# Salviarin, a New Diterpenoid from *Salvia splendens*

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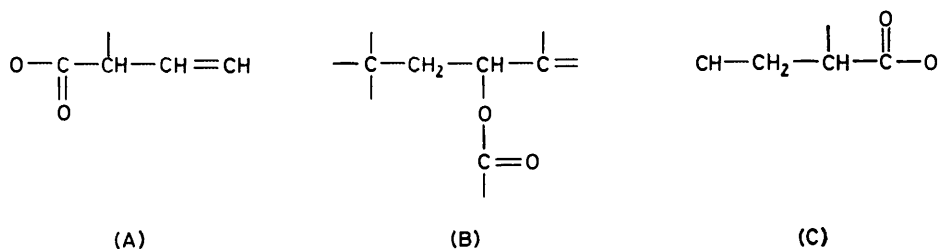
Salviarin has been shown by a combination of spectroscopic and X-ray methods to be 15,16-epoxy-*trans*-cleroda-2,13(16),14-trieno-12,17:19,18-dilactone (1).

Salvia species (Labiatae) are widespread in both the temperate and the tropical zones and a number have found local use as medicinal and culinary herbs.[1] A variety of bi- and tri-cyclic diterpenoids have been isolated[2] from these species. *Salvia splendens* is a Brazilian species which is now widely used for ornamental purposes. Extraction of the leaves has afforded ursolic
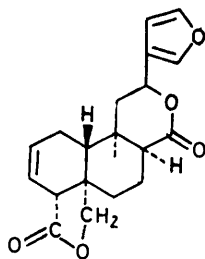
(1)

acid and a new diterpenoid, salviarin, $C_{20}H_{22}O_5$, to which we assign structure (1).† This had i.r. absorptions characteristic of a γ-lactone (1 775 cm⁻¹), a δ-lactone

signal at δ 2.78, collapsing this to a broad singlet. The position of the signal at δ 5.35 ($CH \cdot O \cdot CO$) was clearly due to deshielding by a second functional group. Irradiation at this frequency removed a 5 Hz coupling from a doublet of doublets at δ 2.24 and a 12 Hz coupling from the signal at δ 1.72. These signals showed a geminal coupling of 15 Hz and no further coupling. There was also a clear triplet (δ 1.35, J 15 Hz) which was coupled to signals at δ 1.85 and 1.99. The signal at δ 1.85 was in turn coupled to that of one of two protons at δ 2.47. These decoupling experiments suggested the presence of the groupings (A), (B), and (C). The ^{13}C n.m.r. spectrum (see Table 1) contained signals arising from a methyl group, five methylene carbons, four methine carbons, two olefinic carbon atoms, four furanoid carbons, two quaternary carbon atoms, and two lactone carbonyl groups. Whereas it is difficult to accommodate these spectral data on a labdane skeleton, they may be accommodated readily in the clerodane formulation (1). A related structure (2) has been assigned to a diterpenoid from *Salvia rubescens*.[2f] However it was not possible to distinguish between *cis*- and

(A)   (B)   (C)

(1 725 cm⁻¹), and a furan ring (875 cm⁻¹) thus accounting for the oxygen atoms. The ¹H n.m.r. spectrum showed a $C \cdot CH_3$ signal (δ 1.01), an AB quartet (δ 4.25, J 13 Hz) assigned to $C \cdot CH_2 \cdot O \cdot CO \cdot$, a doublet of doublets (δ 5.36, J 5 and 12 Hz) assigned to $CH \cdot O \cdot CO$ signals for a *cis*-disubstituted olefin (δ 5.64 and 6.00, J 10 Hz) and the characteristic but deshielded signals from a β-substituted furan ring (δ 6.43, 7.43, and 7.48). Proton spin-decoupling studies at 220 MHz indicated the relationship between these protons. Thus irradiation at δ 6.00 removed the 10 Hz coupling from the signal at δ 5.64. Irradiation at δ 5.64, apart from confirming this, removed a 3 Hz coupling from a

trans-clerodane skeletons. Consequently the full structure was determined by X-ray analysis.

The X-ray analysis confirmed structure (1). All the

² (a) *Salvia sclarea*: L. Ruzicka and M. M. Janot, *Helv. Chim. Acta*, 1931, **14**, 645; D. P. Popa and G. V. Lazurveski, *Zhur. obshchei Khim.*, 1963, **33**, 303; D. P. Popa and L. A. Salei, *Khim. prirod. Soedinenii*, 1974, 405; (b) *S. miltiorrhiza*: M. Nakao and T. Fukushima, *J. Pharm. Soc. Japan*, 1934, **54**, 154; F. Von Wessely, *Ber.*, 1940, **73**, 19; 1942, **75**, 958; A. C. Baillie and R. H. Thomson, *J. Chem. Soc. (C)*, 1968, 48; H. Kakisawa, T. Hayashi, I. Okazaki, and M. Ohashi, *Tetrahedron Letters*, 1968, 3231; (c) *S. officinalis* and *S. triloba*: C. H. Brieskorn and A. Fuchs, *Chem. Ber.*, 1962, **95**, 3034; (d) *S. nemorosa*: A. S. Romanova, G. F. Pribylova, P. I. Zakharov, V. I. Scheichenko, and A. I. Ban'lorskii, *Khim. prirod. Soedinenii*, 1971, 199; (e) *S. canariensis*: A. G. Gonzalez, B. M. Fraga, J. G. Luis, and A. G. Ravelo, *Experientia*, 1973, **29**, 1471; *Anales de Quim.*, 1975, **71**, 701; (f) *S. rubescens, S. truxillensis*, and *S. pseudococcinea*: C. Brieskorn and T. Stehle, *Chem. Ber.*, 1973, **106**, 922; (g) *S. ballotaeflora*, W. H. Watson, Z. Taira, X. A. Dominguez, H. Gonzales, M. Guiterrez, and R. Aragon, *Tetrahedron Letters*, 1976, 2501.

† Structure (1) is drawn to represent the relative, but not necessarily the absolute, stereochemistry of salviarin.

¹ 'A Dictionary of Plants Used by Man,' G. Usher, Constable, London, 1974, p. 520.

bond lengths and angles (Tables 2—4) were close to those expected for a *trans*-clerodane structure. The presence of a double bond between C(2) and C(3)

TABLE 1

N.m.r. signals of salviarin (in p.p.m. from SiMe$_4$)

Carbon atom	^{13}C signal (25.15 MHz)	SFORD multiplicity	^{1}H signal (220 MHz)	Multiplicity (J/Hz)
1	18.9 [a]	t	*d*	
2	128.8 [b]	d	6.00	m
3	121.2 [b]	d	5.64	d (10)
4	52.1	d	2.78	m
5	41.4	s		
6	32.4	t	1.35 [e] (1 H)	t (15)
7	21.9 [a]	t	1.85 and 1.99	m
8	49.0	d	2.47	m
9	35.1	s		
10	38.2	d	2.47	m
11	40.8	t	1.72	dd (5 and 15)
			2.24	dd (12 and 15)
12	70.5	d	5.36	dd (5 and 12)
13	124.7	s		
14	108.3	d	6.43	m
15	143.8	d	7.48	m
16	139.6	d	7.43	m
17	175.4 [c]	s		
18	171.4 [c]	s		
19	70.0	t	4.25	q (13) (2 H)
20	23.7	q	1.01	s (3 H)

[a-c] These assignments may be interchanged. [d] The signals for these protons were not identified. [e] The signal for only one of these protons was identified.

caused ring A to assume a half-chair conformation. The δ-lactone ring also exists in a half-chair conformation. The presence of a 2,3- rather than a 3,4-double bond requires an additional hydride shift from C(3) to C(4) in
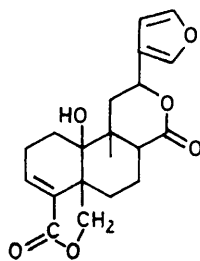
(2)

the biosynthesis of salviarin. In structure (1) there is a *trans*-relationship involving C(20), H(10), C(19), and H(4) which might arise through a concerted rearrangement. However the hydrogen atom at C(8) bears a *cis*-relationship to the methyl group at C(9) as in columbin,[3] suggesting that this hydrogen atom may not be involved in this ' friedo ' rearrangement. There are however a number of labdanes (*e.g.* marrubiin) which possess a hydroxy-group at C(9) having a *trans*-relation-

[3] K. H. Overton, N. G. Weir, and A. Wylie, *J. Chem. Soc.* (C), 1966, 1482.
[4] G. Savona, F. Piozzi, J. R. Hanson, and M. Siverns, *J.C.S. Perkin I*, 1976, 1607.

ship to both H(8) and C(20). The use of this hydroxy-group, or a derivative, as a leaving group could then generate the *trans*-clerodane skeleton shown by salviarin. The migration of a hydrogen atom to C(4) permits the relief of strain introduced by the 18,19-γ-lactone ring which would be present in a *trans*-clerodane with a $\Delta^{3,4}$ double bond.

EXPERIMENTAL

General experimental details have been described previously.[4]

Salvia splendens (1.7 kg, dry flowers and leaves, obtained in October 1976 from the Botanical Gardens, University of Palermo) was extracted with acetone (10 l) at room temperature for 1 week. The solution was evaporated and the residue was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give a gum which was subjected to dry column chromatography on silica gel. Elution with light petroleum gave plant waxes. Elution with 15% ethyl acetate–light petroleum gave ursolic acid containing traces of oleanolic acid (2.0 g) which was identified by g.l.c. of the methyl esters against authentic samples (3% OV-1; 260 °C; N₂ carrier gas at 20 ml min⁻¹; Varian Aerograph 1440). Elution with 30% ethyl acetate–light petroleum gave *salviarin* (120 mg) which crystallized from ethyl acetate–light petroleum as needles, m.p. 218 °C, $[\alpha]_D$ −85° (*c* 2.7) (Found: C, 70.0; H, 6.5. $C_{20}H_{22}O_5$ requires C, 70.2; H, 6.4%); $v_{max.}$ 1 775, 1 725, 1 660, 1 210, 1 190, 1 160, 1 020, 950, 875, 790, and 710 cm⁻¹; for n.m.r. data see Table 1; *m/e* 342, 217, 203, 159, 145, 131, 117, 105, 94, and 77.

Crystal Data.—$C_{20}H_{22}O_5$, $M = 342.4$. Orthorhombic, $a = 11.817(8)$, $b = 17.625(5)$, $c = 8.011(7)$ Å, $U = 1 668.8$ Å³, $Z = 4$, $D_c = 1.363$ g cm⁻³, $F(000) = 728$, space group $P2_12_12_1$ (no. 19) [5] from the systematic absences $0k0$ for k odd, $h00$ for h odd, and $00l$ for l odd. Mo-$K_{\alpha 1}$ radiation, $\lambda = 0.709\ 26$ Å, $\mu(\text{Mo-}K_\alpha) = 0.8$ cm⁻¹.

Crystallographic measurements. A colourless needle-shaped crystal of dimensions *ca.* 0.45 × 0.1 × 0.1 mm was used for data collection on a Hilger and Watts four-circle diffractometer. Accurate cell dimensions were calculated from the setting angles for 12 reflections. Intensity data were collected by an ω—2θ step scan for the octant *hkl* in two consecutive shells, 2—22 and 22—25°, with Mo-K_α radiation. Each reflection was measured in 60 steps of 0.5 s each and background counts of 15 s were made at each end of the scan. Three standard reflections, measured after every 100 reflections, remained constant over the data collection. After correction for Lorentz and polarization effects, but not for absorption, the data were termed significant if $I > 3\sigma(I)$ based on counting statistics. After averaging of equivalent reflections, there were 584 significant reflections out of a total of 1 729 measured.

Structure determination. All data were converted to normalized structure factors ($|E|$) and phases were derived by multiple-start tangent formula procedures [6] using the 261 reflections with $|E| > 1.20$. Two fused six-membered rings and a five-membered ring were revealed, giving rough atom positions for 18 non-hydrogen atoms. The remaining non-hydrogen atoms were found by tangent refinement of partial structures [7] using the 18 atom positions to obtain

[5] ' International Tables for X-Ray Crystallography,' Kynoch Press, Birmingham, 1962.
[6] G. Germain and M. M. Woolfson, *Acta Cryst.*, 1968, **B24**, 91.
[7] J. Karle, *Acta Cryst.*, 1968, **B24**, 182.

TABLE 2

Final position parameters ($\times 10^4$), with estimated standard deviations in parentheses

(a) Non-hydrogen atoms

	x	y	z
O(1)	−1 868(10)	4 755(7)	12 383(15)
O(2)	0 453(8)	4 590(5)	8 313(13)
O(3)	1 385(9)	5 098(6)	6 305(14)
O(4)	3 507(9)	1 857(6)	4 275(14)
O(5)	2 455(11)	1 576(7)	2 066(17)
C(1)	1 161(13)	2 058(7)	8 165(19)
C(2)	0 794(13)	1 481(8)	6 922(20)
C(3)	0 949(13)	1 537(8)	5 292(18)
C(4)	1 590(13)	2 176(7)	4 527(17)
C(5)	2 237(13)	2 676(8)	5 776(19)
C(6)	2 495(15)	3 456(8)	4 940(19)
C(7)	3 064(13)	4 012(9)	6 082(20)
C(8)	2 373(12)	4 126(7)	7 693(17)
C(9)	2 086(11)	3 387(7)	8 591(16)
C(10)	1 586(12)	2 805(7)	7 366(17)
C(11)	1 309(11)	3 588(8)	10 017(17)
C(12)	0 231(11)	3 966(7)	9 494(18)
C(13)	−0 427(12)	4 301(7)	10 879(19)
C(14)	−0 059(14)	4 562(8)	12 461(21)
C(15)	−0 938(15)	4 829(8)	13 279(21)
C(16)	−1 537(16)	4 441(9)	10 854(24)
C(17)	1 378(13)	4 618(8)	7 372(19)
C(18)	2 523(16)	1 843(9)	3 493(23)
C(19)	3 348(13)	2 210(8)	5 934(19)
C(20)	3 208(12)	3 066(8)	9 385(18)

	x	y	z	Bonded to
H(1)	045	219	897	C(1)
H(2)	184	182	890	C(1)
H(3)	037	098	738	C(2)
H(4)	060	110	449	C(3)
H(5)	096	251	388	C(4)
H(6)	171	370	452	C(6)
H(7)	304	336	388	C(6)
H(8)	389	380	640	C(7)
H(9)	315	455	545	C(7)
H(10)	291	442	857	C(8)
H(11)	083	310	697	C(10)
H(12)	327	178	689	C(19)
H(13)	405	258	623	C(19)
H(14)	383	299	841	C(20)
H(15)	307	253	1 001	C(20)
H(16)	351	348	1 028	C(20)
H(17)	176	397	1 085	C(11)
H(18)	110	307	1 068	C(11)
H(19)	−003	351	894	C(12)
H(20)	−210	433	982	C(16)
H(21)	−091	507	1 451	C(15)
H(22)	−080	455	1 246	C(14)

TABLE 3

Bond lengths (Å) and angles (°), with estimated standard deviations in parentheses

(a) Bond lengths

O(1)−C(16)	1.40(2)		C(5)−C(10)	1.51(2)
O(1)−C(15)	1.32(2)		C(5)−C(19)	1.55(2)
O(2)−C(12)	1.48(2)		C(6)−C(7)	1.50(2)
O(2)−C(17)	1.33(2)		C(7)−C(8)	1.54(2)
O(3)−C(17)	1.20(2)		C(8)−C(9)	1.53(2)
O(4)−C(18)	1.32(2)		C(9)−C(10)	1.54(2)
O(4)−C(19)	1.48(2)		C(9)−C(20)	1.58(2)
O(5)−C(18)	1.24(2)		C(9)−C(11)	1.51(2)
C(1)−C(2)	1.49(2)		C(11)−C(12)	1.50(2)
C(1)−C(10)	1.55(2)		C(12)−C(13)	1.48(2)
C(2)−C(3)	1.32(2)		C(17)−C(8)	1.48(2)
C(3)−C(4)	1.49(2)		C(13)−C(16)	1.34(2)
C(4)−C(5)	1.54(2)		C(13)−C(14)	1.42(2)
C(4)−C(18)	1.50(2)		C(15)−C(14)	1.32(2)
C(5)−C(6)	1.56(2)			

TABLE 3 (Continued)

(b) Bond angles

C(10)−C(1)−C(2)	113.6(1.2)		C(5)−C(10)−C(1)	112.7(1.0)
C(3)−C(2)−C(1)	124.7(1.5)		C(9)−C(10)−C(1)	115.4(1.1)
C(4)−C(3)−C(2)	122.2(1.4)		C(9)−C(10)−C(5)	116.4(1.1)
C(5)−C(4)−C(3)	114.8(1.1)		C(12)−C(11)−C(9)	114.3(1.1)
C(18)−C(4)−C(3)	107.7(1.2)		C(13)−C(12)−C(11)	114.5(1.2)
C(18)−C(4)−C(5)	102.6(1.3)		C(16)−C(13)−C(12)	125.4(1.5)
C(10)−C(5)−C(4)	112.5(1.2)		C(14)−C(13)−C(12)	129.8(1.3)
C(10)−C(5)−C(6)	109.3(1.1)		C(14)−C(13)−C(16)	104.8(1.6)
C(19)−C(5)−C(4)	99.8(1.1)		C(15)−C(14)−C(13)	108.7(1.5)
C(19)−C(5)−C(6)	109.6(1.2)		C(15)−O(1)−C(16)	106.5(1.3)
C(19)−C(5)−C(10)	116.3(1.2)		C(17)−O(2)−C(12)	122.5(1.1)
C(7)−C(6)−C(5)	113.7(1.3)		C(12)−O(4)−C(18)	108.8(1.3)
C(8)−C(7)−C(6)	111.0(1.3)		O(1)−C(16)−C(13)	109.5(1.7)
C(9)−C(8)−C(7)	113.7(1.1)		O(3)−C(17)−C(8)	122.0(1.5)
C(17)−C(8)−C(7)	110.5(1.2)		O(3)−C(17)−O(2)	115.7(1.4)
C(17)−C(8)−C(9)	113.9(1.2)		O(2)−C(12)−C(11)	111.1(1.1)
C(10)−C(9)−C(8)	110.7(1.0)		O(2)−C(12)−C(13)	106.0(1.0)
C(20)−C(9)−C(8)	108.1(1.1)		O(4)−C(18)−C(4)	112.2(1.4)
C(20)−C(9)−C(10)	110.0(1.1)		O(5)−C(18)−C(4)	127.7(1.8)
C(11)−C(9)−C(8)	106.9(1.1)		O(5)−C(18)−O(4)	120.1(1.8)
C(11)−C(9)−C(10)	113.9(1.1)		O(4)−C(19)−C(5)	104.8(1.2)
C(11)−C(9)−C(20)	106.9(1.1)			

the best 30 phases. The atom positions with isotropic temperature factors were refined by full-matrix least squares using the 584 significant reflections with unit
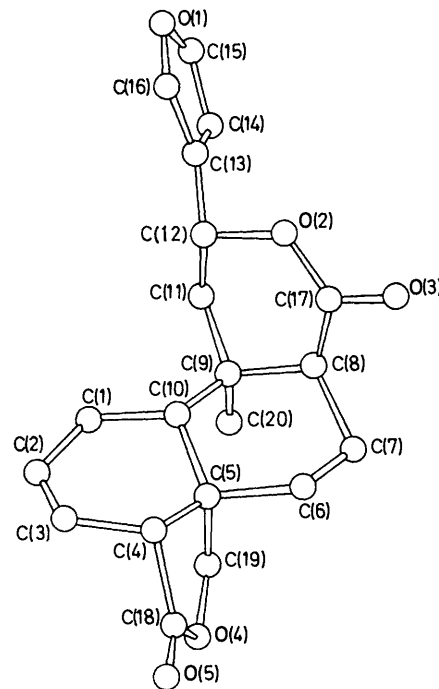
A perspective view of salviarin

weight. Ambiguities between oxygen and carbon atoms were resolved on the basis of temperature factors and bond lengths. The R value at this point was 0.10. The positions of the 22 hydrogen atoms were calculated geometrically. The methyl groups were refined as rigid bodies, and the remaining hydrogen atoms were made to ride on the corresponding carbon atoms. The methyl hydrogen atoms were given individual isotropic temperature factors; the other hydrogen atoms were given the temperature factors of their corresponding carbon atoms. Four cycles of least-squares refinement of all atoms with isotropic temperature factors and a weighting scheme defined as $w = K/[\sigma^2(F) +$

$0.001(F)^2$] gave convergence. The refinement was terminated at R 0.070 and R' 0.072, when the maximum value of shift-to-e.s.d. for any non-hydrogen parameter was 0.19.

Initial data processing was done with local programs. Data were then converted into a format suitable for the SHEL-X program.[8] Scattering factors for C, O, and H atoms were taken from ref. 9 and no allowance was made for anomalous scattering. The final atom co-ordinates are listed in Table 2, and the bond lengths and angles in Table 3.

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue.

[8] ' SHEL-X,' program for crystal structure determination, G. Sheldrick.

A perspective view of the molecule is shown in the Figure. The final structure factors are listed in Supplementary Publication No. SUP 22246 (8 pp.), together with the torsion angles and thermal parameters.*

[9] D. T. Crommer and J. J. Mann, *Acta Cryst.*, 1968, **A24**, 321; R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **43**, 3175.