Unsaturated Diterpenoids with a Novel Carbocyclic Skeleton from *Salvia xalapensis*

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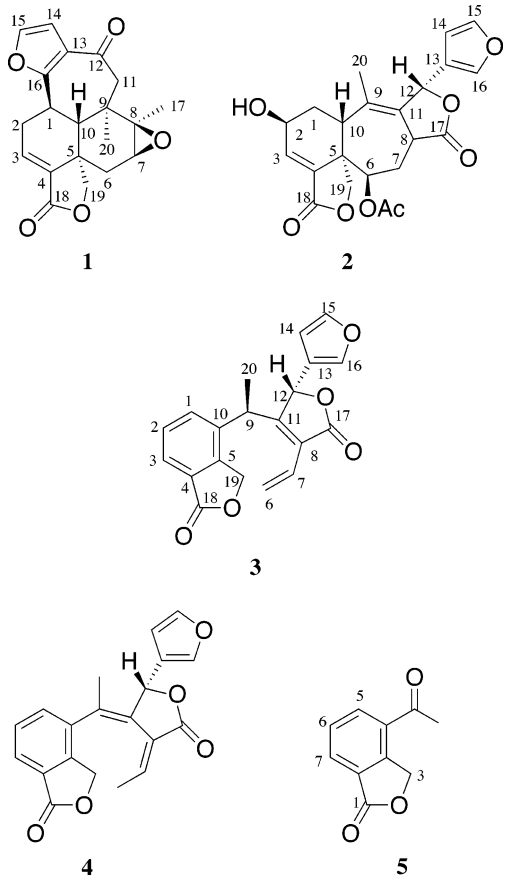
Two diterpenoids with an unprecedented carbocyclic skeleton, salvixalapadiene (**3**) and isosalvixalapadiene (**4**), have been obtained from the leaves of *Salvia xalapensis.* The rearranged skeleton of these products may be derived biogenetically from a salvigenane precursor. In addition, two new rearranged diterpenoids (**1** and **2**) belonging to already known skeletons were isolated. The structures of the new compounds (**1**−**4**) were elucidated on the basis of spectroscopic data interpretation.

Plants of the genus *Salvia* (Labiatae) have attracted much attention owing to a variety of medicinal properties and biological activities attributed to them. For example, antibacterial, antioxidant, antidiabetic, and antitumor properties have been described for these plants and their constituents.[1] One of the most distinguishing features of *Salvia* species studied until now is the number of rearranged diterpenoid derivatives produced belonging to different carbocyclic skeletons, of which most can be related biogenetically to clerodane precursors, although some rearranged abietane and pimarane derivatives have also been isolated.[2] As part of our continuing investigations of Mexican *Salvia* species, we describe herein the diterpenoid constituents of *Salvia xalapensis* Benth. (*Salvia* subgenus *Jungia*, section *Angulatae*).[3] Six rearranged diterpenoids were isolated from the leaves of this plant. Whereas diterpenoids **1** and **2** belong to the already known languidulane and salvigenane skeletons, diterpenoids **3** and **4** are based on an unprecedented rearranged skeleton, which has been named salvixalapane.

The acetone extract of the leaves of *S. xalapensis* was repeatedly chromatographed over silica gel to afford six compounds. Two of them were already known, namely, salvisousolide, a languidulane-type diterpenoid previously isolated from *Salvia sousae*,[4] and salvigenolide, originally obtained from *Salvia fulgens.*[5] The latter compound was identified by comparison with an authentic sample.

A new languidulane derivative, named salvixalapoxide (**1**), was isolated as a crystalline solid, mp 280−281 °C. HRMS indicated $C_{20}H_{20}O_5$ as the molecular formula. Its IR spectrum showed the presence of a furan ring, an α,β-unsaturated γ-lactone moiety, and an α,β-unsaturated ketone group. The ^{1}H and ^{13}C NMR data of **1** supported the presence of an α,β-substituted furan ring characteristic of a languidulane-type diterpenoid with a carbonyl group at C-12 and an α,β-unsaturated γ-lactone bound to the A-ring, as in languiduline, salvisousolide, and related languidulane derivatives.[2] An AB system, observed in the ^{1}H NMR spectrum of **1** at δ 4.72 and 4.09 (J = 8.0 Hz), was assigned to the C-19 methylene protons. The pro-*S* H-19 signal (δ 4.09) showed an additional long-range coupling of 2.5 Hz with the H-6β signal. This observation indicated the lack of any substituent at the C-6β position and the axial orientation of the C-19 methylene group.[6] A doublet at δ 2.43 (J = 11 Hz) was assigned to H-10, with the coupling constant suggesting an axial orientation for this proton and therefore an A/B *trans* fusion for salvixalapoxide (**1**). A one-proton doublet at δ 3.27 (J = 6.0 Hz) in the ^{1}H NMR spectrum of **1** was ascribed to the proton of an oxirane ring. The chemical shift observed for the methyl protons at C-17 (δ 1.41) suggested that the oxirane ring is located at the C-7 and C-8 positions. The coupling constant apparent for H-7 indicated a β-orientation for the oxirane ring according to the equation of Tori et al.[7] The upfield shift observed for C-10 in the ^{13}C NMR spectrum of **1** (δ 47.9), compared with the same signal in savisousolide (δ 51.8), supported the β-orientation proposed for the oxirane ring.[4]



Compound **2**, named 2β-hydroxysalvigenolide, was isolated as an amorphous powder, $[\alpha]^{20}_D$ −52° (c 0.1, $CHCl_3$)

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Table 1. ^{1}H NMR Data for Compounds **1**−**4**

position	**1**[a]	**2**[b]	**3**[a]	**4**[b]
1	2.87 dt (11.0, 3.0)[c]	α: 1.56 ddd (13.8, 6.9, 2.4) *β*: 1.90−2.16 m	7.41 dd (7.5, 1.5)	7.60 m
2	α: 3.31 ddd (18.0, 8.0, 3.0) *β*: 2.39 ddd (18.0, 11.0, 2.5)	4.50 dt (6.9, 4.0)	7.45 t (7.5)	7.60 m
3	6.92 dd (8.0, 2.5)	7.10 d (6.9)	7.77 dd (7.5 1.5)	7.90 dd (8, 3)
6	α: 2.44 dd (14.5, 6.0) *β*: 1.74 dd (14.5, 2.5)	5.30 t (3.3)	pro-*Z*: 6.63 dd (17.5, 5.0) pro-*E*: 5.71 dd (8.0, 5.0)	0.94 d (3H) (7.8)
7	3.27 d (6.0)	α: 1.90−2.16 m *β*: 2.50 dt (15.0, 3.9)	6.59 dd (17.5, 8.0)	6.71 q (7.8)
8		3.83−3.90 m		
9			4.08 q (7.0)	
10	2.43 d (11.0)	3.83−3.90 m		
11	α: 3.06 d (16.5) *β*: 2.90 d (16.5)			
12		6.05 s	5.68 br s	6.07 s
14	6.72 d (2.0)	6.29 dd (1.5, 1.2)	5.84 dd (1.8, 1.0)	6.35 dd (1.8, 0.9)
15	7.33 d (2.0)	7.49 m	7.17 t (1.8)	7.44 t (1.8)
16		7.49 m	7.24 t (1.0)	7.47 dd (0.9, 1.8)
17	1.41 s			
19	pro-*S*: 4.09 dd (8.0, 2.5)	pro: 3.73 d (9.0)	a: 5.15 d (15.3)	a: 5.16 d (14.5)
	pro-*R*: 4.72 d (8.0)	pro: 4.00 d (9.0)	b: 4.99 d (15.3)	b: 5.12 d (14.5)
20	1.01 s	1.63 s	1.66 d (7.0)	2.13 s
21		2.10 s		
OH		4.60 br s		

[a] Recorded at 500 MHz. [b] Recorded at 300 MHz, $CDCl_3$, TMS. [c] Coupling constants (*J* in Hz) in parentheses.

and proved to have a salvigenane skeleton. The ^{1}H NMR spectrum of **2** was almost identical to that reported for salvigenolide.[5] The observed differences were consistent with the presence of a hydroxyl group at the C-2*β* position. A one-proton double triplet at *δ* 4.50 (*J* = 4 and 6.9 Hz) was assigned to the geminal proton of the hydroxyl group and a doublet at *δ* 7.10 (*J* = 6.9 Hz) to the vinylic H-3. The coupling constant observed for H-2 was in agreement with the *β*-orientation of the hydroxyl group.

Compound **3**, named salvixalapadiene, was isolated as colorless needles, mp 170−171 °C, $[\alpha]^{20}_D$ +54° (*c* 0.1, $CHCl_3$). The HRMS agreed with a $C_{20}H_{16}O_5$ molecular formula, indicating a high degree of unsaturation, which was supported by the UV spectrum. The IR spectrum showed bands due to α,*β*-unsaturated *γ*-lactone groups and a *β*-substituted furan group. The ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2, respectively) were in agreement with the structure depicted as **3**. Three one-proton signals at *δ* 7.41 (dd, *J* = 7.5, 1.5 Hz), 7.45 (t, *J* = 7.5 Hz), and 7.77 (dd, *J* = 7.5, 1.5 Hz) were assigned to the aromatic protons H-1, H-2, and H-3, respectively (Table 1). These signals indicated the presence of a phthalide moiety in **3**. This group is found in ryacophane-derived diterpenoids such as ryacophyline and salvireptanolide.[8,9] A three-proton doublet at *δ* 1.66 (*J* = 7.0 Hz) was assigned to the C-20 methyl group. The chemical shift of this signal is consistent with the allylic and benzylic nature of this moiety. In agreement with this assignment, the signal for H-9 was observed at *δ* 4.08 (q, *J* = 7.0 Hz). A broad singlet at *δ* 5.68 was ascribed to H-12. The signals of a monosubstituted double bond were observed at *δ* 6.63 (1H, dd, *J* = 17.5, 5.0 Hz), 5.71 (1H, dd, *J* = 8.0, 5.0), and 6.59 (1H, dd, *J* = 17.5, 8.0), which were assigned to H-6 pro-*Z*, H-6 pro-*E,* and H-7, respectively. Two sp^2 singlets at *δ* 124.4 and 160.6 in the ^{13}C NMR spectrum of **3** (Table 2) were attributed to C-8 and C-11. A doublet at *δ* 123.2 and a triplet at *δ* 124.1 were ascribed to C-7 and C-6, respectively. The HMBC spectrum of **3** showed correlations between C-11 (*δ* 160.6) and the signals ascribed to H-12, H-9, and H-20. Cross-peaks were also observed for C-1 (*δ* 131.8) and C-10 (*δ* 135.5) with H-9. These HMBC correlations confirmed the connectivity of C-11 to C-1 through C-9. Additional cross-peaks were observed for C-8 (*δ* 124.4) with H-7 and H-6. The signal ascribed to C-17 (*δ* 170.6) correlated with H-7, thus confirming the connectivity of C-6, C-7, C-8, and C-17. Additional relevant HMBC correlations are shown in Figure 1. The relative configuration of **3** was established with the aid of a NOE difference spectroscopy experiment. Nuclear Overhauser enhancement effects were observed between the C-20 methyl group and the protons at C-12 and C-7. In addition, strong NOE enhancements were observed between H-6 pro-*E* with the C-19 methylene protons and H-9 with H-16. These results indicated that in one of the possible minimum energy conformations of **3** the monosubstituted double bond between C-6/C-7 lies out of the plane formed by the C-17, C-8, and C-11 atoms and H-7 points toward the C-20 methyl group, which is spatially close to H-12. In this conformation, H-9 is close to the furan

Table 2. ^{13}C NMR Data for Compounds **1**−**4**

carbon	**1**[b]	**2**[a]	**3**[a]	**4**[b]
1	36.9 (d)	32.1 (t)	131.8 (d)	133.8 (d)
2	33.1 (t)	61.9 (d)	129.8 (d)	130.1 (d)
3	134.3 (d)	137.1 (d)	124.9 (d)	125.4 (d)
4	135.6 (s)	132.3 (s)	144.8 (s)	143.6 (s)
5	45.2 (s)	47.8 (s)	126.0 (s)	126.6 (s)
6	34.7 (t)	70.7 (d)	124.1 (t)	16.2 (q)
7	60.3 (d)	30.0 (t)	123.2 (d)	138.8 (d)
8	63.7 (s)	39.2 (d)	124.4 (s)	126.0 (s)
9	37.5 (s)	136.0 (s)	35.1 (d)	132.3 (s)
10	47.9 (d)	31.1 (d)	135.5 (s)	138.0 (s)
11	53.8 (t)	135.0 (s)	160.6 (s)	131.4 (s)
12	193.3 (s)	75.0 (d)	74.4 (d)	73.9 (d)
13	123.2 (s)	123.9 (s)	120.2 (s)	122.6 (s)
14	109.5(d)	108.1(d)	107.2 (d)	108.6 (d)
15	142.1 (d)	144.9 (d)	144.3 (d)	144.4 (d)
16	158.2 (d)	140.7 (d)	141.6 (d)	140.7 (d)
17	18.8 (q)	176.4 (s)	170.6 (s)	169.6 (s)
18	167.8 (s)	168.2 (s)	170.4 (s)	170.4 (s)
19	71.9 (t)	68.6 (t)	68.6 (t)	69.4 (t)
20	16.8 (q)	15.9 (q)	18.7 (q)	16.2 (q)
21 (Ac)		168.8 (s)		
22 (Me)		20.9 (q)		

[a] Recorded at 125 MHz. [b] Run at 75 MHz.

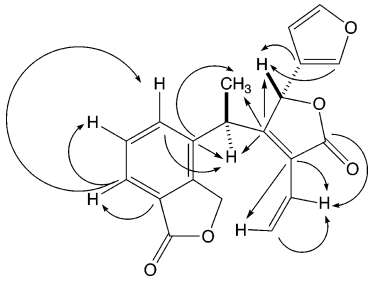

Figure 1. Selected HMBC correlations for compound **3**.

ring. Careful inspection of a molecular model of **3** indicated a free rotation around the axis of the C-9/C-11 bond and a partially restricted one around the C-9/C-10 bond. Interatomic distances calculated after AM1 energy minimization were H-12···Me-20 = 2.4 Å and H-7···Me-20 = 2.04 Å.[10] Figure S1 (Supporting Information) shows one of the most stable conformations of **3**. The configuration at C-12 as *R* could be proposed on the basis of biogenetic grounds, since this is the configuration found, by X-ray analysis, for the same center in several diterpenoids isolated from *Salvia* species, such as salvigenolide, that coexist in the same plant. On the basis of the previous proposal and the results from a NOE experiment, we assigned a C-9*R* configuration as depicted for **3**, thus accounting for the observed NOE correlation observed between the C-20 methyl group and H-12. To the best of our knowledge, this is the first report of a 5,6-*seco*-salvigenane derivative, and the name salvixalapane has been accorded to this new carbocyclic arrangement. A biogenetic pathway to **3** is outlined in Scheme S1 (Supporting Information), starting from a hypothetical salvigenane precursor **7**, which could lead to compound **3** through aromatization of ring A with the concomitant rupture of the C-5/C-6 bond. The presence of salvigenane derivatives in *S. xalapensis* supports the biogenetic hypothesis depicted. Moreover, precursor **7** could be derived from an isosalvigenane derivative such as blepharolide A (**6**). This interesting diterpenoid has been recently isolated from *Salvia blepharophylla*, a Mexican species belonging to the section *Brandegeia* of the subgenus *Jungia*.[11] Compound **3** was unstable under atmospheric conditions and decomposed in the presence of air. From a sample of decomposed **3**, the new phthalide, 4-acetylisobenzofuran-1(3H)-one (**5**), was isolated, suggesting the participation of oxygen in the process of degradation.

Compound **4** (isosalvixalapadiene) was obtained as a crystalline compound, mp 154−155 °C. Spectroscopic data interpretation indicated that **4** is an isomer of salvixalapadiene (**3**). The ^{1}H NMR spectrum of **4** was similar to that obtained for **3** (Table 1). The observed differences were consistent with the presence of two vinylic methyl groups in **4**, which could be obtained from **3** via [1,5]H sigmatropic rearrangement as outlined in Scheme S1 (Supporting Information). The upfield shift observed for the C-6 methyl group (δ 0.94) could be explained after careful inspection of a molecular model of **4** since in one of the possible minimum energy conformations of isosalvixalapadiene the C-6 methyl group points toward the shielding zone of the aromatic ring, thus accounting for the chemical shift observed. In the case of compound **4**, the calculated distance between the aromatic ring and the C-6 methyl group is about 3.082 Å.[10]

Mexican *Salvia* species are a rich source of both *cis*- and *trans*-neoclerodane diterpenoids and also of novel carbocyclic skeletons biogenetically derived from clerodane, abietane, and pimarane precursors. Some salvigenane-derived diterpenoids were recently isolated from a Chinese collection of *Salvia dugesii*.[12] This is the first report of salvixalapane (5,6-*seco*-salvigenane) derivatives and the cooccurrence of several rearranged neoclerodane-derived diterpenoids in a single *Salvia* species.

Experimental Section

General Experimental Procedures. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 polarimeter. IR spectra ($CHCl_3$) were obtained on a FT-IR Magna 750 spectrophotometer. UV spectra (MeOH) were determined on a Perkin-Elmer 552 apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using a Varian Unity Plus 500 apparatus (at 500 and 125 MHz) and a Varian Unity 300 instrument (at 300 and 75 MHz). Chemical shifts (δ values) are reported with respect to residual $CHCl_3$ (δ 7.25) for ^{1}H and to the solvent signal (δ 77.0) for ^{13}C. ^{13}C NMR assignments were confirmed with the aid of HMQC and HMBC spectra. EIMS were obtained on a JEOL JMS-AX505HA and HRMS on a JEOL JMS-SX102A apparatus. Vacuum-column chromatography was performed on standard grade silica gel 60 for TLC without binder. Flash chromatography was carried out on silica gel 60, 200−400 mesh. Analytical TLC separations were run on Alugram Sil G/UV254 sheets.

Plant Material. The aerial parts of *S. xalapensis* were collected in the city of Xalapa, State of Veracruz, Mexico, in December 1999. A voucher specimen (MEXU 996326) has been deposited in the National Herbarium of the Institute of Biology, National Autonomous University of Mexico.

Extraction and Isolation. Air-dried, pulverized leaves (1.2 kg) of *S. xalapensis* were extracted with Me_2CO at room temperature for 5 days. The solvent was removed in vacuo to yield 55 g of a gummy extract, which was partitioned between hexane and MeOH−H_2O (4:1). The MeOH−H_2O-soluble portion (4.6 g) was subjected to vacuum-column chromatography, using mixtures of petroleum ether−EtOAc as eluents. From the fractions eluted with petroleum ether−EtOAc (9:1) betulinol[13] (21 mg) and betulinic acid[14] (25 mg) were isolated. Ursolic acid[15] (50 mg) was obtained from several fractions eluted with petroleum ether−EtOAc (8:2). Fractions eluted with petroleum ether−EtOAc (1:1) were combined and subjected to flash chromatography (CH_2Cl_2−Me_2CO, 4:1) to provide naringenin[16] (6 mg), salvixalapoxide (**1**) (13 mg), and salvigenolide (22 mg). Further fractions eluted with petroleum ether−EtOAc (1:1) was subjected to flash chromatography (petroleum ether−EtOAc, 9:1) to yield 75 mg of salvixalapadiene (**3**) and 15 mg of isosalvixalapadiene (**4**). Fractions eluted with petroleum ether−EtOAc (4:6) from the original vacuum-column chromatography were subjected to flash chromatography using an isocratic mixture of CH_2Cl_2−MeOH (95:5) and provided isosalipurpol[17] (6 mg). Fractions eluted with petroleum ether−EtOAc (1:4) afforded, by precipitation, 2β-hydroxysalvigenolide (**2**) (26 mg), as an amorphous powder. Additional fractions with the same polarity were subjected to further chromatographic purification by flash chromatography (CH_2Cl_2−Me_2CO, 4:1) to afford salvisousolide (12 mg). Compound **3** proved to be unstable to atmospheric conditions and was stored under Ar in the dark. From a sample of pure **3** (15 mg) exposed to ambient conditions for a week, after flash chromatography purification ($C_6H_5CH_3$−MeOH, 99:1), 4-acetylisobenzofuran-1(3H)-one (**5**) (5 mg) was isolated as a crystalline solid.

Salvixalapoxide (1): crystalline solid; mp 280−281 °C (Me_2CO); $[\alpha]^{20}_D$ −309° (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1774, 1660, 1602, 1529, 1384, 1315, 1271, 1136, 1008, 979, 881 cm^{-1} ; UV λ_{max} nm (log ϵ) (MeOH) 264 (3.69), 238 (3.41); ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); EIMS *m/z* 340 (85), 162 (100); HREIMS *m/z* 340.1307 (calcd for $C_{20}H_{20}O_5$ 340.1311).

2β-Hydroxysalvigenolide (2): amorphous powder; $[\alpha]^{20}_D$ −52° (*c* 0.1, $CHCl_3$); IR ν_{max} (film) 3467, 3140, 1766, 1504, 873 cm^{-1}; UV λ_{max} nm (log ϵ) (MeOH) 207 (3.90); ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); EIMS *m/z* 414 (6.6), 129 (25), 95 (40), 91 (31), 55 (37), 43 (100); HREIMS *m/z* 414.1318 (calcd for $C_{22}H_{22}O_8$ 414.1315).

Salvixalapadiene (3): crystalline solid; mp 170−171 °C (Me_2CO); $[\alpha]^{20}_D$ +54° (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$) 1762, 1651, 1597, 1413, 1298, 1056, 1024, 1006, 873 cm^{-1}; UV λ_{max} nm (log ϵ) (MeOH) 236.5 (4.25), 227 (4.55); ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); EIMS *m/z* 336 (75), 268 (27), 175 (100), 161 (50), 95 (76); HREIMS *m/z* 336.0999 (calcd for $C_{20}H_{16}O_5$ 336.0998).

Isosalvixalapadiene (4): crystalline solid; mp 154−155 °C (Me_2CO); IR ν_{max} ($CHCl_3$) 1764, 1646, 1436, 1256, 1050, 1022, 999, 875 cm^{-1}; ^{1}H NMR (Table 1); ^{13}C NMR (Table 2); EIMS *m/z* 336 (100), 307 (70), 197 (50), 95 (42); HREIMS *m/z* 336.0996 (calcd for $C_{20}H_{16}O_5$ 336.0998).

4-Acetylisobenzofuran-1(3*H*)-one (5): crystalline solid; mp 143 °C; IR ν_{max} ($CHCl_3$) 1766, 1682, 1596, 1484, 1447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (1H, dd, J = 7.5, 1.0 Hz, H-7), 8.13 (1H, br d, J = 7.5 Hz, H-5), 7.70 (1H, t, J = 7.5 Hz, H-6), 5.65 (2H, s, OCH_2), 2.69 (3H, s, $COCH_3$); EIMS *m/z* 176 $[M]^+$ (100), 161 (20), 148 (25), 133 (35), 105 (70), 43 (30); HREIMS *m/z* 176.0470 (calcd for $C_{10}H_8O_3$ 176.0473).

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Supporting Information Available: Biogenetic pathway to compounds **3** and **4** and Figure S1 (minimum energy conformation of compound **3**). This information is available free of charge via the Internet at http://pubs.acs.org.

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