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ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · FEBRUARY 2007

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Neo-clerodane Diterpenes from the Hallucinogenic Sage *Salvia divinorum*

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Received September 15, 2006

Seven new neo-clerodane diterpenes, salvidivins A (**2**), B, (**3**), C (**4**), and D (**5**), salvinorins H (**6**) and I (**7**), and divinorin F (**8**), along with eight known neo-clerodane diterpenes, salvinorins A (**1**)−F, divinatorins A and B, and seven other constituents, were isolated from the hallucinogenic sage *Salvia divinorum*. The structures of **1**−**7** were elucidated on the basis of 2D NMR spectroscopic studies.

The Mexican hallucinogenic sage *Salvia divinorum* Epling & Játiva (Laminaceae), which is called "diviner's sage" or "magic mint", contains the neo-clerodane diterpene salvinorin A (**1**) as a hallucinogenic active constituent.[1,2] Recently, due to an increase in the popularity of this hallucinogenic plant as a recreational drug, a number of countries have begun to regulate either or both *S. divinorum* and salvinorin A (**1**) as controlled substances.[3] Salvinorin A (**1**) is a potent naturally occurring non-nitrogenous κ-opioid selective agonist, and hence it is considered to be of interest for the development of novel therapeutic agents for Alzheimer's disease.[4] After the hallucinogenic actions of **1** were revealed, several research groups have studied *S. divinorum* and the salvinorins, and this has resulted in an increasing number of reports on the isolation and synthesis of new neo-clerodane diterpenes during the past few years.[5−18] Recently, two new neo-clerodane diterpenes, salvinicins A and B, were isolated from this same plant material, and it was demonstrated that salvinicin A is a partial κ-opioid agonist, whereas salvinicin B is the first μ-opioid antagonist having a neo-clerodane skeleton.[19,20] Such research reports have shown further possibilities for the use of *S. divinorum* as a resource for new bioactive compounds, and this encouraged us to attempt the isolation of new salvinorin-like diterpenoids from this hallucinogenic sage. Herein, we report a study on the isolation and structure determination of the new compounds **1**−**7** from this plant.

Results and Discussion

A dichloromethane-soluble portion (72 g) of the methanol extract (123 g) of the commercially available dried leaves (970 g) of *S. divinorum* was subjected to silica gel open-column chromatography using an *n*-hexane−ethyl acetate solvent mixture to afford 12 fractions. The fractions, which showed pink to purple spots on silica gel TLC using a vanillin−phosphoric acid reagent, were further separated by ODS-medium-pressure liquid chromatography (MPLC) using aqueous methanol as elution solvent. These additional fractions were then applied repeatedly to ODS-HPLC using aqueous acetonitrile as elution solvent to yield seven new neo-clerodane diterpenes, named salvidivins A (**2**), B (**3**), C (**4**), and D (**5**), salvinorins H (**6**) and I (**7**), and divinorin F (**8**). In addition to these substances, eight known neo-clerodane diterpenes, salvinorins A (**1**)−F[1,2,5,7] and divinatorins A and B,[6] as well as six other constituents that have not been reported from this plant, nepetoidin B,[21,22] dehydrovomifoliol,[23] isololiolide,[24] methyl caffate, methyl 3,4-dihydroxybenzoate, and 3,4-dihydroxybenzaldehyde, along with a previously reported compound, loliolide,[25] were also isolated. The structures of these known compounds were identified by comparison with their published data or with commercially available compounds.

Compounds **2** and **3** gave pseudomolecular ion peaks at *m*/*z* 465.1789 and 465.1765 $[M + H]^+$, respectively, in the HRESIMS, suggesting a molecular formula of $C_{23}H_{29}O_{10}$ in each case. The solubility of both compounds in several deuterated solvents such as $CDCl_3$, CD_3OD, and pyridine-d_5 was low, and the ^{1}H NMR spectra measured in DMSO-d_6 showed broadened peaks. Therefore, the NMR spectra for their structure elucidation were measured in $CDCl_3$−CD_3OD (ca. 1:1) mixtures. Even in this solvent mixture, some of the peaks were broadened in both the ^{1}H and ^{13}C NMR spectra, especially in the olefinic regions. Comparison of the ^{1}H and ^{13}C NMR spectra of **2** and **3** with those of salvinorin A (**1**) suggested that these compounds are structurally similar. In fact, the chemical shift assignments for the A and B rings, and their respective substituents of **2** and **3**, could be assigned readily by comparison to **1**; this was confirmed by analysis of the HMBC spectrum, as shown in Figure 1. The biggest problem with both the ^{1}H and ^{13}C NMR spectra of **2** and **3** was that the signals that should have been assignable to the furan ring of **1** were extremely broad. Only one of the four carbon signals assignable to a furan ring unit of **2** appeared as a peak at δ_C 171.4 in the ^{13}C NMR spectrum. In the HSQC spectrum of **2**, a broad methine proton signal at δ_H 6.10 showed a cross-peak with a broad carbon signal that appeared at δ_C 117.8, and another broad signal at δ_H 6.18 exhibited a cross-peak with an extremely broad signal at around δ_C 98. Also in the HMBC spectrum of **2** a cross-peak was observed between one methylene proton of C-11 at δ_H 1.68 and an extremely broad carbon signal at around δ_C 167.5. In the case of **3**, all four carbon signals corresponding to the furan ring unit could not be observed as discrete peaks. In the HSQC spectrum of **3**, a broad methine proton at δ_H 7.20 showed a cross-peak with a broad carbon signal that appeared around δ_C 147.5. On the other hand, in the HMBC spectrum of **3**, the H-12 methine proton at δ_H 5.40 showed cross-peaks with broad carbon signals around δ_C 136, 147.5, and 170. However, the remaining extremely broad carbon signal at around δ_C 98 did not exhibit any cross-peaks. Although only limited information could be obtained for the furan derivative moieties of **2** and **3**, the signals around δ_C 170 were assigned to carbonyl carbons. Further, a quaternary carbon at C-13 (δ_C 167.5 for **2**, δ_C 136 for **3**) suggested one double bond in the moiety, and the remaining carbon signal around δ_C 98 could be assigned to a hemiacetal. From the HMBC correlations depicted in Figure 1, the structures of **2** and **3** were assigned as shown. Therefore, it is concluded that the furan derivative moieties of both **2** and **3** represent a pair of geometrical isomers of the γ-hydroxy-α,β-unsaturated γ-lactone, which differ from each other at the linkage position to C-12; **2** is linked at the β-position, whereas **3** is linked at the α-position from the carbonyl carbon of the lactone. The relative configuration of **2** and **3** was determined by ROESY NMR correlations, as shown in Figure 1, except for the hemiacetal proton,

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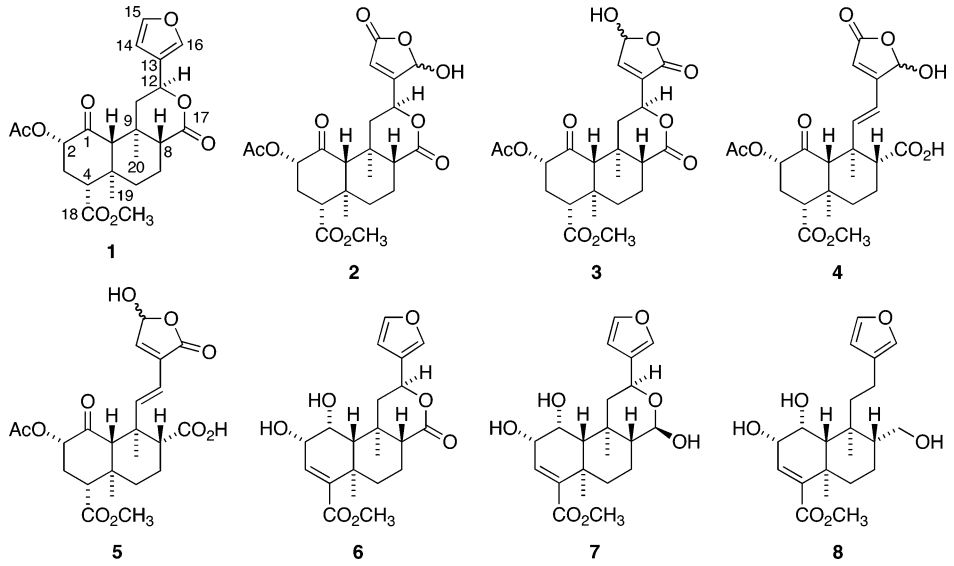
10.1021/np060456f CCC: $33.50
Published on Web 11/17/2006

Chart 1



which did not result in any informative cross-peaks. Thus, structures **2** and **3**, respectively, were proposed for salvidivins A and B.

Compounds **4** and **5** were confirmed to have the same molecular formula as **2** and **3**, respectively, by measurement of their HRESIMS data. Their NMR spectra obtained in CD_3OD showed essentially the same pattern; further, **4** and **5** showed differences in the chemical shifts in the low-field region in both their ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra, one set of *trans* olefinic protons (δ_H 6.33, 6.50, $J = 16.3$ Hz for **4**; δ_H 6.13, 6.72, $J = 16.2$ Hz for **5**) was observed, and these were assigned as protons of a double bond between C-11 and C-12 since HMBC correlations were observed with C-8, C-9, C-10, and C-20. These olefinic protons also had HMBC correlations with carbons at δ_C 99.9 and 164.3 for **4** and at δ_C 133, 144.5, and 172.1 for **5**, as shown in Figure 2; these carbons were assigned as furan ring resonances connected to C-12. Further, HMBC NMR spectroscopic analysis revealed the presence of the same γ-hydroxy-α,β-unsaturated γ-lactone moiety in **2** and **3**. The HMBC spectrum of **5** also confirmed a C-17 carboxylic acid group instead of the lactone ring in the case of **1**−**3**, whereas the HMBC spectrum of **4** failed to give long-range correlations from any proton to a carbon at δ_C 172.6 assigned to C-17. Similar to the ROESY NMR spectra of **2** and **3**, the ROESY spectra of **4** and **5** revealed the same relative configuration for the A and B rings as **1**, as shown in Figure 2. From these data, the structures of **4** and **5** were determined for salvidivins C and D, respectively. In the ^1H NMR spectrum of **4**, H-10 had a split peak, and broad signals of H-8 and H-12 were observed. H-12 showed ROESY correlations with H-14, H-16, and H-20, whereas H-11 exhibited correlations with H-8, H-10, H-14, H-16, and H-20 in the ROESY spectrum of **4**. These observations suggested that rotational conformers with respect to bonds between C-9 and C-11 and between C-12 and C-13 are evident. A similar consideration also applied to **5**, in which both H-11 and H-12 showed ROESY correlations with H-8, H-10, H-14, and H-20. The same applied to **2** and **3**, which showed broad signals around the γ-lactone moiety.

Compound **6** gave a pseudomolecular ion peak at *m/z* of 391.1779 $[M + H]^+$ in the HRESIMS, suggesting a molecular formula of $C_{21}H_{27}O_7$. In the ^1H NMR spectrum, four olefinic protons, of which three were a pair of normal furan rings as in **1**, an absence of acetyl methyl protons, and one additional oxymethine proton were assigned by a general comparison with **1**. Moreover, in the ^{13}C NMR spectrum, the absence of a carbonyl carbon, which was assignable to C-1, and the appearance of one additional double bond were evident by comparison with **1**. Further, observations from the HMBC and ROESY NMR spectra, shown in Figure 3, supported the structure of **6** as salvinorin H, which is the deacetylated derivative of salvinorins C−E.[5,7]

Compound **7** showed pseudomolecular ion peaks at *m/z* 807.3 $[2M + Na]^+$ and 415.2 $[M + Na]^+$ in the ESIMS and a peak at *m/z* 415.1783 $[M + Na]^+$ in the HRESIMS, suggesting a molecular formula of $C_{21}H_{28}O_7$. In the ^1H NMR spectrum, the appearance of two oxymethine protons assignable to H-1 and H-2 and four olefinic protons assignable to a furan ring and the H-3 methine resembled those of **6** fairly closely. One oxymethine proton assignable to H-12 was shifted upfield and one additional oxymethine appeared at δ_H 4.72, in contrast to **6**. The additional oxymethine signal was finally assigned as H-17, since HMBC correlations were observed between the oxymethine proton and C-8, and C-9 and between the oxymethine carbon at δ_C 95.5 and H-8, as shown in Figure 3. Therefore, it was concluded that the lactone ring in **6** is partially reduced to a cyclic acetal in the case of **7**. The relative stereochemistry of the acetal hydroxyl group was assigned with β-orientation since ROESY NMR correlations were observed between H-12,

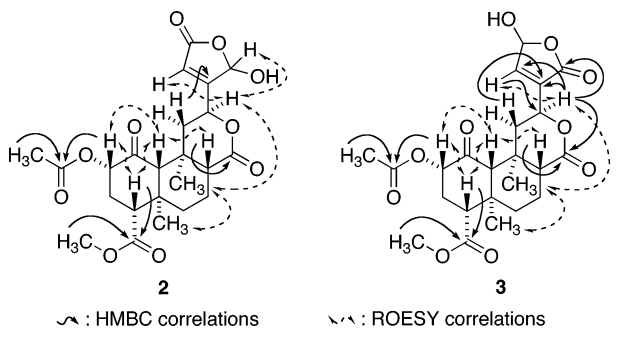


Figure 1. Principal HMBC and ROESY correlations of **2** and **3**.

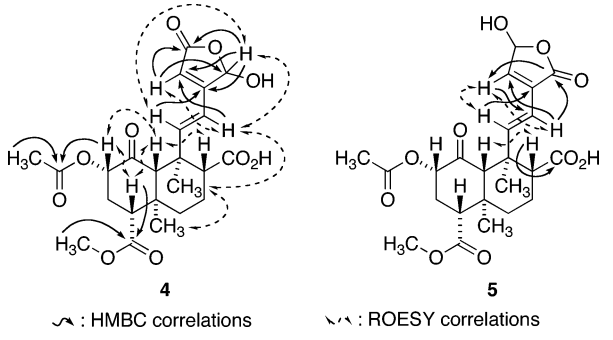
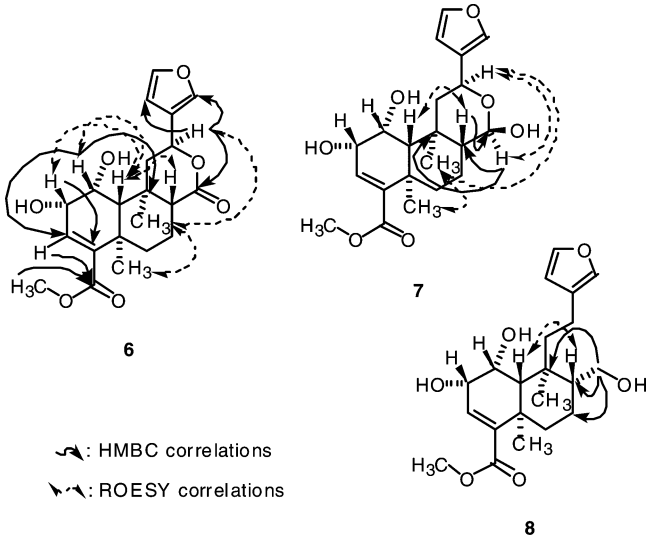


Figure 2. Principal HMBC and ROESY correlations of **4** and **5**.



6 **7** **8**

Figure 3. Principal HMBC and ROESY correlations of **6**−**8**.

H-17, and H-20. On the basis of these data, the structure **7** was proposed for salvinorin I.

Compound **8** was assigned a molecular formula of $C_{21}H_{30}O_6$, as suggested from the pseudomolecular ion peaks at *m*/*z* of 779.4 [2M + Na]$^+$ and 401.2 [M + Na]$^+$ in the ESIMS and a peak at *m*/*z* of 401.1952 [M + Na]$^+$ in the HRESIMS. In the ^{1}H NMR spectrum, the appearance of two oxymethine protons assignable to H-1 and H-2 and four olefinic protons assignable to a furan ring and H-3 methines closely resembled those of **6** and **7**, although one set of oxymethylene protons was observed instead of the disappearance of the H-12 oxymethine proton. A detailed HMBC spectroscopic analysis led to the conclusion that **8** is a divinatorin-type neo-clerodane diterpene that possesses a decalin ring and a furan ring without a lactone ring.[6,12] ROESY NMR spectroscopic analyses confirmed the relative stereochemistry of this isolate. Consequently, the structure **8** was proposed for divinatorin F.

In conclusion, seven new neo-clerodane diterpenes have been isolated from commercially available *S. divinorum*. Salvidivins A (**2**), B (**3**), C (**4**), and D (**5**) are unique neo-clerodane diterpenes that possess a γ-hydroxy-α,β-unsaturated γ-lactone moiety, and the pairs **2** and **3**, and **4** and **5**, respectively, are geometrical isomers at the γ-lactone moiety. It appears that **2** and **3** are important precursors of salvinicins A and B; salvinicin A is described as being a partial agonist of the κ-opioid receptor, whereas salvinicin B is reported to be the first μ-opioid antagonist having a neo-clerodane skeleton.[19,20] Salvinorin H (**6**) has a 1,2-dihydroxy substitution on the A ring. The occurrence of salvinorin H (**6**) was predicted previously;[13] this is because similar salvinorins acetylated at C-1 (salvinorin D), at C-2 (salvinorin E), or at both sites (salvinorin C) have already been isolated from *S. divinorum*.[5,7] Salvinorin I (**7**) is a derivative of **6**, which is partially reduced at C-17, while divinatorin F (**8**) seems to be a precursor of **6**; these three substances have the same A, B ring substitution pattern in their molecules. It would be interesting to ascertain whether or not any of these new compounds also exhibit agonist/antagonist activities against various types of opioid receptors.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanaco MP-J3 micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO P-1030 polarimeter. UV, CD, and IR spectra were obtained with a JASCO V-560 UV/vis spectrophotometer, a JASCO J-820 spectropolarimeter, and a JASCO FT/IR-6300 spectrometer with ATR option, respectively. 1D and 2D ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity INOVA 500 spectrometer at 300 K using Varian standard pulse sequences. Phase-sensitive ROESY experiments were conducted with a mixing time of 300 ms. A 3.57 ms (140 Hz) delay was used to optimize one-bond coupling in the HSQC spectra and suppress it in the HMBC spectra, and the evolution delay for long-range couplings in the HMBC spectra was set to 62.5 ms (8 Hz). ESITOFMS and HRESITOFMS were obtained on a Q-TOF micro-mass spectrometer (Micromass/Waters). Silica gel open-column chromatography was performed on silica gel 60 (Merck). Medium-pressure liquid chromatography (MPLC)

Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Spectroscopic Data for **2** and **3**

	salvidivin A (**2**) in $CDCl_3$−CD_3OD, 1:1		salvidivin B (**3**) in $CDCl_3$−CD_3OD, 1:1	
position	δ_C, mult.	δ_H, mult. (*J* in Hz)	δ_C, mult.	δ_H, mult. (*J* in Hz)
1	203.4, qC		203.4, qC	
2	76.0, CH	5.20, dd (7.3, 12.2)	76.0, CH	5.20, dd (7.6, 12.5)
3	31.3, CH_2	2.27, q-like (13.2)	31.4, CH_2	2.25, q-like (12.9)
		2.34, ddd (3.9,7.6, 13.2)		2.31,[d] dt (3.7, 7.6)
4	53.6, CH	2.90, dd (3.7, 13.2)	53.6, CH	2.92, dd (3.7, 13.2)
5	42.6		42.6, qC	
6	38.3, CH_2	1.68,[c] br-t (12.5)	35.9, CH_2	1.68,[c] br-t (12.2)
		1.79, br-dd (2.9, 10.0)		1.79, br-dt (3.1, 13.1)
7	18.7, CH_2	1.62, br-dt (2.9, 13.2)	18.7, CH_2	1.61, br-dt (3.5, 13.3)
		2.12, br-d (10.5)		2.12, br-dd (3.2, 13.7)
8	51.2,[a] CH	2.36, br-dd (2.7, 11.5)	51.1, CH	2.35,[d] br-dd (3.4, 10.5)
9	35.9,[a] qC		38.4, qC	
10	63.4, CH	2.45,[d] s	63.5, CH	2.47, s
11	41.0,[a] CH_2	1.68,[c] br-t (12.5)	40.6, CH_2	1.68,[c] br-t (12.2)
		2.45,[d] br-s		2.46, dd (5.7, 13.4)
12	73.9,[a] CH	5.49, br-s	72.6,[a] CH	5.40, dd (5.7, 11.8)
13	167.5,[b] qC		136,[b] qC	
14	117.8,[a] CH	6.10, br-s	147.5,[b] CH	7.20, br-s
15	171.4, qC		98,[b] qC	6.18, br-s
16	98,[b] CH	6.18, br-s	170,[b] CH	
17	172.1, qC		172.6, qC	
18	172.8, qC		172.9, qC	
19	16.7, CH_3	1.11, s	16.6, CH_3	1.10, s
20	15.3,[a] CH_3	1.43, s	15.2, CH_3	1.43, s
$OCOCH_3$ (2)	171.2, qC		171.0, qC	
$OCOCH_3$ (2)	20.7, CH_3	2.18, s	20.6, CH_3	2.15, s
$COOCH_3$ (4)	52.3, CH_3	3.74, s	52.2, CH_3	3.73, s

[a] Carbon signal appeared as a broad signal. [b] Carbon signal extremely broad or did not appear clearly; chemical shift value determined from HSQC and/or HMBC spectra. [c] Signals superimposed on each other. [d] Assignments may be exchanged with each other.

Table 2. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Spectroscopic Data for **4** and **5**

	salvidivin C (**4**) in CD_3OD		salvidivin D (**5**) in CD_3OD	
position	δ_C, mult.	δ_H, mult. (*J* in Hz)	δ_C, mult.	δ_H, mult. (*J* in Hz)
1	203.9, qC		203.9, qC	
2	77.0, CH	5.19, dd (71, 12.2)	76.9, CH	5.20, dd (7.2, 12.6)
3	32.2, CH_2	2.15, q-like (13.0)	32.2, CH_2	2.15, q-like (12.9)
		2.29, ddd (3.5, 7.2, 13.1)		2.28, ddd (3.5, 7.2, 12.9)
4	54.1,[a] CH	3.01, dd (3.4, 13.4)	54.0, CH	3.02, dd (3.5, 13.3)
5	43.6, qC		43.4, qC	
6	38.8, CH_2	1.73,[a] m	38.8, CH_2	1.72, br-d (7.3)
		1.73,[a] m		1.72, br-d (7.3)
7	22.0, CH_2	1.78, br-ddd (3.2, 3.4, 11.1)	22.1, CH_2	1.75, br-dd (3.4, 13.4)
		1.95, br-ddt (5.9, 12.5, 12.7)		1.94, m
8	54.1,[a] CH	2.42, br-s	54.2, CH	2.41, dd (2.9, 12.5)
9	42.5, qC		42.1, qC	
10	61.6, CH 61.3, CH	2.81, 2.87, br-s	61.7, CH	2.81, s
11	152.6, CH	6.50, d (16.3)	147.5, CH	6.72, d (16.2)
12	120.4, CH	6.33, br-d (16.3)	118.2, CH	6.13, d (16.2)
13	164.3, qC		133.0, qC	
14	116.5, CH	5.92, s	144.5, CH	7.03, s
15	173.7,[b] qC		98.4, CH	6.04, br-s
16	99.9, CH	6.13, s	172.1, qC	
17	176.2, qC		176.3, qC	
18	173.6,[b] qC		173.7, qC	
19	16.4, CH_3	1.05, s	16.5, CH_3	1.06, s
20	15.9, CH_3	1.56, s	15.8, CH_3	1.55, s
O*C*OCH_3 (2)	171.6, qC		171.5, qC	
OCO*CH*$_3$ (2)	20.5, CH_3	2.09, s	20.5, CH_3	2.08, s
COO*CH*$_3$ (4)	52.2, CH_3	3.70, s	52.2, CH_3	3.70, s

[a] Signals superimposed on each other. [b] Assignments may be exchanged with each other.

Table 3. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Spectroscopic Data for **6**−**8**

	salvinorin H (**6**) in $CDCl_3$−CD_3OD = 1:1		salvinorin I (**7**) in CD_3OD		divinatorin F (**8**) in $CDCl_3$	
position	δ_C, mult.	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)
1	66.1, CH	4.25, d (4.9)	66.5, CH	4.22, d (4.8)	66.3, CH	4.30, d (4.6)
2	70.3, CH	4.17, dd (2.2, 4.9)	71.1, CH	4.14, dd (2.2, 4.8)	70.0, CH	4.24, dd (2.3, 4.8)
3	138.1, CH	6.49, d (2.2)	138.6, CH	6.45,[b] d (2.2)	135.3, CH	6.45, d (2.3)
4	141.9, qC		142.7, qC		143.0, qC	
5	38.3,[a] qC		39.2, qC		38.0, qC	
6	37.7, CH_2	1.18, dt (3.4, 13.2)	39.3, CH_2	1.13, br-dt (1.1, 8.6)	37.7, CH_2	1.15, dt (3.5, 12.9)
		2.44, dt (3.4, 13.2)		2.39, dt (3.4, 12.9)		2.32, dt (3.3, 12.9)
7	19.3, CH_2	1.77, br-dq (2.8, 13.5)	19.4, CH_2	1.53, dq (3.4, 13.4)	21.8, CH_2	1.54, dq (3.4, 12.9)
		2.00, br-dq (3.4, 14.4)		1.78, dq (3.4, 13.5)		1.85, m
8	52.2, CH	2.44, br-dd (2.7, 12.2)	54.7, CH	1.19, br-dt (2.2, 5.8)	44.5, CH	1.60, m
9	38.2,[a] qC		38.3, qC		38.8, qC	
10	54.5, CH	1.28, br-s	56.2, CH	1.16, br-s	48.1, CH	1.42, br-s
11	44.6, CH_2	1.69, br-d (10.3)	46.9, CH_2	1.26, br-t (12.1)	38.9, CH_2	1.78, br-dt (4.4, 12.7)
		2.51, dd (6.1, 13.2)		1.95, dd (3.2, 12.1)		1.88, br-dt (5.1, 15.1)
12	73.3, CH	5.63, dd (5.9, 11.0)	67.6, CH	4.98, dd (2.3, 11.6)	18.3, CH_2	2.07, br-dt (4.7, 13.5)
						4.84, br-dt (4.2, 13.5)
13	126.8, qC		128.7, qC		124.8, qC	
14	109.3, CH	6.47, d (1.5)	110.1, CH	6.46,[b] t (0.9)	110.9, CH	6.25, d (0.7)
15	144.7, CH	7.45, d (1.7)	144.1, CH	7.42, t (1.6)	142.9, CH	7.34, d (1.6)
16	140.6, CH	7.52, t (0.7)	140.4, CH	7.48, d (0.7)	138.5, CH	7.20, s
17	174.5, qC		95.5, CH	4.72, d (9.0)	63.9, CH_2	3.38, dd (8.1, 10.5)
						3.83, dd (3.7, 10.5)
18	168.1, qC		168.5, qC		167.1, qC	
19	22.2, CH_3	1.68, s	22.8, CH_3	1.68, s	21.9, CH_3	1.65, s
20	16.4, CH_3	1.44, s	16.5, CH_3	1.45, s	21.2, CH_3	1.18, s
COO*CH*$_3$ (4)	51.9, CH_3	3.69, s	51.9, CH_3	3.69, s	51.6, CH_3	3.72, s

[a] Assignments may be exchanged with each other. [b] Signals superimposed on each other.

was performed with a prepacked glass column (Ultra Pack: 26 mm i.d. × 300 mm for medium-scale separation, 50 mm i.d. × 300 mm for large-scale separation; Yamazen Corporation, Kyoto, Japan) packed with 50 μm octadecyl silica gel (ODS). HPLC was performed with an Inertsil PREP-ODS column (6 mm i.d. × 250 mm for analysis, 20 mm i.d. × 250 mm for preparative; GL Science Inc., Tokyo, Japan) packed with 10 μm ODS. TLC was conducted on precoated silica gel 60 F_{254} (Merck) and/or RP-18 F_{254s} (Merck), and the spots were detected by heating after spraying with vanillin−phosphoric acid reagent.

Plant Material. Dried *S. divinorum* leaves were purchased in June 2005 from Ethnogens.com (Lawrence, KS). Voucher specimens were deposited at the Medicinal Herbarium, Faculty of Pharmaceutical Sciences at Kagawa campus, Tokushima Bunri University, specimen # 050601-001.

Extraction and Isolation. Commercial dried *S. divinorum* leaves (970 g) were powdered and extracted with MeOH three times around 40 to 50 °C, and the MeOH solution was evaporated in vacuo under 40 °C to yield a MeOH extract (123 g). The extract was partitioned between CH_2Cl_2 and water three times and evaporated to give a CH_2Cl_2-soluble portion (72 g). The CH_2Cl_2-soluble portion was then chromatographed over a silica gel open column (0.6 kg; 50 × 540 mm) eluted with an *n*-hexane−EtOAc gradient solvent system (10:0, 8:2, 1:1, 0:10, then MeOH) to yield 12 fractions. Fraction (Fr.) numbers 4 to 10 showed pink to purple spots by TLC (*n*-hexane−

EtOAc, 1:1) by spraying with vanillin−phosphoric acid spray reagent. The positive fractions were separated by ODS MPLC with aqueous MeOH as elution solvent. The MPLC-derived fractions were further purified by ODS HPLC with aqueous acetonitrile as elution solvent to yield seven new compounds: salvidivins A (**2**, 85 mg) and B (**3**, 80 mg) from Fr. 5−8 eluted with 35% acetonitrile; salvidivins C (**4**, 41 mg) and D (**5**, 42 mg) from Fr. 5 eluted with 33% acetonitrile; salvinorin H (**6**, 120 mg) from Fr. 5−7 eluted with 35% acetonitrile; and salvinorin I (**7**, 6.5 mg) and divinorin F (**8**, 15 mg) from Fr. 5 eluted with 33% and 35% acetonitrile, respectively. The known salvinorins A (**1**, 2.0 g), B (37 mg), C (176 mg), D (180 mg), E (28 mg), and F (100 mg) and divinatorins A (219 mg) and B (29 mg) were also isolated from Fr. 4−10. Along with them, seven other known constituents, nepetoidin B (15 mg), dehydrovomifoliol (1.5 mg), isololiolide (5.4 mg), methyl caffeate (11 mg), methyl 3,4-dihydroxybenzoate (2.9 mg), 3,4-dihydroxybenzaldehyde (2.7 mg), and loliolide (26 mg), were isolated from Fr. 4−10.

Salvidivin A (2): amorphous solid; mp 217−222 °C; $[\alpha]^{24}_{D}$ −69.6 (*c* 0.28, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 206 (4.07), 253 (sh, 2.88) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 292 (−1.6), 225 (−3.9) nm; IR (ATR) 3324, 2932, 1725, 1456, 1376, 1277, 1230, 1198, 1165, 1134, 1083, 1048, 951, 893, 861, 783, 688, 605 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD, 1:1, 500 MHz) and ^{13}C NMR ($CDCl_3$−CD_3OD, 1:1, 125 MHz), see Table 1; ESITOFMS *m*/*z* 929.4 (15, $[2M + H]^+$), 465.2 (7, $[M + H]^+$), 447.2 (100, $[M - H_2O]^+$); HRESITOFMS *m*/*z* 465.1789 (calcd for $C_{23}H_{29}O_{10}$, 465.1761).

Salvidivin B (3): amorphous solid; mp 216−221 °C; $[\alpha]^{24}_{D}$ −54.2 (*c* 0.28, MeOH); UV (MeOH) λ_{max} (log ϵ) 203.5 (3.92), 248 (sh, 3.15) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 291.5 (−1.9), 222 (−4.4) nm; IR (ATR) 3462, 2955, 1772, 1729, 1702, 1456, 1378, 1276, 1210, 1164, 1147, 1092, 1048, 1005, 935, 886, 770 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD, 1:1, 500 MHz) and ^{13}C NMR ($CDCl_3$−CD_3OD, 1:1, 125 MHz), see Table 1; ESITOFMS *m*/*z* 929.4 (55, $[2M + H]^+$), 465.2 (17, $[M + H]^+$), 387.1 (100, $[M - H_2O - CO_2Me]^+$); HRESITOFMS *m*/*z* 465.1765 (calcd for $C_{23}H_{29}O_{10}$, 465.1761).

Salvidivin C (4): amorphous solid; mp 123−127 °C; $[\alpha]^{22}_{D}$ −133.3 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 269 (3.93) nm; CD (MeOH) λ_{max} nm ($\Delta\epsilon$) 303 (0.2), 266.5 (−3.3), 226 (1.4); IR (ATR) 2953, 1717, 1645, 1437, 1375, 1234, 1169, 1126, 1048, 948, 889, 772 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz), see Table 1; ESITOFMS *m*/*z* 929.4 (15, $[2M + H]^+$), 465.2 (14, $[M + H]^+$), 447.2 (100, $[M - H_2O]^+$); HRESITOFMS *m*/*z* 465.1765 (calcd for $C_{23}H_{29}O_{10}$, 465.1761).

Salvidivin D (5): amorphous solid; mp 185−193 °C; $[\alpha]^{24}_{D}$ −107.2 (*c* 0.27, MeOH); UV (MeOH) λ_{max} (log ϵ) 261 (3.95) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 261.5 (−3.2), 225 (−3.6) nm; IR (ATR) 3381, 2953, 1770, 1729, 1705, 1684, 1438, 1384, 1340, 1281, 1225, 1082, 1009, 928, 774, 662 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz), see Table 1; ESITOFMS *m*/*z* 929.4 (2, $[2M + H]^+$), 465.2 (12, $[M + H]^+$), 387.1 (100, $[M - H_2O - CO_2Me]^+$); HRESITOFMS *m*/*z* 465.1772 (calcd for $C_{23}H_{29}O_{10}$, 465.1761).

Salvinorin H (6): amorphous solid; mp 95−103 °C; $[\alpha]^{22}_{D}$ 29.1 (*c* 0.22, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 209.5 (4.03) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 257.5 (−1.5), 228 (7.0), 203.5 (−8.6) nm; IR (ATR) 3444, 2952, 1715, 1507, 1435, 1375, 1314, 1225, 1142, 1071, 1026, 949, 875, 787, 686, 601 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD, 1:1, 500 MHz) and ^{13}C NMR ($CDCl_3$−CD_3OD, 1:1, 125 MHz), see Table 2; ESITOFMS *m*/*z* 391.2 (42, $[M + H]^+$), 373.2 (100, $[M - H_2O]^+$); HRESITOFMS *m*/*z* 391.1779 (calcd for $C_{21}H_{27}O_7$, 391.1757).

Salvinorin I (7): amorphous solid; mp 217−220 °C; $[\alpha]^{22}_{D}$ −4.2 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ϵ) 210.5 (3.99) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 258.5 (−1.1), 228 (9.2), 203 (−6.9) nm; IR (ATR) 3400, 2945, 1692, 1541, 1507, 1438, 1240, 1174, 1130, 1085, 1039, 1022, 1000, 968, 875, 808, 684, 602 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz), see Table 2; ESITOFMS *m*/*z* 807.3, (30, $[2M + Na]^+$), 415.2 (32, $[M + Na]^+$), 375.2 (22, $[M - H_2O]^+$), 255.1 (100); HRESITOFMS *m*/*z* 415.1783 (calcd for $C_{21}H_{28}O_7Na$, 415.1733).

Divinatorin F (8): amorphous solid; mp 97−99 °C; $[\alpha]^{23}_{D}$ 8.4 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 213 (3.99) nm; CD (MeOH) λ_{max} ($\Delta\epsilon$) 260.5 (−0.9), 227.5 (10.2), 202 (−8.9) nm; IR (ATR) 3395, 2928, 2878, 1704, 1434, 1226, 1164, 1055, 1026, 1007, 873, 777, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 2; ESITOFMS *m*/*z* 779.4, (18, $[2M + Na]^+$), 401.2 (45, $[M + Na]^+$), 343.2 (61), 311.2 (100); HRESITOFMS *m*/*z* 401.1952 (calcd for $C_{21}H_{30}O_6Na$, 401.1940).

Acknowledgment. This work was supported in part by research grants from Research on Regulatory Science of Pharmaceuticals and Medical Devices, H16-iyaku-060 (to O.S.) and H16-iyaku-030 (to S.S.), from the Ministry of Health, Labour and Welfare, Japan.

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NP060456F