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neo-Clerodane Diterpenes from *Salvia herbacea*

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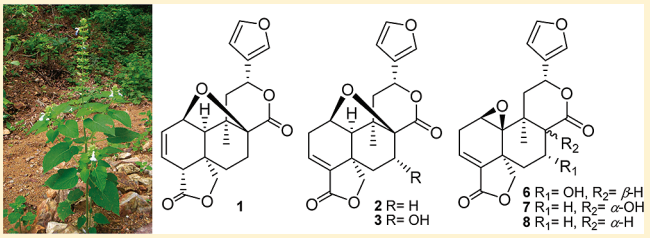
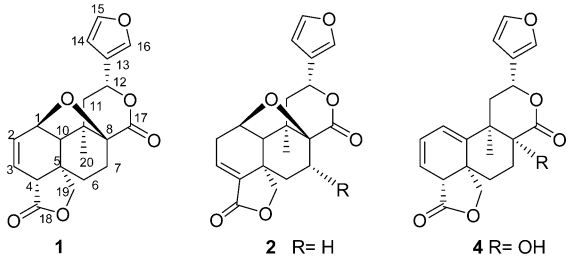
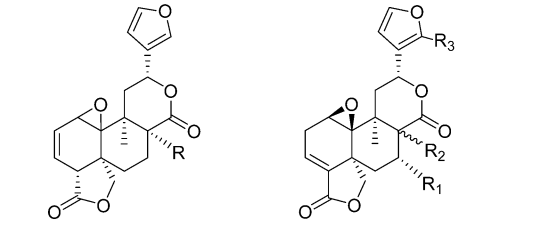
Supporting Information

ABSTRACT: Chemical investigation of the aerial parts of *Salvia herbacea* led to the isolation of eight new *neo*-clerodane diterpenes (**1**–**8**), named tehuanins A–H, and three known compounds. The structures of these compounds were determined by analysis of their spectroscopic data. Three of the new diterpenes possess a 1,8-epoxy group (**1**–**3**). This unusual structural feature was confirmed by X-ray diffraction of **1**. The structure of the previously isolated 1α,10α-epoxysalviarin was revised. The absolute configuration of **6** was established by X-ray diffraction analysis of its bromo derivative **6a**. Cytotoxic and anti-inflammatory activities of these diterpenes were examined. None of the compounds were considered to be cytotoxic; however, compound **7** exhibited anti-inflammatory activity comparable to that of indomethacin.



Salvia is one of 224 genera in the family Lamiaceae. This subcosmopolitan genus comprises about 900 species, including some that are used for ornamental, culinary, or medicinal purposes.[1] *Salvia* species have been utilized in traditional Mexican medicine to treat dysentery, diarrhea, and insomnia and for their abortive, expectorant, and antipyretic properties.[2] Metabolites reported from this genus include triterpenes,[3] flavonoids,[4] sesterterpenes,[5] and diterpenes. Diterpenes from *Salvia* are mainly abietanes and *neo*-clerodanes, many of them with modified skeletons.[6] Some of these diterpenes have shown cytotoxic,[7] antiprotozoal,[8] and phytotoxic activities,[9] and one of them, salvinorin A, is a nonalkaloidal, naturally occurring hallucinogen and also the first non-nitrogenous κ-opioid selective agonist.[10] Salvinorin A was isolated from *Salvia divinorum*,[11] a hallucinogenic plant used by Mazatec healers in magical rites of divination. As a part of our ongoing study of diterpenes from *Salvia*, we have now investigated the aerial parts of *Salvia herbacea* Benth. (Lamiaceae, subgenus *Calosphace*), a herbaceous plant that grows on the Isthmus of Tehuantepec in Southern Mexico. Herein, we report the structural elucidation of the isolates from this plant and the results of tests of their cytotoxic and anti-inflammatory activities.





RESULTS AND DISCUSSION

Fractionation of a Me_2CO extract of aerial parts of *S. herbacea* led to the isolation of eight new diterpenes, tehuanins A–H (**1**–**8**), together with the known 1(10)-dehydrosalviarin (**9**),[12] 1α,10α-epoxysalviarin (**10**), previously isolated from *Salvia lineata*,[13] and 5,6,3′-trihydroxy-7,4′-dimethoxyflavone.[14] The published structure of compound **10** will be discussed.

Tehuanin A (**1**) was isolated as colorless crystals. It has the molecular formula $C_{20}H_{20}O_6$, as deduced from the $[M + H]^+$ ion at m/z 357.1330 in the HRFABMS. Its ^{13}C NMR spectrum showed 20 signals, and the IR spectrum indicated the presence of γ- and δ-lactones and a furan ring. This information together with previous studies of the chemistry of genus *Salvia* subgenus *Calosphace*[6a] suggested that **1** had a *neo*-clerodane skeleton. The ^1H and ^{13}C NMR spectra of **1** (Table 1) showed the presence of a tertiary methyl group (δ_H 1.30 s, δ_C 23.6, CH_3-20), a furan ring (δ_H 6.45, H-14; δ_H 7.44, H-15; δ_H 7.51, H-16), a 18,19-γ-lactone (δ_C 172.8, C-18; δ_C 76.3, δ_H 4.68, 4.10, CH_2-19), and a

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

	1[b]		2		3[d]		3a[e]	
position	δ_H mult. (J in Hz)	δ_C	δ_H mult. (J in Hz)	δ_C	δ_H mult. (J in Hz)	δ_C	δ_H mult. (J in Hz)	δ_C
1	4.49 t (5.0)	71.6 CH	4.55 ddd (8.0, 4.0, 1.0)	75.3 CH	4.54 ddd (8.0, 4.0, 1.0)	75.3 CH	4.58 m[c]	75.3 CH
2a	6.26 ddd (10.0, 5.0, 2.0)	126.6 CH	3.08 ddd (21.0, 8.0, 6.0)	31.0 CH_2	3.06 ddd (20.5, 8.0, 6.5)	30.8 CH_2	3.08 ddd (21.0, 8.0, 6.5)	30.7 CH_2
2b			2.78 ddd (21.0, 2.5, 1.0)		2.70 ddd (20.5, 2.5, 1.0)		2.75 br dd (21.0, 2.5)	
3	6.10 dd (10.0, 6.0)	122.9 CH	6.88 dd (6.0, 2.5)	134.0 CH	6.88 dd (6.5, 2.5)	133.4 CH	6.90 dd (6.5, 2.5)	133.8 CH
4β	3.00 dd (6.0, 2.0)	49.2, CH		137.1 C		137.5 C		136.9 C
5		40.3 C		41.1, C		40.2 C		40.2 C
6α	1.87 m[c]	25.3 CH_2	2.02 m[c]	31.6 CH_2	2.20 br d (16.0)[c]	39.5 CH_2	2.13 m[c]	38.9 CH_2
6β	2.03 m[c]		1.67 dddd (14.5, 12.0, 8.0, 1.0)		2.03 dd (16.0, 4.0)[c]		2.13 m[c]	
7α	1.90 m[c]	25.4 CH_2	1.91 m[c]	25.8 CH_2		69.1 CH		68.1 CH
7β	2.15 dd (13.0, 8.5)		2.21 dd (14.5, 8.0)		4.42 dd (8.0, 2.0)		5.49 t (4.5)	
8		82.4 C		82.2 C		81.3 C		80.4 C
9		44.8 C		44.9 C		45.0 C		45.0 C
10α	2.06 d (5.0)[c]	46.6 CH	1.91 d (4.0)[c]	57.5 CH	1.96 d (4.0)	57.6 CH	1.99 d (4.0)	57.5 CH
11α	2.06 m[c]	43.2 CH_2	2.02 m[c]	43.7 CH_2	2.10 m[c]	44.7 CH_2	2.13 m[c]	44.4 CH_2
11β	2.06 m[c]		2.02 m[c]		2.04 m[c]		2.06 m[c]	
12β	5.81 dd (11.5, 5.0)	71.7 CH	5.78 dd (12.0, 4.5)	72.0 CH	5.75 dd (12.0, 4.0)	72.3 CH	5.68 dd (12.0, 4.0)	71.6 CH
13		123.7 C		124.3 C		123.9 C		124.1 C
14	6.45 dd (2.0, 1.0)	107.8 CH	6.44 dd (2.0, 1.0)	108.4 CH	6.45 dd (2.0, 0.5)	108.3 CH	6.44 dd (2.0, 1.0)	108.3 CH
15	7.44 dd (2.0, 1.5)	143.1 CH	7.43 t (2.0)	143.8 CH	7.44 t (1.5)	143.9 CH	7.44 t (2)	143.9 CH
16	7.51 m	139.2 CH	7.49 m	139.8 CH	7.50 m	140.0 CH	7.49 m	139.9 CH
17		168.9 C		169.7 C		171.0 C		169.1 C
18		172.8 C		168.2 C		168.2 C		167.1 C
19 *pro-R*	4.10 d (9.5)	76.3 CH_2	4.50 d (9.5)	79.3 CH_2	4.69 d (9.5)	80.4 CH_2	4.57 d (9.0)	79.8 CH_2
19 *pro-S*	4.68 d (9.5)		4.24, dd (9.5, 1.0)		4.29 dd (9.5, 0.5)		4.30 d (9.0)	
20	1.30 s	23.6 CH_3	1.21 s	22.9 CH_3	1.49 s	23.3 CH_3	1.49 s	23.5 CH_3

[a]Spectra taken in $CDCl_3$ at 500 MHz for ^{1}H and 125 MHz for ^{13}C. [b]$CDCl_3$–DMSO-d_6. [c]Overlapped signal. [d]OH signal at δ_H 2.95 (br s). [e]MeCO signals at δ_H 2.05 (s), δ_C 21.0 (CH_3), 168.0 (C).

17,12-δ-lactone (δ_C 168.9, C-17; δ_C 71.7, δ_H 5.81, CH-12). In the HMBC spectrum, the signal at δ_H 3.00 (dd, J = 6.0, 2.0 Hz) correlated with the γ-lactone carbonyl (C-18), and it was assigned to H-4. In the COSY spectrum the last proton signal showed cross-peaks with the signals at δ_H 6.26 (ddd, J = 10.0, 5.0, 2.0 Hz, H-2) and 6.10 (dd, J = 10.0, 6.0 Hz, H-3), indicating the presence of a double bond at C-2. The COSY spectrum also showed cross-peaks between H-2 and the signal at δ_H 4.49 (br t, J = 5.0 Hz, H-1) and between H-1 and the signal at δ_H 2.06 (d, J = 5.0 Hz, H-10). These assignments were confirmed by the HMBC correlations shown in Figure 1. The chemical shifts of H-1 and C-1 (δ_C 71.6) indicated an oxygenated function at this position. In addition, the ^{13}C NMR spectrum showed a signal for an oxygenated non-protonated carbon at δ_C 82.4. HMBC correlations from H_2-6, H_2-7, H_3-20, and H-10 and/or H_2-11 (superimposed signals at δ_H 2.06) to the last mentioned carbon signal allowed its assignment to C-8. Thus, both C-1 and C-8 were bonded to oxygenated functions. However, five of the six oxygen atoms contained in the molecular formula of **1** were part of the lactones and the furan ring; therefore the sixth one must be present as an 1,8-epoxy group. This proposal was consistent with the molecular formula of **1** (degree of unsaturation of 11). Regarding the relative configuration of **1**, the H-12 coupling constants ($J_{11\alpha\text{-}12}$ = 11.5 Hz, $J_{11\beta\text{-}12}$ = 5.0 Hz) established its axial disposition, its NOE correlations with H-1, its β-orientation, and also the β-orientation of the 1,8-epoxy group. NOESY correlations from H_3-20 to H-7α and H-19$_{pro\text{-}S}$ and those of H-19$_{pro\text{-}R}$ with H-4 and H-6α indicated the β-orientation of H-4 and, therefore, a *cis*-fused γ-lactone. Thus, structure **1** was established for tehuanin A. This structure was confirmed by X-ray diffraction analysis of **1** (Figure 2).

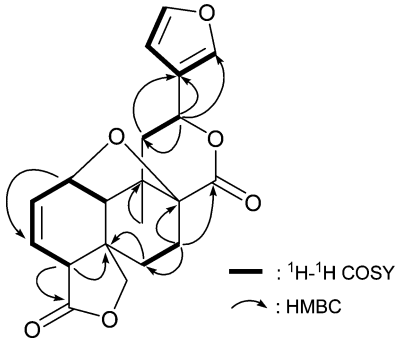

Figure 1. Key ^{1}H−^{1}H COSY and HMBC correlations of **1**.

Tehuanine B (**2**) was an isomer of compound **1** ($C_{20}H_{20}O_6$, by HRFABMS). Comparison of the NMR spectra of these compounds indicated that they differed only in the position of the double bond in ring A, which in **2** was conjugated with the γ-lactone. This was deduced from the chemical shift of the γ-lactone carbonyl of **2** (δ_C 168.2, C-18), as well as from the

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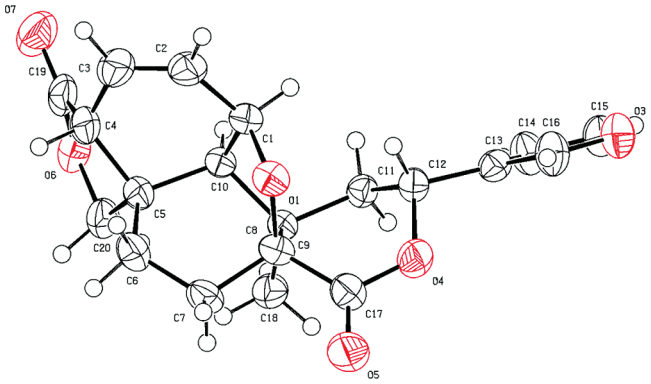

Figure 2. ORTEP diagram (crystallographic numbering) of tehuanine A (**1**).

signals of a trisubstituted double bond (δ_H 6.88, dd, J = 6.0, 2.5 Hz, δ_C 134.0, CH-3; δ_C 137.1, C-4). In the COSY spectrum, H-3 showed cross-peaks with the protons of a methylene at δ_H 3.08 (ddd, J = 21.0, 8.0, 6.0 Hz) and 2.78 (ddd, J = 21.0, 2.5, 1.0 Hz), which were assigned to H-2a and H-2b, respectively. In turn H-2a correlated with a proton geminal to the 1,8-epoxy group (δ_H 4.55 ddd, J = 8.0, 4.0, 1.0 Hz, H-1). The above-mentioned was confirmed by HMBC correlations from H-1 to C-3 and C-5 (δ_C 41.1) and those from H-3 to C-1 (δ_C 75.3), C-2 (δ_C 31.0), C-5, and C-18. NOESY correlations from H-1 to H-2a (α-oriented), H-2b (weak), H-10, and H-12, from H-19$_{pro\text{-}R}$ to H-6α and H$_3$-20, and from H-19$_{pro\text{-}S}$ to H-10 and H$_3$-20 established that tehuanin B (**2**) had the same relative configuration as compound **1**.

Tehuanine C (**3**) showed a $[M + H]^+$ ion at m/z 373.1281, which was consistent with the molecular formula $C_{20}H_{20}O_7$, indicating that **3** contained one oxygen more than **2**. The IR spectrum of **3** showed, in addition to the absorptions for γ- and δ-lactones and a furan ring, a band indicative of an OH group at 3497 cm^{-1}. The NMR spectra of **2** and **3** were similar. The main differences were signals for an oxygenated methine in the spectra of **3** (δ_H 4.42, δ_C 69.1) instead of those for a methylene in **2**. The methine signals were attributed to CH-7 on the basis of the HMBC correlations from H-7 to C-5, C-8, and C-9 and from H$_2$-6 to C-7. The COSY spectrum showed a cross-peak between H-7 and a broad OH singlet at δ_H 2.95, thus placing the OH at C-7. The H-7 coupling constants (dd, J = 8.0, 2.0 Hz) indicated its equatorial disposition and, therefore, α-axial orientation of the OH. The latter was supported by preparation of the acetyl derivative **3a**. Compound **3a** exhibited a $[M + H]^+$ ion at m/z 415.1394, in agreement with the molecular formula $C_{22}H_{22}O_8$. The ^{1}H and ^{13}C NMR spectra of **3a** showed the presence of an acetyl group and a low-field shift of H-7. Thus, the structure of tehuanin C was established as **3**.

Tehuanine D (**4**) had the molecular formula $C_{20}H_{20}O_6$; $[M + H]^+$ at m/z 357.1335 in the HRFABMS. The ^{13}C NMR spectrum showed 20 signals, and the IR spectrum indicated the presence of an OH, γ- and δ-lactones, and a furan ring, suggesting that **4** also possessed a clerodane-type skeleton. Its ^{1}H and ^{13}C NMR spectra (Tables 2 and 3) showed the presence of a tertiary methyl group (δ_H 1.21 s, CH$_3$-20) and a furan ring (δ_H 6.47, H-14; δ_H 7.43, H-15; δ_H 7.50, H-16). The 1(10),2-diene system was deduced from the three olefinic proton signals (δ_H 6.11, 6.19, and 5.63), which were assigned to H-1, H-2, and H-3, respectively, on the basis of HMBC correlations. Compound **4** also possesses a 18,19-γ-lactone (δ_C 177.0, C-18; δ_C 75.8, δ_H 4.48 and 4.01, CH$_2$-19) and a 17,12-δ-lactone (δ_C 172.5, C-17; δ_C 71.2, δ_H 5.54, CH-12). All these structural features were the same as those of 1(10)-dehydrosalviarin (**9**),[13] but whereas in **9** C-8 was a methine (δ_C 48.5, δ_H 2.55, CH-8), in **4** C-8 was bonded to an OH group (IR 3432 cm^{-1}). This was evident from the chemical shift of the

Table 2. ^{1}H NMR Data of Compounds 4–8 and 11 (500 MHz, CDCl$_3$)

position	4	5[a]	6[c]	7	8[d]	11[a]
1	6.11 d (6.0)	3.63 dd (4.5, 1.5)	3.55 br s	3.46 br s	3.62 br s	3.59 dd (4.5, 2.0)
2a	6.19 ddd (9.5, 6.0, 3.0)	6.29 ddd (9.5, 4.5, 3.0)	2.95 ddd (21.0, 3.0, 1.5)	2.96 ddd (21.0, 3.0, 1.0)	2.96 ddd (21.2, 3.2, 1.2)	6.28 ddd (9.5, 4.5, 3.0)
2b			2.75 ddd (21.0, 4.0, 2.5)	2.76 ddd (21.0, 4.0, 2.5)	2.76 ddd (21.2, 4.0, 2.4)	
3	5.63 ddd (9.5, 3.0, 0.5)	5.66 dt (9.5, 1.5)[b]	6.41 m[b]	6.38 ddd (4.0, 3.0, 1.0)	6.43 m	5.66 dt (9.5, 2.0)[b]
4β	3.08 t (3.0)	2.85 br t (3.0)				2.87 br t (3.0)
6α	1.94 dt (14.5, 3.5)	2.03 dt (14.0, 4.5)	2.41 dd (14.0, 2.0)	2.34 dt (13.5, 8.5)	2.03 m[b]	1.86 m
6β	1.35 dddd (14.5, 14.5, 3.5, 2.0)	1.75 m[b]	1.98 ddd (14.0, 3.5, 2.0)	1.97 m[b]	1.94 m[b]	1.79 m[b]
7α	2.03 td (13.5, 3.5)	1.95 ddd (13.5, 12.0, 4.5)		1.94 m[b]	2.03 m[b]	2.03 m
7β	2.47 dt (13.5, 3.5)	2.65 dt (13.5, 4.5)	4.67 br dt (3.5, 2.0)	2.52 dt (14.0, 9.0)	2.60 m[b]	2.62 m[b]
8			3.07 d (3.5)		2.63 m[b]	2.60 m[b]
11α	2.65 dd (15.5, 12.5)	2.26 dd (15.0, 12.0)	1.47 dd (13.5, 10.5)	1.60 dd (15.0, 11.5)	1.68 dd (14.8, 11.2)	1.74 dd (15.0, 10.0)
11β	2.24 dd (15.5, 3.5)	1.77 dd (15.0, 4.5)[b]	2.14 dd (13.5, 7.0)	1.90 dd (15.0, 2.0)	2.11 dd (14.8, 3.6)	2.16 dd (15.0, 5.0)[b]
12β	5.54 dd ((12.5, 3.5)	5.63 dd (12.0, 4.5)[b]	5.26 dd (10.5, 7.0)	5.74 dd (11.5, 2.0)	5.57 dd (11.2, 3.6)	5.76 dd (10.0, 5.0)[b]
14	6.47 ddd (2.0, 1.0, 0.5)	6.48 dd (2.0, 1.0)	6.42 dd (2.0, 1.0)[b]	6.41 dd (2.0, 1.0)	6.40 dd (1.6, 0.8)	6.39 br s
15	7.43 td (1.5, 0.5)	7.40 t (2.0)	7.45 t (2.0)	7.43 t (2.0)	7.42 t (1.6)	7.42 m
16	7.50 m	7.46 m	7.47 m	7.49 m	7.44 m	7.43 m
19 *pro-R*	4.48 d (8.5)	4.50 d (8.5)	5.65 d (7.0)	5.32 d (7.5)	4.58 d (8.0)	4.47 d (9.0)
19 *pro-S*	4.01 dd (8.5, 2.0)	4.16 dd (8.5, 2.0)	3.93 dd (7.0, 2.0)	4.02 dd (7.5, 2.0)	4.06 dd (8.0, 1.6)	4.15 dd (9.0, 1.5)
20	1.21 s	1.11 s	1.40 s	1.07 s	1.20 s	1.22 s

[a]In CDCl$_3$–DMSO-d_6. [b]Overlapped. [c]7-OH signal at δ_H 4.15 (br s). [d]Determined at 400 MHz.

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Table 3. ^{13}C NMR Data (δ) of Compounds 4–8 and 11 (125 MHz, $CDCl_3$)

position	4	5[a]	6	7	8[b]	11[a]
1	120.7 CH	48.9 CH	57.3 CH	53.4 CH	55.4 CH	49.0 CH
2	124.6 CH	125.6 CH	27.2 CH_2	27.3 CH_2	27.2 CH_2	125.69 CH
3	119.1 CH	125.3 CH	127.7 CH	126.2 CH	128.1 CH	125.72 CH
4	51.5 CH	51.0 CH	133.8 C	134.0 C	132.7 C	50.7 CH
5	42.1 C	42.9 C	42.7 C	41.1 C	43.2 C	43.3 C
6	32.0 CH_2	30.0 CH_2	33.9 CH_2	26.3 CH_2	27.2 CH_2	29.3 CH_2
7	28.0 CH_2	27.2 CH_2	66.0 CH	30.9 CH_2	20.2 CH_2	18.0 CH_2
8	75.0 C	73.2 C	48.1 CH	74.6 C	46.9 CH	45.4 CH
9	42.1 C	41.4 C	39.5 C	41.8 C	38.2 C	36.9 C
10	139.4 C	67.6 C	63.7 C	63.9 C	64.9 C	66.7 C
11	34.4 CH_2	34.7 CH_2	37.5 CH_2	40.2 CH_2	39.3 CH_2	38.1 CH_2
12	71.2 CH	71.6 CH	71.2 CH	72.9 CH	71.9 CH	71.4 CH
13	124.6 C	125.8 C	123.8 C	123.9 C	125.1 C	125.1 C
14	108.5 CH	108.1 CH	108.4 CH	108.1 CH	108.2 CH	107.6 CH
15	143.8 CH	143.0 CH	144.1 CH	143.9 CH	143.8 CH	143.1 CH
16	139.9 CH	139.3 CH	139.8 CH	140.0 CH	139.5 CH	138.7 CH
17	172.5 C	171.8 C	174.2 C	176.4 C	172.2 C	170.7 C
18	177.0 C	174.6 C	168.7 C	168.8 C	168.1 C	174.3 C
19	75.8 CH_2	71.2 CH_2	73.1 CH_2	75.1 CH_2	72.5 CH_2	70.2 CH_2
20	26.1 CH_3	20.0 CH_3	23.4 CH_3	22.7 CH_3	26.0 CH_3	25.3 CH_3

[a]In $CDCl_3$–DMSO-d_6. [b]Determined at 100 MHz.

C-8 signal (δ_C 75.0) and confirmed by the HMBC correlations from H-6β, H-7α, H-7β, H-11α, H-11β, and H_3-20 to C-8. The low-field shift of the signals for carbons in a β-position to the OH, C-7 (δ_C 28.0) and C-9 (δ_C 42.1), compared with those of compound **9** (δ_C 19.1, C-7; δ_C 37.7, C-9), supported this assumption. NOESY correlations from H-7α to H_3-20 and H-19$_{pro\text{-}R}$ indicated α-axial dispositions of C-19 and C-20. A NOESY correlation between H-4 and H_2-6 was observed. Molecular models showed that this correlation is possible only if H-4 is β-oriented and, therefore, in a *syn*-relationship to C-6. Consequently the γ-lactone was *cis*-fused and α-oriented. The axial disposition of H-12 was deduced from its coupling constants ($J_{11\alpha-12}$ = 12.5 Hz, $J_{11\beta-12}$ = 3.5 Hz), and its β-orientation from its NOE correlations to H-1 and H-11β. The upfield shift of the signals of C-11 (δ_C 34.4) and C-20 (δ_C 26.1) of **4**, with respect to the corresponding signals of **9** (δ_C 40.7, C-11; δ_C 32.1, C-20),[12,13] can be explained only by a γ-gauche effect of the 8-OH group, which requires α-orientation of this group. Thus, structure **4** was established for tehuanin D.

Tehuanine E (**5**) showed IR absorptions for OH (3428 cm^{-1}), γ-lactone (1757 cm^{-1}), δ-lactone (1718 cm^{-1}), and a furan ring (3150, 1504, and 875 cm^{-1}). Its molecular formula was determined by HRFABMS as $C_{20}H_{20}O_7$ ($[M + H]^+$ at m/z 373.1282). NMR data of this compound (Tables 2 and 3) were very similar to those described for a compound isolated from *S. lineata,* to which the structure 1α,10α-epoxysalviarin (**10**) was assigned.[13] This compound was also isolated in this work. The only difference between **5** and **10** was the presence of an α-oriented OH group at C-8 in **5**. This was evident from the chemical shift of C-8 (δ_C 73.2), as well as by the effects that this group causes on the chemical shifts of the β- (C-7, C-9) and γ-carbons (C-11, C-20) (Table 3). The NOESY correlation from H-4 to H-6β and that from H-6α to H-19$_{pro\text{-}S}$, together with those from H_3-20 to H-7α, H-11α, and H_2-19, indicated an α-oriented *cis*-fused γ-lactone. The β-orientation of H-12 was deduced from its NOESY correlations with H-1, H-7β, and H-11β. NOESY correlations from H-1 to H-2, H-11α, H-11β, H-12, and H_3-20 were not sufficient to determine the orientation of the 1,10-epoxy group, since inspection of molecular models revealed that H-1 can exhibit the same NOESY interactions independent of the orientation of this group. Thus, β-orientation of the epoxy group was confirmed by an X-ray diffraction analysis of **5** (Figure 3). This analysis also confirmed the proposed structure **5** for tehuanin E.

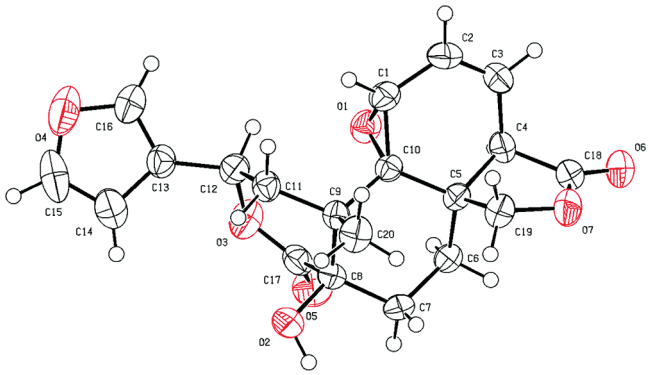

Figure 3. ORTEP diagram of tehuanine E (**5**).

The above results and the close similarity of the ^1H and ^{13}C NMR data of **5** and **10**, especially those concerning ring A, indicated that they have the same configuration. Therefore the structure of compound **10** must be revised to 1β,10β-epoxysalviarin (**11**).

The IR spectrum of tehuanine F (**6**) showed absorptions for OH, γ- and δ-lactones, a double bond, and a furan ring. The ^{13}C NMR spectrum showed 20 signals, which, in accordance with DEPT and HSQC experiments, corresponded to one methyl, four methylene, eight methine, and seven nonprotonated carbons. The HRFABMS spectrum showed a $[M + H]^+$ ion at 373.1288, consistent with the molecular formula $C_{20}H_{20}O_7$, indicating that **6** was an isomer of **5**. The ^1H and ^{13}C NMR signals confirmed the presence of a furan ring (δ_H 6.42, H-14; 7.45, H-15; 7.47, H-16), a 18,19-γ-lactone (δ_C 168.7, C-18; δ_H

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5.65 d, J = 7.0 Hz; δ_H 3.93 dd, J = 7.0, 2.0 Hz, δ_C 73.1, CH_2-19), and a 17,12-δ-lactone (δ_C 71.2, δ_H 5.26 dd, J = 10.5, 7.0 Hz, H-12; δ_C 174.2, C-17). The signal at δ_H 3.07 (d, J = 3.5 Hz) was assigned to H-8 since, in the HMBC spectrum, it correlated with C-17, and in the COSY experiment with H-7. The chemical shift of the H-7signal (δ_H 4.67) revealed an OH at C-7. The 1,10-epoxy group was deduced from the signals for C-10 (δ_C 63.7) and CH-1 (δ_C 57.3, δ_H 3.55). COSY cross-peaks of H-1 with H-2β and those of H-2α and H-2β with the olefinic proton at δ_H 6.41 showed that a double bond was located at C-3 in **6** and that the γ-lactone was α,β-unsaturated. This was confirmed by the chemical shift of the lactone carbonyl (δ_C 168.7). The α-axial disposition of CH_3-20 and CH_2-19 was deduced from the NOESY correlations of H-11α to H_3-20 and those of H_3-20 to H_2-19. NOESY correlations from H-12 to H-8 and H-11β and those from H-8 to H-6β, H-7, H-11β, and H-12 established a β-orientation of H-8 and α-orientations of both the furan ring and the 7-OH group. The orientation of the epoxy group could not be deduced from the NOESY correlations from H-1 to H_2-2 and H-11β; only the weak interaction from H-1 to the α-oriented CH_3-20 seems to account for a β-epoxy group. In order to confirm this point and also to establish the absolute configuration of **6**, a single-crystal X-ray diffraction analysis of its 16-bromo derivative **6a** (NMR data in Experimental Section) was carried out. The results (Figure 4) confirmed the above-mentioned, including β-orientation of the epoxy group, and also established that tehuanin F (**6**) has the configuration of a *neo*-clerodane diterpene.

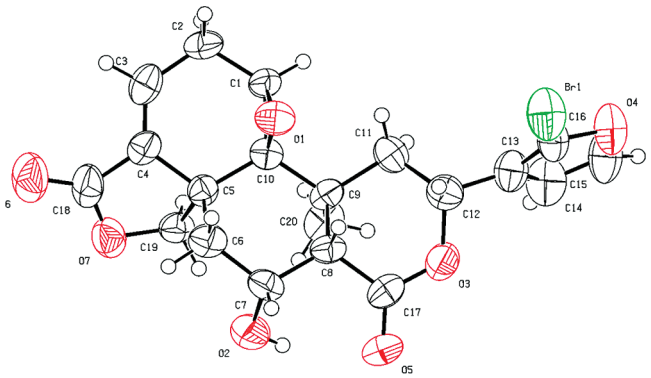

Figure 4. ORTEP diagram of 16-bromotehuanine F (**6a**).

Tehuanine G (**7**) had the same molecular formula as **6**, and the same functional groups in the IR spectrum. The NMR spectra of both compounds were quite similar, except that **7** had a tertiary OH group at C-8, instead of the secondary 7-OH group of **6**. This was established by the chemical shift of C-8 (δ_C 74.6) and the HMBC correlations from H_2-6, H-7α, H-11β, and H_3-20 to this carbon. The NOESY correlations from H-12 to H-7β and H-11β indicated the α-orientation of the OH group.

The HRFABMS spectrum of tehuanine H (**8**) showed a pseudomolecular ion at m/z 357.1347 ($C_{20}H_{20}O_6$). The IR spectrum showed absorptions typical of a furan ring, γ- and δ-lactones, and a double bond. The NMR spectra of **7** and **8** were quite similar, but compound **8** lacked the OH group of **7**. This was evident from the signals at δ_C 46.9 and δ_H 2.63, which were attributed to CH-8 on the basis of the correlations from H-6β and H-11β to C-8, observed in the HMBC spectrum of **8**. The α-orientation of H-8 was deduced from its NOESY interactions with H-19$_{pro\text{-}R}$ and H_3-20, as well as those of H-12 with H-1, H-7β, and H11β. The NOESY spectrum also revealed that **7** and **8** had the same relative configuration in all the other stereogenic centers common to both compounds.

Cytotoxicity of the isolated diterpenes was evaluated against six human cancer cell lines: HCT-15, MCF-7, K-562, U-251, PC-3, and SKLU-1.[15] Only compound **6** showed a marginal cytotoxicity against U251 (IC_{50} 41.86 ± 1.4 μM) and SKLU-1 (IC_{50} 38.92 ± 4.1 μM) cell lines. The anti-inflammatory activity of compounds **4**–**9** and **11** was evaluated using the TPA-induced ear edema model.[16] Compound **7** exhibited anti-inflammatory activity (IC_{50} 0.24 μM/ear) comparable to that of the reference compound (indomethacin). This result suggests the need of a more extensive study of the anti-inflammatory properties of compound **7**.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points (uncorrected) were determined on a Fisher-Johns apparatus. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. UV spectra were recorded on a Shimadzu UV 160U spectrophotometer. IR spectra were obtained on a Bruker Tensor 27 spectrometer. 1D and 2D NMR experiments were performed on a Varian Unity Plus 500 or on a Bruker Avance III spectrometer. Chemical shifts were referred to TMS. EIMS were obtained on a JEOL JMS-AX505HA mass spectrometer. FABMS and HRFABMS were determined on a JEOL JMS-SX102A mass spectrometer. Column chromatography (CC) assisted with vacuum was performed on silica gel 60 (Merck G) or on a bentonitic clay[17] (Tonsil Mexicana). Silica gel 230–400 mesh (Macherey-Nagel) was used for flash chromatography. TLC was carried out on precoated Macherey-Nagel Sil G/UV254 plates of 0.25 thickness. X-ray crystallographic analyses were carried out on a Bruker Smart Apex CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å).

Plant Material. Aerial parts of *S. herbacea* were collected at Tehuantepec, Oaxaca State, México, in August 2009. A voucher specimen (MEXU-1 039 699) was deposited at the National Herbarium.

Extraction and Isolation. The dried and powered aerial parts of *S. herbacea* (4.55 kg) were extracted with Me_2CO. The extract was concentrated at reduced pressure to obtain 308 g of residue, which was defatted by partition between hexane and MeOH–H_2O, 4:1. The hexane fraction was concentrated to obtain 125 g of residue. The MeOH–H_2O fraction was concentrated to one-fifth of its volume and extracted with EtOAc. The EtOAc fraction (172 g) was submitted to CC eluted with hexane–CH_2Cl_2, 1:1 (fractions A and B), CH_2Cl_2 (fraction C), CH_2Cl_2–Me_2CO, 95:5 (fraction D), CH_2Cl_2–Me_2CO, 9:1 (fraction E), CH_2Cl_2–Me_2CO, 7:3 (fraction F), and Me_2CO (fraction G). Fraction B (53.9 g) was separated by CC on bentonitic clay[17] as follows: B1 (hexane, 0.15 g); B2 (hexane–CH_2Cl_2, 1:1; 32.58 g); B3 (EtOAc, 10.88 g). Fractions B2 and B3 were combined and purified by silica gel CC eluted with hexane–EtOAc, 4:1 (B2a, 8.4 g), 3:1 (B2b, 16.5 g), and 7:3 (B2c, 8.9 g). Fraction B2b was subjected to CC eluted with hexane–Me_2CO, 4:1 and 7:3, to obtain fractions B2b1 and B2b2, respectively. Compound **4** (6.18 g) was isolated from fraction B2b1 by crystallization from Me_2CO–hexane. Fraction B2b2 (5.1 g) was a mixture of compounds **4** and **9**. This fraction was purified by CC eluted with $CHCl_3$–EtOAc (98:2 to 70:30). Fractions eluted with $CHCl_3$–EtOAc, 98:2, gave 0.93 g of **4** and 0.48 g of **9**. Fraction B2c was subjected to flash chromatography ($CHCl_3$–EtOAc, 95:5) to give compounds **6** (363.6 mg), **7** (371.1 mg), and **10** (26.9 mg). CC of fraction C eluted with hexane–EtOAc, 7:3 and 6:4, gave C1 (5.55 g) and C2 (22.6 g). Fraction C1 was purified by CC eluted with $CHCl_3$–EtOAc, 95:5, to obtain **4** (2.26 g). Fraction C2 was submitted to CC eluted with hexane–EtOAc, 4:1 (C2a, 0.81 g), 7:3 (C2b, 2.19 g), and 4:6 (C2c, 19.68 g). Compound **4** (726.3 mg) was obtained from fraction C2a. Fraction C2b was purified by CC on bentonitic clay

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to obtain 473.7 mg of **4** eluted with hexane−EtOAc, 7:3, and 449.8 mg of **5** eluted with hexane−EtOAc, 6:4. Fractions C2c1 (2.69 g), C2c2 (8.77 g), and C2c3 (3.25 g) were eluted, respectively, with hexane−EtOAc, 3:2, 2:3, and 7:3, from a bentonitic clay CC of fraction C2c. Fraction C2c1 was purified by bentonitic clay CC eluted with hexane−EtOAc, 3:1 (C2c1a), 7:3 (C2c1b), and 3:7 (C2c1c). Fraction C2c1a gave compound **4** (307 mg). Fraction C2c1b was purified by successive CCs eluted with hexane−EtOAc, 3:1, and $CHCl_3$−EtOAc, 19:1, to obtain compound **1** (17.9 mg). Compounds **2** (34.9 mg) and **5** (477.7 mg) were obtained after two successive CCs of fraction C2c1c (hexane−EtOAc, 7:3; hexane−EtOAc, 19:1). Silica gel CC of fraction C2c2 ($CHCl_3$−EtOAc, 19:1) gave **8** (650.4 mg), while CC of fraction C2c3 ($CHCl_3$−EtOAc, 19:1) gave 225.5 mg of **6** and the mixture of compounds **1**, **6**, and **8**, which were purified by CC eluted with hexane−EtOAc mixtures of increasing polarity; 82.2 mg of **1**, 69.4 mg of **6**, and 55.9 mg of **8** were obtained. 5,6,3′-Trihydroxy-7,4′-dimethoxyflavone (492 mg) was obtained by crystallization (MeOH) from fraction D. Its mother liquors were purified by CC eluted with hexane−EtOAc, 3:2 and 2:3, to obtain fractions D1 and D2, respectively. Fraction D1 (11.3 g) was subjected to CC on bentonitic clay using hexane−EtOAc, 3:2 and 2:3, to obtain D1a and D1b. Silica gel CC ($CHCl_3$−EtOAc, 9:1) of D1b yielded **3** (34.5 mg).

*Tehuanin A (**1**):* colorless crystals (Me_2CO−hexane); mp 240−242 °C; $[\alpha]^{25}_D$ −56.4 (*c* 0.11, Me_2CO); UV (MeOH) λ_{max} (log ε) 207 (3.91), 307 (2.88) nm; IR (KBr) ν_{max} 1772, 1747, 1504, 895 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; FABMS *m*/*z* 357 $[M + H]^+$; HRFABMS *m*/*z* 357.1330 (calcd for $C_{20}H_{21}O_6$, 357.1338).

X-ray Single-Crystal Structure Determination of 1 (ref 18). Crystal data were collected from a colorless block (0.314 × 0.184 × 0.082 mm) at 298(2) K: $C_{20}H_{20}O_6$, MW = 356.36, monoclinic, space group $P2_1$, unit cell dimensions a = 7.344(2) Å, b = 12.490(3) Å, c = 8.907(2) Å, $\alpha = \gamma = 90°$, β = 90.641(5)°; V = 817.0(4) Å^3, Z = 2, D_c = 1.449 Mg/m^3, $F(000)$ = 376. A total of 2036 reflections were collected in the range 2.29° < θ < 27.89°, with 2036 independent reflections [R(int) = 0.0637]; completeness to θ_{max} was 99.5%. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, with anisotropic temperature factors for non-hydrogen atoms converging at final R indices [$I > 2\sigma(I)$], R_1 = 0.0513, wR_2 = 0.1114; R indices (all data), R_1 = 0.0700, wR_2 = 0.1190.

*Tehuanin B (**2**):* amorphous powder; $[\alpha]^{25}_D$ −40.8 (*c* 0.24, Me_2CO); UV (MeOH) λ_{max} (log ε) 212 (4.10) nm; IR (film) ν_{max} 1750, 1505, 875 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; EIMS *m*/*z* 356 $[M]^+$ (6); HRFABMS *m*/*z* 357.1335 (calcd for $C_{20}H_{21}O_6$, 357.1338).

*Tehuanin C (**3**):* amorphous powder; $[\alpha]^{25}_D$ −50.0 (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 212 (3.36), 265 (2.53) nm; IR (film) ν_{max} 3497, 1754, 1505, 875 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; EIMS *m*/*z* 372 $[M]^+$ (14); HRFABMS *m*/*z* 373.1281 (calcd for $C_{20}H_{21}O_7$, 373.1287).

*Acetyltehuanin C (**3a**).* A solution of **3** (17.4 mg, 0.05 mmol) in pyridine (0.2 mL) and Ac_2O (0.2 mL) was stirred for 24 h at 50 °C. The reaction mixture was worked up as usual to obtain a residue, which was purified by CC (hexane−EtOAc, 3:2) to give 4.5 mg (23%) of **3a** as an amorphous solid: ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; HRFABMS *m*/*z* 415.1394 (calcd for $C_{22}H_{23}O_8$, 415.1393).

*Tehuanin D (**4**):* colorless crystals (Me_2CO−hexane); mp 224−226 °C; $[\alpha]^{25}_D$ −174 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 209 (3.93), 266 (3.90), 273 (3.89) nm; IR (KBr) ν_{max} 3432, 3148, 1757, 1718, 1505, 872 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Tables 2 and 3; EIMS *m*/*z* 356 $[M]^+$ (16); HRFABMS *m*/*z* 357.1335 (calcd for $C_{20}H_{21}O_6$, 357.1338).

*Tehuanin E (**5**):* colorless crystals (EtOAc−hexane); mp 247−249 °C; $[\alpha]^{25}_D$ −30 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 210 (3.97) nm; IR (KBr) ν_{max} 3428, 3150, 1757, 1718, 1504, 875 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$+ DMSO-d_6) see Tables 2 and 3; EIMS *m*/*z* 372 $[M]^+$ (5); HRFABMS *m*/*z* 373.1282 (calcd for $C_{20}H_{21}O_7$, 373.1287).

X-ray Single-Crystal Structure Determination of 5 (ref 18). Crystal data were collected from a colorless prism (0.314 × 0.228 × 0.218 mm) at 298(2) K: $C_{20}H_{20}O_7$, MW = 372.36, orthorhombic, space group $P2_12_12_1$, unit cell dimensions a = 7.163(1) Å, b = 15.233(2) Å, c = 15.892(3) Å, V = 1734.1(5) Å^3, Z = 4, D_c = 1.426 Mg/m^3, $F(000)$ = 784. A total of 11 482 reflections were collected in the range 1.85° < θ < 27.89°, with 2371 independent reflections [R(int) = 0.0548]; completeness to θ_{max} was 99.8%. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, with anisotropic temperature factors for non-hydrogen atoms converging at final R indices [$I > 2\sigma(I)$], R_1 = 0.0545, wR_2 = 0.1110; R indices (all data), R_1 = 0.0768, wR_2 = 0.1205.

*Tehuanin F (**6**):* colorless crystals (MeOH−H_2O); mp 206−208 °C; $[\alpha]^{25}_D$ −93.9 (*c* 0.23, Me_2CO); UV (MeOH) λ_{max} (log ε) 210 (4.02) nm; IR (KBr) ν_{max} 3519, 1767, 1731, 1678, 1512, 871 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Tables 2 and 3; EIMS *m*/*z* 372 $[M]^+$ (18); HRFABMS *m*/*z* 373.1288 (calcd for $C_{20}H_{21}O_7$, 373.1287).

*16-Bromotehuanin F (**6a**).* A 0.2 mL (0.16 mmol) amount of a solution of bromine (0.2 mL) in CH_2Cl_2 (5.0 mL) was dropwise added to a stirred solution of **6** (35.4 mg, 0.095 mmol) in CH_2Cl_2 (10 mL) at 0 °C, under N_2. The reaction mixture was kept at 0 °C for 1 h, then at room temperature for 1 h. The reaction was washed with saturated $NaHCO_3$ (3 × 5 mL), dried over anhydrous Na_2SO4, and concentrated under reduced pressure to yield an oil, which was purified by silica gel CC ($CHCl_3$/AcOEt, 9:1) to give 8.5 mg (19.8%) of **6a** as colorless crystals (EtOAc/hexane): mp 230−232 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (1H, d, J = 2.5 Hz, H-15), 6.50 (1H, d, J = 2.5 Hz, H-14), 6.41 (1H, m, H-3), 5.65 (1H, d, J = 7.5 Hz, H-19$_{pro\text{-}R}$), 5.16 (1H, dd, J = 10.5, 7.5 Hz, H-12), 4.68 (1H, m, H-7), 4.13 (1H, br s), 3.93 (1H, dd, J = 7.5, 2.5 Hz, H-19$_{pro\text{-}S}$), 3.52 (1H, br s, H-1), 3.10 (1H, d, J = 3.0 Hz, H-8), 2.95 (1H, ddd, J = 21.0, 3.0, 1.5 Hz, H-2a), 2.74 (1H, ddd, J = 21.0, 4.0, 2.5 Hz, H-2b), 2.42 (1H, dd, J = 14.0, 2.5 Hz, H-6α), 2.08 (1H, dd, J = 13.5, 7.5 Hz, H-11β), 2.00 (1H, ddd, J = 14.0, 3.5, 2.0 Hz, H-6β), 1.43 (1H, dd, J = 13.5, 10.5 Hz, H-11α), 1.42 (3H, s, H-20); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1 (C, C-17), 168.7 (C, C-18), 145.3, (CH, C-15), 134.2 (C, C-4), 127.7 (CH,C-3), 122.5 (C, C-13), 121.6 (C, C-16), 111.0 (CH, C-14), 73.3, (CH_2, C-19), 71.3 (CH, C-12), 66.3 CH, C-7), 63.9 (C, C-10), 57.6 (CH, C-1), 48.4 (CH, C-8), 43.1 (C, C-5), 39.8 (C, C-9), 37.3 (CH_2, C-11), 34.3 (CH_2, C-6), 27.5 (CH_2, C-2), 23.7 (CH_3, C-20); HRFABMS *m*/*z* 451.0398 (calcd for $C_{20}H_{20}O_7{}^{79}Br$, 451.0392).

X-ray Single-Crystal Structure Determination of 6a (ref 18). Crystal data were collected from a colorless prism (0.458 × 0.092 × 0.062 mm) at 298(2) K: $C_{20}H_{19}BrO_7$, MW = 451.26, orthorhombic, space group $P2_12_12_1$, unit cell dimensions a = 7.503(1) Å, b = 8.168(2) Å, c = 31.10(1) Å, V = 1906.2(6) Å^3, Z = 4, D_c = 1.572 Mg/m^3, $F(000)$ = 920. A total of 13 237 reflections were collected in the range 2.58° < θ < 25.34°, with 3473 independent reflections [R(int) = 0.0735]; completeness to θ_{max} was 99.8%. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, with anisotropic temperature factors for non-hydrogen atoms converging at final R indices [$I > 2\sigma(I)$], R_1 = 0.0579, wR_2 = 0.1381; R indices (all data), R_1 = 0.1120, wR_2 = 0.1636.

*Tehuanin G (**7**):* colorless crystals (EtOAc−hexane); mp 180−182 °C; $[\alpha]^{25}_D$ −76 (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 210 (4.25) nm; IR (KBr) ν_{max} 3409, 1759, 1718, 1505, 873 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Tables 2 and 3; EIMS *m*/*z* 372 $[M]^+$, (0.2); HRFABMS *m*/*z* 373.1285 (calcd for $C_{20}H_{21}O_7$, 373.1287).

*Tehuanin H (**8**):* colorless crystals (EtOAc−hexane); mp 243−245 °C; $[\alpha]^{25}_D$ −58.5 (*c* 0.13, Me_2CO); UV (MeOH) λ_{max} (log ε) 210 (4.05) nm; IR (KBr) ν_{max} 3397, 1772, 1708, 1501, 874 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Tables 2 and 3; FABMS *m*/*z* 357 $[M + H]^+$; HRFABMS *m*/*z* 357.1347 (calcd for $C_{20}H_{21}O_6$, 357.1338).

Cytotoxicity Assay. Cytotoxic activity was evaluated by the sulforhodamine B method (SRB), following protocols established by the NCI.[15] All the isolates were screened *in vitro* against six human cancer cell lines: HCT-15 (colorectal adenocarcinoma), K-562 (chronic myelogenous leukemia), MCF-7 (mammary adenocarcinoma), PC-3 (prostatic adenocarcinoma), U-251 (glioblastoma), and SKLU-1 (lung adenocarcinoma) cell lines, supplied by the National Cancer Institute (NCI, USA). Cell lines were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 000 units/mL penicillin G sodium, 10 000 μg mL^{-1} streptomycin sulfate, 25 μg mL^{-1} amphotericin B (Gibco), and 1%

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nonessential amino acids (Gibco). Cells were maintained at 37 °C in a humidified atmosphere with 5% CO_2. Viability of the cells used in the experiments exceeded 95%, as determined by the trypan blue assay. The cells were removed from the tissue culture flasks by treatment with trypsin and diluted with fresh media. Cell suspensions (100 μL, containing 5000 or 7500 cells per well) were placed into 96-well microtiter plates (Costar) and incubated at 37 °C for 24 h in a 5% CO_2 atm. A 100 μL aliquot of the test compounds at concentrations ranging from 1×10^{-3} to 50 μM was added to each well. Camptothecin was used as reference. The cultures were exposed to the drug for 48 h. After the incubation period, cells were fixed by addition of 50 μL of cold 50% aqueous trichloroacetic acid. The plates were incubated at 4 °C for 1 h, washed with tap H_2O, and air-dried. The cells were stained with 0.4% SRB, washed with 1% aqueous acetic acid, and air-dried. Bound dye was solubilized with 10 mM unbuffered Tris base (pH 10.5, 100 μL). The plates were placed on a shaker for 5 min, and the absorption was determined at 515 nm using an ELISA plate reader (Bio-Tex Instruments).

Anti-inflammatory Activity. Anti-inflammatory activity was evaluated in the 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced ear edema model as previously described.[16] Groups of five male CD-1 mice weighing 25−30 g (in accord with the Mexican official norm MON-062-Z00-1999) were anaesthetized with sodium pentobarbital. TPA (2.5 μg) dissolved in EtOH (10 μL) was topically applied to both sides of the right ear of the mice (5 μL each side). The left ear received only EtOH (10 μL). After 10 min, doses of 0.1 to 1.0 μM of the test compounds or indomethacin (reference compound) dissolved in 20 μL of acetone were applied to the right ear (10 μL each side). Control animals received only vehicle (20 μL). Four hours later the animals were sacrificed by cervical dislocation, and a plug (7 mm diameter) was removed from each ear. The swelling was assessed as the difference in weight between the left and the right ear. The percent of inhibition was calculated by the following equation: $\% = [(A - B)/A]100$; A = edema induced by TPA; B = edema induced by TPA plus sample. Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's test. The IC_{50} values were estimated from the linear regression equation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

1D and 2D NMR spectra of compounds **1**−**8**, **3a**, **6a**, and **11**, together with ^1H and ^{13}C NMR data of compound **9**, are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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