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Hypophyllins A–D, Labdane-Type Diterpenoids with Vasorelaxant Activity from *Hypoestes phyllostachya* "Rosea"

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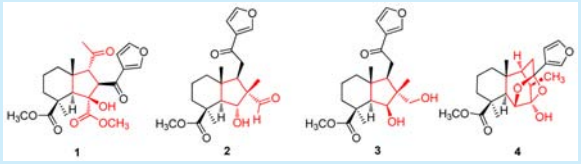
Supporting Information

ABSTRACT: Three rearranged labdane-type diterpenoids, hypophyllins A–C (**1**–**3**), and a caged labdane diterpenoid possessing a 8,9-dioxatricyclic[4.2.1.1^{3,7}]decane moiety, hypophyllin D (**4**), as well as two new biogenetically related diterpernoids, hypophyllins E (**5**) and F (**6**), were isolated from the aerial parts of *Hypoestes phyllostachya* "Rosea". The absolute configurations of **1**–**4** were determined by X-ray diffraction analysis. The plausible biogenetic pathway for **1**–**4** was also proposed. Compounds **4** and **5** showed potent vasorelaxant activity on endothelium-intact thoracic aorta rings precontracted with KCl.



Labdane-type diterpenoids are a large group of naturally occurring secondary metabolites found in terrestrial plants, microbes, insects, and marine organisms.[1] Some of them have been reported to exhibit a wide variety of bioactivities, such as antimicrobial, antitumor, anti-inflammatory, and analgesic activities.[2] Particularly, andrographolide, a major constituent of *Andrographis paniculata*, shows potent anti-inflammatory activity and has been widely used in clinics for the treatment of upper respiratory infections.[3] In addition, some labdanes have attracted great interest from the organic synthetic, pharmacological communities due to their unique structures and intriguing biological activities.[4]

Hypoestes species are a rich source of diterpenoids with diverse skeletons, including labdane,[5] isopimarane,[6] dolabellane,[7] fusicoccane,[8] and verticillane[9] types, some of which display potent antifungal,[6,7] anti-inflammatory,[10] antimalarial,[11] and antitumor[12] activities. However, no chemical constituents have been investigated from *H. phyllostachya*, which has many different cultivars with an uncommon characteristic of dark green foliage covered with pink, white, or red spots and is cultivated as an ornamental plant.[13] As part of a program to search structurally unique and bioactive natural products, the chemical constituents of *H. phyllostachya* "Rosea" (8 kg) were investigated. As a result, hypophyllins A–C (**1**–**3**, 0.00011%, 0.00028%, and 0.0001%, respectively), three new labdane-type diterpenoids with unprecedented carbon skeletons, hypophyllin D (**4**, 0.00035%), a unique labdane diterpenoid having a 6/6/6/5-fused ring system, as well as two new biogenetically related diterpenoids, hypophyllins E (**5**, 0.00025%) and F (**6**, 0.00044%), were isolated. It is noteworthy that **1** is a rearranged diterpenoid featuring a unique 7,8-seco-6,11-cyclolabdane skeleton, and **2** and **3** are the first example of 6(7 → 8)-abeo-labdane diterpenoids. Compound **4** is a caged labdane diterpenoid with characteristic ketal and hemiketal units between ring B and the furan-containing side chain, forming a unique 8,9-dioxatricyclic[4.2.1.1^{3,7}]decane moiety. Herein, we describe the isolation, structure elucidation, and vasorelaxant activities of **1**–**6**.

Hypophyllin A (**1**) was obtained as colorless crystals. Its molecular formula was determined to be $C_{22}H_{28}O_8$ on the basis of the HRESIMS at m/z 443.1676 [M + Na]$^+$ (calcd 443.1682), corresponding to nine degrees of unsaturation. Absorption bands at 1724, 1697, and 3419 cm^{-1} in the IR spectrum of **1** were assigned to ketone, ester carbonyl, and hydroxy groups, respectively. The ^{1}H NMR data (Table 1) of **1** displayed diagnostic signals for two methoxy groups (δ_H 3.68 and 3.75), three methyls [δ_H 2.16 (s, H_3-17), 1.11 (s, H_3-18), and 1.31 (s, H_3-20)], and a typical β-substituted furan ring [δ_H 6.65 (dd, J = 1.8, 0.7 Hz, H-14), 7.59 (t, J = 1.8 Hz, H-15), and 7.91 (dd, J = 1.8, 0.7 Hz, H-16)]. The ^{13}C NMR and DEPT spectra (Table 1) exhibited 22 carbon resonances comprising five methyls (including two methoxy groups), three methylenes, six methines (including three olefinic ones), and eight quaternary carbons (including two ketone, two ester carbonyl, one oxygenated, and one olefinic ones). Among them, the ketone, ester carbonyl, and furan ring functionalities accounted for seven out of the nine degrees of unsaturation, requiring that **1** had to possess two additional rings.

Construction of the gross structure for **1** was established by interpretation of 2D NMR spectra, especially HMBC and ^{1}H–^{1}H COSY data. The HMBC correlations (Figure 2A) from H_2-1 to C-5 and C-10, from H_2-3 to C-4 and C-5, from H-5 to C-4 and C-10, from H_3-18 to C-4 and C-19, and from one methoxy (δ_H 3.75) to C-19, as well as ^{1}H–^{1}H COSY correlations of H_2-1/H_2-2/H_2-3, suggested that a six-membered ring A with a methyl

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Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data for 1 and 2 in Acetone-d_6 (δ in ppm, J in Hz)

	1		2	
no.	δ_H	δ_C	δ_H	δ_C
1α	1.25 (td, 12.6, 3.8)	37.9	1.20 (td, 13.2, 4.0)	40.2
1β	1.76 (m)		1.73 (m)	
2α	1.56 (m)	20.9	1.75 (m)	20.5
2β	1.80 (m)		1.48 (m)	
3α	1.07 (td, 13.7, 4.4)	38.4	1.07 (td, 13.6, 4.4)	38.9
3β	2.15 (m)		2.15 (m)	
4		47.2		44.8
5	2.16 (s)	61.9	1.70 (d, 11.1)	61.1
6		84.5	4.57 (dd, 11.1, 5.8)	84.6
7		177.4	9.57 (s)	203.8
8		209.4		55.8
9	3.86 (d, 6.4)	60.6	2.64 (dd, 10.5, 3.8)	48.8
10		46.1		42.7
11a	4.44 (d, 6.4)	60.7	2.87 (dd, 17.5, 10.5)	36.6
11b			2.79 (dd, 17.5, 3.8)	
12		190.4		194.3
13		129.2		128.3
14	6.65 (dd, 1.8, 0.7)	109.6	6.71 (dd, 1.8, 0.8)	109.1
15	7.59 (t, 1.8)	145.2	7.62 (t, 1.8)	145.4
16	7.91 (dd, 1.8, 0.7)	147.9	8.42 (dd, 1.8, 0.8)	148.9
17	2.16 (s)	32.9	1.04 (s)	17.7
18	1.11 (s)	27.7	1.32 (s)	29.0
19		180.5		177.7
20	1.31 (s)	25.1	0.72 (s)	15.9
6-OH	5.81 (s)		4.38 (d, 5.8)	
7-OCH_3	3.68 (s)	52.7		
19-OCH_3	3.75 (s)	53.6	3.63 (s)	51.5

ester carbonyl and a methy group at C-4 was established. The HMBC cross-peaks of H-9 with C-5 and C-10, and of H-11 with C-5 and C-6, coupled with the $^{1}H-^{1}H$ COSY correlations of H-9/H-11, indiated the existence of a five-membered ring B fused with ring A through the positions between C-5 and C-10. Subsequently, the HMBC correlations of H_3-20 with C-1, C-5, C-9, and C-10 suggested the connection of the Me-20 with C-10. One hydroxy and another methyl ester carbonyl were located at C-6 by the correlations from H-5 and H-11 to C-6 and C-7, from 6-OH to C-6 and C-11, and from the methoxy (δ_H 3.68) to C-7 in the HMBC spectrum. Additionally, one acetyl and one 3-furanoyl were attached to C-9 and C-11, respectively, by the HMBC correlations of H-9, H-11, and H_3-17 with C-8 and of H-9, H-11, H-14, and H-16 with C-12. Consequently, the planar structure of **1** was established as shown in Figure 1.

The relative configuration of **1** was elucidated by a ROESY experiment. The ROESY correlations (Figure S6) of H-5/H-11, H-5/H_3-18, H-9/H_3-20, and 6-OH/H_3-20 indicated the α-orientation of H-5, H-11, and H_3-18, and the β-orientation of 6-OH, H-9, and H_3-20. Finally, the absolute configuration of **1** was established by a single X-ray diffraction study (Figure 2B), which further confirmed the deduced structure. The final refinement on the Cu Kα data resulted in Flack and Hooft parameters of 0.2(3) and −0.05(7), respectively, allowing unambiguous assignment of the absolute configuration of **1** to be 4*S*, 5*R*, 6*S*, 9*R*, 10*S*, 11*R*.

Hypophyllin B (**2**), colorless crystals, had a molecular formula of $C_{21}H_{28}O_6$ with eight degrees of unsaturation, based on the pesudomolecular ion peak at m/z 399.1788 $[M + Na]^+$ (calcd 399.1784) in its HRESIMS. The IR spectrum showed absorption bands at 1722 and 3431 cm^{-1}, reminiscent of the presence of

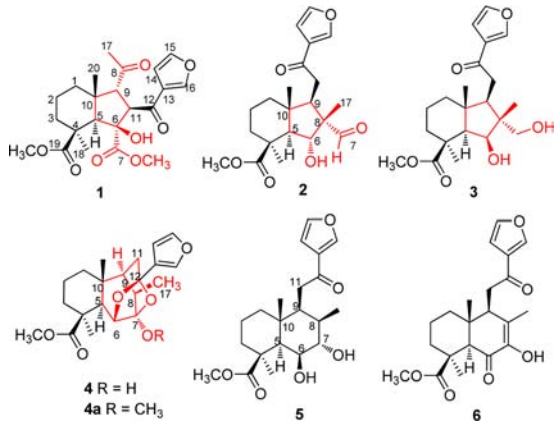

Figure 1. Structures of hypophyllins A–F (**1**–**6**).

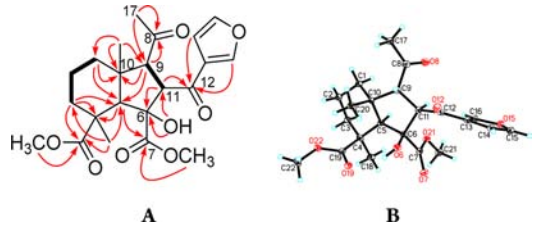

Figure 2. (A) $^{1}H-^{1}H$ COSY (bold) and selected HMBC (arrows) correlations of **1**. (B) X-ray crystallography structure of **1**.

carbonyl and hydroxy groups. Comparison of the ^{1}H and ^{13}C NMR data of **2** (Table 1) with those of methyl 12-oxo-lambertianate[14] revealed that they shared the same ring A and side chain but a different ring B. A five-membered ring B was deduced by the HMBC correlations (Figure S12) from H-5 to C-8, C-9, and C-10, and from H-9 to C-8 and C-10, along with the correlations between H-5 and H-6 in the $^{1}H-^{1}H$ COSY spectrum. The HMBC correlations of 6-OH (4.38, d, J = 5.8 Hz) with C-5 and C-6 suggested the location of one hydroxy group at C-6. Furthermore, the HMBC cross-peaks of H-7 (δ_H 9.57) with C-8, C-9, and C-17 and of H_3-17 with C-6, C-7, C-8, and C-9 indicated that the C-17 methyl and one formyl group were connected to C-8. Therefore, compound **2** was deduced to possess a 6(7 → 8)-abeo-labdane carbon skeleton. The ROESY correlations (Figure S13) of H-5 with H-9 and H_3-18 suggested that these protons were α-oriented. Meanwhile, the β-orientation of H-6, H_3-17, and H_3-20 were determined by the ROESY cross-peaks of H-6 with H_3-17 and H_3-20, together with the large coupling constant for $J_{5,6}$ (11.1). Finally, X-ray diffraction analysis (Figure 3) using Cu Kα radiation ambiguously established the absolute configuration of **2** as 4*S*, 5*R*, 6*R*, 8*S*, 9*R*, 10*R*.

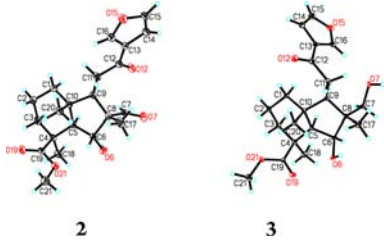

Figure 3. X-ray crystallography structures of **2** and **3**.

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The HRESIMS data of hypophyllin C (**3**) exhibited a pseudomolecular ion at m/z 401.1941 $[M + Na]^+$ (calcd 401.1940), indicating a molecular formula of $C_{21}H_{30}O_6$. The ^1H and ^{13}C NMR data of **3** (Table S1) showed close similarity to those of **2**, except for the replacement of the formyl unit with a hydroxymethyl group at C-8. This deduction was verified by the HMBC cross-peaks (Figure S19) of H_2-7 with C-6, C-8, C-9, and C-17. The ROESY correlations (Figure S20) of H-5/H-9, H-6/H_2-7, and H_2-7/H-9 suggested that H-6 and the hydroxymethyl group were α-oriented. The X-ray diffraction experiment (Figure 3) with Cu Kα radiation further corroborated the planar structure and fully determined its absolute configuration to be 4*S*, 5*R*, 6*S*, 8*R*, 9*R*, 10*R*.

Hypophyllin D (**4**) was obtained as colorless crystals, and its molecular formula was determined to be $C_{21}H_{28}O_6$ on the basis of the HREIMS at m/z 376.1893 $[M]^+$ (calcd 376.1886), corresponding to eight degrees of unsaturation. The IR spectrum showed the presence of ester carbonyl and hydroxy at 3433 and 1727 cm^{-1}, respectively. Analysis of the ^1H NMR data (Table S1) of **1** revealed the occurrence of a methoxy (δ_H 3.59), a secondary methyl [δ_H 1.16 (d, J = 6.3 Hz, H_3-17)], two tertiary methyls [δ_H 1.19 (s, H_3-18) and 1.05 (s, H_3-20)], and a typical β-substituted furan ring [δ_H 6.53 (dd, J = 1.7, 0.7 Hz, H-14), 7.50 (t, J = 1.7 Hz, H-15), and 7.63 (dd, J = 1.7, 0.7 Hz, H-16)]. The ^{13}C NMR and DEPT spectra (Table S1) revealed 21 carbon resonances comprising four methyls (including one methoxy), four methylenes, seven methines (including one oxygenated and three olefinic ones), and six quaternary carbons (including one ester carbonyl, one olefinic, and two doubly oxygenated ones). The aforementioned data indicated a highly oxygenated labdane diterpenoid with five ring systems for **4**.

Inspection of the 1D NMR data of **4** with those of **1** showed a similar moiety for ring A. The remaining part of the structure was established by analysis of the HMBC and $^1H-^1H$ COSY spectra (Figure 4A). The HMBC correlations from H-6, H-8, H_3-17, and

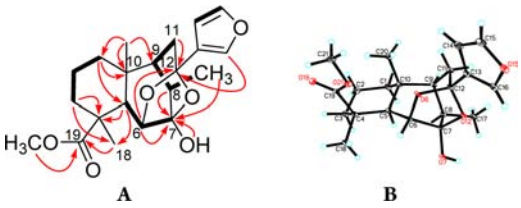


Figure 4. (A) $^1H-^1H$ COSY (bold) and selected HMBC (arrows) correlations of **4**. (B) X-ray crystallography structure of **4**.

7-OH to C-7 (δ_C 107.3) indicated the presence of a hemiketal group at C-7 connected with C-6 and C-8. While, in the case of the ether linkage, both C-6 and C-7 with C-12 form a ketal group based on the key HMBC correlations from H-6 and H_2-11 to C-12 (δ_C 105.2), as well as the remaining degrees of unsaturation. Furthermore, the location of the furanyl unit at C-12 was established by the HMBC correlation between H-16 and C-12. Consequently, the planar structure of **1** was assigned as a caged labdane diterpenoid possessing a 8,9-dioxatricyclic[4.2.1.$1^{3,7}$]-decane moiety.

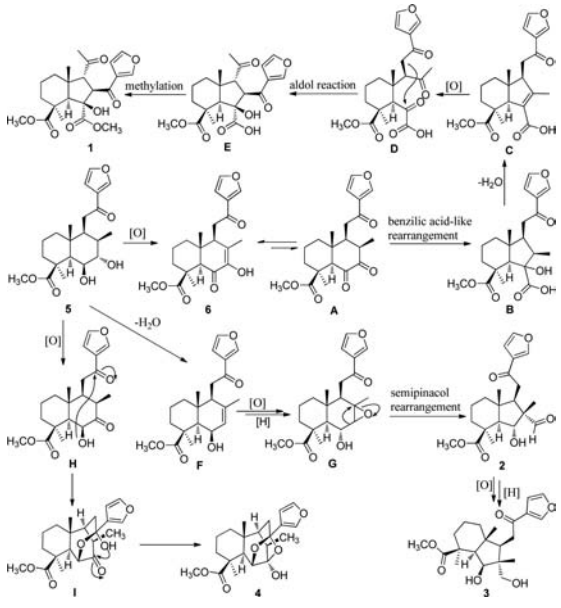
The ROESY correlations (Figure S27) of H-5/H-8, H-5/H_3-18, H-6/H_3-18, and H-6/7-OH indicated that they were cofacial and arbitrarily assigned as α-oriented. In addition, the cross-peaks of H-11a/H_3-20 and H_3-20/OMe in the ROESY spectrum demonstrated that H-9 was α-oriented, while H_3-20 possessed a β-orientation. Finally, a single crystal X-ray diffraction analysis (Figure 4B) was carried out to further confirm the planar structure and demonstrate the absolute configuration of **4** to be 4*S*, 5*R*, 6*S*, 7*R*, 8*R*, 9*S*, 10*R*, 12*R* as shown in Figure 1.

Hypophyllin E (**5**) exhibited a pseudomolecular ion peak at m/z 401.1946 $[M]^+$ in the HRESIMS spectrum, indicating the molecular formula of $C_{21}H_{30}O_6$. Detailed analysis of the ^1H and ^{13}C NMR data (Table S2) suggested that **2** was a furanolabdane diterpenoid with one ketone and two hydroxy groups. The HMBC correlations (Figure S33) from H_2-11, H-14, and H-16 to C-12 (δ_C 195.5) permitted the assignment of the ketone group at C-12, while HMBC correlations from H-6 and H-7 to C-5 and C-8 led to the location of two hydroxy groups at C-6 and C-7, respectively. In addition, one methoxy was linked to the ester carbonyl group at C-18, as deduced from the HMBC correlations of H_2-3, H-5, and the methoxy with C-18. ROESY correlations (Figure S34) of H-5/H-9, H-5/H_3-18, and 7-OH/H-9, along with the small coupling constant of $J_{5,6}$ (1.6), indicated that H-5, H-6, 7-OH, H-9, and H_3-19 were α-oriented. The β-orientation of H_3-17 and H_3-20 were determined by the ROESY cross-peaks of H_3-17/H-11b and H-11a/H_3-20.

The molecular formula of hypophyllin F (**6**) was determined to be $C_{21}H_{26}O_6$ based on the HRESIMS (m/z 397.1629 $[M + Na]^+$) data. Comparing the 1D NMR data (Table S2) with those of **5** revealed their structural similarity, except for the changes occurring at ring B. Instead of one sp^3 and two oxygenated methines in **5**, an α-hydroxy-α,β-unsaturated ketone unit (δ_C 126.6, 145.2, and 193.1) at C-5, C-6, and C-7 in **6** was recognized, which was confirmed by the HMBC networks (Figure S40) from H-5 to C-6 and C-7, from H_3-17 to C-7 and C-8, and from 7-OH to C-6, C-7, and C-8. The relative configurations of C-4, C-5, C-9, and C-10 in **6** were identical to those in **5** by analysis of the ROESY experiment.

Biogenetically, compounds **1**–**4** should be derived from **5**, a co-occurring labdane diterpenoid in *H. phyllostachya* "Rosea" (Scheme 1). Compound **5** might undergo oxidation and benzilic acid-like rearrangement[15] to form an intermediate (**B**), which then converted into **1** through a sequence of dehydration, oxidation, aldol reaction,[16] and methylation. Compound **2** could be derived from **6** via dehydration, oxidation, reduction, and

Scheme 1. Plausible Biosynthetic Pathway for 1–4



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followed by semipinacol rearrangement.[17] Then, compound **2** was transformed to **3** through oxidation and reduction. Finally, compound **4** was formed by oxidation and intramolecular nucleophilic addition from **6**.

Some *Hypoestes* species, such as *H. serpens*,[6,7] *H. forskalei*,[8b] and *H. verticillaris*,[8a] have been used as folk medicines to treat hypertension and heart disease in Madagascar and Saudi Arabia. Therefore, the vasorelaxant effects on endothelium-intact thoracic aorta rings precontracted with KCl for **1**−**6** and the methylation derivative of **4** (**4a**) were evaluated. As a result, compounds **1**, **4**−**6**, and **4a** exhibited potent vasorelaxant activity at 100 μM with the maximum relaxant values as shown in Table 2. Moreover, compounds **4**, **4a**, and **5** showed a higher vasorelaxant effect than other compounds with the maximum relaxant values of 64.28 ± 13.38%, 62.18 ± 1.27%, and 63.83 ± 5.65%, respectively. Interestingly, both compounds **4** and **4a** share a unique 8,9-dioxatricyclic[4.2.1.1^{3,7}]decane core, indicating that this caged moiety is probably an important pharmacophore for vasorelaxant activity. In addition, compound **5** possesses two hydroxy groups between C-6 and C-7, suggesting that the vicinal diol system might also be critical to the vasorelaxant effect for the furanolabdane diterpenoids.

Table 2. Vasorelaxant Effect of Compounds on KCl Induced Precontraction in Rat Aorta Rings[a]

	maximum relaxant ratio (%)[a]	
compounds (100 μM)	30 min	1 h
1	9.04 ± 1.53	31.27 ± 1.79[e]
4	34.26 ± 8.56[c]	64.28 ± 13.38[e]
4a	41.54 ± 1.62[d]	62.18 ± 1.27[e]
5	36.80 ± 1.02[d]	63.83 ± 5.65[e]
6	14.54 ± 4.24[c]	34.77 ± 5.06[e]
DMSO	0.76 ± 0.79	3.87 ± 0.72
nifedipine[b]	91.67 ± 3.02[d]	92.78 ± 3.46[e]

[a]Data expressed as means ± SD (n = 3). [b]Positive control. [c]$p < 0.05$ vs DMSO group at 30 min. [d]$p < 0.01$ vs DMSO group at 30 min. [e]$p < 0.01$ vs DMSO group at 1 h.

In conclusion, six labdane-type diterpenoids, including three rearranged labdane-type diterpenoids with unprecedented scaffolds (hypophyllins A−C, **1**−**3**) and a caged labdane-type diterpenoid (hypophyllin D, **4**) were isolated from the aerial parts of *H. phyllostchya* "Rosea". The discovery of the fascinating structures (**1**−**4**) will attract great interest from synthetic and biosynthetic communities. In addition, hypophyllins D (**4**) and E (**5**) also exhibited potent vasorelaxant activity, which made them promising lead compounds for the treatment of hypertension, heart disease, and stroke.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03388.

Detailed experimental procedures; 1D, 2D NMR, and HRMS spectra of **1**−**6** and **4a** (PDF)
X-ray data for compound **1** (CIF)
X-ray data for compound **2** (CIF)
X-ray data for compound **3** (CIF)
X-ray data for compound **4** (CIF)

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Notes

The authors declare no competing financial interest.

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