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Tigliane-Type Diterpenoid Glycosides from *Euphorbia fischeriana*

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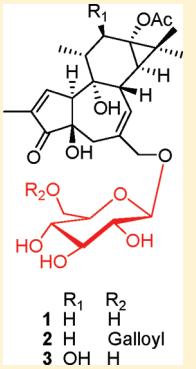
Supporting Information

ABSTRACT: Investigation of whole plants of *Euphorbia fischeriana* afforded three new tigliane-diterpenoid glycosides, fischerosides A−C (**1**−**3**), together with 11 known diterpenoids. Fischerosides A−C (**1**−**3**) are the first tigliane-type diterpenoid glucosides. Their structures were determined by a combination of 1D and 2D NMR, MS, and acid hydrolysis. Inhibitory activity against HIV-1 was assessed for compounds **1**−**5**. The new compound **3** showed an EC_{50} value of 0.02 μM and a therapeutic index (TI) of 17.50, while prostratin (**4**) and 12-deoxyphorbol-13,20-diacetate (**5**) showed significantly greater anti-HIV-1 activity.



Euphorbia fischeriana Steud (Euphorbiaceae), with the Chinese name "lang-du", is a perennial herbaceous plant with a milky juice and is distributed mainly in northeastern China. It has been used as a remedy for the treatment of edema, ascites, and cancer in Traditional Chinese Medicine for a long time.[1] Qin's group and others have reported a variety of structurally interesting diterpenoids from the roots of *E. fischeriana*.[2−8] Among these diterpenoids, jolkinolides A (**11**) and B (**13**) showed cytotoxic activities toward sarcoma 180, Ehrlich ascites, and HeLa cells, while 17-hydroxyjolkinolide B (**14**) was claimed to be a promising anticancer drug candidate as a potent STAT3 signaling inhibitor.[9−11] Perhaps the most interesting compound from *E. fishceriana* and other species of Euphorbiaceae is prostratin (**4**, 12-deoxyphorbol-13-acetate), a non-tumor-promoting 12-deoxytigliane diterpenoid that exhibits potent in vitro activity in inducing HIV expression in latently infected cell lines and primary cells.[12−14] Although the mechanism of action has not yet been completely elucidated, prostratin has been advanced into preclinical trials. The challenge of its semi- or total synthesis has drawn great interest in recent years.[15,16]

These results encouraged us to investigate the whole plants of *E. fischeriana* for new analogues of prostratin[8,12−14] and led to the isolation of three new tigliane-type diterpenoid glycosides, fischerosides A−C (**1**−**3**). Eleven known diterpenoids were also isolated: prostratin (**4**),[8] 12-deoxyphorbol-13,20-diacetate (**5**),[17] 12-deoxyphorbol-13-hexadecanoate (**6**),[8] 12-deoxyphorbaldehyde-13-hexadecanoate (**7**),[8] langduin A (**8**),[3] langduin D (**9**),[6] *ent*-13*S*-hydroxy-16-atisene-3,14-dione (**10**),[18] jolkinolide A (**11**),[9] 17-hydroxyjolkinolide A (**12**),[4] jolkinolide B (**13**),[9] and 17-hydroxyjolkinolide B (**14**).[9] Fischerosides A−C (**1**−**3**) are the first tigliane-type diterpenoid glucosides. This paper describes the isolation, structural elucidation, and anti-HIV-1 activities of the new compounds.

Compound **1** was isolated as a white, amorphous powder and had the molecular formula $C_{28}H_{40}O_{11}$, deduced from its high-resolution electrospray ionization mass spectrometry (HRESIMS) at m/z 575.2464 $[M + Na]^+$ (calcd 575.2468) and ^{13}C NMR data (Table 1), indicating nine degrees of unsaturation. The absorption bands in the IR spectrum at 1705 and 1629 cm^{-1} and the UV maximum at 210 nm indicated the presence of an α,β-unsaturated carbonyl functionality in **1**, as in prostratin (**4**). The ^1H NMR spectrum of **1** (Table 1) showed four methyl protons at δ_H 1.12 (d, J = 6.0 Hz), 1.17 (s), 1.19 (s), and 1.64 (s), two trisubstituted olefinic proton signals at δ_H 6.06 (d, J = 5.2 Hz) and 7.67 (br s), one acetate proton signal at δ_H 2.05 (s), and an anomeric proton at δ_H 4.87 (d, J = 7.8 Hz). The ^{13}C and DEPT NMR spectrum (Table 1) displayed signals of two carbonyls, two double bonds, and five methyl, three methylene (one oxygenated one), four methine, and four quaternary carbons (three oxygenated ones). Glucopyranosyl signals were also identified at δ_C 104.6 (d), 75.2 (d), 78.7 (d), 71.9 (d), 78.6 (d), and 62.7 (t), which was confirmed by the results of acid

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Table 1. ^{1}H and ^{13}C NMR Data for Compounds 1−3

	1[a]		2[b]		3[b]	
position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	7.67 br s	160.1, CH	7.47 br s	161.3, CH	7.57 br s	161.1, CH
2		133.6, C		134.9, C		134.5, C
3		209.4, C		210.8, C		210.7, C
4		74.2, C		74.7, C		74.8, C
5	3.01 br s (2H)	39.1, CH_2	2.50 m	39.0, CH_2	2.52 d (18.1)	39.0, CH_2
			2.53 m		2.57 d (18.1)	
6		138.6, C		138.8, C		139.7, C
7	6.06 d (5.2)	132.2, CH	5.63 d (5.1)	133.6, CH	5.68 d (4.8)	132.4, CH
8	3.64 m	39.7, CH	3.07 t (4.9)	40.0, CH	3.27 m	40.2, CH
9		76.5, C		77.9, C		79.9, C
10	3.65 m	57.3, CH	3.19 m	57.1, CH	3.16 m	57.7, CH
11	2.45 m	37.1, CH	1.96 m	37.5, CH	2.01 m	46.1, CH
12	1.91 dd (11.0, 14.5)	33.1, CH_2	1.52 dd (10.9, 14.7)	33.0, CH_2	3.91 d (9.9)	77.6, CH
	2.32 dd (6.6, 14.4)		2.07 dd (7.0, 14.7)			
13		64.6, C		64.6, C		69.5, C
14	1.06 d (5.7)	32.5, CH	0.80 d (5.8)	32.9, CH	1.07 m	36.6, CH
15		23.5, C		24.2, C		27.2, C
16	1.17 s	23.3, CH_3	1.11 s	23.3, CH_3	1.21 s	17.5, CH_3
17	1.19 s	15.9, CH_3	1.02 s	15.9, CH_3	1.22 s	24.1, CH_3
18	1.12 d (6.0)	19.4, CH_3	0.86 d (6.5)	19.1, CH_3	1.05 d (6.6)	15.5, CH_3
19	1.64 s	10.5, CH_3	1.60 d (1.5)	10.2, CH_3	1.74 d (1.5)	10.2, CH_3
20	4.22 m	75.3, CH_2	4.12 d (11.8)	76.6, CH_2	4.07 d (11.7)	76.0, CH_2
	4.59 d (11.5)		4.16 d (11.8)		4.22 d (11.7)	
Ac		173.0, C		175.0, C		176.0, C
	2.05 s	21.2, CH_3	2.04 s	21.1, CH_3	2.10 s	21.1, CH_3
1′	4.87 d (7.8)	104.6, CH	4.28 d (7.8)	103.5, CH	4.26 d (7.8)	103.9, CH
2′	3.99 m	75.2, CH	3.22 m	75.1, CH	3.15 dd (7.8, 9.0)	75.2, CH
3′	3.89 m	78.7, CH	3.37 m	77.9, CH	3.31 m	78.1, CH
4′	4.18 m	71.6, CH	3.41 m	71.5, CH	3.24 m	71.7, CH
5′	4.20 m	78.6, CH	3.47 m	75.5, CH	3.22 m	78.1, CH
6′	4.35 dd (5.3, 12.0)	62.7, CH_2	4.34 dd (5.3, 11.9)	65.1, CH_2	3.61 dd (5.1, 11.9)	62.8, CH_2
	4.53 dd (2.0, 12.0)		4.55 dd (1.7, 11.9)		3.83 d (12.4)	
1″				168.2, C		
2″				121.4, C		
3″, 7″			7.06 s	110.1, CH		
4″, 6″				146.5, C		
5″				139.8, C		

[a] Recorded in pyridine-d_5, 400 MHz for δ_H, 100 MHz for δ_C. [b] Recorded in methanol-d_4, 500 MHz for δ_H, 125 MHz for δ_C.

hydrolysis. Comparison of the NMR spectroscopic data of **1** (Table 1) with those obtained for prostratin (**4**) indicated that compound **1** is a glycoside derivate of prostratin, which was supported by the $^{1}H-^{1}H$ COSY, HMBC (Figure 1), and ROESY spectra. The glucopyranosyl moiety attached to C-20 could be determined by the HMBC correlations from H-1′ (δ_H 4.87) to C-20 (δ_C 75.3). Thus, the structure of **1** was deduced as prostratin 20-*O*-β-D-glucopyranoside, named fischeroside A. This is first example of a tigliane-type diterpenoid glycoside.

Compound **2** gave a molecular formula of $C_{35}H_{44}O_{15}$ by its HRESIMS at m/z 727.2587 $[M + Na]^+$ (calcd 727.2577) and ^{13}C NMR data (Table 1). The NMR data (Table 1) were similar to those of **1**, with an apparent difference being the presence of a galloyl group [δ_H 7.06, (s, H-3″ and H-7″); δ_C 168.2 (s, C-1″), 121.4 (s, C-2″), 110.1 (d, C-3″ and C-7″), 146.5 (s, C-4″ and -6″), and 139.8 (s, C-5″)] in **2**, which was confirmed by the mass difference of m/z 152 ($C_7H_4O_4$) between the two compounds. Furthermore, the position of the galloyl group at C-6′ of the glucopyranosyl moiety was determined by the HMBC correlations (Figure 1) from H_2-6′ [δ_H 4.34 (dd, J = 5.3, 11.9 Hz) and 4.55 (dd, J = 1.7, 11.9 Hz)] to C-1″ (δ_C 168.2). On the basis of the above evidence, the structure of **2** was proved to be prostratin 20-*O*-(6′-galloyl)-β-D-glucopyranoside, named fischeroside B.

Compound **3** exhibited a molecular formula of $C_{28}H_{40}O_{12}$ as derived from the quasimolecular ion peak at m/z 591.2413 $[M + Na]^+$ (calcd 591.2417) in the HRESIMS and ^{13}C NMR data (Table 1), indicating one additional oxygen atom in comparison to compound **1**. The ^{1}H and ^{13}C NMR data of **3** (Table 1) were

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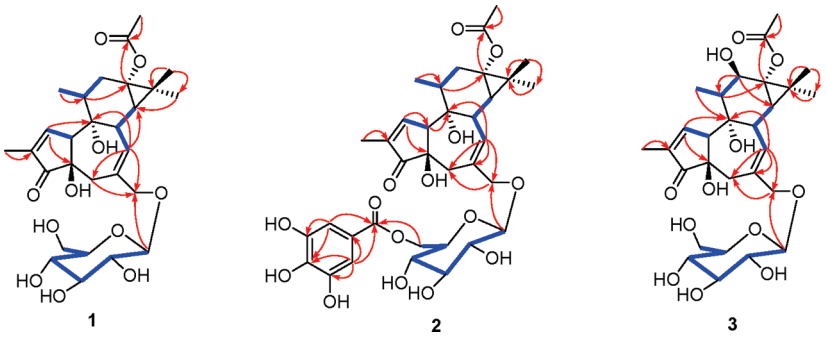

Figure 1. $^{1}H-^{1}H$ COSY (blue lines) correlations and key HMBC (red arrows) for **1**−**3**.

Table 2. Anti-HIV-1 Activities of Compounds 1−5

compound	cytotoxicity, CC_{50} (μM)	anti-HIV-1 activity, EC_{50} (μM)	therapeutic index (TI), CC_{50}/EC_{50}
1	>0.36	0.17	>2.12
2	>0.28	0.07	>4.00
3	>0.35	0.02	>17.50
4	>0.51	0.00006	>8500
5	0.11	0.0003	>366.67
AZT	4.07	0.000004	1017500

similar to those of **1** except for the absence of a methylene and the presence of a hydroxy group located at C-12 (δ_C 77.6) and an oxymethine proton (δ_H 3.91, d, J = 9.9 Hz) in compound **3**. Therefore, it was supposed that the aglycone of compound **3** was phorbol-13-acetate. This was confirmed by the proton spin system comprising H-11 (δ_H 2.01) with H-12 (δ_H 3.91) and Me-18 (δ_H 1.05) in the $^{1}H-^{1}H$ COSY spectra and the HMBC correlations (Figure 1) from H-12 (δ_H 3.91) to C-11 (δ_C 46.1), C-13 (δ_C 69.5), C-15 (δ_C 27.2), and Me-18 (δ_C 15.5). The ROESY correlations of H-12 with H-14 and Me-18 suggested the β-orientation for OH-12. As a result, the structure of **3** was elucidated as phorbol-13-acetate 20-*O*-β-D-glucopyranoside, named fischeroside C.

Compounds **1**−**5** were tested for cytotoxicities against C8166 cells (CC_{50}), and anti-HIV-1 activities were evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}), using AZT as a positive control. The results are summarized in Table 2. Compound **3** showed weak activity in preventing the cytopathic effects of HIV-1 in C8166 cells with an EC_{50} of 0.02 μM and a therapeutic index (TI) of 17.50. 12-Deoxyphorbol-13,20-diacetate (**5**) displayed significant anti-HIV-1 activity, with an EC_{50} of 0.003 μM and a TI of 366.67, while prostratin (**4**) showed the strongest anti-HIV-1 activity, with an EC_{50} of 0.00006 μM and a TI of 8500. This assay demonstrated that introducing an *O*-acetyl or glucopyranosyl moiety at C-20 of prostratin (**4**) may dramatically reduce its anti-HIV-1 activity.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were recorded on a Horiba SEAP-300 polarimeter. UV spectra were obtained on a Shimadzu UV-2401PC spectrophotometer. IR spectra were measured on a Bio-Rad FTS-135 spectrometer with KBr pellets. NMR spectra were recorded on Bruker AM-400 and DRX-500 instruments. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. ESIMS and HRESIMS were carried out on an API QSTAR TOF spectrometer. Semipreparative HPLC was performed on an Agilent 1100 liquid chromatograph with a Zorbax SB-C_{18} (9.4 mm × 25 cm) column. Column chromatography was performed on either silica gel (200−300 mesh, Qindao Marine Chemical Inc., Qingdao, People's Republic of China), RP-18 gel (LiChroprep, 40−63 μm, Merck, Darmstadt, Germany), or Sephadex LH-20 (Amersham Biosciences, Sweden). Fractions were monitored by TLC, and spots were detected with a UV_{254} lamp and by spraying with 10% H_2SO_4 in EtOH followed by heating at 120 °C for 5 min.

Plant Material. Whole plants of *E. fischeriana* were collected in June 2009 from Panshi, Jilin Province, People's Republic of China, and identified by Dr. En-De Liu of Kunming Institute of Botany. A voucher specimen (No. HY0004) was deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China.

Extraction and Isolation. The dried and powdered plant material (24 kg) was extracted with 90% EtOH (3 × 60 L) under reflux for a total of 6 h. After removal of the solvent in vacuo, the residue (4.7 kg) was suspended in H_2O (20 L) and successively extracted with EtOAc (3 × 20 L). The solvent was removed to give the EtOAc extract (2.25 kg), which was subjected to column chromatography over silica gel eluting with petroleum ether−acetone (from 50:1 to 2:1) to give four fractions, A−D. Fraction D (434 g) was subjected to an MCI gel CHP20P column eluted with a MeOH−H_2O gradient system (7:3 to 9:1) to give two subfractions, D_1 and D_2. Fraction D_1 (67.0 g) was separated on a silica gel column ($CHCl_3$−MeOH, 80:1 to 10:1) to afford six further fractions, $D_{11}-D_{16}$. Fraction D_{11} (1.78 g) was purified by semipreparative HPLC (MeOH−H_2O, 80:20; flow rate 3 mL/min) to give **5** (25 mg). Fraction D_{12} (8.94 g) was chromatographed on silica gel eluting with petroleum ether−EtOAc (10:1 to 5:1) to afford compound **4** (75 mg). Compound **8** (1.34 g) was obtained from fraction D_{13} (6.97 g) after being purified on silica gel eluting with $CHCl_3$−MeOH (30:1 to 20:1). Fraction D_{14} (8.47 g) was chromatographed on MPLC eluted with petroleum ether−EtOAc (5:1 to 0:1) to afford **1** (59 mg). Fraction D_{15} (2.73 g) was subjected to a silica gel column eluted with EtOAc, followed by a Sephadex LH-20 column (MeOH), to yield **3** (25 mg). Fraction D_{16} (1.25 g) was passed through a Sephadex LH-20 column (MeOH) and further purified by semipreparative HPLC (MeOH−H_2O, 45:55; flow rate 3 mL/min) to give **2** (23 mg). Fraction D_2 (230 g) was separated on a silica gel column ($CHCl_3$−MeOH, 100:1 to 10:1) to afford three combined fractions, $D_{21}-D_{23}$. Fraction D_{21} (16.49 g) was passed through a Sephadex LH-20 column (MeOH) followed by silica gel eluting with petroleum ether−EtOAc (100:1 to 40:1) to give **9** (163 mg). Compound **7** (74 mg) was obtained from fraction D_{22} by a Sephadex LH-20 column (MeOH). Fraction D_{23} (5.52 g) was subjected to silica gel, eluting with petroleum ether−EtOAc (10:1 to 1:1), to give **6** (65 mg). Fraction C (9.73 g) was subjected to an MCI gel column eluted with a MeOH−H_2O gradient system (70% and 90%) to

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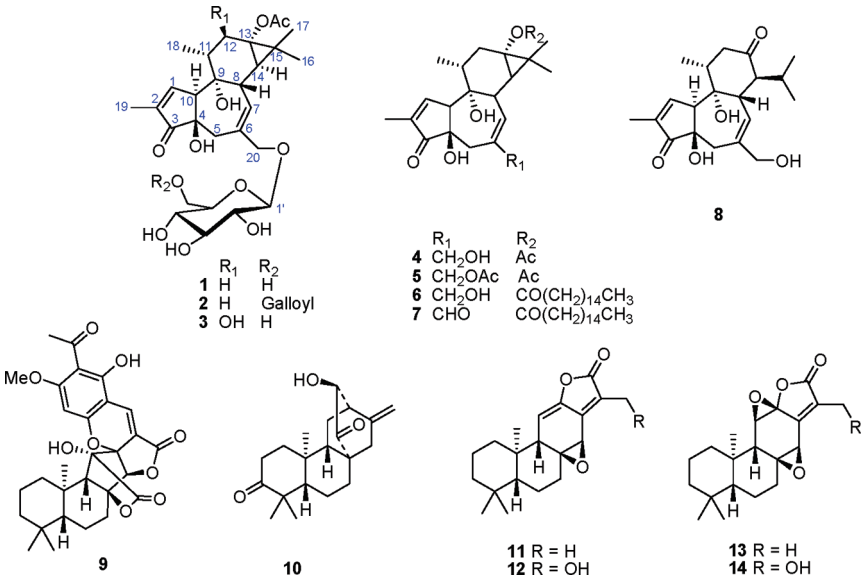
Chart 1



give two subfractions, C_1 and C_2. Fraction C_1 (4.5 g) was separated on a silica gel column ($CHCl_3$−MeOH, 100:1 to 10:1) to afford two combined fractions, C_{11} and C_{12}. Compound **10** (51 mg) was obtained after being crystallized in MeOH from fraction C_{11}. Fraction C_{12} was purified on silica gel eluting with $CHCl_3$−MeOH (150:1 to 30:1) to give **14** (32 mg). Compounds **11** (231 mg), **12** (1.087 g), and **13** (179 mg) were obtained after being crystallized in petroleum ether−$CHCl_3$ from fractions A, B, and C_2, respectively.

*Fischeroside A (**1**):* white, amorphous powder; $[\alpha]^{17}_D$ +15.2 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ε) 238 (3.35), 210 (3.38) nm; IR (KBr) ν_{max} 3420, 2983, 1705, 1629, 1378, 1263, 1078, 1044 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 575 $[M + Na]^+$; positive HREIMS *m/z* 575.2464 $[M + Na]^+$ (calcd for $C_{28}H_{40}O_{11}Na$, 575.2468).

*Fischeroside B (**2**):* white, amorphous powder; $[\alpha]^{17}_D$ +16.2 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 272 (3.64), 218 (4.09) nm; IR (KBr) ν_{max} 3423, 2824, 1700, 1616, 1450, 1378, 1333, 1233, 1077, 1039 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 727 $[M + Na]^+$; positive HREIMS *m/z* 727.2587 $[M + Na]^+$ (calcd for $C_{35}H_{44}O_{15}Na$, 727.2577).

*Fischeroside C (**3**):* white, amorphous powder; $[\alpha]^{17}_D$ +38.0 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 232 (3.41), 210 (3.51) nm; IR (KBr) ν_{max} 3423, 2824, 1700, 1628, 1378, 1264, 1078, 1043 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; positive ESIMS *m/z* 591 $[M + Na]^+$; positive HREIMS *m/z* 591.2413 $[M + Na]^+$ (calcd for $C_{28}H_{40}O_{12}Na$, 591.2417).

Acid Hydrolysis of Compounds 1−3. Compound **1** (10 mg) was hydrolyzed with 4 M TFA−dioxane (1:1 v/v, 2 mL) for 4 h at 90 °C. After cooling, the reaction mixture was neutralized with 1 M NaOH and filtered. The filtrate was extracted with $CHCl_3$. Through TLC comparison with an authentic sample using $CHCl_3$−MeOH−H_2O (8:2:0.2) as a developing system, D-glucose was detected in the water layer (R_f = 0.11). The aqueous solution was further concentrated to dryness and subjected to silica gel chromatography eluting with $CHCl_3$−MeOH (9:1) to give D-glucose (2 mg), $[\alpha]^{17}_D$ +40.0 (*c* 0.2, MeOH). By the same method used for **1**, the sugar moiety in compounds **2** and **3** was identified as D-glucose.

Anti-HIV-1 Assay. Cytotoxicity against C8166 cells (CC_{50}) was assessed using the MTT method, and anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50}).[19] AZT (zidovudine) was used as the positive control anti-HIV-1 drug.

■ ASSOCIATED CONTENT

Supporting Information. 1D and 2D NMR (HSQC, COSY, HMBC, ROESY) spectra for fischerosides A−C (**1**−**3**) are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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