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FIVE NEW HIGHLY OXIDIZED NEOCLERODANE DITERPENES, SALVILEUCALINS E-I FROM *SALVIA LEUCANTHA*

Yutaka Aoyagi,[1*] Yutaka Nakazato,[2] Akira Yamazaki,[2] Haruna Kondo,[2] Ayana Ninomiya,[2] Mari Tokuda,[2] Haruhiko Fukaya,[2] Reiko Yano,[1] Koichi Takeya,[2] and Yukio Hitotsuyanagi[2*]

[1]College of Pharmacy, Kinjo Gakuin University, 2-1723 Omori, Moriyama-ku, Nagoya 463-8521, Japan; E-mail: yutaka@kinjo-u.ac.jp [2]School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan; E-mail: yukioh@toyaku.ac.jp

Abstract – Five new rearranged neoclerodane diterpenes (salvileucalins E-I) were isolated from *Salvia leucantha* (Lamiaceae), whose structures were elucidated by spectroscopic analysis and X-ray crystallographic analysis.

INTRODUCTION

The genus *Salvia* (Lamiaceae) is a large genus consisting of over 1000 species.[1] Many plants of this genus are used as folk medicine in China and also in traditional Chinese medicinal prescriptions.[2] From the aerial parts of *Salvia leucantha* Cav. (common name "Mexican bush sage"), an evergreen herbaceous perennial plant, are isolated some rearranged neoclerodane diterpenes[3] and a highly rearranged diterpene, spiroleucantholide.[4] In our previous paper, we reported the isolation of highly rearranged neoclerodane

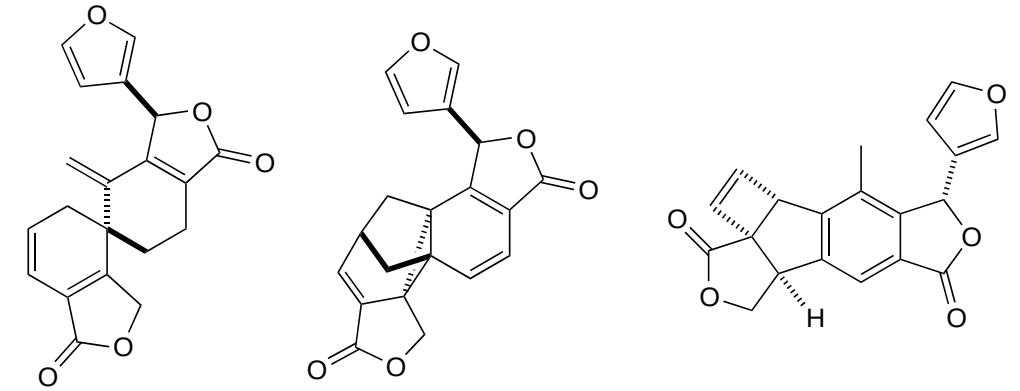


Figure 1. Previously reported rearranged neoclerodane diterpenes, salvileucalins A-C (**1**-**3**)

diterpenes, salvileucalins A (**1**) and B (**2**),[5] and a neoclerodane diterpene having a cyclobutane unit, salvileucalin C (**3**),[6] from *S. leucantha* (Figure 1).

In the present study, from the aerial parts of the same plant, *S. leucantha*, five novel highly oxidized neoclerodane diterpenes, salvileucalins E-I (**4**-**8**) (Figure 2) were isolated and their chemical structures were elucidated by the spectroscopic methods and X-ray crystallographic analysis.

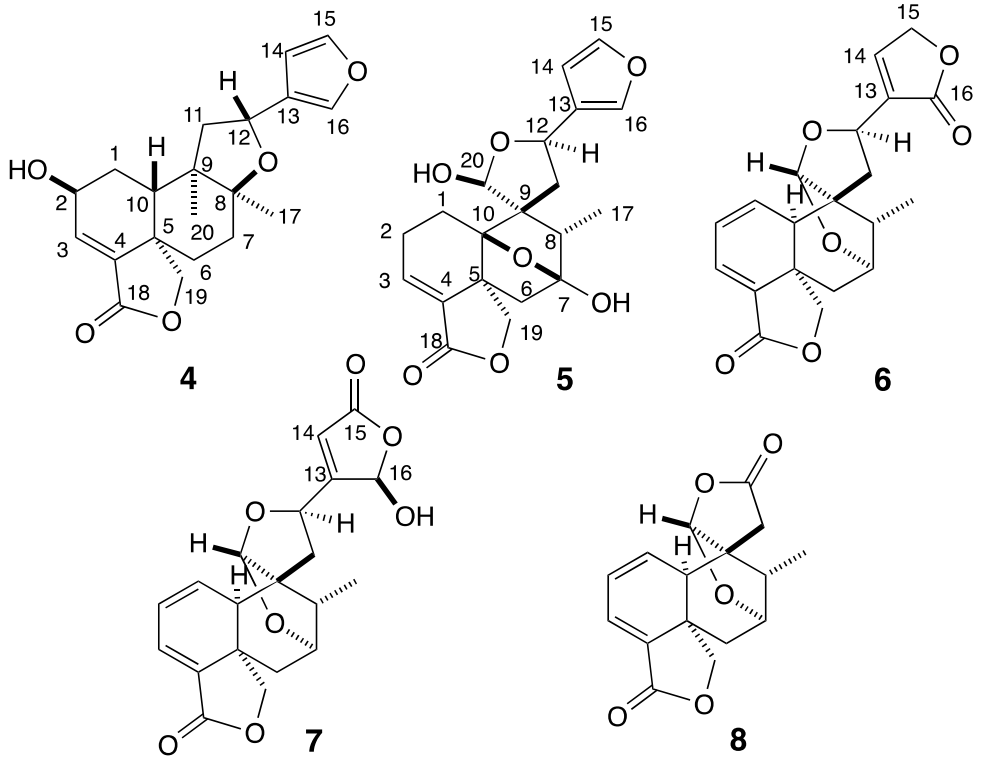


Figure 2. Newly isolated highly oxidized neoclerodane diterpenes, salvileucalins E-I (**4**-**8**) from *S. leucantha*

RESULTS AND DISCUSSION

By Diaion HP-20 resin column chromatography and the following repeated silica gel chromatography and ODS-HPLC, an acetone extract of the air-dried aerial parts of *S. leucantha* gave compounds **4**-**8**, which were named salvileucalins E-I, respectively.

Salvileucalin E (**4**) was obtained as a colorless amorphous solid. The $[M+H]^+$ ion peak at *m/z* 345.1704 in HRESIMS determined its molecular formula to be $C_{20}H_{24}O_5$, implying that it had 9 degrees of unsaturation. The IR absorption spectrum showed bands of hydroxy (3375 cm^{-1}) and of carbonyl (1765 cm^{-1}) groups. On the basis of ^1H and ^{13}C NMR, and DEPT spectral studies, the compound was shown to have 20 carbons assignable to three sp^2 and three sp^3 quaternary carbons, four sp^2 and three sp^3 methine carbons, five sp^3 methylene carbons, and two sp^3 methyl carbons (Table 1). The ^1H and ^{13}C NMR spectra showed the presence of one furan unit (δ_C 108.7, 128.4, 139.1, and 143.4; δ_H 6.36, 7.37, and 7.38), one

γ-lactone carbonyl carbon（δ_C 168.9), and a hydroxymethine carbon (δ_C 69.8 and δ_H 5.09), suggesting that it was a neoclerodane diterpene with one γ-lactone unit. The HMBC correlations from H-12 to C-8, C-13, C-14, and C-16 implied that the furan unit was attached to C-12. The HMBC correlations from H-3, H-6, and H-19 to C-5 suggested that **4** had a cyclohexene substructure fused to the γ-lactone (Figure 3). Relative configurations were established by the NOESY correlations observed between H-16/H-17, H-12/H-10, H-20/H-17, and H-19/H-20 (Figure 4). Finally, the crystals obtained by recrystallization from *n*-hexane-ethyl acetate were subjected to X-ray crystallographic analysis, which showed the relative structure of salvileucalin E (**4**) was as shown in Figure 5. Thus, the structure of salvileucalin E was elucidated to be the 2-epimer of salvisplendin D (**9**)[7] (Figure 6).

Salvileucalin F (**5**) was obtained as a colorless amorphous solid. The $[M+Na]^+$ ion peak at *m/z* 397.1248 in HRESIMS determined its molecular formula to be $C_{20}H_{22}O_7$, having 10 degrees of unsaturation. The IR absorption spectrum showed the presence of hydroxy (3392 cm^{-1}) and of carbonyl (1748 cm^{-1}) groups. On the basis of its ^1H and ^{13}C NMR, and DEPT spectral data, the 20 carbons of the molecule were assigned to three sp^2 and four sp^3 quaternary carbons, four sp^2 and three sp^3 methine carbons, five sp^3 methylene carbons, and one sp^3 methyl carbon (Table 1). The ^1H and ^{13}C NMR spectra further showed the presence of one furan unit (δ_C 108.8, 126.3, 139.9, and 143.7, δ_H 6.41, 7.40, 7.42), one γ-lactone carbonyl carbon（δ_C 169.3), one hemiacetal unit (δ_C96.6 and δ_H 5.14) and one hemiketal unit (δ_C 107.4), suggesting that **5** was a neoclerodane diterpene with one γ-lactone, one hemiacetal, and one hemiketal units. The HMBC correlations from H-12 to C-13, C-14, C-16, and C-20 implied that the furan unit was attached to C-12 and that the hemiacetal carbon was C-20. The HMBC correlations from H-8 and H-6 to C-7 showed that the hemiketal carbon was C-7. The HMBC correlations from H-3, H-6, and H-19 to C-5 suggested that in this molecule the cyclohexene substructure and the γ-lactone fused together (Figure 3). The relative configurations were established by the NOESY correlations observed between H-12/H-8, H-12/H-20, and H-17/H-19 (Figure 4). Finally, the crystals recrystallized from acetonitrile were subjected to X-ray crystallographic analysis, which showed the relative structure of salvileucalin F (**5)** was as shown in Figure 5.

Salvileucalin G (**6**) was obtained as a colorless amorphous solid. The $[M+Na]^+$ ion peak at *m/z* 379.1158 in HRESIMS determined its molecular formula to be $C_{20}H_{20}O_6$, implying it had 11 degrees of unsaturation. The IR absorption spectrum showed a band of carbonyl group (1749 cm^{-1}). On the basis of ^1H and ^{13}C NMR, and DEPT spectral studies, **6** was shown to have 20 carbons assignable to four sp^2 and two sp^3 quaternary carbons, four sp^2 and five sp^3 methine carbons, four sp^3 methylene carbons, and one sp^3 methyl carbon (Table 1). The ^1H and ^{13}C NMR spectra further showed the presence of two γ-lactone carbonyl carbons（δ_C 172.0 and 169.4), and one acetal carbon (δ_C 110.2), implying that **6** was a

neoclerodane diterpene with two γ-lactone and one acetal units. The HMBC correlations from H-12 to C-13, C-14, C-16, and C-20, and from H-7 to C-20 implied that one γ-lactone unit was linked to C-12 and that C-20 was the acetal carbon. The HMBC correlations from H-3, H-6, and H-19 to C-5 suggested that this compound had a cyclohexadiene substructure fused to one γ-lactone (Figure 3). The relative configurations of **6** was established by the NOESY correlations observed between H-12/H-17, H-10/H-19, H-10/H-20, and H-14/H-20 (Figure 4). Finally, the crystals recrystallized from *n*-hexane-ethyl acetate were subjected to X-ray crystallographic analysis, which showed the relative structure of salvileucalin G (**6**) to be as shown in Figure 5.

Salvileucalin H (**7**) was obtained as a colorless amorphous solid. The $[M+H]^+$ ion peak at *m/z* 373.1302 in HRESIMS determined its molecular formula to be $C_{20}H_{20}O_7$, implying it had 11 degrees of unsaturation. The IR absorption spectrum showed bands of hydroxy (3331 cm^{-1}) and carbonyl (1754 cm^{-1}) groups. The ^1H and ^{13}C NMR, and DEPT spectral studies assigned 18 of the 20 carbons of the molecule: two sp^2 and three sp^3 quaternary carbons, four sp^2 and five sp^3 methine carbons, three sp^3 methylene carbons, and one sp^3 methyl carbons (Table 1), leaving two carbons unassigned. The ^1H and ^{13}C NMR spectra further showed the presence of two γ-lactone carbonyl carbons（δ_C173.1 and 171.3) and one acetal carbon (δ_C 110.8), which suggested that **7** was a neoclerodane diterpene with two γ-lactone and one acetal units. The HMBC correlations from H-12 and H-7 to C-20 implied that one γ-lactone unit was attached to C-12 and that C-20 was the acetal carbon. The HMBC correlations from H-3, H-6, and H-19 to C-5 suggested that the compound had a cyclohexadiene substructure fused to one γ-lactone (Figure 3). Finally, the crystals recrystallized from *n*-hexane-ethyl acetate were subjected to X-ray crystallographic analysis, which showed the relative structure of salvileucalin H (**7**) to be as shown in Figure 5.

Salvileucalin I (**8**) was obtained as a colorless amorphous solid. The $[M+H]^+$ ion peak at *m/z* 289.1076 in HRESIMS determined its molecular formula to be $C_{16}H_{16}O_5$, implying it had 9 degrees of unsaturation. The IR absorption spectrum showed a band of carbonyl group (1751 cm^{-1}). On the basis of the ^1H and ^{13}C NMR, and DEPT spectral studies, **8** was shown to have 16 carbons assignable to three sp^2 and two sp^3 quaternary carbons, three sp^2 and four sp^3 methine carbons, three sp^3 methylene carbons, and one sp^3 methyl carbon (Table 1). The ^1H and ^{13}C NMR spectra further showed the presence of two γ-lactone carbonyl carbons（δ_C 172.0 and 168.6), and one acetal carbon (δ_C 108.2), implying that **8** was a neoclerodane diterpene with two γ-lactone and one acetal units, and with one furan substructure. The HMBC correlations from H-20 to C-12, from H-11 to C-12, and from H-7 to C-20 implied that the carbons C-12 was a γ-lactone carbonyl carbon and the C-20 was an acetal carbon. The HMBC correlations from H-3, H-19, H-6 to C-5 suggested that **8** had a cyclohexadiene substructure fused to one γ-lactone unit (Figure 3). The relative configurations of **8** were established by the NOESY correlations

observed between H-10/H-19, H-10/H-11, H-10/ H-20, and H-11/H-17 (Figure 4). Finally, the crystals recrystallized from acetonitrile were subjected to X-ray crystallographic analysis, which showed the relative structure of salvileucalin I (**8**) to be as shown in Figure 5.

Thus, in the present study, five new neoclerodane diterpenes, salvileucalins E-I (**5**-**8**), were isolated from the aerial parts of *Salvia leucantha* and their structures were determined. Of them, salvileucalin E (**4**) was shown to be the C-2 epimer of salvisplendin D (**9**),[7] whereas, salvileucalins F (**5**), G (**6**), H (**7**), and I (**8**), to be salvifaricin (**10**)[8] (Figure 6)-related compounds, possibly biosynthesized from salvifaricin (**10**) via the routes shown in Scheme 1.

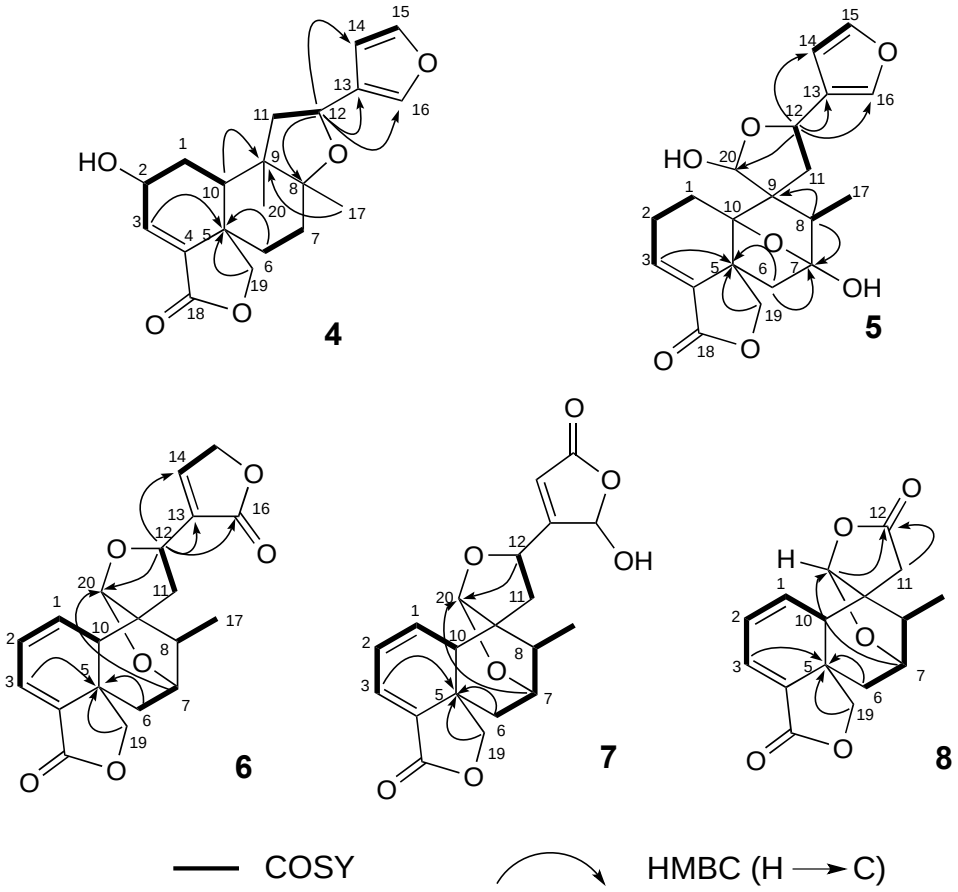


Figure 3. Selected COSY and HMBC correlations noted in salvileucalins E-I (**4**-**8**)

Table 1. ^{13}C- and ^{1}H-NMR data of salvileucalins E-I (**4**-**8**)[1]

position	**4**		**5**		**6**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	29.1 (t)	1.84 (1H, brd, 13.8)	25.3 (t)	1.75 (1H, m)	132.8 (d)	5.83 (1H, dd, 2.0, 9.5)
		1.37 (1H, ddd, 3.1, 13.8, 13.8)		2.15 (1H, ddd, 1.8, 3.2, 13.9)		
2	63.8 (d)	4.59 (1H, ddd, 2.7, 2.7, 6.5)	22.2 (t)	2.32 (1H, m)	124.0 (d)	6.29 (1H, ddd, 3.0, 5.2, 9.5)
				2.45 (1H, ddd, 2.3, 7.4, 12.9)		
3	131.6 (d)	6.77 (1H, d, 6.4)	134.7 (d)	6.88 (1H, dd, 2.1, 7.3)	127.6 (d)	6.91 (1H, d, 5.2)
4	142.7 (s)		134.8 (s)		130.0 (s)	
5	45.2 (s)		51.8 (s)		39.1 (s)	
6	29.7 (t)	1.79 (1H, brd, 14.8)	44.3 (t)	1.75 (1H, m)	39.1 (t)	2.12 (1H, dd, 4.2, 14.2)
		1.63 (1H, m)		2.49 (1H, d, 12.4)		1.29 (1H, d, 14.2)
7	30.6 (t)	2.05 (1H, brm)	107.4 (s)		84.7 (d)	4.39 (1H, d, 4.2)
		1.74 (1H, m)				
8	84.0 (s)		50.3 (d)	2.05 (1H, dd, 2.0, 7.6)	41.8 (d)	2.03 (1H, q, 7.1)
9	46.6 (s)		60.8 (s)		58.2 (s)	
10	35.4 (d)	2.68 (1H, d, 12.1)	83.7 (s)		48.6 (d)	2.92 (1H, br, m)
11	44.1 (t)	2.44 (1H, dd, 6.8, 13.2)	42.9 (t)	2.09 (1H, dd, 4.9, 11.7)	35.5 (t)	2.79 (1H, dd, 8.2, 13.3)
		1.91 (1H, dd, 10.2, 13.2)		2.62 (1H, m)		1.94 (1H, dd, 7.7, 13.3)
12	69.8 (d)	5.09 (1H, dd, 6.8, 10.2)	71.1 (d)	4.89 (1H, dd, 5.3, 10.8)	75.5 (d)	5.11 (1H, d, 8.0)
13	128.4 (s)		126.3 (s)		135.6 (s)	
14	108.7 (d)	6.36 (1H, dd, 1.1, 1.1)	108.8 (d)	6.41 (1H, d, 1.1)	145.4 (d)	7.36 (1H, d, 1.3)
15	143.4 (d)	7.38 (1H, s)	143.7 (d)	7.40 (1H, dd, 1.6, 1.6)	70.3 (t)	4.86 (1H, d, 19.2)
						4.83 (1H, d, 19.2)
16	139.1 (d)	7.37 (1H, s)	139.9 (d)	7.42 (1H, d, brs)	172.0 (s)	
17	26.6 (q)	1.21 (3H, s)	11.5 (q)	1.22 (3H, d, 7.6)	14.6 (q)	1.35 (3H, d, 7.1)
18	168.9 (s)		169.3 (s)		169.4 (s)	
19	69.4 (t)	4.33 (1H, d, 8.1)	74.5 (t)	4.36 (1H, d,8.0)	80.7 (t)	4.98 (1H, d, 8.0)
		3.92 (1H, dd, 1.8, 8.1)		4.44 (1H, d, 8.0)		4.15 (1H, dd, 1.8, 8.0)
20	17.2 (q)	0.84 (3H, s)	96.6 (d)	5.14 (1H, s)	110.2 (d)	5.35 (1H, s)

position	**7**		**8**	
	δ_C	δ_H	δ_C	δ_H
1	133.4 (d)	6.04 (1H, dd, 2.0, 9.5)	131.0 (d)	5.78 (1H, dd, 2.2, 9.5)
2	123.3 (d)	6.36 (1H, ddd, 3.0, 5.2, 9.5)	124.8 (d)	6.35 (1H, ddd, 3.0, 5.2, 9.5)
3	127.8 (d)	6.94 (1H, d, 5.2)	127.8 (d)	6.94 (1H, d, 5.2)
4	129.7 (s)		129.8 (s)	
5	38.8 (s)		38.7 (s)	
6	38.9 (t)	2.06 (1H, brm)	38.9 (t)	2.18 (1H, dd, 4.3, 14.4)
		1.35 (1H, brm)		1.37 (1H, d, 14.4)
7	84.9 (d)	4.38 (1H, d, 4.1)	84.3 (d)	4.46 (1H, d, 4.3)
8	41.7 (d)	2.11 (1H, dd, 7.1, 14.2)	41.8 (d)	2.20 (1H, dd, 7.3, 14.4)
9	57.9 (s)		54.2 (s)	
10	48.5 (d)	2.98 (1H, brm)	48.4 (d)	2.92 (1H, brm)
11	35.4 (t)	2.92 (1H, dd, 8.3, 13.1)	36.6 (t)	2.98 (1H, d, 17.4)
		2.06 (1H, dd, 4.4, 14.2)		2.54 (1H, d, 17.4)
12	76.5 (d)	5.22 (1H, br)	172.0 (s)	
13	not detected			
14	116.0 (d)	6.14 (1H, br)		
15	171.3 (s)			
16	not detected	6.25 (1H, br)		
17	13.5 (q)	1.37 (3H, d, 7.1)	13.5 (q)	1.21 (3H, d, 7.2)
18	170.2 (s)		168.6 (s)	
19	80.8 (t)	4.92 (1H, d, 8.2)	80.0 (t)	4.92 (1H, d, 7.9)
		4.24 (1H, d, 7.5)		4.09 (1H, dd, 2.0, 7.9)
20	110.8 (d)	5.33 (1H, s)	108.2 (d)	5.40 (1H, s)

[1] Salvileucalin E (**4**), G (**6**), and I (**8**) ($CDCl_3$, 150 MHz and 600 MHz); salvileucalin F (**5**) ($CDCl_3$, 125 MHz and 500 MHz); salvileucalin H (**7**) (CD_3OD, 150 MHz and 600 MHz).

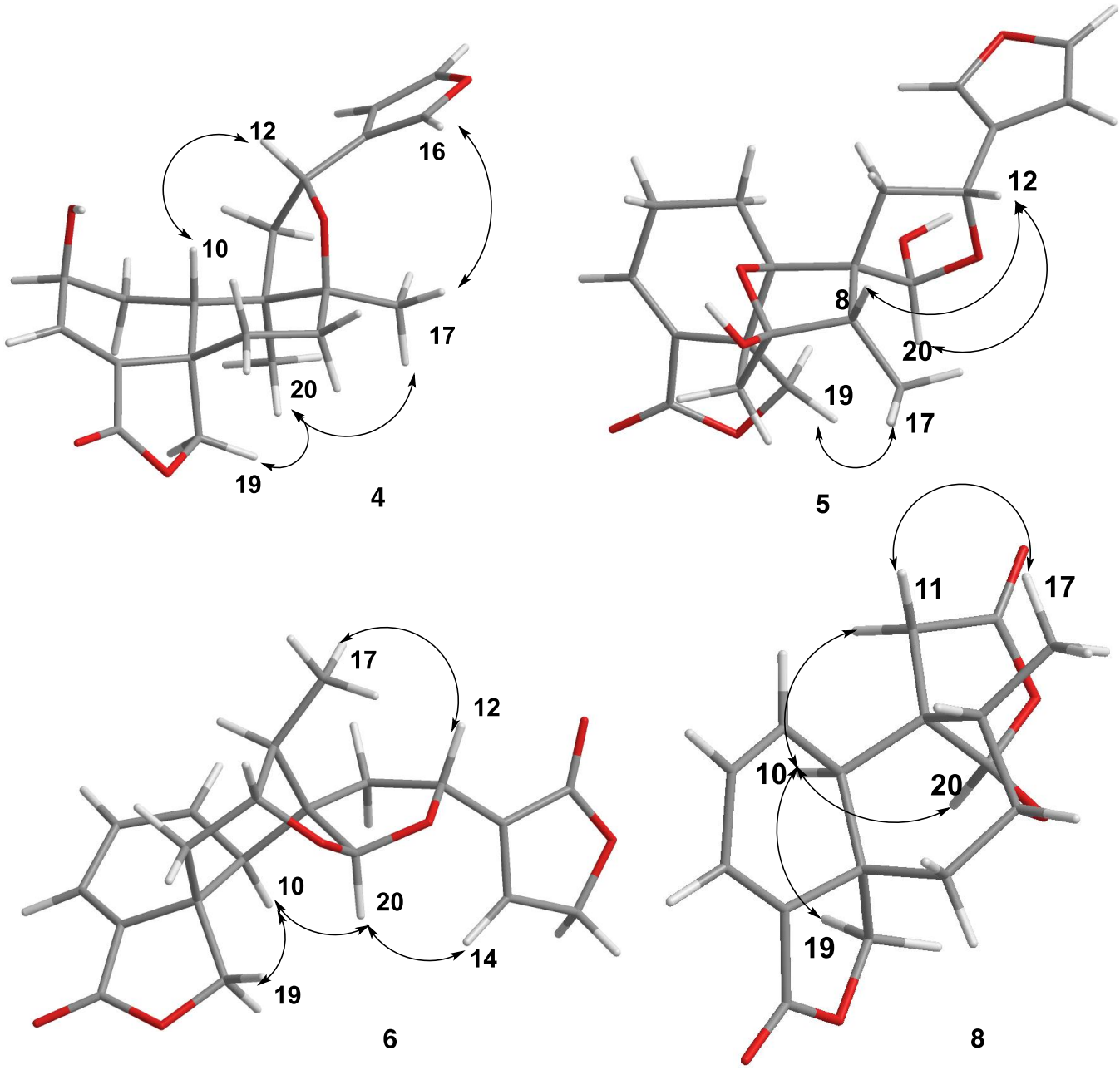


Figure 4. Selected NOESY correlations for salvileucalins E-G (**4**-**6**) and I (**8**)

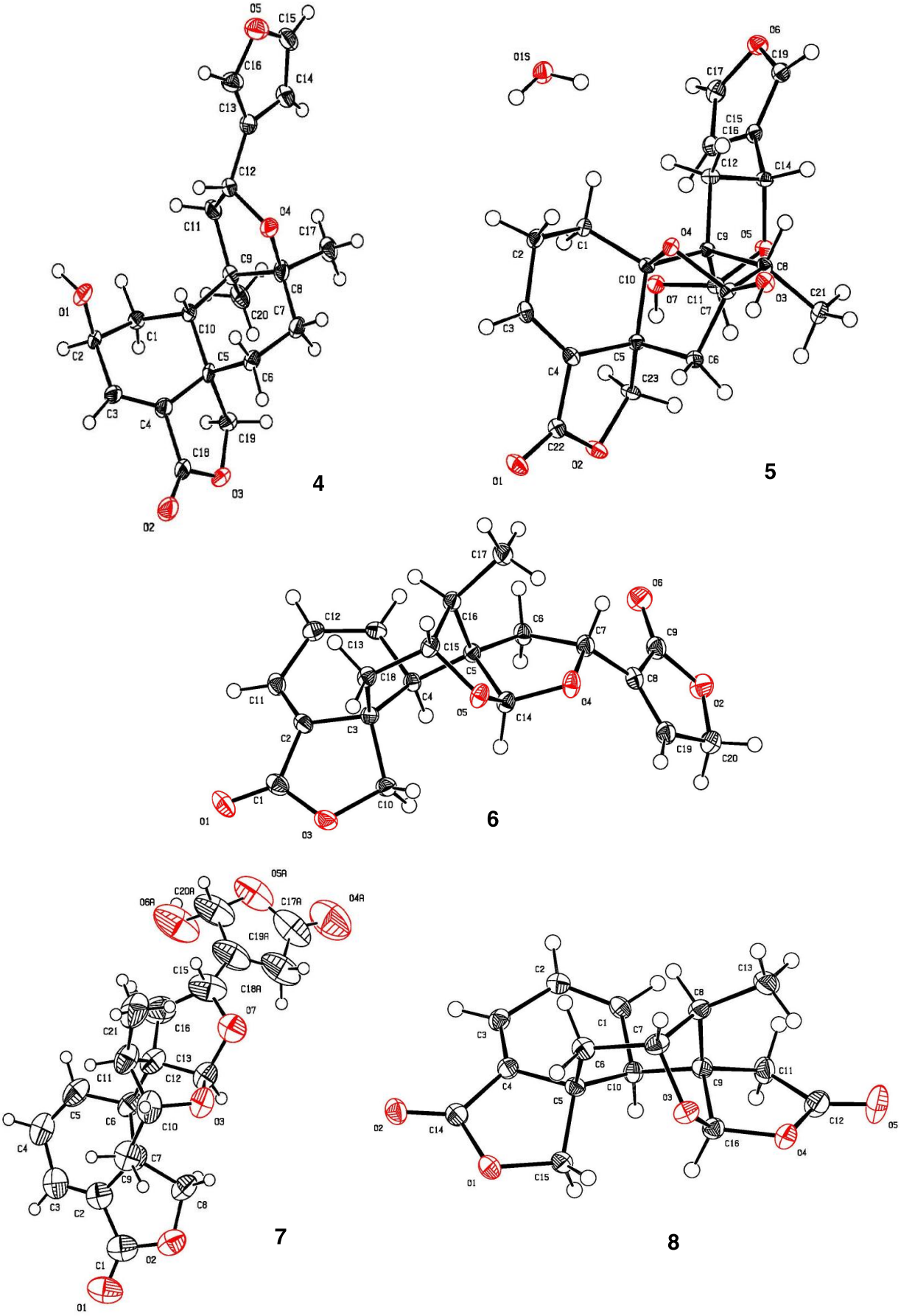


Figure 5. ORTEP representation of salvileucalins E-I (**4-8)**

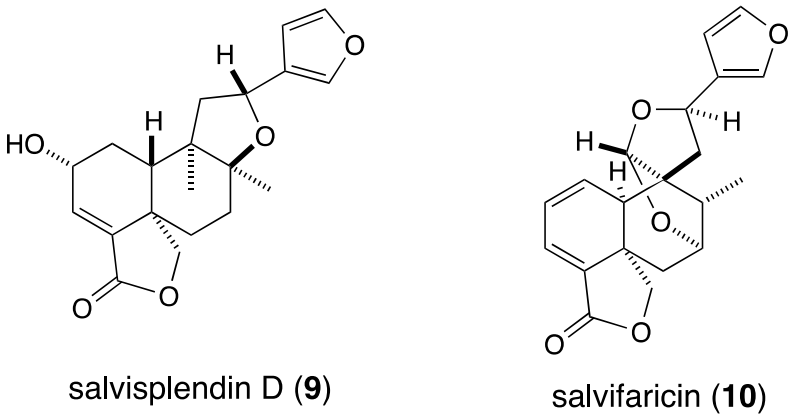
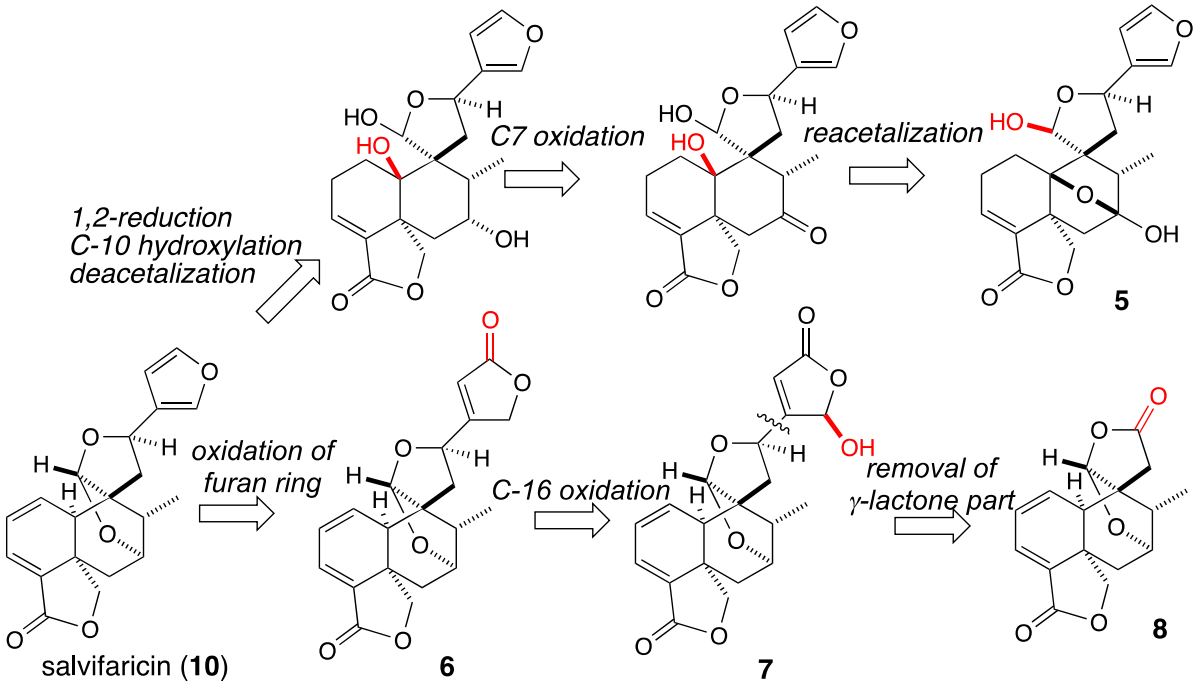


Figure 6. Previously isolated neoclerodane diterpenes, salvisplendin D (**9**) and salvifaricin (**10**)



Scheme 1. Possible biosynthetic pathway for salvileucalins F-I (**5-8)**

EXPERIMENTAL

General Experimental Procedures. Optical rotations were determined on a JASCO DIP-360 digital polarimeter and IR spectra were recorded on a JASCO FT/IR 620 spectrophotometer. NMR spectra were obtained on a Bruker DRX-500 or a DRX-600 spectrometer at 300 K. The chemical shifts (δ) are reported for ^{1}H-NMR in ppm relative to the residual $CHCl_3$ resonance at 7.26 ppm and to the residual CD_2HOD resonance at 3.31 ppm and for ^{13}C-NMR to the $CDCl_3$ resonance at 77.0 ppm and to the CD_3OD resonance at 49.2 ppm. Mass spectra were obtained with a VG AutoSpec E spectrometer. Preparative HPLC was carried out on a JASCO PU-980 pump equipped with a UV-875 detector (λ 220 nm) and a Inertsil® PREP-ODS column, (10 μm, 20 × 250 mm).

Plant Material. The aerial part of *Salvia leucantha* Cav. grown in the medicinal botanical garden of Tokyo University of Pharmacy & Life Sciences, Tokyo, Japan, was collected in November 2005 and 2006. A voucher specimen has been deposited in the herbarium of Tokyo University of Pharmacy and Life Sciences. (05JCP01).

Extraction and Isolation. The air-dried aerial parts of *Salvia leucantha* (18.66 kg) was extracted with acetone (3 x 40 L) at room temperature. The combined acetone extract was concentrated and subjected to Diaion HP-20 resin column chromatography eluting sequentially with H_2O, 50% MeOH, 80% MeOH, 100% MeOH, and acetone. The fraction eluted with 80% MeOH was then subjected to repeated silica gel column chromatography (solvent system: *n*-hexane-AcOEt, $ChCl_3$-MeOH, and *n*-hexane-acetone) and repeated ODS-HPLC (solvent system: H_2O-MeOH or H_2O-MeCN) to give compounds **4** (1.3 mg), **5** (7.3 mg), **6** (4.8 mg), **7** (4.8 mg), and **8** (2.9 mg).

Salvileucalin E (**4**) colorless amorphous solid, mp 215-218 °C (*n*-hexane-AcOEt); $[\alpha]_D$ -60.0 (*c* 0.07, MeOH). IR (film) λ_{max}: 3375 (OH), 1765 (C=O) cm^{-1}. ^1H and ^{13}C data are listed in Table 1. HRESIMS calcd for $C_{20}H_{25}O_5$ (M+H) 345.1702; found 345.1704.

Salvileucalin F (**5**) colorless amorphous solid, mp 174-176 °C (MeCN); $[\alpha]_D$ -46.9 (*c* 0.10, $CHCl_3$). IR (film) λ_{max}: 3392 (OH), 1748 (C=O) cm^{-1}. ^1H and ^{13}C data are listed in Table 1. HRESIMS calcd for $C_{20}H_{22}O_7Na$ (M+Na) 397.1263; found 397.1248.

Salvileucalin G (**6**) colorless amorphous solid, mp 160-162 °C (*n*-hexane-AcOEt); $[\alpha]_D$ -57.0 (*c* 0.10, MeOH). IR (film) λ_{max}: 1749 (C=O) cm^{-1}. ^1H and ^{13}C data are listed in Table 1. HRESIMS calcd for $C_{20}H_{20}O_6Na$ (M+Na) 379.1121; found 379.1158.

Salvileucalin H (**7**) colorless amorphous solid, mp 159-162 °C (*n*-hexane-AcOEt); $[\alpha]_D$ -51.8 (*c* 0.10, MeOH). IR (film) λ_{max}: 3331 (OH), 1754 (C=O) cm^{-1}. ^1H and ^{13}C data are listed in Table 1. HRESIMS calcd for $C_{20}H_{21}O_7$ (M+H) 373.1287; found 373.1302.

Salvileucalin I (**8**) colorless amorphous solid, mp 230-233 °C (MeCN); $[\alpha]_D$ -194.4 (*c* 0.09, $CHCl_3$). IR (film) λ_{max}: 1750 (C=O) cm^{-1}. ^1H and ^{13}C data are listed in Table 1. HRESIMS calcd for $C_{16}H_{17}O_5$ (M+H) 289.1099; found 289.1076.

X-Ray Crystallographic Studies.

Crystal data for Salvileucalin E (**4**) : $C_{20}H_{24}O_5$, fw 344.39, unit cell dimension *a*= 8.024(2) Å, *b*= 10.445(3) Å, *c*=10.150(3) Å, *V*=850.3(4) $Å^3$, *Z*=2, *T*=90K, *R*(all data)= 0.0691.

Crystal data for Salvileucalin F (**5**) : $C_{20}H_{22}O_7$, fw 392.39, unit cell dimension *a*= 6.5286(8) Å, *b*=

7.6463(9) Å, *c*=36.093(4) Å, *V*=1801.8(4) Å^3, *Z*=4, *T*=90K, *R*(all data)= 0.0325.

Crystal data for Salvileucalin G (**6**) : $C_{20}H_{20}O_6$, fw 356.36, unit cell dimension *a*= 11.3114(14) Å, *b*= 11.3418(14) Å, *c*=12.7803(15) Å, *V*=1639.6(3) Å^3, *Z*=4, *T*=90K, *R*(all data)= 0.0345.

Crystal data for Salvileucalin H (**7**) : $C_{20}H_{20}O_7$, fw 372.36, unit cell dimension *a*= 8.4280(11) Å, *b*= 8.2396(11) Å, *c*=12.9095(17) Å, *V*=868.8(2) Å^3, *Z*=2, *T*=90K, *R*(all data)= 0.0984.

Crystal data for Salvileucalin I (**8**) : $C_{16}H_{16}O_5$, fw 288.29, unit cell dimension *a*= 8.0943(14) Å, *b*= 8.2716(14) Å, *c*=19.825(3) Å, *V*=1327.4(4) Å^3, *Z*=4, *T*=90K, *R*(all data)= 0.0465.

Crystallographic data for compounds **4**, **5**, **6**, **7**, and **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1941952, CCDC 1941950, CCDC 1941949, CCDC 1941953, and CCDC 1941951. Copies of the data can be obtained, free of charge, on application to the Director, CCDC (e-mail: deposit@ccdc.cam.ac.uk).

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Conflict of Interest The authors declare no conflict of interest.

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