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Salvinorin C, a New Neoclerodane Diterpene from a Bioactive Fraction of the Hallucinogenic Mexican Mint *Salvia divinorum*

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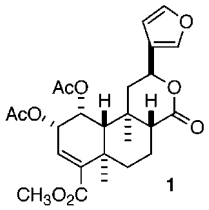
ABSTRACT



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Salvinorin C (1), a minor component from a biologically active TLC fraction, was isolated from the leaves of the Mexican mint *Salvia divinorum*. Its structure was elucidated on the basis of extensive proton and C-13 NMR experiments, as well as by comparison of the NMR data with those of the mono- and diacetate derivatives 5–7 of the major $NaBH_4$-reduction product of salvinorin A (2).

As part of our continuing investigations[1−6] of the psychotropic Mexican labiate *Salvia divinorum* (Epling & Jativá-M.), we report the isolation and structure of a new *trans*-neoclerodane diterpene, salvinorin C (**1**). Previous studies of the mint led to the isolation of salvinorins (divinorins) A (**2**) and B (**3**),[2,7] as well as the unambiguous determination of their absolute stereochemistry[6] by the use of the exciton chirality circular dichroism method.[8] Salvinorin A exhibits activity paralleling that of mescaline, the prototype hallucinogen, in the modified open field bioassay.[2,5,9] Research in humans has shown that, although essentially inactive when taken orally, vaporizing and inhaling 200−500 μg of salvinorin A induces profound hallucinations.[10] Salvinorin A is the first diterpene to be identified as a hallucinogen in humans and is one of the most potent naturally occurring compounds thus far isolated.[11] We have discussed the effects of *S. divinorum* and salvinorin A in animals and humans

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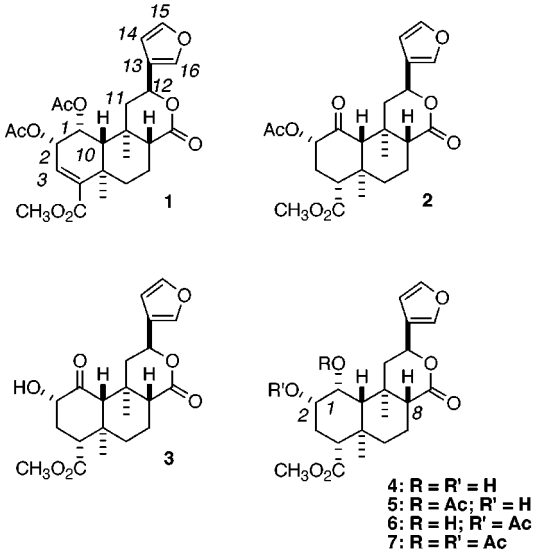
and warned of their potential to become drugs of abuse.[5] During our research on *S. divinorum*, salvinorin A was first isolated from a single pharmacologically active TLC band using a solvent system of 100/10/1 $CHCl_3$/MeOH/H_2O. Differences in potency between the purified diterpene and the original TLC fraction led us to surmise that the latter contained other strongly bioactive compounds that co-chromatographed with salvinorin A during the chromatographic separation. Upon changing the solvent system to 1/1 hexanes/EtOAc, the minor component became separated from salvinorin A. Even though it is estimated that salvinorin C comprises only about 10% of the pharmacologically active TLC fraction, the rest being salvinorin A, the fraction was significantly more potent than an equivalent amount of salvinorin A alone. This seems to indicate that the new diterpene may also have strong psychotropic activity.

Air-dried, pulverized leaves (0.49 kg) of *S. divinorum* were extracted as before[2] with ether, and salvinorins were isolated by repeated flash column chromatography. Final purification of salvinorin C was achieved by HPLC.[12] Repeated recrystallization from hexanes/EtOAc provided pure salvinorin C (**1**)[13] (38.5 mg): mp 196−198 °C, $[\alpha]^{22}_D$ +49.3 (*c* 0.61, $CHCl_3$).



Salvinorin C (**1**) has the molecular formula $C_{25}H_{30}O_9$, and its IR spectrum suggests the presence of an α,β-unsaturated ester (1715 cm^{-1}), as well as another ester and a δ-lactone (1755 and 1735 cm^{-1}, respectively). Its complete structure was elucidated by the use of ^1H and ^{13}C NMR spectroscopy. NMR data were compared with those of salvinorin A (**2**) and the acetate derivatives of the major product obtained by the $NaBH_4$-reduction of salvinorin A. Partial structures deduced by the analysis of NMR data are indicated in connecting thick lines (Figure 1). Although no splitting was

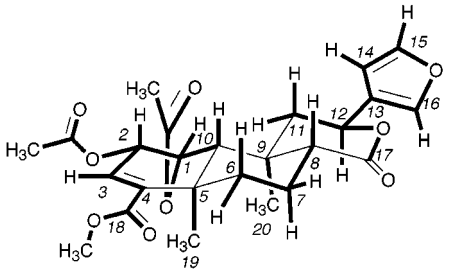


Figure 1. Partial structures and their connectivity (bold lines) established by ^1H and ^{13}C NMR spectroscopy.

visible between H-1 and H-10 in the ^1H NMR spectrum of salvinorin C ($J_{1,10}$ < 0.8 Hz), irradiation of the H-1 peaks sharpened the H-10 singlet. In addition, at the same time the H-3 peaks collapsed into a doublet, confirming the presence of the W-shape coupling between H-1 and H-3 (J = 1.4 Hz). The connectivity between the C-12 and the furan group was established by the detection of the weak coupling between H-12 and H-16 ($^4J_{12,16}$ = 0.8 Hz).

In an effort to further ascertain the structure of salvinorin C, salvinorin A (**2**) was reduced with $NaBH_4$ in isopropyl alcohol (35 °C, 2.5 h). As we reported earlier,[2] the reaction produced a 2.3:1 mixture of *cis*-diol **4** and its C-8 epimer[14] in 87% combined yield. Attempts at directly forming the 1,2-diacetate from diol **4** proved virtually impossible with Ac_2O/pyridine, even at elevated temperatures, presumably as a result of the severe steric hindrance of the 1α-OH imposed by the two 1,3-diaxially juxtaposed methyl groups. Instead, the formation of 2-monoacetate **6**[2] was observed. Therefore, in analogy to a similar situation encountered in our study on forskolin,[15] diol **4** was first treated with trimethyl orthoacetate at 100 °C in the presence of a catalytic amount of acetic acid. Immediate acid-catalyzed hydrolysis of the resulting 1,2-cyclic orthoacetate provided 1-monoaceate **5**[16] in 83% yield, consistent with the general observation on the selective formation of the axial monoester of diols obtainable upon acid hydrolysis of their cyclic ortho ester derivatives.[17] Acetylation of **5** under standard conditions then afforded the desired 1,2-diacetate **7**[18] in 94% yield.

Comparison of the ^{13}C NMR chemical shifts of salvinorin C (**1**), monoacetates **5** and **6**, and diacetate **7** (Table 1) gave

(12) A 10-μm Radial Pak Microporasil silica gel column (10 cm × 8 mm id) eluted with an isocratic solvent mixture of 10% acetonitrile, 30% methyl-*tert*-butyl ether, and 60% hexanes with a flow rate of 1.5 mL/min.

(13) Salvinorin C (**1**): IR (KBr) 3150, 2950, 2920, 2850, 1755, 1735, 1715, 1635, 1430, 1370, 1310, 1225, 1140, 1070, 1035, 955, 905, 870, 785, 765 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{25}H_{30}O_9$ 474.1890, found 474.1865.

(14) Data for the 8-epimer of diol **4**: mp 234−235 °C (EtOH); $[\alpha]^{22}_D$ +8.8 (*c* 0.24, MeOH); ^1H NMR (400 MHz, acetone−d_6) δ 0.97 (d, 1H, J = 1.1 Hz), 1.33 (s, 3H), 1.43 (ddd, 1H, J = 13.7, 4.5, 3.9 Hz), 1.60 (ddd, 1H, J = 13.7, 13.6, 5.0 Hz), 1.58−1.68 (m, 1H), 1.70 (s, 3H), 1.82 (dd, 1H, J = 12.1, 11.6 Hz), 1.91 (dddd, 1H, J = 13.6, 13.3, 4.7, 3.9 Hz), 2.03 (dddd, 1H, J = 13.3, 5.0, 4.5, 1.9 Hz), 2.14 (dd, 1H, J = 11.6, 1.9 Hz), 2.16 (dd, 1H, J = 9.7, 1.9 Hz), 2.17 (ddd, 1H, J = 12.0, 11.5, 9.7 Hz), 2.60 (dd, 1H, J = 4.7, 1.9 Hz), 2.86 (s, 1H, 1-OH), 2.89 (s, 1H, 2−OH), 3.60 (ddd, 1H, J = 11.5, 4.5, 2.3 Hz), 3.62 (s, 3H), 4.09 (dd, 1H, J = 2.3, 1.1 Hz), 5.49 (ddd, 1H, J = 12.1, 1.9, 1.2 Hz), 6.58 (dd, 1H, J = 1.8, 0.7 Hz), 7.57 (dd, 1H, J = 1.8, 1.7 Hz), 7.66 (ddd, 1H, J = 1.7, 1.2, 0.7 Hz); ^{13}C NMR (75 MHz, acetone-d_6) δ 17.36 (q), 18.91 (t), 26.59 (q), 29.77 (t), 37.43 (s), 37.51 (s), 37.85 (t), 46.85 (d), 49.67 (t), 51.15 (q), 55.38 (d), 55.48 (d), 70.08 (d), 70.21 (d), 71.93 (d), 109.66 (d), 125.90 (s), 140.80 (s), 144.38 (d), 173.75 (s), 174.31 (s). Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.60; H, 7.23. Found: C, 64.14; H, 7.18.

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Table 1. NMR Data for **1** and **5**−**7** in $CDCl_3$ [a]

	salvinorin C (**1**)		1-OAc **5**	2-OAc **6**	diacetate **7**
	δ_H	δ_C	δ_C	δ_C	δ_C
1	5.76 br d (5.1)	69.40	71.29	71.70	71.78
2	5.55 dd (5.1, 2.4)	64.36	70.10	67.33	67.34
3	6.50 dd (2.4, 1.4)	132.62	28.77	24.90	25.79
4		143.02	52.98	54.99	52.82
5[b]		38.25	37.22	37.86	37.54
6α	2.60 ddd (12.9, 3.3, 3.2)	37.19	40.74	40.65	40.74
6*β*	1.23 ddd (12.9, 12.8, 3.9)				
7α	1.82 dddd (14.2, 12.8, 12.4, 3.2)	18.53	18.80	18.72	18.74
7*β*	2.09−2.18 m				
8	2.13 dd (12.4, 3.3)	52.82	51.47	52.55	51.52
9[b]		37.38	37.49	36.95	37.38
10	1.50 br s	51.93	54.87	55.91	54.77
11α	2.49 dd (12.9, 5.9)	44.43	44.48	44.39	44.31
11*β*	1.69 dd (12.9, 11.4)				
12	5.54 dd (11.4, 5.9)	71.92	71.84	74.61	71.78
13		125.81	125.85	125.99	125.68
14	6.42 dd (1.9, 1.1)	108.63	108.51	108.44	108.51
15	7.43 dd (1.5, 1.1)	144.19	143.83	143.71	143.78
16	7.45 dd d (1.9, 1.5, 0.8)	139.75	139.55	139.35	139.55
17		170.12	171.62	171.55	171.19
18		166.14	172.55	172.35	172.17
19	1.23 s	21.86	17.66	16.81	17.66
20	1.73 s	15.79	16.20	17.90	16.14
CO_2CH_3	3.78 s	51.99	55.15	51.29	54.99
$OCOCH_3$	2.05 s	20.07	21.45	21.11	20.69
	2.13 s	21.10			21.24
$OCOCH_3$		170.79	171.35	169.51	169.89
		171.68			170.32

[a] 400 MHz for ^1H and 75 MHz for ^{13}C NMR, *J* values (Hz) are given in parentheses. [b] The ^{13}C chemical shift assignments for C-5 and C-9 may be interchanged in each column.

further credence to the proposed structure of salvinorin C. In addition, examination of the ^1H NMR spectra of salvinorin C (**1**) and diacetate **7** was informative in deducing the A-ring stereochemistry of both compounds. A long-range W-type coupling (1.2 Hz) was observed between the two equatorial Hs at C-1 and C-3 in diacetate **7** as in the case of salvinorin C (vide ante).

These salvinorin compounds from *S. divinorum* closely resemble a large number of neoclerodane diterpenes isolated from Latin American *Salvia* plants.[19] It would be interesting to examine if any of those compounds also exhibit psychotropic activity.

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(16) Data for **5**: mp 206−209 °C (hexanes/EtOAc); $[\alpha]^{22}_D$ +7.1 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.36 (s, 3H), 1.42 (ddd, 1H, J = 13.9, 13.0, 3.6 Hz), 1.47 (d, 1H, J = 1.7 Hz), 1.60 (dddd, 1H, J = 14.1, 13.9, 12.1, 2.9 Hz), 1.62 (d, 1H, J = 1.7 Hz), 1.72 (ddd, 1H, J = 13.0, 3.5, 2.9 Hz), 1.73 (dddd, 1H, J = 13.0, 4.9, 2.8, 1.0 Hz), 1.90 (dd, 1H, J = 13.2, 11.7 Hz), 2.00 (dddd, 1H, J = 14.1, 3.6, 3.5, 3.2 Hz), 2.07 (s, 3H), 2.11 (ddd, 1H, J = 13.2, 13.0, 12.1 Hz), 2.32 (dd, 1H, J = 13.2, 2.8 Hz), 2.35 (dd, 1H, J = 12.1, 3.2 Hz), 2.48 (dd, 1H, J = 13.2, 5.4 Hz), 3.64 (s, 1H, OH), 3.65 (s, 3H), 3.68 (ddd, 1H, J = 12.1, 4.9, 1.7 Hz), 5.54 (dd, 1H, J = 11.7, 5.4 Hz), 5.60 (ddd, 1H, J = 1.7, 1.7, 1.0 Hz), 6.59 (dd, 1H, J = 1.8, 0.8 Hz), 7.57 (dd, 1H, J = 1.8, 1.5 Hz), 7.68 (ddd, 1H, J = 1.5, 0.8, 0.8 Hz). Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.42; H, 7.00.

(17) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754−1769.

(18) Data for **7**: mp 211−214 °C (hexanes/EtOAc); $[\alpha]^{22}_D$ −7.5 (*c* 0.81, $CHCl_3$); ^1H NMR (400 MHz, acetone-d_6) δ 1.16 (s, 3H), 1.38 (s, 3H), 1.50 (dddd, 1H, J = 14.0, 12.8, 12.2, 2.6 Hz), 1.62 (d, 1H, J = 1.7 Hz), 1.63 (ddd, 1H, J = 13.0, 12.8, 3.2 Hz), 1.76 (dddd, 1H, J = 12.9, 4.8, 2.8, 1.2 Hz), 1.78 (ddd, 1H, J = 13.0, 3.2, 3.0 Hz), 1.90 (s, 3H), 1.94 (dd, 1H, J = 13.2, 11.7 Hz), 2.02 (dddd, 1H, J = 14.0, 3.3, 3.2, 3.0 Hz), 2.14 (s, 3H), 2.23 (ddd, 1H, J = 13.2, 12.9, 12.4 Hz), 2.32 (dd, 1H, J = 13.2, 5.5 Hz), 2.40 (dd, 1H, J = 12.2, 3.3 Hz), 2.45 (dd, 1H, J = 13.2, 2.8 Hz), 3.67 (s, 3H), 4.81 (ddd, 1H, J = 12.4, 4.8, 3.4 Hz), 5.56 (dd, 1H, J = 11.7, 5.5 Hz), 5.68 (ddd, 1H, J = 3.4, 1.7, 1.2 Hz), 6.58 (dd, 1H, J = 1.8, 0.8 Hz), 7.56 (dd, 1H, J = 1.8, 1.5 Hz), 7.66 (ddd, 1H, J = 1.5, 0.8, 0.8 Hz). Anal. Calcd for $C_{25}H_{32}O_9$: C, 63.01; H, 6.77. Found: C, 62.87; H, 6.71.

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