ent-Kaurane Diterpenoids from *Isodon phyllostachys*

by **Xian Li**[a])[b]), **Zhi-Ying Weng**[a])[b]), **Yong Li**[c]), **Jian-Xin Pu**[a]), **Sheng-Xiong Huang**[a]), **Wei-Lie Xiao**[a]), and **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, Yunnan, P. R. China (phone: +86-871-5223251; fax: +86-871-5216343; e-mail: hdsun@mail.kib.ac.cn)

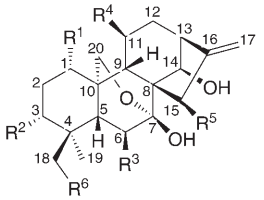
[b]) School of Pharmacy, Kunming Medical College; Kunming 650031, Yunnan, P. R. China

[c]) The 5th Affiliated Hospital, Kunming Medical College; Gejiu 661000, Yunnan, P. R. China

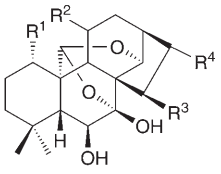
Phytochemical investigation of the medicinal plant *Isodon phyllostachys* led to the isolation of four new *ent*-kaurane diterpenoids, phyllostacins F–I (**1**–**4**, resp.), together with 11 known compounds, rosthorin A (**5**), rabdoternin C (**6**), enmenol (**7**), oridonin (**8**), lasiocarpanin (**9**), xerophilusin B (**10**), ponicidin (**11**), macrocalin B (**12**), phyllostachysin A (**13**), sculponeatin C (**14**), and macrocalyxoformin E (**15**). The structures of the new compounds were established by spectroscopic methods, including extensive 1D- and 2D-NMR analyses. Compounds **1**, **2**, **7**, **10**, and **13** were evaluated for their inhibitory activity against K562 and HepG2 cell lines.

Introduction. – The genus *Isodon* (Labiatae), a rich source of *ent*-kaurane diterpenoids, is a folk medicine well-known for its antibacterial, anti-inflammatory, and antitumor activity [1]. *I. phyllostachys*, which is distributed throughout the northwest district of the Yunnan Province of China, has been used as an antiphlogistic and antibiotic agent by the local inhabitants. In previous investigations, three C(20)-oxygenated *ent*-kauranoids, phyllostachysins A–C, have been reported from the plant of *I. phyllostachys* [2–4]. Interestingly, we isolated other types of *ent*-kauranoids (C(20)-non-oxygenated) named as phyllostachysins D–H from this plant before, which was collected from different region [5]. This new discovery may be attributable to the different ecological environment, which represents a promising strategy for the discovery of other new diterpenoids. Therefore, in our continued investigation of *I. phyllostachys* collected in Lijiang County of Yunnan Province, China, resulted in the isolation of 15 compounds including four new *ent*-kaurane diterpenoids, named phyllostacins F–I (**1**–**4**), together with 11 known compounds, rosthorin A (**5**) [6], rabdoternin C (**6**) [7], enmenol (**7**) [8], oridonin (**8**) [9], lasiocarpanin (**9**) [10], xerophilusin B (**10**) [11], ponicidin (**11**) [9], macrocalin B (**12**) [12], phyllostachysin A (**13**) [2], sculponeatin C (**14**) [13], and macrocalyxoformin E (**15**) [14]. The known compounds **5**–**15** were identified by comparison with authentic samples or literature data.

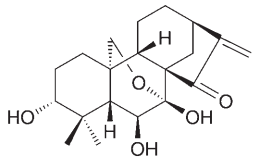
Results and Discussion. – Phyllostacin F (**1**), obtained as white amorphous powder, showed a pseudo-molecular ion peak $[M+Na]^+$ at *m/z* 387.1779 in its HR-ESI mass spectrum, corresponding to the molecular formula $C_{20}H_{28}O_6$. This was corroborated by



	R^1	R^2	R^3	R^4	R^5	R^6
1	H	OH	OH	H	=O	H
5	H	H	OH	OH	=O	H
6	H	H	AcO	H	AcO	H
7	H	H	OH	H	OH	H
8	OH	H	OH	H	=O	H
9	H	H	OH	H	=O	OH
16	H	H	OH	H	=O	H



	R^1	R^2	R^3	R^4
3	H	H	=O	β-CH_2OMe
4	H	α-OH	OH	$=CH_2$
10	H	H	=O	$=CH_2$
11	OH	H	=O	$=CH_2$
12	H	β-OH	=O	$=CH_2$



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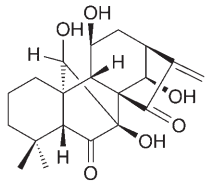

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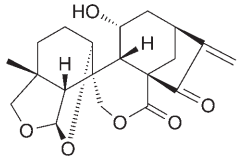

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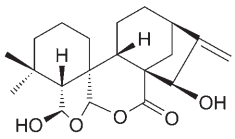

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the ^{13}C-NMR spectrum, which exhibited signals for the 20 C-atoms of the diterpene skeleton (*Table*). The presence of a five-membered ketone conjugated with an *exo*-methylene group in **1** was evident from the following data: UV (MeOH) 225 (3.99); IR (KBr) 1720 and 1648 cm^{-1}; ^{1}H-NMR δ(H) 6.27 and 5.49 (br. *s*, each 1 H); ^{13}C-NMR δ(C) 208.8 (*s*), 152.9 (*s*) and 119.5 (*t*). In addition, the ^{13}C-NMR data of compound **1** showed the characteristic signals of two Me groups (δ(C) 29.3 (C(18)) and 16.3 (C(19))), three CH groups (δ(C) 61.0 (C(5)), 52.1 (C(9)), and 43.9 (C(13))), three quaternary C-atoms (δ(C) 62.6 (C(8)), 40.3 (C(4)) and 36.4 (C(10))), a hemiketal quaternary C-atom (δ(C) 98.5 (C(7))), and an oxygenated CH_2 group (δ(C) 66.2 (*t*), δ(H) 4.24 and 3.97 (*d*, $J = 9.8$, each 1 H) attributed to C(20)/CH_2(20)), suggesting a 7β-hydroxy-7α,20-epoxy-*ent*-kaur-16-en-15-one diterpenoid skeleton typically found in *Isodon* plants, substituted by three OH groups, similar to longikaurin A (**16**) [15].

Comparison of the spectroscopic data of **1** and **16** revealed close similarities, and the only difference was that **1** had one more OH group. The additional OH group was positioned at C(3) due to the signals shifted to lower field at 28.1 (C(2)) and 40.3 (C(4)) in **1**, compared to those of compound **16** showing the corresponding signals at 17.3

Table. *^{13}C-NMR Data of Compounds* **1**–**4** *and* **16** (100 MHz, C_5D_5N, δ in ppm)[a])

Position	**1**	**2**	**3**	**4**	**16**
1	29.1 (*t*)	28.7 (*t*)	27.4 (*t*)	28.7 (*t*)	31.3 (*t*)
2	28.1 (*t*)	28.1 (*t*)	18.9 (*t*)	19.1 (*t*)	17.3 (*t*)
3	77.5 (*d*)	77.8 (*d*)	41.3 (*t*)	41.5 (*d*)	42.1 (*t*)
4	40.3 (*s*)	40.4 (*s*)	33.8 (*s*)	33.8 (*s*)	34.5 (*s*)
5	61.0 (*d*)	61.8 (*d*)	63.5 (*d*)	64.8 (*d*)	53.1 (*d*)
6	73.6 (*d*)	73.9 (*d*)	72.9 (*d*)	72.9 (*d*)	74.8 (*d*)
7	98.5 (*s*)	96.2 (*s*)	101.8 (*s*)	101.3 (*s*)	98.9 (*s*)
8	62.6 (*s*)	60.2 (*s*)	57.6 (*s*)	51.2 (*s*)	63.2 (*s*)
9	52.1 (*d*)	50.2 (*d*)	44.4 (*d*)	49.1 (*d*)	61.4 (*d*)
10	36.4 (*s*)	36.6 (*s*)	42.7 (*s*)	43.1 (*s*)	37.1 (*s*)
11	16.8 (*t*)	16.8 (*t*)	17.3 (*t*)	64.0 (*d*)	19.6 (*t*)
12	30.2 (*t*)	29.7 (*t*)	19.1 (*t*)	37.0 (*t*)	30.8 (*t*)
13	43.9 (*d*)	35.1 (*d*)	35.7 (*d*)	42.2 (*d*)	44.4 (*d*)
14	73.8 (*d*)	26.7 (*t*)	71.2 (*d*)	71.0 (*d*)	74.1 (*d*)
15	208.8 (*s*)	210.5 (*s*)	210.9 (*s*)	71.2 (*d*)	209.3 (*s*)
16	152.9 (*s*)	154.0 (*s*)	53.1 (*d*)	155.6 (*s*)	153.5 (*s*)
17	119.5 (*t*)	116.4 (*t*)	68.5 (*t*)	111.8 (*t*)	120.1 (*t*)
18	29.3 (*q*)	29.4 (*q*)	31.7 (*q*)	31.6 (*q*)	34.2 (*q*)
19	16.3 (*q*)	16.3 (*q*)	23.3 (*q*)	23.4 (*q*)	23.0 (*q*)
20	66.2 (*t*)	66.0 (*t*)	98.3 (*d*)	98.1 (*d*)	66.8 (*t*)
MeO			58.6 (*q*)		

[a]) The assignments were based on DEPT, HMQC, and HMBC experiments.

(C(2)) and 34.5 (C(4)). The HMBC correlations (*Fig. 1*) of H–C(3) (δ(H) 3.55 (*dd*, $J = 11.0, 3.5$)) with C(2), C(5) and C(19) confirmed the above assignment. The ROESY correlations (*Fig. 1*) of H_β–C(3) with H_β–C(5) and Me(18), of H_α–C(6) with Me(19) and of H_α–C(14) with H_b–C(20) ((δ(H) 3.97 (*d*, $J = 9.8$)) suggested that the substituents at C(3), C(6) and C(14) had α-, β-, and β-orientations, respectively. Therefore, compound **1** was elucidated as (3α,5β,6β,7β,9β,10α,13α,14β)-3,6,7,14-tetrahydroxy-7,20-epoxy-*ent*-kaur-16-en-15-one.

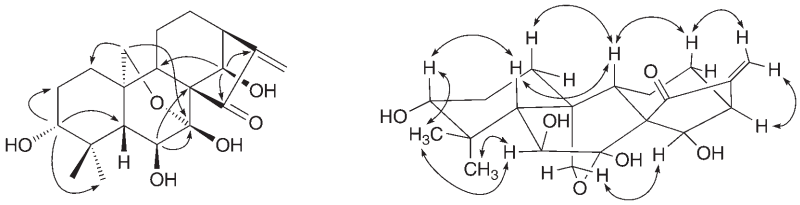

Fig. 1. *Selected HMBC* (H → C)*and ROESY* (H ↔ H) *correlations of* **1**

Phyllostacin G (**2**) has the molecular formula $C_{20}H_{28}O_5$, as established by its HR-ESI mass spectrum. The NMR data indicated that **2** was very similar to **1**, except for the substitution pattern at C(14), now being a CH_2-group (δ(C) 26.7 (*t*), δ(H) 2.45–2.49 and 2.26–2.28 (*m*, each 1 H)), instead of the former CH–O group. Moreover, the correlations in the ROESY experiment in **2** indicated that the corresponding

substituents in compound **2** had the same relative configurations as those in **1**. Thus, **2** was determined to be (3α,5β,6β,7β,9β,10α,13α)-3,6,7-trihydroxy-7,20-epoxy-*ent*-kaur-16-en-15-one.

Phyllostacin H (**3**), a white amorphous powder, has the molecular formula $C_{21}H_{30}O_6$, as established by HR-ESI mass spectrum. It showed no α,β-unsaturated ketone group absorption in its UV and IR spectra. On the basis of the characteristic signals of a hemiketal quaternary C-atom (δ(C) 101.8 (C(7))), and a significant oxygenated methine (δ(C) 98.3 (*d*), δ(H) 5.48 (br. *s*, 1 H) attributable to C(20)/H–C(20)), along with the structures of the compounds isolated from this plant at the same time, we assumed that **3** should to be a 7β-hydroxy-7α,20 : 14α,20-diepoxy-*ent*-kaurane diterpenoid, similar to xerophilusin B (**10**). The NMR spectra of **3** were identical to those of **10** except for the *D*-ring signals. The methine (δ(C) 53.1 (*d*), δ(H) 2.86–2.88 (*m*) assignable to C(16)/H–C(16)) and a $MeOCH_2$ group (δ(C) 58.6 (MeO) and 68.5 (C(17)); δ(H) 3.22 (MeO), 3.89 and 3.62–3.66 (CH_2(17))) in **3** replaced the *exo*-methylene group in **10**, as also confirmed by the HMBC spectrum (*Fig. 2*). The β-orientation of the $MeOCH_2$ group in **3** was deduced from the unusual upfield shift of δ(C) 19.1 (C(12)). The ROESY correlations of H_α–C(16) with H_α–C(13) further confirmed the above conclusion. The configuration of the remaining substituents in **3** was the same as in **10**, as observed in the ROESY spectra. Hence, **3** was determined to be (6β,7β,14α,16*R*)-6,7-dihydroxy-16-(methoxymethyl)-7,20 : 14,20-diepoxy-*ent*-kaur-15-one, and is most likely an artefact from the isolation (β-addition of MeOH to the enone system of **10**).

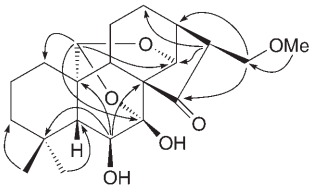

Fig. 2. *Selected HMBC correlations of* **3**

Phyllostacin I (**4**) was also determined to be a 7β-hydroxy-7α,20 : 14α,20-diepoxy-*ent*-kaurane diterpenoid by the analysis of its NMR data, and the molecular formula was $C_{20}H_{28}O_6$, as observed in the positive HR-ESI mass spectrum. Thus, it possessed seven degrees of unsaturation. This compound also showed no characteristic absorption bands above 220 nm in the UV spectrum, but showed the presence of an exocyclic CH_2 moiety (δ(C) 155.6 (*s*), 111.8 (*t*); δ(H) 5.54 and 5.36 (br. *s*, each 1 H)) in the NMR spectrum. Therefore, the CO group at C(15) must be absent in **4**. Careful analysis of 2D-NMR data led to the conclusion that the C(6), C(11) and C(15) positions were substituted by β-, α- and β-OH groups, respectively, on the basis of its HMBC correlations of H–C(6) with C(4), C(8) and C(10), of H–C(11) with C(8), C(10) and C(13), and of H–C(15) with C(9), C(14) and C(17), and its ROESY correlations of H_α–C(6) with Me(19), of H_β–C(11) with H_β–C(9) and of H_α–C(15) with H_α–C(13). Therefore, (6β,7β,11α,14α,15β)-6,7,11,15-tetrahydroxy-7,20 : 14,20-diepoxy-*ent*-kaur-16-en was assigned to **4**.

The cytotoxicities of compounds **1**, **2**, **7**, **10**, and **13** were tested against K562, and HepG2 cell lines using the method described in the literature [16]. Compound **10** was the most active against K562 and HepG2 cells with IC_{50} values of 0.05, and 0.18 μg/ml, respectively. Compounds **1**, **2**, and **13** showed less activity in these test systems, while compound **7** was completely inactive ($IC_{50} > 100$ μg/ml), which suggested that the cyclopentanone conjugated with an *exo*-methylene group is the decisive pharmacophore [17].

Experimental Part

General. Column chromatography (CC) on silica gel (SiO_2; 200–300 mesh, *Qingdao Marine Chemical Factory*, Qingdao, P. R. China), *Lichroprep RP-18* gel (40–63 μm, *Merck*, Darmstadt, Germany) and *MCI* gel (75–150 μm, *Mitsubishi Chemical Corporation*, Japan). Semipreparative HPLC: *Agilent 1100* apparatus equipped with a UV detector and a *Zorbax SB-C-18* column. Optical rotations: *Horiba SEPA-300* polarimeter. UV Spectra: *Shimadzu UV-2401A* spectrophotometer. IR Spectra: *Tenor27* spectrophotometer using KBr pellets. 1D- and 2D-NMR spectra: *Bruker AM-400* and *DRX-500* spectrometers with TMS as internal standard. The chemical shifts (δ) were expressed in ppm with reference to the solvent signals. MS Spectra: *VG Autospec-3000* spectrometer and a *Finnigan MAT 90* instrument.

Plant Material. The aerial parts of *I. phyllostachys* were collected in Lijiang County of Yunnan Province, P. R. China, in August 2005 and identified by Prof. *Xi-Wen Li*. A voucher specimen (KIB 05081958) was deposited in State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. The air-dried and powdered aerial parts of *I. phyllostachys* (3.0 kg) were extracted with acetone (3 × 15 l, 24 h) at r.t. and filtered. The filtrate was evaporated to give a residue, which was suspended in H_2O (2.5 l) and then extracted with AcOEt (3 × 3 l). The AcOEt extract (88.0 g) was decolorized on *MCI* gel, eluted with 90% MeOH/H_2O, to yield a yellowish gum (75.0 g). The gum was subjected to CC over SiO_2 (200–300 mesh), eluted with $CHCl_3$/Me_2CO (1:0 → 0:1 gradient system), to obtain five fractions (*Frs. A–E*). Furthermore, compound **5** (105 mg) was obtained by recrystallization in MeOH from *Fr. B* (15.0 g). *Fr. A* (20.0 g) was applied to SiO_2 and eluted with a petroleum ether (PE)/PrOH (15:1 → 3:1) gradient to provide four subfractions (*Frs. A_1–A_4*). *Fr. A_2* (8.0 g) was further separated by *RP-18* (35% → 75% MeOH/H_2O gradient system) and normal-phase SiO_2 (PE/PrOH, 10:1) to yield **15** (7.0 mg), **7** (6.0 mg), **12** (25.0 mg), and **13** (25.0 mg), respectively. *Fr. A_3* (5.0 g) was purified over SiO_2 ($CHCl_3$/MeOH, 25:1), then by preparative HPLC with 55% MeOH/H_2O, to yield **11** (20.0 mg). *Fr. B* (15.0 g) afforded **3** (4.0 mg), **6** (15.0 mg), and **10** (6.0 mg) by repeated SiO_2 CC eluted with PE/AcOEt (3:2), and provided **8** (25.0 mg), and **9** (15.0 mg) by following semiprep. HPLC (47% MeOH/H_2O) purification. *Fr. C* (8.0 g) afforded **2** (5.0 mg) and **4** (4.0 mg). *Fr. D* (14.0 g) was passed through *RP-18* to yield two main subfractions (*Fr. D_1* and *D_2*), eluted with 40% → 85% gradient system MeOH/H_2O. *Fr. D_1* was subjected to SiO_2 CC with PE/Me_2CO to yield **1** (5.0 mg). *Fr. D_2* was purified by SiO_2 CC eluted with $CHCl_3$/MeOH 20:1, then followed by semipreparative HPLC (38% MeOH/H_2O) to yield **14** (10.0 mg).

Cytotoxicity Bioassay. The cytotoxicity of the compounds against suspended tumor cells was determined by the trypan blue exclusion method, and against adherent cells by sulforhodamine B (SRB) assay. Cells were plated in a 96-well plate 24 h before treatment and continuously exposed to different concentrations of the compounds for 72 h. After treatments, cells were counted (suspended cells) or fixed and stained with SRB (adherent cells) as described in the literature [16].

Phyllostacin F (*=(3α,5β,6β,7β,9β,10α,13α,14β)-3,6,7,14-Tetrahydroxy-7,20-epoxy*-ent-*kaur-16-en-15-one*; **1**). White amorphous powder. $[\alpha]_D^{17.7} = -82.5$ ($c = 1.09$, C_5H_5N). UV (MeOH): 225 (3.99). IR (KBr): 3425, 2928, 1720, 1648, 1370, 1089. ^{1}H-NMR (400 MHz, (D_5)pyridine): 6.27 (br. *s*, H_a–C(17)); 5.49 (br. *s*, H_b–C(17)); 5.03 (br. *s*, H_α–C(14)); 4.37–4.39 (*m*, H_α–C(6)); 4.24 (*d*, $J = 9.8$, H_a–C(20)); 3.97 (*d*, $J = 9.8$, H_b–C(20)); 3.55 (*dd*, $J = 11.0, 3.5$, H_β–C(3)); 3.16–3.18 (*m*, H_α–C(13)); 2.31–2.35 (*m*,

H_α–C(12)); 1.75–1.77 (*m*, H_β–C(2)); 1.67–1.68 (*m*, H_α–C(2)); 1.64–1.66 (overlapped, H_β–C(9), H_α–C(11)); 1.59 (*s*, Me(18)); 1.51–1.55 (overlapped, H_β–C(5), H_β–C(12)); 1.32 (*s*, Me(19)); 1.20–1.24 (overlapped, H_α–C(1), H_β–C(11)); 1.05–1.07 (*m*, H_β–C(1)). ^{13}C-NMR: *Table*. FAB-MS (pos.): 365 ($[M+H]^+$). HR-ESI-MS (pos.): 387.1779 ($[M+Na]^+$, $C_{20}H_{28}NaO_6^+$; calc. 387.1783).

Phyllostacin G (=*(3α,5β,6β,7β,9β,10α,13α)-3,6,7-Trihydroxy-7,20-epoxy*-ent-*kaur-16-en-15-one*; **2**). White amorphous powder. $[\alpha]_D^{17.5} = -122.4$ ($c = 0.43$, C_5H_5N). UV (MeOH): 239 (3.68). IR (KBr): 3416, 3273, 2946, 1700, 1640, 1451, 1080. ^{1}H-NMR (500 MHz, (D_5)-pyridine): 5.98 (br. *s*, H_a–C(17)); 5.28 (br. *s*, H_b–C(17)); 4.36–4.40 (*m*, H_α–C(6)); 4.17 (*d*, $J = 9.8$, H_a–C(20)); 3.94 (*d*, $J = 9.8$, H_b–C(20)); 3.54–3.56 (*m*, H_β–C(3)); 2.88–2.90 (*m*, H_α–C(13)); 2.45–2.49 (*m*, H_α–C(14)); 2.26–2.28 (*m*, H_β–C(14)); 2.10–2.14 (*m*, H_α–C(12)); 1.76–1.78 (*m*, H_β–C(2)); 1.64–1.66 (*m*, H_α–C(2)); 1.59 (*s*, Me(18)); 1.54–1.56 (*m*, H_β–C(5)); 1.50–1.54 (overlapped, H_β–C(9), H_α–C(11)); 1.31 (*s*, Me(19)); 1.25–1.27 (*m*, H_α–C(1)); 1.19–1.23 (overlapped, H_β–C(11), H_β–C(12)); 1.06–1.08 (*m*, H_β–C(1)). ^{13}C-NMR: *Table*. ESI-MS (pos.): 371 ($[M+Na]^+$). HR-ESI-MS (pos.): 371.1830 ($[M+Na]^+$, $C_{20}H_{28}NaO_5^+$, calc. 371.1834).

Phyllostacin H (=*(6β,7β,14α,16R)-6,7-Dihydroxy-16-(methoxymethyl)-7,20 : 14,20-diepoxy*-ent-*kaur-15-one*; **3**). White amorphous powder. $[\alpha]_D^{18.1} = -109.8$ ($c = 0.54$, C_5H_5N). UV (MeOH): 201 (3.41). IR (KBr): 3431, 2925, 1733, 1090, 974. ^{1}H-NMR (400 MHz, (D_5)pyridine): 5.48 (br. *s*, H–C(20)); 5.03 (*d*, $J = 4.7$, H_β–C(14)); 4.19 (br. *s*, H_α–C(6)); 3.89 (*dd*, $J = 10.0$, 4.0, H_a–C(17)); 3.62–3.66 (*m*, H_b–C(17)); 3.22 (*s*, MeO), 2.86–2.88 (overlapped, H_α–C(13), H_α–C(16)); 2.64 (*d*, $J = 4.5$, H_β–C(9)); 2.09–2.11 (*m*, H_α–C(12)); 1.64–1.68 (overlapped, H_α–C(1), H_α–C(11)); 1.60–1.62 (overlapped, H_β–C(2), H_β–C(12)); 1.48 (br. *s*, H_β–C(5)); 1.41–1.45 (overlapped, H_α–C(2), H_β–C(11)); 1.34–1.36 (*m*, H_β–C(3)); 1.09–1.11 (*m*, H_α–C(3)); 1.02 (*s*, Me(18)); 0.99–1.01 (*m*, H_β–C(1)); 0.89 (*s*, Me(19)). ^{13}C-NMR: *Table*. FAB-MS (pos.): 379 ($[M+H]^+$). HR-ESI-MS (pos.): 401.1948 ($[M+Na]^+$, $C_{21}H_{30}NaO_6^+$, calc. 401.1940).

Phyllostacin I (=*(6β,7β,11α,14α,15β)-6,7,11,15-Tetrahydroxy-7,20 : 14,20-diepoxy*-ent-*kaur-16-en*; **4**). White amorphous powder. $[\alpha]_D^{18.1} = -82.0$ ($c = 0.62$, C_5H_5N). UV (MeOH): 205 (3.95). IR (KBr): 3387, 2931, 1632, 1430, 1088, 1008. ^{1}H-NMR (400 MHz, (D_5)pyridine): 5.54 (br. *s*, H_a–C(17)); 5.36 (br. *s*, H_b–C(17)); 5.41–5.45 (overlapped, H_α–C(15), H–C(20)); 4.69 (*d*, $J = 5.9$, H_β–C(14)); 4.27–4.29 (*m*, H_β–C(11)); 4.20 (br. *s*, H_α–C(6)); 3.02 (br. *s*, H_β–C(9)); 2.94 (br. *s*, H_α–C(13)); 2.59–2.61 (*m*, H_α–C(12)); 2.05–2.07 (*m*, H_β–C(12)); 1.69–1.71 (*m*, H_α–C(1)); 1.66 (br. *s*, H_β–C(5)); 1.48–1.52 (*m*, H_β–C(2)); 1.42–1.44 (*m*, H_α–C(2)); 1.32–1.34 (*m*, H_β–C(3)); 1.21–1.25 (*m*, H_β–C(1)); 1.09–1.11 (*m*, H_α–C(3)); 1.00 (*s*, Me(18)); 0.89 (*s*, Me(19)). ^{13}C-NMR: *Table*. FAB-MS (pos.): 365 ($[M+H]^+$). HR-ESI-MS (pos.): 387.1794 ($[M+Na]^+$, $C_{20}H_{28}NaO_6^+$; calc. 387.1783).

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