ORGANIC LETTERS

2012
Vol. 14, No. 1
302–305

New Bicyclo[3.1.0]hexane Unit *ent*-Kaurane Diterpene and Its *seco*-Derivative from *Isodon eriocalyx* var. *laxiflora*

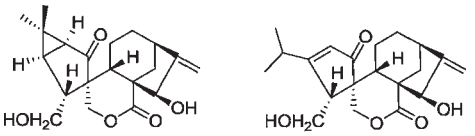
Wei-Guang Wang,[†,‡] Xue Du,[†] Xiao-Nian Li,[†] Hai-Yan Wu,[†] Xu Liu,[†] Shan-Zhai Shang,[†,‡] Rui Zhan,[†,‡] Cheng-Qin Liang,[†,‡] Ling-Mei Kong,[†,‡] Yan Li,[†] Jian-Xin Pu,[*,†] and Han-Dong Sun[*,†]

State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, Yunnan, P. R. China, and Graduate School of the Chinese Academy of Sciences, Beijing 100039, P. R. China

pujianxin@mail.kib.ac.cn; hdsun@mail.kib.ac.cn

Received November 14, 2011

ABSTRACT



Neolaxiflorin A (1), an unprecedented *ent*-kaurane diterpenoid with a bicyclo[3.1.0]hexane unit, and its *seco*-derivative, neolaxiflorin B (2), along with two known compounds 3 and 4 were isolated from the leaves of *Isodon eriocalyx* var. *laxiflora*. The absolute configuration of 1 was determined by spectral methods and single crystal X-ray diffraction analysis. Compound 4 and the synthesized compound 5 exhibited significant cytotoxicity.

The molecules containing bicyclo[3.1.0]hexane and its heteroanalogues including nitrogen, oxygen, or sulfur atoms in the five-membered ring unit have been recognized as interesting core structures with diverse biological activities.[1] Some of them have been prepared by metal-catalyzed synthesis,[2] atom-economic synthesis,[3] cross metathesis,[4] a chemicoenzymatic approach,[5] and other methods.[1c,6]

As an important group of terpenoids, the structural scaffold diversity of *ent*-kaurane-type diterpenoids is just as much a characteristic as their biological diversity.[7] For example, bisrubescensins A–C,[8] maoecrystal Z,[9] and maoecrystal V[10] have been reported as unique structures. Meanwhile, maoecrystal V has been repeatedly synthesized due to the challenge posed by the unusual skeleton.[11] Some compounds such as pharicins A[12] and B,[13] eriocalyxin B,[14] oridonin,[15] and ponicidin,[16] have brought great attention to their potential application in antitumors.[7]

[†] Kunming Institute of Botany.
[‡] Graduate School of the Chinese Academy of Sciences.

(1) (a) Foulke-Abel, J.; Agbo, H.; Zhang, H.; Mori, S.; Watanabe, C. M. H. *Nat. Prod. Rep.* **2011**, *28*, 693–704. (b) Kumar, T. S.; Zhou, S. Y.; Joshi, B. V.; Balasubramanian, R.; Yang, T. H.; Liang, B. T.; Jacobson, K. A. *J. Med. Chem.* **2010**, *53*, 2562–2576. (c) Comin, M. J.; Agbaria, R.; Ben-Kasus, T.; Huleihel, M.; Liao, C.; Sun, G.; Nicklaus, M. C.; Deschamps, J. R.; Parrish, D. A.; Marquez, V. E. *J. Am. Chem. Soc.* **2007**, *129*, 6216–6222. (d) Mamane, V.; Gress, T.; Krause, H.; Furstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (e) Jeong, L. S.; Buenger, G.; McCormack, J. J.; Cooney, D. A.; Hao, Z.; Marquez, V. E. *J. Med. Chem.* **1998**, *41*, 2572–2578. (f) Decosta, B. R.; Mattson, M. V.; George, C.; Linders, J. T. M. *J. Med. Chem.* **1992**, *35*, 4704–4712. (g) Kamata, S.; Haga, N.; Tsuri, T.; Uchida, K.; Kakushi, H.; Arita, H.; Hanasaki, K. *J. Med. Chem.* **1990**, *33*, 229–239. (h) Rynbrand, R.; Schmidt, F. L.; Dutton, F. E. *J. Med. Chem.* **1972**, *15*, 424–426.

(2) (a) Liu, R. S.; Vasu, D.; Hung, H. H.; Bhunia, S.; Gawade, S. A.; Das, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911–6914. (b) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452–3453. (c) Monnier, F.; Vovard-Le Bray, C.; Castillo, D.; Aubert, V.; Derien, S.; Dixneuf, P. H.; Toupet, L.; Ienco, A.; Mealli, C. *J. Am. Chem. Soc.* **2007**, *129*, 6037–6049. (d) Kerber, W. D.; Gagne, M. R. *Org. Lett.* **2005**, *7*, 3379–3381. (e) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.

(3) (a) Feng, J. J.; Zhang, J. *J. Am. Chem. Soc.* **2011**, *133*, 7304–7307. (b) Xu, F.; Murry, J. A.; Simmons, B.; Corley, E.; Fitch, K.; Karady, S.; Tschaen, D. *Org. Lett.* **2006**, *8*, 3885–3888.

(4) Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E. *Org. Lett.* **2006**, *8*, 705–708.

(5) Moon, H. R.; Ford, H.; Marquez, V. E. *Org. Lett.* **2000**, *2*, 3793–3796.

(6) (a) Terrazas, M.; Avino, A.; Siddiqui, M. A.; Marquez, V. E.; Eritja, R. *Org. Lett.* **2011**, *13*, 2888–2891. (b) Li, J.; Lowary, T. L. *Org. Lett.* **2008**, *10*, 881–884. (c) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787–4790. (d) Renslo, A. R.; Gao, H. W.; Jaishankar, P.; Venkatachalam, R.; Gordeev, M. F. *Org. Lett.* **2005**, *7*, 2627–2630.

10.1021/ol203061z
Published on Web 12/19/2011

In thousands of new *ent*-kaurane diterpenoids identified previously, compounds containing the bicyclo[3.1.0]hexane unit in this type of diterpenoids have not been reported. Recently, two new *ent*-kaurane-type of diterpenoid derivatives, neolaxiflorins A and B (**1** and **2**), together with two known 6,7-*seco*-*ent*-kaurane diterpenoids, laxiflorins A and B (**3** and **4**),[7] have been isolated from *I. eriocalyx* var. *laxiflora* which are distributed in southwest China (Figure 1). Compound **1** is an *ent*-kaurane diterpenoid which bears an infrequent bicyclo[3.1.0]hexane unit, and **2** has an α,β-unsaturated ketone in its five-membered ring A which is biogenetically related to **1**. Meanwhile, compound **5**, a significant cytotoxic diterpenoid, was synthesized from **1** to investigate the structure−activity relationship of these compounds. Here, we report their isolation, structure elucidation including absolute stereochemistry, derivatization, and cytotoxic activities.

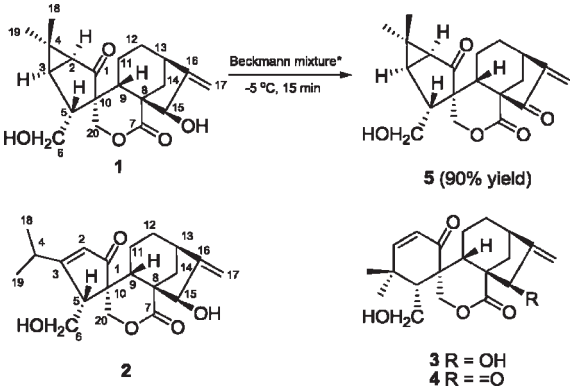


Figure 1. Chemical structures of compounds **1**–**5**. *1:1:3 $K_2Cr_2O_7$–H_2SO_4–H_2O.

Neolaxiflorin A (**1**) was obtained as colorless needles. The molecular formula, $C_{20}H_{26}O_5$, with eight unsaturations, was established by HR-ESI-MS ($[M + Na]^+$, 369.1685, calcd 369.1677) and NMR spectral features (Tables 1 and 2).

Table 1. ^{13}C NMR Spectroscopic Data (δ in ppm) of Neolaxiflorins A−C (**1**, **2**, and **5**) (Pyridine-d_5, δ in ppm)[a]

no.	1	2	5
1	212.7 s	208.8 s	212.5 s
2	39.0 d	127.6 d	39.3 d
3	33.2 d	186.5 s	32.8 d
4	29.0 s	29.7 d	29.5 s
5	40.3 d	52.9 d	39.4 d
6	60.5 t	58.4 t	61.5 t
7	175.6 s	175.6 s	170.8 s
8	52.3 s	52.2 s	58.8 s
9	35.2 d	38.7 d	42.6 d
10	62.3 s	53.1 s	62.4 s
11	18.7 t	19.1 t	19.9 t
12	31.3 t	33.0 t	30.7 t
13	36.5 d	36.9 d	35.7 d
14	33.3 t	32.0 t	30.7 t
15	82.9 d	81.4 d	203.5 s
16	160.1 s	159.9 s	151.6 s
17	109.2 t	108.9 t	119.1 t
18	17.7 q	21.6 q	18.0 q
19	27.6 q	20.3 q	27.8 q
20	69.4 t	68.9 t	70.1 t

[a] Data of compounds **1** and **2** were recorded at 125 MHz, **5** was recorded at 150 MHz, and the assignments were based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

The IR spectrum demonstrated absorptions at 1709 and 1680 cm^{-1}, indicating the existence of a carbonyl group and a carbon−carbon double bond respectively. In the ^1H NMR spectrum (Table 2), there were two tertiary methyl groups at δ_H 0.89 (3H, s) and 1.12 (3H, s), an olefinic methylene (exocyclic double bond) group at δ_H 5.46 (1H, s) and 5.22 (1H, s), and an oxygenated methine group at δ_H 4.98 (1H, s). In addition, it showed resonances due to an ABX group at [δ_H 4.15 (1H, dd, J = 9.8, 5.8 Hz), 4.05 (1H, dd, J = 9.8, 6.6 Hz), and 2.51 (1H, br d, J = 6.6 Hz)] together with an AB methylene group at [δ_H 5.20 (1H, d, J = 11.2 Hz) and 4.70 (1H, d, J = 11.2 Hz)].

Analyses of the ^{13}C NMR and DEPT spectra (Table 1) of **1** revealed the presence of 20 carbons, ascribed to two methyls, six methylenes (two oxygenated ones, one exocyclic double bond), six methines (one oxygenated), and six quaternary carbons (one olefinic group, one ester, and one ketone group), which suggested a pentacyclic diterpenoid with a C_{20} nucleus different from the *ent*-kaurane or 6,7-*seco*-*ent*-kaurane skeletons reported before.

Interpretation of the HMBC spectrum of **1** showed obvious correlations from the geminal methyls Me-18 (δ_H 1.12, s) and Me-19 (δ_H 0.89, s) to C-2, C-3, and C-4. Furthermore, the ABX methylene H_2-6 displayed HMBC

(7) Sun, H. D.; Huang, S. X.; Han, Q. B. *Nat. Prod. Rep.* **2006**, *23*, 673–698.
(8) Huang, S. X.; Xiao, W. L.; Li, L. M.; Li, S. H.; Zhou, Y.; Ding, L. S.; Lou, L. G.; Sun, H. D. *Org. Lett.* **2006**, *8*, 1157–1160.
(9) Han, Q. B.; Cheung, S.; Tai, J.; Qiao, C. F.; Song, J. Z.; Tso, T. F.; Sun, H. D.; Xu, H. X. *Org. Lett.* **2006**, *8*, 4727–4730.
(10) Li, S. H.; Wang, J.; Niu, X. M.; Shen, Y. H.; Zhang, H. J.; Sun, H. D.; Li, M. L.; Tian, Q. E.; Lu, Y.; Cao, P.; Zheng, Q. T. *Org. Lett.* **2004**, *6*, 4327–4330.
(11) (a) Zakarian, A.; Gu, Z. H. *Org. Lett.* **2011**, *13*, 1080–1082. (b) Chen, D. Y. K.; Dong, L.; Deng, L. J.; Lim, Y. H.; Leung, G. Y. C. *Chem.—Eur. J.* **2011**, *17*, 5778–5781. (c) Trauner, D.; Baitinger, I.; Mayer, P. *Org. Lett.* **2010**, *12*, 5656–5659. (d) Thomson, R. J.; Lazarski, K. E.; Hu, D. X.; Stern, C. L. *Org. Lett.* **2010**, *12*, 3010–3013. (e) Nicolaou, K. C.; Dong, L.; Deng, L. J.; Talbot, A. C.; Chen, D. Y. K. *Chem. Commun.* **2010**, *46*, 70–72. (f) Li, C. C.; Gong, J. X.; Lin, G. A.; Sun, W. B.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746. (g) Li, C. C.; Gong, J.; Lin, G.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770–4773. (h) Baran, P. S.; Krawczuk, P. J.; Schone, N. *Org. Lett.* **2009**, *11*, 4774–4776.
(12) Xu, H. Z.; Huang, Y.; Wu, Y. L.; Zhao, Y.; Xiao, W. L.; Lin, Q. S.; Sun, H. D.; Dai, W.; Chen, G. Q. *Cell Cycle* **2010**, *9*, 2897–2907.
(13) Gu, Z. M.; Wu, Y. L.; Zhou, M. Y.; Liu, C. X.; Xu, H. Z.; Yan, H.; Zhao, Y.; Huang, Y.; Sun, H. D.; Chen, G. Q. *Blood* **2010**, *116*, 5289–5297.
(14) (a) Wang, L.; Zhao, W. L.; Yan, J. S.; Liu, P.; Sun, H. P.; Zhou, G. B.; Weng, Z. Y.; Wu, W. L.; Weng, X. Q.; Sun, X. J.; Chen, Z.; Sun, H. D.; Chen, S. J. *Cell Death Differ.* **2007**, *14*, 306–317. (b) Zhang, Y. W.; Jiang, X. X.; Chen, Q. S.; Shi, W. Y.; Wang, L.; Sun, H. D.; Shen, Z. X.; Chen, Z.; Chen, S. J.; Zhao, W. L. *Exp. Hematol.* **2010**, *38*, 191–201.
(15) Fujita, E.; Fujita, T.; Katayama, H.; Shibuya, M. *Chem. Commun.* **1967**, 252–254.
(16) Fujita, E.; Taoka, M.; Shibuya, M.; Fujita, T.; Shingu, T. *J. Chem. Soc., Perkin Trans.* **1973**, 2277–2281.

Table 2. ^{1}H NMR Assignments of Neolaxiflorins A−C (**1**, **2**, and **5**) (Pyridine-d_5, δ in ppm, J in Hz)[a]

no.	1	2	5
2	1.82 br s	6.14 s	1.82 d (6.2)
3	1.82 br s	–	1.48 dd (6.2, 2.8)
4	–	2.73 q (6.8)	–
5β	2.51 br d (6.6)	3.23 br s	2.51 ddd (9.1, 6.0, 2.8)
6a	4.15 dd (9.8, 5.8)	4.14 d (11.2)	4.03 dd (10.8, 6.0)
6b	4.05 dd (9.8, 6.6)	4.02 dd (11.2, 3.8)	3.97 dd (10.8, 9.1)
9β	3.07 dd (13.3, 4.8)	2.93 dd (13.0, 4.8)	2.90 dd (11.9, 6.2)
11α	1.62 m	1.56 m	1.65 m
11β	1.54 m	1.36 m	1.65 m
12α	2.36 d (12.2)	1.43 m	1.22 m
12β	2.41 dd (12.2, 5.0)	1.98 m	1.96 m
13α	2.67 dd (8.0, 5.0)	2.69 m	2.85 dd (9.4, 4.5)
14α	1.97 m	2.22 br s	2.71 d (12.5)
14β	1.40 m	2.22 br s	2.67 dd (12.5, 4.5)
15α	4.98 s	5.21 s	–
17a	5.46 s	5.51 s	5.96 s
17b	5.22 s	5.20 s	5.31 s
18β	1.12 s	1.11 d (6.8)	1.08 s
19α	0.89 s	1.06 d (6.8)	0.88 s
20a	5.20 d (11.2)	5.27 d (11.1)	5.09 d (11.5)
20b	4.70 d (11.2)	5.01 d (11.1)	4.80 d (11.5)

[a] Data of compounds **1** and **2** were recorded at 500 MHz, **5** was recorded at 600 MHz, and the assignments were based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

correlations with C-3, C-5 and C-10, H-5 with C-4, C-9, C-10, and C-20. Other HMBC correlations were noted from H-2 and H-3 (δ_H 1.82, br s) to C-1, C-5, C-10, and C-18. The observed HMBC correlations above, coupled with a proton spin system, H-3/H-5/H$_2$-6, established by ^{1}H−^{1}H COSY correlations, gave partial structure **1a** (Figure 2).

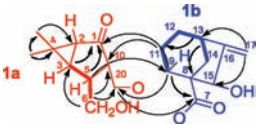


Figure 2. Structural fragments of **1** (→ HMBC).

Detailed analyses of the ^{1}H−^{1}H COSY and HSQC spectra starting from the proton H-9 (δ_H 3.07, dd) revealed the presence of a spin system (CHCH$_2$CH$_2$CHCH$_2$, H-9/H$_2$-11/H$_2$-12/H-13/H$_2$-14) (Figure 2). This information coupled with the key HMBC correlations from H-11β (δ_H 1.54, m) to C-8 and C-13; H-13 (δ_H 2.67, dd) to C-8, C-11, C-14, C-15, and C-16; and H-17a (δ_H 5.46, s) to C-13, C-15, and C-16 further corroborated the structure of fragment **1b** (Figure 2). The HMBC spectrum also showed the following correlations: H-9 with C-1, C-5, C-7, C-8, C-10, C-11, C-12, C-14, C-15, and C-20; the AB methylene group H$_2$-20 with C-1, C-9, and C-10; and H-20b (δ_H 4.20, d) with C-7. This information permitted **1a** and **1b** to be jointed through a C−C connection between C-9 and C-10 and an ester bond between C-7 and C-20. Accordingly, the planar structure of compound **1** could be established.

In the ROESY spectrum of **1**, the cross-peaks observed between H-5/H-9 and H-5/Me-18 demonstrated that H-5, H-9, and Me-18 all possessed the same β-orientations, so Me-19 and hydromethyl at C-5 should be α-orientations (Figure 3). The NOE correlations from H-9/H-11β, H-12α/H-11α, H-13/H-12α, and H-13/H-15 suggested that H-13 and H-15 have the same α-orientations. The structure of **1** was finally confirmed by a single-crystal X-ray diffraction using anomalous scattering of Cu Kα radiation (CCDC 853442),[17] which indicated the absolute stereochemistry of **1** to be 2*S*, 3*R*, 5*R*, 8*S*, 9*S*, 10*S*, 13*R*, 15*R* (Figure 4).

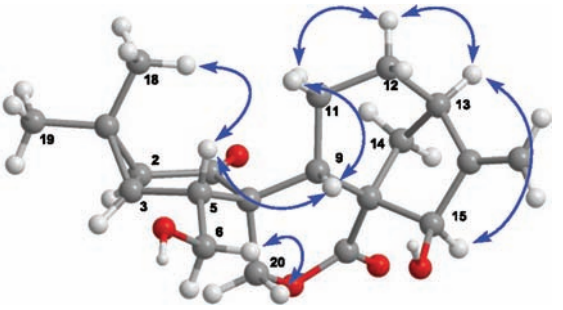


Figure 3. Key ROESY correlations of **1** (blue ↔, ROESY).

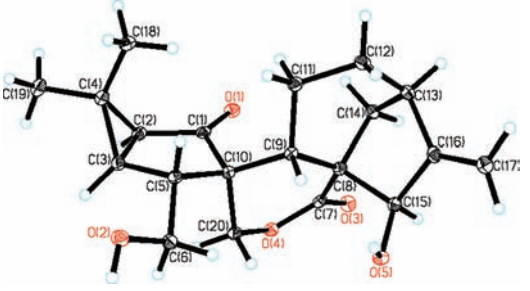


Figure 4. X-ray crystallographic structure of **1**.

Neolaxiflorin B (**2**) had the same molecular formula $C_{20}H_{26}O_5$ as **1**, on the basis of HR-ESI-MS (m/z 369.1673 for $[M + Na]^+$), indicating eight degrees of unsaturation. Its ^{1}H (Table 2) and ^{13}C NMR data (Table 1) indicated that it was very similar to **1**. The most notable difference was that the geminal methyl group [(δ_H 1.12, 3H, s; δ_C 17.7, q)

(17) (a) Flack, H.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908–915. (b) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881.

(Me-18), (δ_H 0.89, 3H, s; δ_C 27.6, q) (Me-19)] at C-4 (δ_C 29.0, s) in **1** changed into an isopropyl group in **2** [(δ_H 2.73, 1H, q, J = 6.8 Hz; δ_C 29.7, d), (δ_H 1.11, 3H, d, J = 6.8 Hz; δ_C 21.6, q), (δ_H 1.06, 3H, d, J = 6.8 Hz; δ_C 20.3, q)] (C-4, Me-18, and Me-19). Then, the other important difference was that the two methines C-2 (δ_C 39.0, d) and C-3 (δ_C 33.2, d) in **1** were placed by a C−C double bond between C-2 (δ_C 127.6, d) and C-3 (δ_C 186.5, s) in **2**. Therefore, **2** might be derived from **1** because the bicyclo[3.1.0]hexane structure in **1** was oxidatively cleaved between C-2 and C-4, followed by formation of a C−C double bond between C-2 and C-3. This conjecture was supported by the HMBC correlations from Me-18 to C-3, C-4, and C-19; Me-19 to C-3, C-4, and C-18; and H-2 (δ_H 6.14, 1H, s) to C-1, C-3, C-4, C-5, and C-10. In addition, other 2D NMR data including ^{1}H−^{1}H COSY, HSQC, HMBC, and ROESY further established the structure of **2** (Figure 1).

Neolaxiflorin C (**5**) had a molecular formula of $C_{20}H_{24}O_5$, as determined by its HR-ESI-MS data (m/z 367.1254 for $[M + Na]^+$), indicating 9 degrees of unsaturation. Comparison of its NMR data (Tables 1 and 3) with those of **1** revealed similarities except for the lack of the signal of H-15 in **1** instead of a carboxy group in **5** at C-15 (δ_C 203.5 s), which was supported by the HMBC correlation from H_2-17 [δ_H (5.96, s), (5.31, s)] to C-13, C-15, and C-16. This evidence, along with other comprehensive NMR and MS spectroscopic analyses, confirmed the structure of compound **5**.

Table 3. Cytotoxic Activity of Compounds **1**−**5**[a]

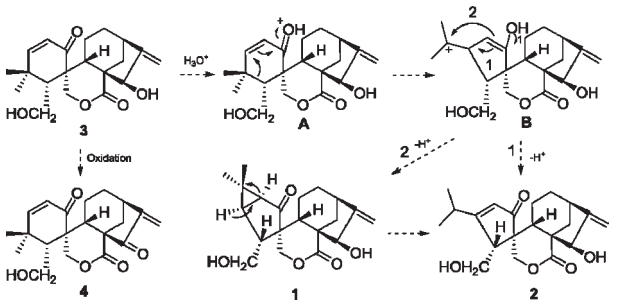
compd	A-549	HL-60	MCF-7	SMMC-7721	SW-480
1	>40	>40	>40	>40	>40
2	>40	>40	>40	>40	>40
3	>40	>40	>40	>40	>40
4	2.02	0.76	1.26	1.03	0.61
5	6.76	4.04	3.24	4.96	2.79
cis-platin	16.02	1.25	16.95	16.18	18.05

[a] Results were expressed as IC_{50} values in μM, data were obtained from triplicate experiments, and *cis*-platin was used as positive control.

In natural products, compounds hybiding a bicyclo-[3.1.0]hexane unit were very rare. **1** was the first example of *ent*-kaurane diterpene bearing a rare 3/5/6/6/5 ring system, and **2** had an α,β-unsaturated ketone unit in its five-membered ring A and represented a new group of *ent*-kaurane diterpene with a 5/6/6/5 ring system. The new skeletons of **1** and **2** were quiet different from the previously reported 6/6/6/5 ring system of 6,7-*seco*-*ent*-kaurane diterpene. The possible biogenetic route of **1** and **2** (Scheme 1) could be plausibly traced back to laxiflorin A (**3**). The formation of intermediate **B** from intermediate **A** by rearrangement involving the carbocation route is the key step to forming the two compounds.

Using the MTT method, **1**−**5** were tested for cytotoxicity in human cancer cell lines: A-549, HL-60, MCF-7, SMMC-7721, and SW-480.[18] The successful synthesis of **5** gave us the opportunity to further confirm the structure−activity relationship reported previously.[19] First, **4** and **5** showed cytotoxicity with an IC_{50} value in the range of 0.61−6.76 μM for the above-mentioned tumor cell lines, while none of compounds **1**, **2**, and **3** showed any inhibitory activity with IC_{50} > 40 μM. The results were consistent with the previous conclusion that the presence of the O=C—C=CH_2 system seems to be critical for cytotoxic activity.[7,20] Second, **4** had a higher cytotoxicity than **5**, suggesting that the presence of a second α,β-unsaturated ketone might increase the potency for antitumor activity.[7] Finally, changes in ring A of **5** did not reduce its cytotoxicity, probably because of the presence of the cyclopentanone conjugated with an exomethylene group.[7]

Scheme 1. Hypothetical Biogenetic Pathway of **1** and **2**



Acknowledgment. The authors are grateful to Prof. Xi-Wen Li of the Kunming Institute of Botany, Chinese Academy of Sciences, for identification of the plant. This project was supported financially by the NSFC-Joint Foundation of Yunnan Province (No. U0832602 to H.D.S.), the National Natural Science Foundation of China (No. 81172939 to J.-X.P.), the Major State Basic Research Development Program of China (No. 2009CB522300), the reservation-talent project of Yunnan Province (2011CI043 to J.-X.P.), the Science and Technology Program of Yunan Province (Nos. 2008IF010 and 2008CD162), and the Major Direction Projection Foundation of CAS Intellectual Innovation Project (No. 2010KIBA05 to J.-X.P.).

Supporting Information Available. Detailed experimental procedures, method of cytotoxicity test, physicochemical properties, 1D and 2D NMR, MS, UV, IR, ORD spectra of compounds **1**−**3**, and X-ray crystal structure of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589–601.

(19) (a) Leung, C. H.; Grill, S. P.; Lam, W.; Gao, W.; Sun, H. D.; Cheng, Y. C. *Mol. Pharmacol.* **2006**, *70*, 1946–1955. (b) Leung, C. H.; Grill, S. P.; Lam, W.; Han, Q. B.; Sun, H. D.; Cheng, Y. C. *Mol. Pharmacol.* **2005**, *68*, 286–297.

(20) Lee, K. H.; Huang, E. S.; Piantado., C; Pagano, J. S.; Geissman, T. A. *Cancer Res.* **1971**, *31*, 1649–1654.