, indicating nine degrees of unsaturation. Its ^{1}H (Table 2) and ^{13}C NMR data (Table 1) indicated that it was structurally very similar to compound **2**. The most notable difference was that the C-17 hydroxymethyl in compound **2** was not present in compound **3**. This structural assignment was supported by the observed HMBC correlations between H-17 (δ_H 2.21, s) with C-13 and C-16 and between H-13 (δ_H 2.75, m) with C-16 and C-17. The relative configuration of compound **3** was discovered to be the same as that observed in compound **2** by analyzing the ROESY spectra and by utilizing single-crystal X-ray diffraction using anomalous scattering of CuK$_\alpha$ radiation (CCDC 861512)[17] (Fig. 5). The relative configuration of compound **3** can be described by the following nomenclature: 7α,20-epoxy-7β-hydroxy-1,16-dioxo-15,16-*seco*-*ent*-kauran-2-en-6β,15β-olide.

Neolaxiflorins G (**4**) and H (**5**) were determined to be an epimeric pair with the same molecular formula, $C_{20}H_{26}O_6$, by HRESIMS

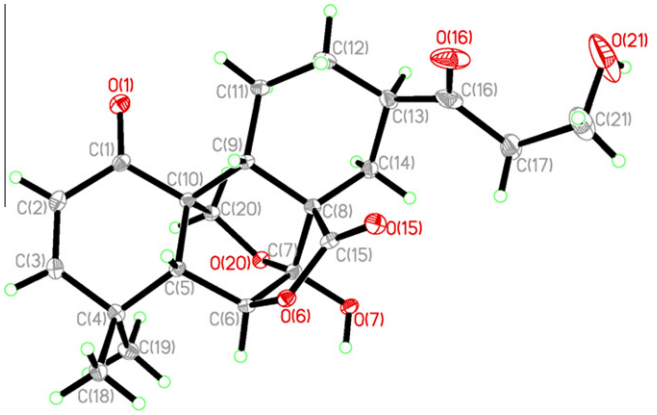

Figure 4. X-ray crystallographic structure of compound **2**.

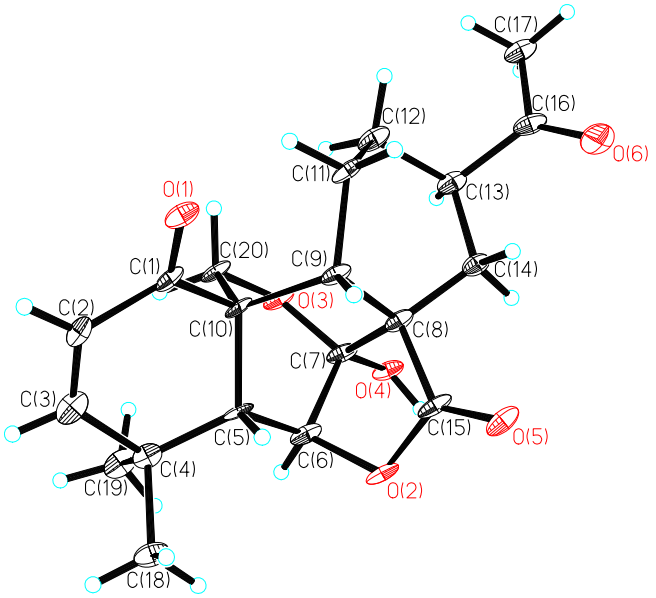

Figure 5. X-ray crystallographic structure of compound **3**.

((**4**, *m*/*z* 385.1621 for [M+Na]$^+$, calcd 385.1627); (**5**, *m*/*z* 385.1625 for [M+Na]$^+$, calcd 385.1627)). The planar structure and relative configurations of the two compounds were obtained by the analysis of 1D and 2D NMR data. The two compounds are structurally similar to eriocalyxin B (**6**)[15] and could be derived from it following a reduction of the C-16/C-17 double bond by addition of a hydroxyl group at C-16 and a hydrogen at C-17. The only difference between the epimers was that the relative configurations of Me-17 was deduced to be α-oriented in compound **4**, but β-oriented in compound **5** (Fig. 1), on the basis of the ROESY correlation data for H-13/H-16 in **4** and H-9/H-17 in **5**. Thus, the relative configurations of the epimeric pair can be described by the following nomenclature: 7α,20-epoxy-6β,7β,16β-trihydroxy-2-en-*ent*-kauran-1,15-dione (**4**) and 7α,20-epoxy-6β,7β,16α-trihydroxy-2-en-*ent*-kauran-1,15-dione (**5**).

Isolation of rubescensin S (**7**)[14] was reported in 2004, and its structure was revised recently to account for an error in assigning the absolute configuration at C-13. The newly discovered caged 15,16-*seco*-*ent*-kauranoids **1–3** may be related biogenetically to each other (Scheme 1).

Compound **1** could have been formed biogenetically through the loss of the side-chain carbons C-16 and C-17 on compound **3**, or by the removal of three carbons (C-16, C-17, and C-21) from compound **2**. With the addition of a C-17 hydromethyl group, compound **2** could also be derived from compound **3**. The formation of the three-membered ring which is composed of C-16-O-C-17 yielded intermediate A and intermediate B, which underwent the cleavage of the C-17-O bond to produce intermediate compounds **4** and **5**.

An oxidative cleavage of the single bond between C-15 and C-16 in the intermediate compounds **4** and **5** formed the key intermediate C. Following the subsequent esterification between C-15 and C-6 in intermediate C was to give intermediate compound **3**. As illustrated in Scheme 1, compound **6** could be a biogenetic precursor of compounds **1** and **2**.

Compounds **1–5** were tested for in vitro cytotoxicity against A-549, HL-60, MCF-7, SMMC-7721, and SW-480 human cancer cell lines using the MTT method.[18] However, none of the compounds showed observable inhibitory activity, all yielding an IC_{50} > 40 μM.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures, cytotoxicity test methods, physicochemical properties, 1D and 2D NMR, MS, UV, IR, and ORD spectra of compounds **1**–**5**, and X-ray crystallographic data for compounds **1**–**3**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.112.

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