Structure Elucidation of Two New Diterpenoids from *Isodon phyllostachys*: Phyllostacins A and B

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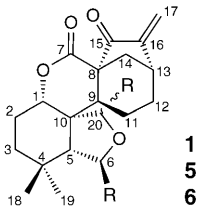
Two new *ent*-kaurane-derived diterpene derivatives, phyllostacins A (**1**) and B (**2**), were isolated from the aerial parts of *Isodon phyllostachy*s, together with two known compounds, irroratin A (**3**) and serrin B (**4**). Both **1** and **2** were found to be present as diastereoisomers. In the case of **1**, the corresponding diastereoisomeric diacetates **5** and **6** were prepared and separated. The structures of the new compounds were elucidated by extensive 1D- and 2D-NMR spectroscopic methods, in combination with MS experiments. In (D_5)pyridine solution, the two epimers of **1** are present in equal amounts, but in $CDCl_3$ or CD_3OD, the (*S*)-epimer predominates in the mixture of hemiacetals.

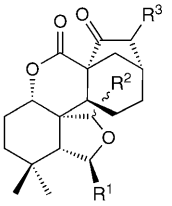
Introduction. – The genus *Isodon* (Labiatae) comprises 150 species, of which more than 100 are distributed in China. In previous studies, *ca*. 650 diterpenoids, including kauranoids, abietanoids, labdanoids, pimaranoids, isopimaranoids, gibberellanoids, and clerodanoids, have been isolated from *Isodon* within the past 30 years [1–3]. *Isodon* diterpenoids continue to intrigue investigators because of their structural complexity, chemical diversity, and biological activities. *Isodon phyllostachys* (DIELS) KUDO is a perennial plant distributed throughout the northwest district of Yunnan Province, China, and is used as an antiphlogistic and antibiotic agent by the local inhabitants. In previous investigations, some *ent*-kauranoids such as phyllostachysins A–C [4–6], and sculponeatins B and C [6] have been reported from this plant.

In our ongoing search for novel bioactive diterpenoids from *Isodon* plants, we re-investigated the chemical constituents of *I. phyllostachys*, collected in Zhongdian County, Yunnan. In this paper, we report the isolation and characterization of two new constituents: phyllostacins A (**1**) and B (**2**), together with two known compounds, irroratin A (**3**) [7] and serrin B (**4**) [8]. Their structures were elucidated by extensive 1D- and 2D-NMR spectroscopic methods, and by chemical derivatization of **1** to the corresponding diacetates **5** and **6**.

Results and Discussion. – The ESI mass spectrum of **1** revealed the $[M+Na]^+$ ion peak at *m*/*z* 385, corresponding to the molecular formula $C_{20}H_{26}O_6$. Although **1** displayed a single spot on TLC (silica gel) in different solvent systems, its ^{13}C-NMR data revealed 20 pairs of signals. Therefore, **1** was expected to be a mixture of two structurally closely related diterpenoids. This hypothesis was rationalized through the sepa-



1 R = OH
5 R = AcO, (20*R*)
6 R = AcO, (20*S*)



	R^1	R^2	R^3
2	OH	OH	α-Me
3	MeO	OH	α-Me
4	MeO	OH	$=CH_2$
7	OH	H	$=CH_2$

ration and identification of two diastereoisomeric compounds upon treatment of **1** with Ac_2O/pyridine. The resulting diacetates **5** and **6** could be identified by MS and NMR-spectroscopic means (see below). From these data, the structure of phyllostacin A (**1**) was elucidated as 6β,20*R*/*S*-dihydroxy-6,7-seco-6,20-epoxy-1α,7-olide-*ent*-kaur-16-en-15-one[1]).

(20*R*)-phyllostacin A diacetate (**5**), obtained as a colorless amorphous powder, exhibited the molecular-ion peak at *m*/*z* 446 in the EI mass spectrum, consistent with the molecular formula $C_{24}H_{30}O_8$, as corroborated by the NMR spectra. The ^{13}C-NMR (DEPT) spectrum of **5** (*Table*) exhibited 24 signals: two Me, six CH_2 (including an olefinic one), six CH (including three oxygenated ones), a lactone C=O group, four quaternary C-atoms, an α,β-unsaturated C=O group, and two pairs of AcO signals at δ(C) 169.2 (*s*) and 20.9 (*q*), and 168.3 (*s*) and 20.8 (*q*), respectively. Considering the structures of diterpenoids previously isolated from the genus *Isodon* [1], along with one characteristic lactone-type C=O signal at δ(C) 170.8 (*s*) assignable to C(7), and three oxygenated CH [δ(C) 75.5 (*d*, C(1)), δ(H) 4.80 (*m*, H–C(1)); δ(C) 100.9 (*d*, C(6)), δ(H) 6.63 (br. *s*, H–C(6); δ(C) 101.8 (*d*, C(20)), δ(H) 6.89 (br. *s*, H–C(20)], compound **5** was assigned an *ent*-kauranoid structure[1]) similar to that of isodocarpin (**7**) [9] [10]. The prominent features distinguishing **5** from **7** were the presence of two additional AcO groups at C(6) and C(20) in **5**, and the replacement of the oxygenated CH_2 at C(20) in **7** [δ(C) 73.9 (*t*), δ(H) 4.06, 3.99 (*AB*-type *d*, *J* = 9.4, H–C(20), 1 H each)] by the oxygenated H–C(20) in **5**. On examination of the HMQC and HMBC spectra of **5** (*Fig. 1*), one AcO group at δ(C) 169.2 (*s*) (δ(H) 20.9 (*q*)) was located at C(6) based on the HMBC correlation with H–C(6); the other AcO group was located at C(20) based on its HMBC correlations with H–C(20).

The observed ROESY correlations from H–C(1) to both H–C(14) and H–C(5), and from H–C(6) to the α-oriented 1-Me group and to H–C(13a), established that the substituents at C(1) and C(6) were in α- and β-orientation, respectively (*Fig. 1*). The significant ROE between H–C(9) at δ(H) 2.41 and H–C(20) in **5** pointed to the (20*R*)-configuration.

The diacetate **6**, obtained as a colorless, amorphous powder, had the molecular formula $C_{24}H_{30}O_8$ (just as **5**), as determined by EI-MS and NMR experiments. Comparison of the ^{1}H- and ^{13}C-NMR spectra of **6** with those of **5**, along with careful inspection of the corresponding 2D-NMR data of **6**, indicated that the constitution of **6** was the same as that of **5**. This information, in combination with the observed ROESY correlations from H–C(1) to both H–C(14) and H–C(5), and from H–C(6) to both the α-oriented

[1]) Arbitrary atom numbering. For systematic names, see the *Exper. Part*.

Table. *^{13}C-NMR Data for Compounds* **1**, **2**, **5**, *and* **6**. At 100 MHz, in C_5D_5N; δ in ppm. Assignments are based on DEPT, HMQC, HMBC, and ROESY spectra.

Atom[1])	(11*S*)-**1**	(11*R*)-**1**	(11*S*)-**2**	(11*R*)-**2**	**5**	**6**
C(1)	76.3 (*d*)	77.5 (*d*)	76.5 (*d*)	77.3 (*d*)	75.5 (*d*)	75.4 (*d*)
C(2)	24.1 (*t*)	25.0 (*t*)	23.5 (*t*)	24.9 (*t*)	24.6 (*t*)	23.4 (*t*)
C(3)	37.6 (*t*)	38.3 (*t*)	37.5 (*t*)	38.1 (*t*)	37.2 (*t*)	36.9 (*t*)
C(4)	31.6 (*s*)	31.6 (*s*)	31.4 (*s*)	31.5 (*s*)	31.4 (*s*)	31.5 (*s*)
C(5)	55.3 (*d*)	54.7 (*d*)	55.0 (*d*)	54.3 (*d*)	52.7 (*d*)	53.6 (*d*)
C(6)	98.6 (*d*)	100.9 (*d*)	98.2 (*d*)	100.7 (*d*)	100.9 (*d*)	98.6 (*d*)
C(7)	172.6 (*s*)	172.0 (*s*)	173.0 (*s*)	172.6 (*s*)	170.8 (*s*)	171.4 (*s*)
C(8)	51.0 (*s*)	57.1 (*s*)	55.8 (*s*)	56.6 (*s*)	56.6 (*s*)	55.6 (*s*)
C(9)	38.4 (*d*)	45.3 (*d*)	38.9 (*d*)	45.7 (*d*)	44.9 (*d*)	38.8 (*d*)
C(10)	51.0 (*s*)	52.4 (*s*)	50.0 (*s*)	51.2 (*s*)	51.5 (*s*)	50.3 (*s*)
C(11)	20.8 (*t*)	19.4 (*t*)	19.1 (*t*)	18.8 (*t*)	19.5 (*t*)	20.9 (*t*)
C(12)	29.8 (*t*)	29.9 (*t*)	19.7 (*t*)	19.2 (*t*)	29.8 (*t*)	29.4 (*t*)
C(13)	34.7 (*d*)	35.3 (*d*)	32.2 (*d*)	32.7 (*d*)	35.2 (*d*)	34.6 (*d*)
C(14)	33.2 (*t*)	33.1 (*t*)	35.0 (*t*)	34.7 (*t*)	33.0 (*t*)	32.8 (*t*)
C(15)	197.7 (*s*)	201.0 (*s*)	212.8 (*s*)	215.4 (*s*)	200.1 (*s*)	198.8 (*s*)
C(16)	152.4 (*s*)	151.5 (*s*)	49.6 (*d*)	49.2 (*d*)	151.0 (*s*)	151.8 (*s*)
C(17)	115.5 (*t*)	117.5 (*t*)	10.4 (*q*)	10.5 (*q*)	118.3 (*t*)	116.4 (*t*)
C(18)	32.8 (*q*)	34.0 (*q*)	32.7 (*q*)	33.8 (*q*)	33.8 (*q*)	32.4 (*q*)
C(19)	23.5 (*q*)	23.3 (*q*)	23.4 (*q*)	23.1 (*q*)	22.2 (*q*)	23.2 (*q*)
C(20)	101.0 (*d*)	104.6 (*d*)	101.2 (*d*)	104.7 (*d*)	101.8 (*d*)	98.8 (*d*)
6-AcO					169.2 (*s*)	170.6 (*s*)
					20.9 (*q*)	21.3 (*q*)
20-AcO					168.3 (*s*)	169.4 (*s*)
					20.8 (*q*)	20.9 (*q*)

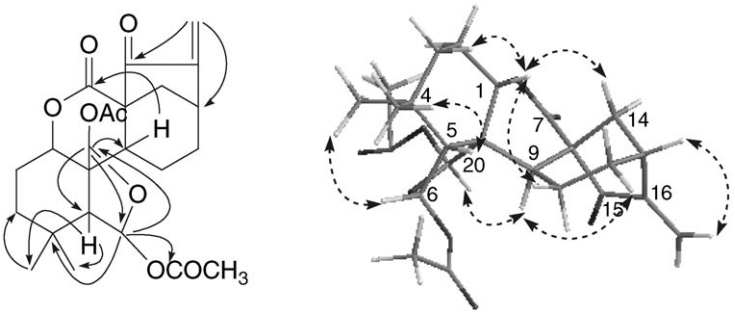


Fig. 1. *Key HMBC and ROESY correlations for* **5**[1])

19-Me group and H–C(5) established the same configurations at C(1) and C(6) as in **5** (*Fig. 2*)[1]). The significant ROESY cross-peak between the α-oriented 19-Me group at δ(H) 0.99 and H–C(20) in **6** was consistent with the (20*S*)-configuration. Therefore, compound **6** was identified as the C(20)-epimer of **5**.

The upfield shift of C(9) (δ(C) 38.4) in (20*S*)-**1** compared to (20*R*)-**1** (δ(C) 45.3) was attributed to the 'γ-gauche steric compression' between 20-OH and H–C(9) [11] (*Fig. 3*)[1]). The lowfield shift of the α-oriented 19-Me group (δ(H) 1.51) in (20*R*)-**1** compared

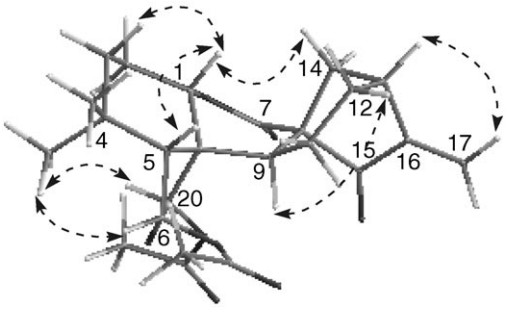


Fig. 2. *Key ROESY correlations for* **6**

to that in (20*S*)-**1** (δ(H) 1.00) is due to the *Van der Waals* force between this Me group and the 20-OH group. These observations further corroborated the structural features of **1**.

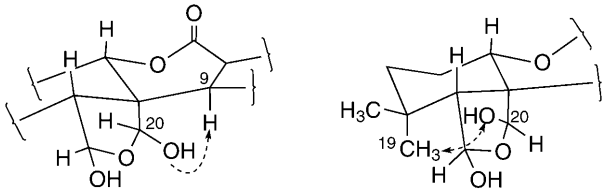


Fig. 3. *'γ-Steric compression effect' in the (20*S*)-epimer of* **1** (left) vs. Van der Waals *interaction in the corresponding (20*R*)-epimer* (right)[1])

Compound **2**, named phyllostacin B, was also obtained as a pair of C(20)-epimers. Careful inspection of the 1D- and 2D-NMR as well as IR spectra of **2** indicated that the prominent difference between **1** and **2** was the replacement of the methylidene (=CH_2) moiety in **1** by a Me group in **2**. This was further confirmed by HMBC correlations of the Me(17) group (δ(H) 0.93 (*d*, *J* = 6.61 Hz)) with C(16) (δ(C) 49.2), C(15) (215.4), and C(13) (32.7)[1]). The same was true for the only slightly different resonances of the corresponding epimer. The α-orientation of the Me(17) group was derived from its ROESY correlations with both H–C(13) and H_α–C(12). Accordingly, compound **2** was identified as 6β-20(*R*/*S*)-dihydroxy-16(*S*)-methyl-6,7-seco-6,20-epoxy-1α,7-olide-*ent*-kaur-15-one[1]).

Two well-resolved sets of signals of equal intensity were observed in both the ^{1}H- and ^{13}C-NMR spectra of **1** and **2**, when recorded in (D_5)pyridine. This suggests that the two epimers exist in equal population in this solvent. However, acetylation of **1** furnished a 4:1 mixture of **6** to **5**. We ascribe this rate-difference to steric hindrance around the 20-OH group of the (20*R*)-configured epimer **5**. To obtain more-detailed insight into the solution structures of **1** and **2**, their ^{1}H-NMR spectra were also recorded in other solvents. Based on the integration data, the (20*S*)/(20*R*) ratios for **1** and **2** were 3:2 and 4:1 in CD_3OD and $CDCl_3$, respectively. Hence, the composition of **1** and **2** in solution is very sensitive to the solvent used.

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Experimental Part

General. Column chromatography (CC): silica gel (100–200 or 200–300 mesh). TLC: silica gel GF_{254}. Semiprep. reverse-phase (RP) HPLC was performed on an *Agilent 1100* liquid chromatograph, with a *Zorbax SB-C18* column. UV Spectra: *Shimadzu 210A* double-beam spectrophotometer; λ_{max} (log ε) in nm. Optical rotations: *Horiba SEPA-300* polarimeter. IR Spectra: *Bio-Rad FTS-135* spectrometer, with KBr pellets; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker AM-400* and *DRX-500* spectrometers, in (D_5)pyridine, δ in ppm rel. to Me_4Si, *J* in Hz. MS: *VG Autospec-3000* magnetic-sector instrument; in *m/z* (rel. %).

Plant Material. Isodon phyllostachys was collected in Zhongdian County, Yunnan Province, P. R. China, in August 2004, and was identified by Prof. *Zhong-Wen Lin*. A voucher specimen (KIB-2004-084 Lin) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, P. R. China.

Extraction and Isolation. The dried and finely powdered aerial parts of *I. phyllostachys* (4.0 kg) were extracted with acetone (3×10 l) at r.t. for 3 d. The resulting extract (dry weight 102 g) was partitioned between AcOEt and H_2O. The AcOEt-soluble part (68 g) was subjected to CC (100–200 mesh, 1.5 kg) eluting with $CHCl_3/Me_2CO$ 1:0 → 0:1: fractions *Fr. 1–4*. *Fr. 2* (2.05 g) was re-subjected to CC (SiO_2; $CHCl_3$/MeOH 20:1) to afford a colorless residue, which was recrystallized from $CHCl_3$ to give **2** (4 mg). *Fr. 3* (10.5 g) was purified by CC (SiO_2; petroleum ether/Me_2CO 3:2) and semiprep. RP-HPLC to afford **1** (55 mg), **3** (25 mg), and **4** (20 mg).

Phyllostacin A (=*(3a*S,*5a*S,*8*R,*10a*S,*10b*R,*11*R/S,*13*R,*13a*R*)-Decahydro-11,13-dihydroxy-1,1-dimethyl-7-methylidene-5*H*-5a,8-methano-11*H*-cyclohepta[*c*]furo[3,4-*e*][1]benzopyran-5,6(7*H*)-dione*; **1**). Colorless, amorphous powder. UV (MeOH): 236 (3.80). $[\alpha]_D^{19.3} = -4.78$ ($c = 0.65$, C_5H_5N). IR (KBr): 3396, 3224, 2936, 2879, 1714, 1649, 1499, 1168, 1064, 912. ^1H-NMR (500 MHz, (D_5)pyridine; (20*S*)-epimer)[1]): 1.00 (*s*, Me(19)); 1.03 (*s*, Me(18)); 1.42–1.45 (*m*, H_β–C(12)); 1.55–1.60 (*m*, CH_2(3)); 1.67–1.70 (*m*, CH_2(11)); 1.91–1.93 (*m*, CH_2(2)); 1.97 (*dd*, *J* = 4.3, 11.8, H_α–C(14)); 2.27–2.30 (*m*, H_α–C(12)); 2.31 (br. *s*, H–C(5)); 2.57 (br. *d*, *J* = 11.8, H_β–C(14)); 2.90 (*dd*, *J* = 4.3, 9.4, H–C(13)); 3.54 (*dd*, *J* = 5.8, 13.6, H–C(9)); 4.74–4.78 (*m*, H–C(1)); 5.21 (br. *s*, 1 H of CH_2(17)); 5.58 (br. *s*, H–C(6)); 5.93 (br. *s*, 1 H of CH_2(17)); 6.23 (*s*, H–C(20)). ^1H-NMR (500 MHz, (D_5)pyridine; (20*R*)-epimer)[1]): 1.13 (*s*, Me(18)); 1.51 (*s*, Me(19)); 1.36–1.39 (*m*, CH_2(3)); 1.42–1.45 (*m*, H_β–C(12)); 1.67–1.70 (*m*, CH_2(11)); 1.91–1.93 (*m*, CH_2(2)); 2.08 (*dd*, *J* = 4.5, 11.8, H_α–C(14)); 2.26 (br. *s*, H–C(5)); 2.27–2.30 (*m*, H_α–C(12)); 2.65 (br. *d*, *J* = 11.8, H_β–C(14)); 2.78 (*dd*, *J* = 5.8, 13.1, H–C(9)); 2.95 (*dd*, *J* = 4.5, 9.4, H–C(13)); 4.74–4.78 (*m*, H–C(1)); 5.29 (br. *s*, 1 H of CH_2(17)); 5.92 (br. *s*, 1 H of CH_2(17)); 6.04 (br. *s*, H–C(6)); 6.28 (*d*, *J* = 3.3, H–C(20)). ^{13}C-NMR: see *Table*. ESI-MS (pos.): 747 ($[2M+Na]^+$), 385 ($[M+Na]^+$), 367 ($[M+Na-H_2O]^+$). HR-ESI-MS: 385.1628 ($[M+Na]^+$, $C_{20}H_{26}NaO_6^+$; calc. 385.1627).

Phyllostacin B (=*(3a*S,*5a*S,*8*R,*10a*S,*10b*R,*11*R/S,*13*R,*13a*R*)-Decahydro-11,13-dihydroxy-1,1,7-trimethyl-5*H*-5a,8-methano-11*H*-cyclohepta[*c*]furo[3,4-*e*][1]benzopyran-5,6(7*H*)-dione*; **2**). Colorless, amorphous powder. UV (MeOH): 230 (3.11). $[\alpha]_D^{23.1} = -0.196$ ($c = 0.99$, C_5H_5N). IR (KBr): 3462, 3376, 2950, 2876, 1754, 1703, 1455, 1260, 1134, 945. ^1H-NMR (500 MHz, (D_5)pyridine; (20*S*)-epimer)[1]): 0.91 (*d*, *J* = 6.4, Me(17)); 0.98 (*s*, Me(19)); 1.00 (*s*, Me(18)); 1.32–1.37 (*m*, C(3)); 1.40–1.45 (*m*, H_β–C(12)); 1.72–1.79 (*m*, H_α–C(12)); 1.86–1.88 (*m*, CH_2(2)); 1.86–1.88 (*m*, CH_2(14)); 2.12–2.19 (*m*, CH_2(11)); 2.26 (br. *s*, H–C(5)); 2.32 (*dd*, *J* = 4.5, 9.4, H–C(13)); 2.33 (br. *s*, H_β–C(16)); 3.30 (*dd*, *J* = 5.8, 13.1, H–C(9)); 4.65–4.72 (*m*, H–C(1)); 5.55 (br. *s*, H–C(6)); 6.21 (br. *s*, H–C(20)). ^1H-NMR (500 MHz, (D_5)pyridine; (20*R*)-epimer)[1]): 0.93 (*d*, *J* = 6.6, Me(17)); 1.11 (*s*, Me(18)); 1.27–1.32 (*m*, CH_2(3)); 1.40–1.45 (*m*, H_β–C(12)); 1.51 (*s*, Me(19)); 1.72–1.79 (*m*, H_α–C(12)); 2.12–2.19 (*m*, CH_2(11)); 2.22 (br. *s*, H–C(5)); 2.37 (*dd*, *J* = 4.3, 9.4, H–C(13)); 2.56 (br. *s*, H_β–C(16)); 2.57 (br. *d*, *J* = 11.8, H_β–C(14)); 2.57–2.59 (*m*, H–C(9)); 2.63 (*dd*, *J* = 4.3, 11.8, H_α–C(14)); 2.81–2.85 (*m*, CH_2(2)); 4.65–4.72

(*m*, H–C(1)); 6.02 (br. *s*, H–C(6)); 6.29 (*d*, *J* = 4.0, H–C(20)). ^{13}C-NMR: see *Table*. FAB-MS (pos.): 729 ($[2M+H]^+$), 365 ($[M+H]^+$), 347 ($[M+H-H_2O]^+$). HR-FAB-MS: 387.1785 ($[M+Na]^+$, $C_{20}H_{28}NaO_6^+$; calc. 387.1783).

Acetylation of **1**. To a soln. of **1** (25 mg) in anh. pyridine (15 ml) was added Ac_2O (0.25 ml), and the mixture was stirred for 36 h at r.t. Then, 10% aq. HCl (60 ml) was added, and the mixture was extracted with AcOEt (4 × 50 ml). The org. layer was washed with H_2O (3 × 50 ml), dried (Na_2SO_4), and evaporated. The crude residue was purified by CC (SiO_2; $CHCl_3$/Me_2CO 9 : 1) to afford a mixture of the diacetates **5** and **6**, which were separated by semiprep. PR-HPLC, yielding 2 mg of pure **5** and 8 mg of pure **6**.

*(20*R*)-Phyllostacin A Diacetate* (**5**). Colorless, amorphous powder. ^{1}H-NMR (500 MHz, (D_5)pyridine)[1]: 1.19 (*s*, Me(19)); 1.23 (*s*, Me(18)); 1.41–1.43 (*m*, H_β–C(3)); 1.50–1.53 (*m*, H_β–C(12)); 1.55–1.58 (*m*, H_α–C(3)); 1.81–1.84 (*m*, CH_2(11)); 1.87 (*s*, 20-AcO); 1.94–1.96 (*m*, CH_2(2)); 2.02 (*s*, 6-AcO); 2.10 (*dd*, *J* = 3.7, 12.0, H_α–C(14)); 2.27 (br. *s*, H–C(5)); 2.38–2.43 (*m*, H–C(9)); 2.38–2.43 (*m*, H_α–C(12)); 2.75 (br. *d*, *J* = 12.0, H_β–C(14)); 3.06–3.09 (*m*, H–C(13)); 4.78–4.81 (*m*, H–C(1)); 5.64 (br. *s*, 1 H of CH_2(17)); 6.06 (br. *s*, 1 H of CH_2(17)); 6.63 (br. *s*, H–C(6)); 6.89 (br. *s*, H–C(20)). ^{13}C-NMR: see *Table* . EI-MS: 446 (3, M^+), 404 (40 $[M-COCH_2]^+$), 362 (22), 298 (77), 270 (100), 255 (70), 133 (34), 105 (54), 91 (53).

*(20*S*)-Phyllostacin A Diacetate* (**6**). Colorless, amorphous powder. ^{1}H-NMR (500 MHz, (D_5)pyridine)[1]: 0.99 (*s*, Me(19)); 1.02 (br. *s*, Me(18)); 1.22–1.28 (*m*, H_β–C(3)); 1.32–1.37 (*m*, H_α–C(3)); 1.48–1.52 (*m*, H_β–C(12)); 1.74–1.76 (*m*, CH_2(11)); 1.83 (*s*, 20-AcO); 1.86–1.87 (*m*, CH_2(2)); 1.94 (*dd*, *J* = 4.1, 12.0, H_α–C(14)); 2.33 (br. *s*, H–C(5)); 2.33–2.37 (*m*, H_α–C(12)); 2.57 (*s*, 6-AcO); 2.64 (br. *d*, *J* = 12.0, H_β–C(14)); 2.98–3.02 (*m*, H–C(9)); 2.98–3.02 (*m*, H–C(13)); 4.76 (*t*-like, *J* = 8.8, H–C(1)); 5.39 (br. *s*, 1 H of CH_2(17)); 6.06 (br. *s*, 1 H of CH_2(17)); 6.29 (br. *s*, H–C(6)); 6.94 (br. *s*, H–C(20)). ^{13}C-NMR: see *Table*. EI-MS: 446 (3, M^+), 404 (40, $[M - COCH_2]^+$), 362 (22), 298 (77), 270 (100), 255 (70), 133 (34), 105 (54), 91 (53).

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