ent-Kaurane Diterpenes and Further Constituents from *Wedelia trilobata*

by **Yin Qiang**[a]), **Dao-Lin Du**[b]), **Yan-Jun Chen**[c]), and **Kun Gao***[a])

[a]) State Key Laboratory of Applied Organic Chemistry and College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China (phone: +86-931-8912592; fax: +86-931-8912582; e-mail: npchem@lzu.edu.cn)

[b]) School of Environment, Jiangsu University, Zhenjiang 212013, P. R. China

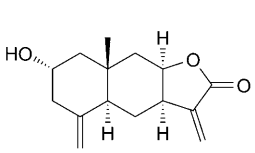
[c]) School of Biotechnology and Chemical Engineering, Ningbo Institute of Technology, Zhejiang University, Ningbo 315100, P. R. China

Two new *ent*-kaurane diterpenes, wedelidins A (**8**) and B (**9**), together with eighteen other constituents, including the sesquiterpenoids **1** and **2**, *ent*-kaurane diterpenes **3**–**7**, triterpenoids **10** and **11**, steroids **12**–**14**, and flavonoids **15**–**17** as well as benzene derivatives **18**–**20**, were isolated from the aerial parts of *Wedelia trilobata*. The structures of wedelidins A (**8**) and B (**9**) were elucidated by extensive spectroscopic analyses (including UV, IR, NMR, and MS). Furthermore, the structures of compounds **2** and **3** were confirmed by X-ray single-crystal diffraction analyses.

Introduction. – *Wedelia trilobata* L. (Asteraceae) is a perennial plant. In traditional herbal medicine, *W. trilobata* has been used for the treatment of fever and malaria in Vietnam [1]. Previous investigations revealed that the secondary metabolites from this plant mainly consisted of terpenoids [1–3], flavonoids [4], and polyacetylenes as well as steroids [5].

As part of our ongoing search for terpenoids and steroids from natural sources [6–8], we investigated the aerial parts of *W. trilobata* from a phytochemical viewpoint, which led to the isolation of the 20 secondary metabolites **1**–**20**, including the two sesquiterpenoids **1** and **2**, the seven *ent*-kaurane diterpenes **3**–**9**, the two triterpenoids **10** and **11**, the three steroids **12**–**14**, and the three flavonoids **15**–**17** as well as the three benzene derivatives **18**–**20**. Among them, compounds **8** and **9**, named wedelidin A and B, resp., are two new *ent*-kaurane diterpenes. Herein, we will report the isolation and structural elucidation of these isolates. In addition, the ^{13}C-NMR data of the five known *ent*-kaurane diterpenes **3**–**7** were completely assigned here by 2D-NMR spectra (^{1}H,^{1}H-COSY, HSQC, and HMBC), and the structures of compounds **2** and **3** were further confirmed by X-ray single-crystal diffraction analyses.

Results and Discussion. – Wedelidin A (**8**) was obtained as a white powder. The negative-ion-mode ESI-MS showed a quasimolecular ion at *m*/*z* 463.1 ($[M-H]^-$), which, combined with analyses of ^{13}C-NMR data and the DEPT experiment, indicated a molecular formula $C_{29}H_{36}O_5$. This hypothesis was also supported by the quasimolecular ion at *m*/*z* 487.2445 ($[M+Na]^+$) in the positive-ion-mode HR-ESI-MS, corresponding to 12 degrees of unsaturation. Its IR spectrum showed absorptions at 3347 (OH), 1708 (C=O), and 1567 and 1470 cm^{-1} (aromatic C=C). The existence of a



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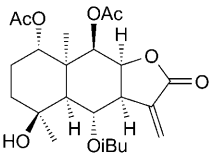

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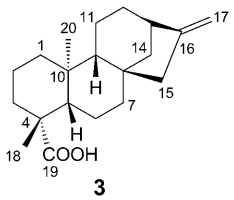

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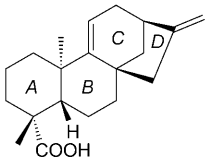

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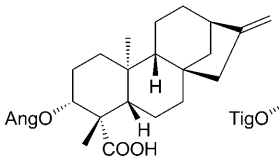

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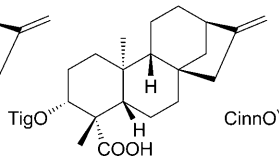

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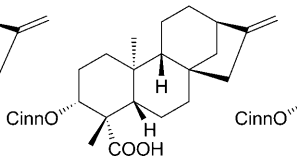

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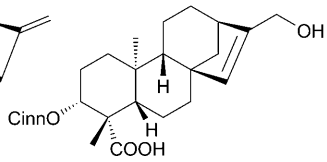

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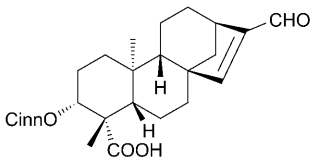

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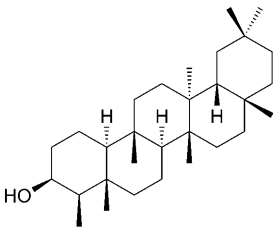

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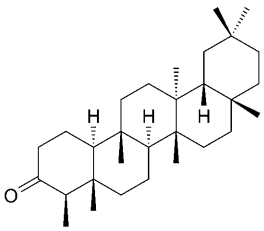

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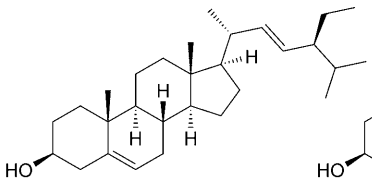

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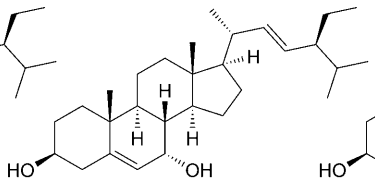

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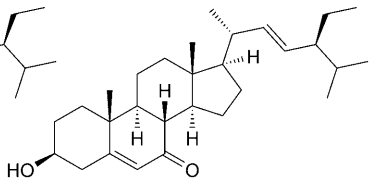

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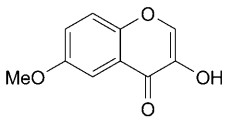

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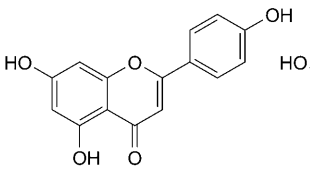

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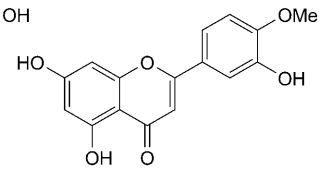

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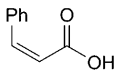

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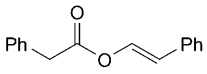

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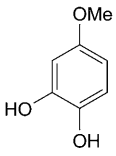

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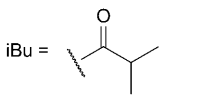

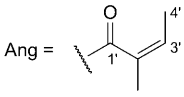

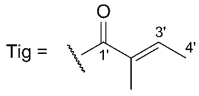

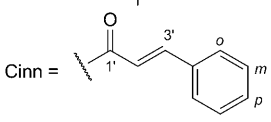

cinnamate (=(2*E*)-3-phenylprop-2-enoate) ester function was supported by the following ^{1}H- and ^{13}C-NMR data: δ(H) 6.47 (*d*, *J* = 15.9 Hz, 1 H), 7.70 (*d*, *J* = 15.9 Hz, 1 H), 7.37–7.39 (overlap, 3 H), and 7.52–7.54 (overlap, 2 H), and δ(C) 166.7 (*s*), 118.3 (*d*), 145.1 (*d*), 134.7 (*s*), 128.1 (*d*), 128.9 (*d*), and 130.3 (*d*) (*Tables 1* and *2*). Besides the above moiety, the remaining twenty C-atoms included a trisubstituted C=C bond (δ(H) 5.53 (br. *s*); δ(C) 137.1 (*d*) and 141.3 (*s*)), a COOH group (δ(C) 180.4 (*s*)), an O-bearing CH group (δ(H) 4.70 (*dd*, *J* = 4.2, 12.0 Hz); δ(C) 78.8 (*d*)), and an O-bearing CH_2 group (δ(H) 4.57 (br. *s*); δ(C) 75.1 (*t*)). Further analyses indicated a closely similar NMR pattern of compound **8** to that of (3α)-3-(cinnamoyloxy)-*ent*-kaur-16-en-19-oic acid (**7**), suggesting the structure of an *ent*-kaurane diterpenoid for **8** [2]. The cinnamate ester moiety should be bonded to the position C(3) based on the HMBC from H–C(3) to C(1′) (*Fig. 1*). The major difference in the NMR data between compounds **8** and **7** was that the signals of the above-described O-bearing CH_2 group and the trisubstituted C=C bond in ring *D* of **8** appeared instead of those of the exocyclic CH_2=C(16) moiety of **7**. The NMR data of ring *D* of **8** were also supported by the HMBC experiment (*Fig. 1*). The relative configuration of compound **8** was established by comparison of its NMR data with those of **7**. The H–C(3) signal of **8** appeared as *dd* (*J* = 4.2 and 12.0 Hz) with a closely similar coupling pattern to that observed for **7** (*dd*, *J* = 4.4 and 12.0 Hz) [2]. So, the cinnamate ester moiety should be α-oriented in compound **8**. Finally, the structure of wedelidin A (**8**) was elucidated as (3α)-3-(cinnamoyloxy)-17-hydroxy-*ent*-kaur-15-en-19-oic acid.

Wedelidin B (**9**) was obtained as a white powder. Its positive-ion-mode HR-ESI-MS revealed a quasimolecular ion at *m*/*z* 463.2483 ($[M+H]^+$), suggesting a molecular

Table 1. *^{1}H-NMR Data* ($CDCl_3$) *of Compounds* **8** *and* **9**. δ in ppm, *J* in Hz.

	8[a])	**9**[b])
CH_2(1)	2.03–2.05 (*m*), 0.99–1.12 (*m*)	2.03–2.06 (*m*), 1.10–1.12 (*m*)
CH_2(2)	2.45 (*q*, *J* = 12.0), 1.81 (overlap)	2.45 (*q*, *J* = 12.0), 1.80 (overlap)
H–C(3)	4.70 (*dd*, *J* = 4.2, 12.0)	4.70 (*dd*, *J* = 4.2, 12.0)
H–C(5)	1.17 (overlap)	1.15 (overlap)
CH_2(6)	1.88–1.91 (*m*), 1.70–1.73 (*m*)	1.88–1.92 (*m*), 1.71–1.75 (*m*)
CH_2(7)	1.93–1.96 (*m*), 1.09–1.11 (*m*)	1.99–2.02 (*m*), 1.14–1.18 (*m*)
H–C(9)	1.21–1.24 (*m*)	1.24–1.29 (*m*)
CH_2(11)	1.55–1.60 (overlap, 2 H)	1.55–1.60 (overlap, 2 H)
CH_2(12)	1.58 (overlap), 1.50 (overlap)	1.60 (overlap), 1.50 (overlap)
H–C(13)	2.62 (br. *s*)	3.06 (br. *s*)
CH_2(14)	1.89–1.91 (*m*), 1.50–1.54 (*m*)	2.06–2.09 (*m*), 1.47–1.51 (*m*)
H–C(15)	5.53 (br. *s*)	6.59 (br. *s*)
CH_2(17) or H–C(17)	4.57 (br. *s*)	9.75 (*s*)
Me(18)	1.35 (*s*)	1.34 (*s*)
Me(20)	1.09 (*s*)	1.09 (*s*)
H–C(2′)	6.47 (*d*, *J* = 15.9)	6.47 (*d*, *J* = 16.2)
H–C(3′)	7.70 (*d*, *J* = 15.9)	7.70 (*d*, *J* = 16.2)
H_o	7.52–7.54 (overlap, 2 H)	7.52–7.54 (overlap, 2 H)
H_m	7.37–7.39 (overlap, 2 H)	7.37–7.39 (overlap, 2 H)
H_p	7.37–7.39 (overlap)	7.37–7.39 (overlap)

[a]) Measured at 300 MHz. [b]) Measured at 600 MHz.

Table 2. *^{13}C-NMR Data* ($CDCl_3$) *of Compounds* **3**–**9**. δ in ppm.

	3[a])	**4**[a])	**5**[a])	**6**[a])	**7**[a])	**8**[b])	**9**[c])
C(1)	41.1 (*t*)	40.7 (*t*)	38.8 (*t*)	38.8 (*t*)	38.9 (*t*)	38.8 (*t*)	39.7 (*t*)
C(2)	19.5 (*t*)	20.1 (*t*)	24.2 (*t*)	24.0 (*t*)	24.2 (*t*)	24.1 (*t*)	24.1 (*t*)
C(3)	38.2 (*t*)	38.2 (*t*)	78.7 (*d*)	78.8 (*d*)	79.0 (*d*)	78.8 (*d*)	78.6 (*d*)
C(4)	44.7 (*s*)	44.7 (*s*)	48.0 (*s*)	48.1 (*s*)	48.1 (*s*)	48.1 (*s*)	48.0 (*s*)
C(5)	57.5 (*d*)	46.6 (*d*)	56.5 (*d*)	56.4 (*d*)	56.5 (*d*)	56.1 (*d*)	55.9 (*d*)
C(6)	22.3 (*t*)	18.4 (*t*)	21.5 (*t*)	21.5 (*t*)	21.6 (*t*)	20.5 (*t*)	20.1 (*t*)
C(7)	41.7 (*t*)	29.7 (*t*)	39.5 (*t*)	39.5 (*t*)	39.5 (*t*)	39.1 (*t*)	38.0 (*t*)
C(8)	44.2 (*s*)	42.3 (*s*)	43.8 (*s*)	43.8 (*s*)	43.9 (*s*)	49.0 (*s*)	50.6 (*s*)
C(9)	55.6 (*d*)	158.5 (*s*)	55.2 (*d*)	55.1 (*d*)	55.2 (*d*)	47.4 (*d*)	46.1 (*d*)
C(10)	40.1 (*s*)	38.8 (*s*)	43.8 (*s*)	43.8 (*s*)	39.4 (*s*)	39.6 (*s*)	38.8 (*s*)
C(11)	18.4 (*t*)	114.9 (*d*)	18.5 (*t*)	18.5 (*t*)	18.5 (*t*)	19.0 (*t*)	18.8 (*t*)
C(12)	33.5 (*t*)	37.9 (*t*)	33.1 (*t*)	33.0 (*t*)	33.1 (*t*)	25.3 (*t*)	25.1 (*t*)
C(13)	44.3 (*d*)	41.2 (*d*)	43.9 (*d*)	43.9 (*d*)	43.8 (*d*)	41.5 (*d*)	37.8 (*d*)
C(14)	40.1 (*t*)	44.9 (*t*)	41.0 (*t*)	41.0 (*t*)	41.0 (*t*)	43.6 (*t*)	42.8 (*t*)
C(15)	49.4 (*t*)	50.3 (*t*)	48.8 (*t*)	48.7 (*t*)	48.8 (*t*)	137.1 (*d*)	161.0 (*d*)
C(16)	156.3 (*s*)	155.9 (*s*)	155.3 (*s*)	155.3 (*s*)	155.3 (*s*)	141.3 (*s*)	148.8 (*s*)
C(17)	103.7 (*t*)	105.5 (*t*)	103.3 (*t*)	103.3 (*t*)	103.3 (*t*)	75.1 (*t*)	189.4 (*d*)
C(18)	29.4 (*q*)	28.2 (*q*)	24.0 (*q*)	23.9 (*q*)	23.9 (*q*)	23.8 (*q*)	23.8 (*q*)
C(19)	184.0 (*s*)	183.3 (*s*)	180.7 (*s*)	180.4 (*s*)	180.6 (*s*)	180.4 (*s*)	180.3 (*s*)
C(20)	16.0 (*q*)	23.6 (*q*)	15.4 (*q*)	15.3 (*q*)	15.4 (*q*)	15.4 (*q*)	15.5 (*q*)
C(1′)			167.7 (*s*)	167.7 (*s*)	166.8 (*s*)	166.7 (*s*)	166.7 (*s*)
C(2′)			128.0 (*s*)	128.8 (*s*)	118.4 (*d*)	118.3 (*d*)	118.2 (*d*)
C(3′)			138.0 (*d*)	137.4 (*d*)	145.1 (*d*)	145.1 (*d*)	145.2 (*d*)
Me(4′) or C_{ipso}			15.7 (*q*)	14.4 (*q*)	134.5 (*s*)	134.7 (*s*)	134.4 (*s*)
Me–C(2′) or C_o			20.6 (*q*)	12.0 (*q*)	128.1 (*d*)	128.1 (*d*)	128.1 (*d*)
C_m					128.8 (*d*)	128.9 (*d*)	128.9 (*d*)
C_p					130.3 (*d*)	130.3 (*d*)	130.3 (*d*)

[a]) Measured at 100 MHz. [b]) Measured at 75 MHz. [c]) Measured at 150 MHz.

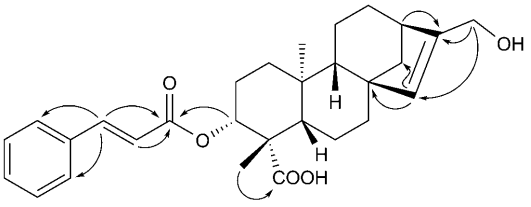

Fig. 1. *Key HMBCs* (H → C) *of compound* **8**

formula $C_{29}H_{34}O_5$, which indicated 13 degrees of unsaturation. The IR spectrum showed absorptions at 3375 (OH), 1710 (C=O), and 1662 and 1453 cm^{-1} (aromatic C=C). The presence of a cinnamate ester moiety was supported by NMR data (*Tables 1* and *2*). Besides this ester moiety, the remaining twenty C-atoms included a trisubstituted C=C bond (δ(H) 6.59 (br. *s*); δ(C) 161.0 (*d*) and 148.8 (*s*)), a COOH group (δ(C) 180.3 (*s*)), an aldehyde C=O group (δ(C) 189.4 (*d*)), and an O-bearing CH group (δ(H) 4.70 (*dd*, $J = 4.8, 12.0$ Hz); δ(C) 78.6 (*d*)). Further analyses demonstrated

that compound **9** showed a closely similar NMR pattern to that of **8**, besides the existence of a CHO instead of an O-bearing CH_2 group, indicating that compound **9** was an *ent*-kaurane diterpenoid. Based on the HMBCs C(17) (δ(C) 189.4 (*s*))/H–C(13) and H–C(15), the position of the CHO group should be assigned to CH(17). The α-orientation of the cinnamate ester moiety of **9** was established by comparison of the H–C(3) coupling pattern (*dd*, $J = 4.8$ and 12.0 Hz) with that of **8** (*dd*, $J = 4.2$ and 12.0 Hz). Thus, the structure of wedelidin B (**9**) was determined as (3α)-3-(cinnamoyloxy)-17-oxo-*ent*-kaur-15-en-19-oic acid.

In addition to the above described two new *ent*-kaurane diterpenes **8** and **9**, 18 secondary metabolites were isolated. Based on the spectroscopic analyses and comparison with the literature data, they were determined as ivalin (**1**) [9], wedeliatrilolactone B (**2**) [10], *ent*-kaur-16-en-19-oic acid (**3**) [11], *ent*-kaura-9(11),16-dien-19-oic acid (**4**) [12], (3α)-3-(angeloyloxy)-*ent*-kaur-16-en-19-oic acid (**5**) [13], (3α)-3-(tiglinoyloxy)-*ent*-kaur-16-en-19-oic acid (**6**) [2], (3α)-3-(cinnamoyloxy)-*ent*-kaur-16-en-19-oic acid (**7**) [2], β-friedelinol (**10**) [14], friedelin (**11**) [15], stigmasterol (**12**) [16], (7α)-7-hydroxystigmasterol (**13**) [17], (3β)-3-hydroxystigmasta-5,22-dien-7-one (**14**) [18], 3-hydroxy-6-methoxychromen-4-one (**15**) [19], apigenin (**16**) [20], diosmetin (**17**) [21], benzeneacetic acid 2-phenylethenyl ester (**18**) [22], isocinnamic acid (**19**) [23], and 4-methoxycatechol (**20**) [24]. Among these isolates, compounds **1**, **4**, and **11**–**20** are reported as secondary metabolites from *W. trilobata* for the first time. The structures of compounds **2** and **3** were further confirmed by an X-ray single-crystal diffraction experiment for the first time (*Fig. 2*). Crystals of **2** and **3** were obtained from a solution of $CHCl_3$/MeOH 1:1. The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre*[1]).

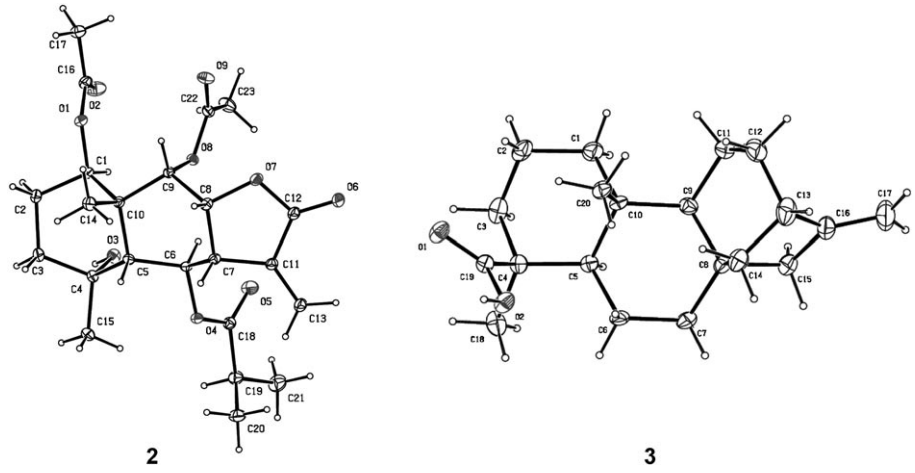

Fig. 2. *X-Ray single-crystal structures of compounds* **2** *and* **3**. Arbitrary atom numbering.

[1]) CCDC-778708 (for **2**) and 782281 (for **3**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

This work was supported by the *Basic Research Program* (*973 Program*) *of China* (No. 2007CB108903), the *National Science Foundation of China* (No. 20972062 and No. 30970556), and the *111 Project*.

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh; *Qingdao Marine Chemical Factory*, Qingdao, P. R. China). TLC: SiO_2 *GF_{254}* (10–40 μm, *Qingdao Marine Chemical Factory*); detection at 254 nm, and by heating after spraying with 98% H_2SO_4 soln./EtOH 5:95 (*v*/*v*). Optical rotations: *Perkin-Elmer-341* polarimeter; in MeOH at 25°. UV Spectra: *NewCentury-Pgeneral-T6* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet-Nexus-670* FT-IR spectrometer; with KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian-Inova-300*, *Bruker-Avance-III-400*, and *Varian-Inova-600* instruments; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Bruker-Esquire-6000* (ESI) and *Bruker-Apex-II* (HR-ESI) instrument; in *m*/*z*.

Plant Material. The plant material was collected in Haikou City, Hainan Province, China, in June 2008 and authenticated by advanced lab assistant *Qiong-Xin Zhong* of the College of Biology, Hainan Formal University. A voucher specimen (20070805) was deposited with the College of Chemistry and Chemical Engineering, Lanzhou University.

Extraction and Isolation. The air-dried whole plant of *W. trilobata* (4600.3 g) was powdered and extracted with 95% EtOH (15 l) three times (each for 7 d) at r.t. and the soln. concentrated to give a crude extract (671.2 g), which was suspended in H_2O (2.5 l) and then extracted with petroleum ether (60–90°; 3 × 2.5 l) and $CHCl_3$ (4 × 2.0 l) successively. The petroleum ether extract (180.1 g) was subjected to CC (SiO_2, petroleum ether/AcOEt 40:1, 20:1, 10:1, 5:1, 2:1, and 0:1): *Fractions 1–6* (monitored by TLC). *Fr. 1* (60.7 g) was repeatedly applied to CC (SiO_2, petroleum ether/AcOEt 50:1 → 10:1): **3** (10.8 g) and **4** (68.6 mg). *Fr. 2* (10.5 g) was also applied to CC (SiO_2, petroleum ether/AcOEt 25:1): **5** (2.1 mg) and a crude crystalline product. The latter was recrystallized from petroleum ether/AcOEt 1:1: **9** (3.8 g). *Fr. 3* (20.4 g) was subjected to repeated CC (SiO_2, petroleum ether/AcOEt 20:1 → 5:1): *Frs. 3.1* and *3.2*. *Fr. 3.1* (10.2 g) was further purified by CC (SiO_2, petroleum ether/AcOEt 10:1): **6** (8.2 mg), **7** (20.6 mg), and **8** (4.6 mg). *Fr. 3.2* (0.6 g) was subjected to prep. TLC ($CHCl_3$/AcOEt 15:1): **10** (4.7 mg) and **11** (33.2 mg). *Fr. 4* (3.8 g) was applied to CC (SiO_2, petroleum ether/AcOEt 10:1 → 2:1): *Frs. 4.1–4.3*. *Fr. 4.1* (1.0 g) was further subjected to CC (SiO_2, $CHCl_3$/AcOEt 15:1 → 5:1): **13** (2.9 mg), **15** (6.8 mg), and **17** (9.2 mg). *Fr. 4.2* (1.8 g) was also further purified by CC (SiO_2, $CHCl_3$/AcOEt 10:1 → 2:1): **1** (1.1 mg), **2** (4.2 mg), and **12** (6.2 mg). *Fr. 5* (1.6 g) was subjected to repeated CC (SiO_2, $CHCl_3$/AcOEt 15:1 → 3:1): **16** (8.3 mg), **19** (10.4 mg), and **20** (5.1 mg). The $CHCl_3$ extract (5.6 g) was subjected to repeated CC (SiO_2, $CHCl_3$/acetone 50:1 → 2:1): *Frs. a–d* (by TLC). *Fr. c* (1.9 g) was further purified with CC (SiO_2, $CHCl_3$/CH_3OH 20:1): **14** (3.0 mg) and **18** (5.6 mg).

Wedelidin A (=*(3α)-3-(Cinnamoyloxy)-17-hydroxy*-ent-*kaur-15-en-19-oic Acid* = *(3α)-17-Hydroxy-3-{[(2*E*)-1-oxo-3-phenylprop-2-en-1-yl]oxy}*-ent-*kaur-15-en-19-oic Acid*; **8**): White amorphous powder. $[\alpha]_D^{25} = -8.2$ (*c* = 0.1, MeOH). UV (MeOH): 207 (3.25), 274 (3.37). IR (KBr): 3347, 2962, 2931, 2868, 1708, 1567, 1470, 1311, 812. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75 MHz, $CDCl_3$): *Table 2*. HR-ESI-MS: 487.2445 ($[M + Na]^+$, $C_{29}H_{36}NaO_5^+$; calc. 487.2455).

Wendelidin B (=*(3α)-3-(Cinnamoyloxy)-17-oxo*-ent-*kaur-15-en-19-oic Acid* = *(3α)-17-Oxo-3-{[(2*E*)-1-oxo-3-phenylprop-2-en-1-yl]oxy}*-ent-*kaur-15-en-19-oic Acid*; **9**): White amorphous powder. $[\alpha]_D^{25} = -6.1$ (*c* = 0.1, MeOH). UV (MeOH): 215 (3.11), 275 (3.09). IR (KBr): 3375, 2925, 1710, 1662, 1453, 1070, 1026, 768. ^{1}H-NMR (600 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (150 MHz, $CDCl_3$): *Table 2*. HR-ESI-MS: 463.2483 ($[M + H]^+$, $C_{29}H_{35}O_5^+$; calc. 463.2479).

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Received August 10, 2010