Clerodane Diterpenoids from *Salvia splendens*

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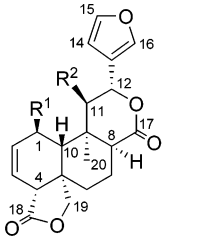
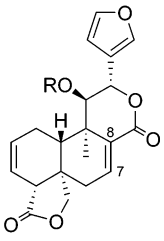
Four new clerodane diterpenoids, salvisplendins A−D (**1**−**4**), have been isolated from an acetone extract of the flowers of *Salvia splendens*, together with an artifact (**5**), arising from salvisplendin D (**4**) by addition of diazomethane, and the already known clerodane olearin (**6**). The structures of the new compounds (**1**−**5**) were established mainly by 1D and 2D NMR spectroscopic studies and, in the case of salvisplendin A (**1**), by chemical correlation with splenolide B (**7**). Complete ^{1}H and ^{13}C NMR assignments for olearin (**6**), not published hitherto, are also reported.

Some clerodane diterpenoids, and particularly those found[1−3] in *Salvia divinorum* Epling & Játiva (Labiatae), have attracted interest in recent years on account of their interesting biological properties as potent and selective κ-opioid receptor agonists in vitro and in vivo.[4−8] The diterpene constituents of *Salvia splendens* Sellow ex Roem. & Schult.[9−11] are clerodanes with functionalities closely related to those exhibited by the diterpenoids found in *S. divinorum*; therefore they could also be interesting as psychoactive compounds.

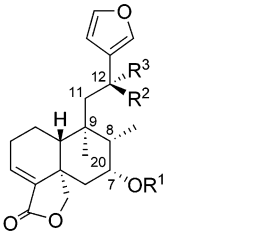
We have carried out an extraction of the flowers of *S. splendens* to isolate its diterpene constituents. These substances are intended for use as starting materials for semisynthetic derivatives, in order to explore whether such compounds may be useful as neuropharmacological agents. In this paper, we report on the isolation and structure elucidation of four new clerodane diterpenoids, salvisplendins A−D (**1**−**4**, respectively), together with the artifact **5**, that results from salvisplendin D (**4**) by the treatment of the crude extract with diazomethane[9] (see Experimental Section), the previously known[12,13] clerodane olearin (**6**), and splenolide B,[11] salviarin,[9] splenolide A,[11] and splendidin[10] (**7**−**10**, respectively), all of them previously found in *S. splendens*.



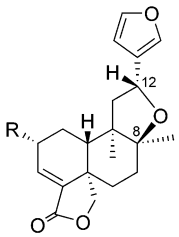
1 R^1 = H, R^2 = OH
7 R^1 = H, R^2 = OAc
8 R^1 = R^2 = H
9 R^1 = OH, R^2 = H
10 R^1 = R^2 = OAc



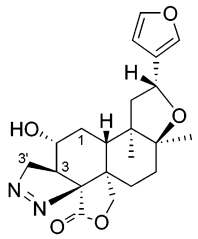
2 R = H
11 R = Ac



3 R^1 = R^2 = H, R^3 =OAc
12 R^1 = R^3 = H, R^2 = OH
13 R^1 = Ac, R^2 = H, R^3 = OAc



4 R = OH
14 R = OAc
15 R = H



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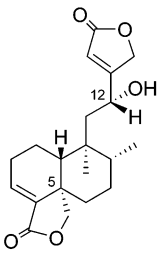

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Results and Discussion

In order to facilitate the isolation of the diterpenes of *S. splendens*, the acetone extract of the flowers of this plant was treated initially with an excess of an ethereal solution of diazomethane, for transforming the triterpene acids into their methyl ester derivatives.[9] Repeated chromatographic processes on the extract yielded compounds **1**−**6**.

The physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, and mass spectra) data of **6** were identical to those reported[13] for olearin, a clerodane diterpene previously found in *Olearia heterocarpa* S. T. Brake (Compositae), the C-12 configuration of which was not ascertained.[12,13] However, we assume that olearin (**6**) possesses a 12*R*-configuration like marrubiastrol,[14] another clerodane isolated from *Leonurus marrubiastrum* L. that differs from **6** only in the configuration at C-5. This assumption is also supported on biogenetic reasons, because the other clerodanes previously found in *S. splendens* (**7**−**10**)[9−11] possess a configuration at C-12 identical to that of marrubiastrol.[14] The complete and unambiguous assignments of the ^{1}H and ^{13}C NMR spectra of **6** have not been reported previously (see Experimental Section).

Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{20}H_{22}O_6$ for salvisplendin A (**1**), and its IR spectrum showed, among others, hydroxyl (3443 cm^{-1}) absorption. The ^{1}H and ^{13}C NMR spectra of **1** (Table 1) were almost identical to those reported[11] for splenolide B (**7**, $C_{22}H_{24}O_7$), and the observed differences were consistent with the absence in the former of the 11-*O*-acetyl group of the latter. Acetic anhydride−pyridine treatment of **1** gave a monoacetyl derivative, identical in all respects (mp, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, and mass spectra, TLC) with **7**. Therefore, salvisplendin A (**1**) is the 11-*O*-deacetyl derivative of splenolide B (**7**).[11]

Treatment of salvisplendin B (**2**, $C_{20}H_{20}O_6$, IR ν_{max} 3437 cm^{-1}, hydroxyl) with acetic anhydride−pyridine yielded a monoacetyl derivative (**11**, $C_{22}H_{22}O_7$), the IR spectrum of which was devoid of hydroxyl absorptions. The ^{1}H and ^{13}C NMR spectra of **2** and **11** (Table 1) were similar to those of **1** (Table 1) and **7**,[11] and signals

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Table 1. NMR Spectroscopic Data[a] for Salvisplendins A (**1**) and B (**2**) and 11-*O*-Acetylsalvisplendin B (**11**)

	salvisplendin A (**1**)		salvisplendin B (**2**)		11-*O*-acetylsalvisplendin B (**11**)	
position	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)
1	24.0, CH_2	2.03, ddddd (16.0, 12.4, 2.7, 2.5, 2.0)[b] 2.70, ddddd (16.0, 5.6, 4.0, 2.4, 1.2)	22.0, CH_2	2.06, ddddd (18.0, 12.1, 2.8, 2.7, 2.2) 2.21, ddddd (18.0, 7.8, 5.3, 2.8, 1.2)	21.3, CH_2	2.04[c]
2	130.3, CH	5.96, dddd (10.0, 5.6, 2.4, 2.0)	130.2, CH	6.03, ddt (10.0, 7.8, 2.2)	128.6, CH	5.97, dddd (10.0, 7.8, 2.8, 2.2)
3	119.8, CH	5.53, dtd (10.0, 2.7, 1.2)	120.1, CH	5.58, dtd (10.0, 2.8, 1.2)	120.1, CH	5.63, dddd (10.0, 3.0, 2.9, 1.6)
4	52.2, CH	2.74, ddt (2.7, 2.5, 2.4)	52.1, CH	2.91, tdd (2.8, 2.7, 2.2)	51.4, CH	2.89, dddd (3.0, 2.9, 2.8, 2.7)
5	41.7, qC		40.3, qC		39.5, qC	
6	32.1, CH_2	1.81, dtd (14.6, 4.0, 1.0) 1.26, dddd (14.6, 13.8, 4.0, 1.6)	37.6, CH_2	2.63, dd (19.3, 5.8) 2.27, ddd (19.3, 2.3, 2.0)	37.3, CH_2	2.72, dd (19.6, 5.8) 2.23, ddd (19.6, 2.5, 2.2)
7	19.4, CH_2	1.87, ddt (14.6, 13.8, 4.0) 2.36, dtd (14.6, 4.0, 3.0)	138.9, CH	7.03, dd (5.8, 2.3)	138.9, CH	7.18, dd (5.8, 2.5)
8	49.2, CH	2.43, ddd (4.0, 3.0, 1.0)	132.6, qC		130.1, qC	
9	38.6, qC		41.1, qC		39.3, qC	
10	37.9, CH	2.09, dd (12.4, 4.0)	34.7, CH	2.78, dd (12.1, 5.3)	35.0, CH	2.24, dd (11.4, 6.1)
11	77.8, CH	3.51, d (10.4)	72.9, CH	3.92, d (2.7)	73.3, CH	5.22, d (1.3)
12	74.1, CH	5.15, d (10.4)	81.8, CH	5.38, dd (2.7, 1.6)	79.3, CH	5.45, dd (1.4, 1.3)
13	122.9, qC		125.3, qC		124.1, qC	
14	108.4, CH	6.43, dd (1.8, 0.8)	108.5, CH	6.44, dd (1.6, 0.7)	107.9, CH	6.54, dd (1.7, 0.6)
15	143.8, CH	7.41, t (1.8)	144.4, CH	7.44, t (1.6)	143.9, CH	7.43, t (1.7)
16	141.2, CH	7.52, dd (1.8, 0.8)	139.4, CH	7.46, td (1.6, 0.7)	138.7, CH	7.50, ddd (1.7, 1.4, 0.6)
17	170.7, qC		167.1, qC		163.4, qC	
18	176.2, qC		177.6, qC		175.1, qC	
19	70.3, CH_2	4.22, dd (9.1,1.6)[d] 4.20, d (9.1)[e]	72.5, CH_2	4.29, dd (8.8, 2.0)[d] 4.03, d (8.8)[e]	71.1, CH_2	4.22, dd (8.8, 2.2)[d] 3.98, d (8.8)[e]
20	19.6, CH_3	1.07, s	22.5, CH_3	0.83, s	21.2, CH_3	0.87, s
OAc					170.3, qC	
					21.1, CH_3	2.13, s

[a] ^1H and ^{13}C NMR spectra at 400 and 100 MHz, respectively, in $CDCl_3$ (**1** and **11**) or 1:1 $CDCl_3$−CD_3OD (**2**) solution. [b] For methylene groups, the first reported δ value belongs to the α-proton and the second reported δ value is for the β-proton.[18] [c] Overlapped signals, H_2-1. [d] This is the pro-*S* α-hydrogen. [e] This is the pro-*R* β-hydrogen.

for H-7 (δ 7.03), C-7 (δ 138.9), and C-8 (δ 132.6) indicated the presence of a trisubstituted olefin at the 7,8-position in **2**. The HMBC spectrum of **2** showed correlations between the C-8 olefin carbon and the H-11α and Me-20 (δ 3.92 and 0.83, respectively) protons, whereas H-7 was correlated with the C-5, C-6, C-8, C-9, and C-17 carbons (δ 40.3, 37.6, 132.6, 41.1, and 167.1, respectively), thus confirming that **2** is the 7-dehydro derivative of **1**. The UV absorption of **2** (λ_{max} 212 nm, log ϵ 3.88), together with the relative deshielding observed for C-17 (δ 167.1) as compared with that of **1** (δ 170.7), further supported this conclusion.[15]

Since the vicinal coupling constant between H-11 and H-12 of salvisplendin B (**2**, $J_{11,12}$ = 2.7 Hz) was very different from that observed for the same protons in **1** ($J_{11,12}$ = 10.4 Hz), the relative configuration of **2** was established by NOE experiments. Irradiation at the Me-20 protons of **2** (δ 0.83) caused NOE enhancement in the signals of H-1α, H-11α, H-14, H-16, and H_2-19, but not for H-10β. In the case of **1**, only the signals of H-1α, H-7α, H-8α, H-11α, and H_2-19 were enhanced upon irradiation of Me-20 (δ 1.07). Moreover, irradiation of H-10β in **1** and **2** (δ 2.09 and 2.78, respectively) produced NOE enhancements in H-1β, H-4β, H-6β, and H-11α for both compounds. These results established that the configuration of the C-4, C-5, C-10, and C-11 asymmetric centers of **1** and **2** are identical and that the Me-20 and furan groups of **2** are α. The observed differences in coupling constants and NOE in **1** and **2** may be only explained by a conformational difference in the 17,12-δ-lactone ring of these compounds. In salvisplendin A (**1**) this lactone possesses a chair ($^{12}C_8$) conformation, in which the H-11α and H-12β protons are *trans*-diaxially oriented ($J_{11,12}$ = 10.4 Hz), and the furan ring is in an equatorial orientation, far from the Me-20 group. The 17,12-δ-lactone of **2** is in a distorted chair ($^8C_{12}$) conformation, in which the dihedral angle between the H-11α and H-12β protons is close to 90° ($J_{11,12}$ = 2.7 Hz), and the furyl substituent is in a pseudoaxial orientation, closer to the C-20 methyl group than in **1**. This conformational difference must be attributed to the presence in **2** of an sp^2 carbon at C-8. Therefore, salvisplendin B possesses the structure depicted as **2**.

The ^1H NMR spectrum of salvisplendin C (**3**, Table 2, $C_{22}H_{28}O_6$) was almost identical to that of **12** ($C_{20}H_{26}O_5$), a clerodane diterpenoid previously isolated[16] from *Heteropappus altaicus* (Willd.) Novopokrov (Compositae), and the observed differences between these spectra were in agreement with the presence in the former of an acetoxy group at the C-12 position.[16] Acetic anhydride−pyridine treatment of **3** yielded the derivative **13** ($C_{24}H_{30}O_7$). The ^1H NMR spectrum of **13** (Table 2) showed a paramagnetically shifted signal of the equatorial H-7β proton (δ 5.30), whereas the H-12 proton resonated at the same field (δ 5.80) as in **3**. Thus, the acetoxy substituent of **3** was at the C-12 position. This conclusion was also supported by the ^{13}C NMR (Table 2), HSQC, and HMBC spectra of **3**, because the carbonyl carbon of the 12-acetate was HMBC-correlated with H-12 and this proton was HSQC connected with a methine carbon at δ 64.5 (C-12), which, in turn, was HMBC-correlated with H_2-11 (δ 2.20 and 1.77) and with H-14 and H-16 (δ 6.40 and 7.41, respectively).

NOE experiments established the relative configuration of **13** and hence of **3**. Irradiation of Me-20 (δ 0.82) of **13** produced NOE enhancements, among others, in the signals of the H_2-19, Me-17, and OAc-7 protons and not in those of H-8 and H-10. Irradiation of H-7β (δ 5.30) produced a strong NOE enhancement (+7.7%) in the signal of H-8. These results indicated that **13** and **3** possess an α-configuration for H_2-19, Me-17, and OAc-7 and that H-8 and H-10 are in the β-configuration.[17,18]

The configuration of the C-12 asymmetric center of **3** was also established through NOE experiments on its acetyl derivative **13**. Irradiation of Me-20 (δ 0.82) produced NOEs for both methylene protons at C-11 (δ 2.22, H-11a, and δ 1.79, H-11b; +7.6% and +9.7% NOE enhancement, respectively). Therefore, compound **13**

Table 2. NMR Spectroscopic Data[a] for Salvisplendins C (**3**) and D (**4**), 7-*O*-Acetylsalvisplendin C (**13**), and 2-*O*-Acetylsalvisplendin D (**14**)

	salvisplendin C (**3**)		salvisplendin D (**4**)		7-*O*-acetylsalvisplendin C (**13**)		2-*O*-acetylsalvisplendin D (**14**)	
position	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.	d_H (*J* in Hz)
1	19.6, CH_2	1.08, qd (12.5, 4.0)[b] 1.50, dddd (12.5, 4.8, 2.0, 0.6)	31.2, CH_2	1.23, ddd (13.3, 12.9, 10.3) 2.01, dddd (13.3, 4.9, 1.2, 0.6)	19.6, CH_2	1.11, qd (12.1, 4.0) 1.55, dddd (12.1, 4.9, 2.1, 1.0)	27.5, CH_2	1.32, ddd (13.5, 12.8, 10.4) 2.10, m[e]
2	27.2, CH_2	2.28, dddd (18.1, 7.4, 4.0, 2.2) 2.02, dddd (18.1, 12.5, 4.8, 2.2)	69.9, CH	4.46, ddd (10.3, 4.9, 1.4)	27.2, CH_2	2.32, dddd (18.2, 7.5, 4.0, 2.1) 2.09, dddd (18.2, 12.1, 4.9, 2.2)	71.7, CH	5.52, ddd (10.4, 5.1, 1.3)
3	135.2, CH	6.68, dd (7.4, 2.2)	141.8, CH	6.60, dd (1.4, 1.2)	135.9, CH	6.72, dd (7.5, 2.2)	135.6, CH	6.53, dd (1.4, 1.3)
4	138.8, qC		137.6, qC		138.0, qC		139.0, qC	
5	44.9, qC		45.6, qC		44.7, qC		45.0, qC	
6	40.2, CH_2	2.31, dd (14.1, 2.4) 1.39, ddd (14.1, 3.6, 2.2)	30.0, CH_2	1.71, ddd (14.5, 4.7, 2.2) 1.50, tdd (14.5, 5.6, 2.0)	37.8, CH_2	2.26, dd (14.8, 2.3) 1.47, ddd (14.8, 4.0, 2.2)	29.2, CH_2	1.77, ddd (12.9, 4.2, 2.1) 1.56, dddd (12.9, 12.7, 4.0, 2.0)
7	72.5, CH	4.08, ddd (3.7, 3.6, 2.4)	30.7, CH_2	1.76, ddd (14.5, 13.3, 4.7) 1.94, ddd (13.3, 5.6, 2.2)	73.2, CH	5.30, ddd (4.1, 4.0, 2.3)	30.3, CH_2	1.70, ddd (15.0, 12.7, 4.2) 2.01, ddd (15.0, 4.0, 2.1)
8	41.5, CH	1.69, qd (7.1, 3.7)	85.0, qC		40.6, CH	1.86, qd (7.0, 4.1)	83.9, qC	
9	39.3, qC		47.4, qC		39.2, qC		46.8, qC	
10	48.5, CH	1.84, dd (12.5, 0.6)	40.4, CH	2.05, dd (12.9, 0.6)	48.2, CH	1.89, dd (12.1, 1.0)	39.5, CH	2.13, dd (12.8, 1.2)
11	42.7, CH_2	2.20, dd (16.0, 8.2) 1.77, dd (16.0, 3.2)	44.8, CH_2	1.94, dd (13.3, 10.3)[c] 2.45, dd (13.3, 6.9)[d]	42.4, CH_2	2.22, dd (16.0, 8.6) 1.79, dd (16.0, 2.7)	44.4, CH_2	1.90, dd (13.3, 10.1)[c] 2.40, dd (13.3, 6.9)[d]
12	64.5, CH	5.80, dd (8.2, 3.2)	70.6, CH	5.01, dd (10.3, 6.9)	64.4, CH	5.80, dd (8.6, 2.7)	69.8, CH	5.01, dd (10.1, 6.9)
13	126.0, qC		128.6, qC		125.9, qC		128.2, qC	
14	108.6, CH	6.40, dd (1.8, 0.9)	109.2, CH	6.36, dd (1.6, 0.8)	108.5, CH	6.39, dd (1.8, 0.9)	108.6, CH	6.34, dd (1.7, 1.1)
15	143.6, CH	7.38, t (1.8)	144.1, CH	7.38, m[e]	143.6, CH	7.38, t (1.8)	143.4, CH	7.39, t (1.7)
16	139.9, CH	7.41, dd (1.8, 0.9)	139.7, CH	7.38, m[e]	139.9, CH	7.41, dd (1.8, 0.9)	139.0, CH	7.36, dd (1.7, 1.1)
17	12.1, CH_3	1.15, d (7.1)	26.8, CH_3	1.18, s	11.5, CH_3	1.01, d (7.0)	26.5, CH_3	1.17, s
18	169.8, qC		170.6, qC		168.9, qC		168.0, qC	
19	72.6, CH_2	3.86, dd (7.6, 2.2)[c] 5.27, d (7.6)[d]	71.3, CH_2	4.00, dd (8.2, 2.0)[c] 4.38, d (8.2)[d]	71.9, CH_2	3.90, dd (8.0, 2.2)[c] 4.81, d (8.0)[d]	70.0, CH_2	3.96, dd (8.2, 2.0)[c] 4.33, d (8.2)[d]
20	19.2, CH_3	0.85, s	17.2, CH_3	0.84, s	19.0, CH_3	0.82, s	16.9, CH_3	0.82, s
OAc	170.2, qC				170.2, qC		170.2, qC	
	21.3, CH_3	1.99, s			21.2, CH_3	1.99, s	21.0, CH_3	2.10, s
					169.9, qC[f]			
					21.3, CH_3[f]	2.09, s[f]		

[a] ^1H and ^{13}C NMR spectra at 400 and 100 MHz, respectively, in $CDCl_3$ (**3**, **13**, and **14**) or 1:1 $CDCl_3-CD_3OD$ (**4**) solution. [b] For methylene groups, except for C-11 in **3** and **13**, the first reported δ value belongs to the α-proton and the second δ value is assigned to the β-proton.[18] [c] This is the pro-*S* α-hydrogen. [d] This is the pro-*R* β-hydrogen. [e] Signal partially obscured. [f] These signals are those of the acetate at C-7.

has a preferred conformation for its side chain at C-9, further indicated by the coupling constants between H-11a and H-11b, and H-12 ($J_{11a,12}$ = 8.6 Hz, $J_{11b,12}$ = 2.7 Hz). Irradiation of Me-17 (δ 1.01) caused NOE enhancements for H-7β, H-8β, and Me-20. Me-17 also showed an NOE to only one proton at C-11 (H-11a, +4.3%), and this proton showed stronger coupling to H-12 ($J_{11a,12}$ = 8.6 Hz). These coupling and NOE relationships in **13** were identical to those reported[19] for several clerodane derivatives[17] possessing a 12*R*-configuration[18] and an identical side chain at C-9. The corresponding 12*S* epimers, like **12**, reveal a strong NOE between the proton at C-11 showing the smaller $J_{11,12}$ value and Me-17.[16,19] Thus, a 12*R*-configuration is very likely for **13**, and hence for **3**. Biogenetic reasoning also supported this point, because all the other clerodanes isolated from *S. splendens* (**1**−**10**) possess the same configuration at their C-12 asymmetric center.[18]

The last diterpenoid isolated from *S. splendens* (salvisplendin D, **4**, $C_{20}H_{24}O_5$) showed a hydroxy absorption (3454 cm^{-1}) in its IR spectrum and was transformed into a monoacetyl derivative (**14**, $C_{22}H_{26}O_6$, no OH absorptions in its IR spectrum) by treatment with acetic anhydride−pyridine. The ^1H and ^{13}C NMR spectra of **4** (Table 2) displayed signals for a β-substituted furan, an exocyclic α,β-unsaturated-γ-lactone, and a C-20 methyl group as in **3**. In addition, **4** was found to possess a secondary hydroxyl group at the C-2 position (δ_{H-2} 4.46, δ_{C-2} 69.9) and an ether bridge between the C-8 and C-12 carbons (δ_{H-12} 5.01, δ_{C-8} 85.0, δ_{C-12} 70.6), as found in dehydrokerlin (**15**), a clerodane isolated from *Salvia rhyacophila* (Fernald) Epling[20] and *S. polystachya* Ort.[21] These structural features were in agreement with key correlations in the HMBC spectrum of **4**, for example, the correlation observed between H-12 and C-8 and between the H-3 olefinic proton (δ 6.60) and the C-1, C-2, C-4, C-5, and C-18 carbons. The relative configuration of salvisplendin D, as it is depicted in formula **4**, was supported by NOE results in a manner similar to that described for **1**−**3**. Moreover, the 2α-configuration[18] of the secondary hydroxy group of **4** (and hence of the OAc-2α substituent of **14**) was in agreement with the observed vicinal coupling constant values for

the protons belonging to ring A, which must be in a half-chair ($^{10}HC_1$) conformation ($J_{\alpha,2\beta} = 10.3$ Hz, $J_{\alpha,10\beta} = 12.9$ Hz, $J_{\beta,2\beta} = 4.9$ Hz, $J_{\beta,10\beta} = 0.6$ Hz, $J_{\beta,3} = 1.2$ Hz, $J_{\beta,3} = 1.4$ Hz).

Clerodanes possessing an 8,12-ether bridge like **4** are infrequent, and only few examples have been reported up to now.[20−23]

The most polar of the compounds isolated from the extract of *S. splendens* (**5**) possesses the molecular formula $C_{21}H_{26}O_5N_2$, and it was supposed that it is an artifact arising from the initial treatment of the plant extract with diazomethane[24] (see above and Experimental Section). The ^{1}H and ^{13}C NMR data of **5** corresponding to the C-1, C-2, and C-5−C-20 structural parts were identical (see Experimental Section) to those of **4** (Table 2), and the observed differences were consistent with the presence in the former of a pyrazoline part in which the C-3 and C-4 carbons of the latter are involved.[24,25] NOE experiments established a β-configuration for the pyrazoline ring of **5**, because irradiation at δ 2.16 (H-3α proton) produced NOEs in the signals of H-1α, H-3′a, H-3′b, and H-19b.

It is of interest that the facile addition of diazomethane to the α,β-unsaturated-γ-lactone of **4** has been reported previously[23−26] for salvifarin, another clerodane diterpene isolated from *Salvia farinacea* Benth. that also possesses an oxygenated function at the C-2 position.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. UV spectra were recorded on a Perkin-Elmer Lambda 2 UV/vis spectrophotometer. IR spectra were obtained on a Perkin-Elmer Spectrum One spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (**1**, **3**, **11**, **13**, and **14**) or 1:1 $CDCl_3$−methanol-d_4 (**2**, **4**, **5**, and **7**) or methanol-d_4 (**6**) solution on a Varian INOVA 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in the δ scale and are referenced to residual $CHCl_3$ (δ 7.25) or methanol-d_4 (δ 3.30) signals for protons and to the solvent signals (δ_{CDCl_3} 77.00, δ_{CD_3OD} 49.00) for carbons. All the assignments for protons and carbons were in agreement with 2D COSY, gHSQC, gHMBC, and 1D NOESY spectra. Mass spectra were registered in the positive EI (70 eV) or APIES mode on Hewlett-Packard 5973 or MSD-1100 instruments, respectively. Elemental analyses were conducted on a LECO CHNS-932 apparatus. Merck Si gel 7734 (70−230 mesh) deactivated with 15% (w/v) of water was used for gravity column chromatography, and Si gel Merck LiChroprep 15−25/25−40 μm 1/1 was used for flash chromatography (elution under 0.7 psi of Ar). Merck 5554 Kieselgel 60 F_{254} sheets were used for thin-layer chromatographic analysis. Petroleum ether (bp 50−70 °C) was used for column chromatography.

Plant Material. *Salvia splendens* Sellow ex Roem. & Schult. was cultivated in the "Orto Botanico" (Botanic Garden) of the University of Palermo, Italy, where voucher specimens are deposited. Flowers of this species were collected at the beginning of June 2005.

Extraction and Isolation. Dried and finely powdered flowers of *S. splendens* (1 kg) were extracted with Me_2CO (10 L) at room temperature for one week. Filtration followed by evaporation of the solvent under reduced pressure (540 mbar) and low temperature (40 °C) gave a residue (50 g, 5% of dry plant material). This extract was treated with an excess of an ethereal solution of CH_2N_2, in order to transform the triterpene acids into their methyl ester derivatives,[9] and then it was subjected to column chromatography (Si gel Merck 7734, 1 kg). Elution with 4:1 petroleum ether−EtOAc gave waxes, phytosterols, and methyl esters of ursolic and oleanolic acids,[9] and elution with 7:3 and 3:2 petroleum ether−EtOAc gave two fractions containing mixtures of diterpenes (TLC). Further chromatography of the first fraction (flash column, 200 g of Si gel Merck LiChroprep, CH_2Cl_2−MeOH as eluent in a gradient from 0.1 to 0.5% of MeOH) successively yielded salvisplendin C (**3**, 120 mg, 0.012% of dry plant material), salviarin[9] (**8**, 2.0 g, 0.20%), and splenolide B[11] (**7**, 1.2 g, 0.12%). Further chromatography of the second fraction in the same way gave, in order of increasing chromatographic polarity, splendidin[10] (**10**, 700 mg, 0.07%), salvisplendin A (**1**, 85 mg, 0.0085%), splenolide A[11] (**9**, 90 mg, 0.009%), impure salvisplendin B (**2**, 105 mg), salvisplendin D (**4**, 110 mg, 0.011%), and compound **5** (100 mg, 0.01%). Impure **2** (104 mg) was subjected to column chromatography (Si gel Merck 230−400 mesh, 30 g, 1:1 petroleum ether−EtOAc as eluent), yielding pure salvisplendin B (**2**, 70 mg, 0.007%, less polar compound) and olearin[12,13] (**6**, 28 mg, 0.0028%).

The previously known diterpenes olearin,[12,13] splenolide B,[11] salviarin,[9] splenolide A,[11] and splendidin[10] (**6**−**10**, respectively) were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (^{1}H and ^{13}C NMR and mass spectra) data and, in the case of **8** and **10**, also by comparison (TLC) with authentic samples.[9,10]

Salvisplendin A (1): amorphous, white solid; $[\alpha]_D^{18}$ −73.9 (*c* 0.207, MeOH); IR (KBr) ν_{max} 3443, 3146, 2919, 1762, 1732, 1446, 1375, 1180, 1154, 1039, 1018, 875, 742, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m*/*z* 358 $[M]^+$ (28), 340 (76), 312 (10), 262 (100), 244 (17), 234 (47), 233 (41), 159 (45), 143 (56), 129 (49), 117 (49), 105 (44), 97 (64), 91 (87), 81 (41); *anal.* C 67.14%, H 6.23%, calcd for $C_{20}H_{22}O_6$, C 67.02%, H 6.19%.

Salvisplendin B (2): amorphous, white solid; $[\alpha]_D^{20}$ −71.8 (*c* 0.213, MeOH); UV (MeOH) λ_{max} (log ϵ) 212 (3.88) nm; IR (KBr) ν_{max} 3437, 3145, 3033, 2916, 1764, 1719, 1650, 1500, 1423, 1370, 1228, 1177, 1033, 1020, 876, 767 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$−CD_3OD, 400 MHz), see Table 1; ^{13}C NMR (1:1 $CDCl_3$−CD_3OD, 100 MHz), see Table 1; EIMS *m*/*z* 356 $[M]^+$ (3), 260 (40), 232 (15), 231 (19), 171 (12), 157 (15), 143 (27), 129 (36), 128 (34), 115 (26), 105 (20), 97 (100), 91 (66), 81 (24), 67 (14), 53 (21); *anal*. C 67.51%, H 5.71%, calcd for $C_{20}H_{20}O_6$, C 67.40%, H 5.66%.

Salvisplendin C (3): colorless, fine needles (Et_2O−*n*-hexane); mp 137−140 °C; $[\alpha]_D^{18}$ −71.7 (*c* 0.159, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 209 (4.06) nm; IR (KBr) ν_{max} 3507, 3140, 2935, 1765, 1738, 1659, 1433, 1373, 1240, 1207, 1189, 1040, 963, 875, 786, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 2; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 2; EIMS *m*/*z* 388 $[M]^+$ (1), 328 (5), 233 (27), 217 (10), 204 (26), 191 (6), 176 (20), 161 (14), 143 (7), 121 (12), 105 (9), 94 (100), 91 (15), 77 (8), 55 (6); *anal*. C 68.17%, H 7.33%, calcd for $C_{22}H_{28}O_6$, C 68.02%, H 7.27%.

Salvisplendin D (4): colorless, fine needles (EtOAc−*n*-hexane); mp 238−241 °C, $[\alpha]_D^{18}$ +16.9 (*c* 0.361, 1:1 $CHCl_3$−MeOH); UV (MeOH) λ_{max} (log ϵ) 210 (4.19) nm; IR (KBr) ν_{max} 3454, 3146, 3128, 2974, 2557, 1753, 1665, 1508, 1459, 1370, 1207, 1014, 1000, 910, 874, 799, 766, 750 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$−CD_3OD, 400 MHz), see Table 2; ^{13}C NMR (1:1 $CDCl_3$−CD_3OD, 100 MHz), see Table 2; EIMS *m*/*z* 344 $[M]^+$ (10), 329 (61), 273 (2), 255 (9), 215 (6), 164 (45), 159 (12), 148 (11), 133 (14), 121 (100), 105 (15), 91 (22), 81 (22), 55 (11); APIESMS *m*/*z* 345 $[M + H]^+$; *anal.* C 69.81%, H 6.89%, calcd for $C_{20}H_{24}O_5$, C 69.75%, H 7.02%.

Compound 5: white plates (MeOH); mp 120−123 °C; $[\alpha]_D^{18}$ −30.4 (*c* 0.102, MeOH); IR (KBr) ν_{max} 3430, 2972, 1766, 1636, 1471, 1377, 1200, 1155, 1023, 907, 874, 795, 720 cm^{-1}; ^{1}H NMR (1:1 $CDCl_3$−CD_3OD, 400 MHz)[18] δ 7.43 (2H, m, H-15 and H-16), 6.42 (1H, dd, $J_{14,15} = 1.6$ Hz, $J_{14,16} = 1.2$ Hz, H-14), 5.06 (1H, d, $J_{3'a,3'b} = 17.2$ Hz, $J_{3'a,3\alpha} = 0.0$ Hz, pro-S H-3′a), 4.97 (1H, dd, $J_{12,11a} = 7.0$ Hz, $J_{12,11b} = 10.0$ Hz, H-12β), 4.64 (1H, d, $J_{19a,19b} = 9.5$ Hz, pro-R H-19a), 4.47 (1H, dd, $J_{19b,19a} = 9.5$ Hz, $J_{19b,6\beta} = 2.0$ Hz, pro-S H-19b), 4.23 (1H, dd, $J_{3'b,3'a} = 17.2$ Hz, $J_{3'b,3\alpha} = 6.1$ Hz, pro-R H-3′b), 2.88 (1H, ddd, $J_{\beta,1\alpha} = 11.2$ Hz, $J_{\beta,1\beta} = 4.1$ Hz, $J_{\beta,3\alpha} = 10.3$ Hz, H-2β), 2.61 (1H, dddd, $J_{\beta,6\alpha} = 12.8$ Hz, $J_{\beta,7\alpha} = 10.8$ Hz, $J_{\beta,7\beta} = 6.8$ Hz, $J_{\beta,19b} = 2.0$ Hz, H-6β), 2.37 (1H, dd, $J_{11a,11b} = 13.2$ Hz, $J_{11a,12} = 7.0$ Hz, pro-R H-11a), 2.16 (1H, dd, $J_{\alpha,2\beta} = 10.3$ Hz, $J_{\alpha,3'a} = 0.0$ Hz, $J_{\alpha,3'b} = 6.1$ Hz, H-3α), 2.02 (1H, ddd, $J_{\alpha,6\beta} = 12.8$ Hz, $J_{\alpha,7\alpha} = 4.0$ Hz, $J_{\alpha,7\beta} = 2.8$ Hz, H-6α), 1.98 (2H, m, H-7α and H-7β), 1.92 (1H, dd, $J_{11b,11a} = 13.2$ Hz, $J_{11b,12} = 10.0$ Hz, pro-S H-11b), 1.76 (1H, ddd, $J_{\beta,1\alpha} = 12.8$ Hz, $J_{\beta,2\beta} = 4.1$ Hz, $J_{\beta,10\beta} = 2.0$ Hz, H-2β), 1.66 (1H, dd, $J_{10\beta,1\alpha} = 12.8$ Hz, $J_{10\beta,1\beta} = 2.0$ Hz, H-10β), 1.50 (1H, td, $J_{\alpha,1\beta} = J_{\alpha,10\beta} = 12.8$ Hz, $J_{\alpha,2\beta} = 11.2$ Hz, H-1α), 1.20 (3H, s, Me-17), 0.90 (3H, s, Me-20); ^{13}C NMR (1:1 $CDCl_3$−CD_3OD, 100 MHz) δ 171.8 (C, C-18), 144.6 (CH, C-15), 140.6 (CH, C-16), 129.8 (C, C-13), 110.0 (CH, C-14), 98.3 (C, C-4), 85.1 (C, C-8), 80.8 (CH_2, C-3′), 72.9 (CH, C-3), 71.4 (CH, C-12), 70.0 (CH_2, C-19), 47.0 (C, C-9), 45.34 (C, C-5, and CH_2, C-11), 45.2 (CH, C-3), 41.4 (CH, C-10), 31.4 (CH_2, C-1), 30.6 (CH_2, C-7), 28.6 (CH_2, C-6), 27.3 (CH_3, C-17), 17.5 (CH_3, C-20); EIMS *m*/*z* 386 $[M]^+$ (2), 371 $[M - CH_3]^+$ (10), 358 $[M - N_2]^+$ (8), 343 $[M - CH_3 - N_2]^+$ (27), 269 (10), 203 (11), 164 (41), 121 (100), 105 (27), 95 (34), 91 (36), 81 (36), 55 (23); *anal*. C 65.18%, H 6.49%, N 7.39%, calcd for $C_{21}H_{26}O_5N_2$, C 65.27%, H 6.78%, N 7.25%.

Olearin (6): colorless, rectangular plates (EtOAc−*n*-pentane); mp 210−212 °C; $[\alpha]_D^{20}$ −116.7 (*c* 0.048, MeOH); IR and mass spectra identical to those reported previously,[13] Lit.: mp 212−213 °C; $[\alpha]_D$ −120 (*c* 1.0, $CHCl_3$);[13] ^{1}H NMR (CD_3OD, 400 MHz)[18] δ 6.75 (1H, dd, $J_{3,2\alpha} = 7.3$ Hz, $J_{3,2\beta} = 2.2$ Hz, H-3), 5.97 (1H, ddd, $J_{14,12} = 1.2$ Hz, $J_{14,16a} = 0.7$ Hz, $J_{14,16b} = 1.8$ Hz, H-14), 4.99 (2H, dd, $J = 1.8$ and 0.7 Hz, $J_{gem} = 0.0$ Hz, H_2-16), 4.63 (1H, br d, $J_{12,11a} = 9.9$ Hz, H-12), 4.43 (1H, d, $J_{19a,19b} = 8.2$ Hz, pro-*R* H-19a), 4.03 (1H dd, $J_{19b,19a} = 8.2$ Hz, $J_{19b,6\beta} = 2.0$ Hz, pro-*S* H-19b), 2.40 (1H, dddd, $J_{\alpha,2\beta} = 17.9$ Hz, $J_{\alpha,1\alpha} = 3.8$ Hz, $J_{\alpha,1\beta} = 2.1$ Hz, $J_{\alpha,3} = 7.3$ Hz, H-2α), 2.27 (1H, qdd, $J_{\beta,7\alpha} = 11.8$ Hz, $J_{\beta,7\beta} = 3.2$ Hz, $J_{\beta,17} = 6.8$ Hz, H-8*β*), 2.23 (1H, m, H-2*β*), 2.03 (1H, dd, $J_{10\beta,1\alpha} = 12.1$ Hz, $J_{10\beta,1\beta} = 1.0$ Hz, H-10*β*), 1.88 (1H, dd, $J_{11a,11b} = 15.6$ Hz, $J_{11a,12} = 9.9$ Hz, H-11a), 1.86 (1H, ddd, $J_{\alpha,6\beta} = 13.2$ Hz, $J_{\alpha,7\alpha} = 3.2$ Hz, $J_{\alpha,7\beta} = 3.6$ Hz, H-6α), 1.62 (1H, dd, $J_{11b,11a} = 15.6$ Hz, $J_{11b,12} = 1.6$ Hz, H-11b), 1.59 (2H, m, H-7α and H-7*β*), 1.58 (1H, m, H-1*β*), 1.32 (1H, dddd, $J_{\beta,6\alpha} = 13.2$ Hz, $J_{\beta,7\alpha} = 12.0$ Hz, $J_{\beta,7\beta} = 3.1$ Hz, $J_{\beta,19b} = 2.0$ Hz, H-6*β*), 1.21 (1H, dddd, $J_{\alpha,1\beta} = 13.2$ Hz, $J_{\alpha,2\alpha} = 3.8$ Hz, $J_{\alpha,2\beta} = 12.4$ Hz, $J_{\alpha,10\beta} = 12.1$ Hz, H-1α), 0.92 (3H, d, $J_{17,8\beta} = 6.8$ Hz, Me-17), 0.64 (3H, s, Me-20); these assignments are in agreement with the partial ^{1}H NMR data previously reported[13] for olearin (**6**); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.9 (C, C-13), 176.4 (C, C-15), 171.9 (C, C-18), 114.4 (CH, C-14), 140.0 (C, C-4), 137.5 (CH, C-3), 73.4 (CH_2, C-19), 72.9 (CH_2, C-16), 66.2 (CH, C-12), 49.3 (CH, C-10), 47.2 (C, C-5), 43.7 (CH_2, C-11), 40.8 (C, C-9), 38.7 (CH, C-8), 35.5 (CH_2, C-6), 28.9 (CH_2, C-7), 28.4 (CH_2, C-2), 21.0 (CH_2, C-1), 18.0 (CH_3, C-20), 16.5 (CH_3, C-17).

General Procedure for the Acetylation of Compounds 1−4. Treatment of **1** (36 mg, 0.100 mmol), **2** (41 mg, 0.115 mmol), and **4** (68 mg, 0.197 mmol) with Ac_2O−pyridine (1:2, 2 mL) for 24 h at room temperature followed by standard workup yielded quantitatively the acetyl derivatives **7**, **11**, and **14**, respectively. Compound **3** (60 mg, 0.154 mmol) was treated with Ac_2O−pyridine (1:2, 3 mL) for one week at 40 °C. Then, the solvent was removed in vacuo by coevaporation with toluene, giving a residue (65 mg). This residue was chromatographed (Si gel 230−400 mesh column, 20 g, 4:1 petroleum ether−EtOAc as eluent), yielding **13** (37 mg, 0.086 mmol, 55.8%).

Splenolide B (7) from Salvisplendin A (1): colorless needles (EtOAc−*n*-hexane); mp 269−271 °C; $[\alpha]_D^{18}$ −131.8 (*c* 0.861, $CHCl_3$). IR, ^{1}H NMR, and mass spectra identical to those reported previously[11] and those obtained by us in this work for **7**. Comparison (mmp, TLC) with an authentic sample confirmed the identity. Lit.:[11] mp 272−274 °C; $[\alpha]_D^{25}$ −135.5 (*c* 1.09, $CHCl_3$).

11-*O*-Acetylsalvisplendin B (11): colorless needles (EtOAc−*n*-pentane); mp 196−198 °C; $[\alpha]_D^{20}$ −73.8 (*c* 0.618, $CHCl_3$); IR (KBr) ν_{max} 3145, 3033, 2979, 1761 (br), 1722 (br), 1656, 1503, 1381, 1231, 1176, 1025, 877, 800, 782, 734, 693 cm^{-1}: ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS *m*/*z* 398 $[M]^+$ (2), 338 (4), 323 (100), 295 (2), 259 (4), 202 (5), 141 (11), 129 (14), 128 (17), 115 (12), 91 (29), 81 (10), 53 (7); *anal*. C 66.26%, H 5.49%, calcd for $C_{22}H_{22}O_7$, C 66.32%, H 5.57%.

7-*O*-Acetylsalvisplendin C (13): amorphous, white solid; $[\alpha]_D^{18}$ −45.5 (*c* 0.441, $CHCl_3$); IR (KBr) ν_{max} 3140, 2933, 1774, 1738, 1661, 1436, 1374, 1228, 1225, 1186, 1034, 972, 875, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 2; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 2; EIMS *m*/*z* 430 $[M]^+$ (2), 388 (10), 370 (3), 328 (19), 246 (24), 235 (30), 217 (66), 158 (38), 143 (30), 111 (36), 94 (100), 81 (12); *anal*. C 67.10%, H 6.91%, calcd for $C_{24}H_{30}O_7$, C 66.96%, H 7.02%.

2-*O*-Acetylsalvisplendin D (14): amorphous, white solid; $[\alpha]_D^{20}$ +12.8 (*c* 0.219, $CHCl_3$); IR (film) ν_{max} 3146, 2973, 2931, 2251, 1778 (br), 1738, 1667, 1500, 1453, 1373, 1236, 1200, 1040, 976, 911, 874, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 2; ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 2; EIMS *m*/*z* 386 $[M]^+$ (5), 371 (25), 295 (5), 255 (10), 164 (41), 121 (100), 105 (19), 95 (39), 81 (30), 55 (16); *anal*. C 68.29%, H 6.71%, calcd for $C_{22}H_{26}O_6$, C 68.38%, H 6.78%.

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(17) On biogenetic grounds, we assume that salvisplendins A−D (**1**−**4**, respectively) belong to the *enantio* absolute configuration, like the other clerodanes (**7**−**10**)[9−11] co-occurring in the same species. Moreover, the clerodane-type diterpenoids until now isolated from plants of the *Salvia* genus, and whose absolute configuration has rigorously been established, belong to the *enantio* series. (Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 2, pp 750−809. Rodríguez-Hahn, L.; Esquivel, B.; Cárdenas, J. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds; Springer-Verlag: Vienna, 1994; Vol. 63, pp 107−196. Rodríguez-Hahn, L.; Esquivel, B.; Cárdenas, J. In *Phytochemistry of Medicinal Plants*; Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, 1995; Chapter 12, pp 311−332.)
(18) In accordance with the Cahn−Ingold−Prelog convention, the configuration of the C-12 chiral center must be described as 12*R* for **2**−**6**, **8**, and **9** and as 12*S* for **1**, **7**, and **10**, although the spatial arrangement of the substituents of that asymmetric carbon is identical for all these compounds. Moreover, since we assume[17] that **1**−**6** belong to the *enantio* series, the *R*- or *S*-configuration for an asymmetric carbon must be described as *ent*-*S* or *ent*-*R*, respectively (Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 1, pp XV−XVI). However, for clarity we use throughout the text the *R*/*S* nomenclature, omitting the prefix *ent*-, which refers to the absolute configuration of the whole molecule. On the other hand, and also for clarity, the α- or *β*-configuration for a substituent indicates that it is placed, respectively, below or above the plane of the formulas depicted for the described substances. However, since we assume that these compounds belong to the *enantio* series,[17] those configurations should be described as *ent*-*β* or *ent*-α, indicating that the substituent is placed, respectively, below or above the plane of the formulas.
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