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Structure and Stereochemistry of (8*S*,12*R*)-*cis*-Clerodane-1,3,13(16),14-tetraene-15,16-epoxy-12(17);18,19-diolide (Linearolactone), a Diterpene*

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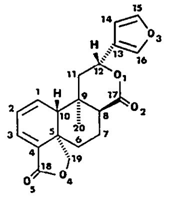
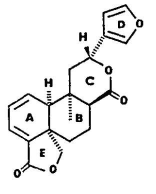
Abstract. $C_{20}H_{20}O_5$, $M_r = 340{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}824\,(2)$, $b = 13{\cdot}555\,(6)$, $c = 15{\cdot}506\,(4)$ Å, $V = 1645\,(1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}37$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}7107$ Å, $\mu = 0{\cdot}092$ mm^{-1}, $F(000) = 720$, $T = 300$ K, $R = 0{\cdot}039$ for 1110 observed reflections. The structure determination establishes the configuration at C(12) to be 12*R*. The *A* and *B* rings are *cis* fused, with 1,3-diplanar and distorted chair conformations, respectively. The γ-lactone ring has a half-chair conformation and the 13(16*H*)-furan ring is planar to within 0·028 (4) Å. The crystal structure is stabilized by intra- and intermolecular C—H···O contacts.

Introduction. In a previous communication (Esquivel, Cárdenas, Ramamoorthy & Rodríguez-Hahn, 1986) the isolation of linearifolin from *Salvia lineata* Bentham and its structure assignment as (1) was described. Both (1) and (2) are possible structures for linearolactone. The structure (1) was assigned mainly on the basis of ^{1}H and ^{13}C NMR data, although structure (2) could not be excluded with certainty based on the NMR spectrum. The configuration at C(12) as 12*R* and the *A*/*B* ring fusion as *trans* were proposed by comparison with related compounds (Savona, Paternostro, Piozzi, Hanson, Hitchcock & Thomas, 1978) and on biogenetic grounds. An X-ray analysis was therefore carried out to provide conclusive evidence for the chemical structure, establish the configuration at C(12), the *A*/*B* ring fusion and to obtain details of the molecular conformation.



(1)



(2)

Experimental. Colourless crystal 0·28 × 0·58 × 0·60 mm. Nicolet *R*3 four-circle diffractometer. Lattice parameters from 25 machine-centred reflections with $5{\cdot}8 < 2\theta < 18{\cdot}1^\circ$. 1269 independent reflections with $3 < 2\theta < 45^\circ$, 1110 with $I > 2{\cdot}5\sigma(I)$, index range $h\,0\rightarrow 8$, $k\,0\rightarrow 14$, $l\,0\rightarrow 16$, ω-scan mode, variable scan speed, scan width $1{\cdot}0^\circ(\theta)$, two standard reflections ($02\bar{1}$; $1\bar{1}2$) monitored every 50 measurements, Lp correction, absorption ignored; structure solved by combination of direct methods and partial structure expansion by iterative *E*-Fourier procedure using *SHELXTL* (Sheldrick, 1981); least-squares anisotropic refinement of all non-H atoms and H atoms riding on bonded C with fixed isotropic $U = 0{\cdot}06$ Å^2, function minimized $\sum w(\Delta F)^2$, $w = [\sigma^2(F_o) + 0{\cdot}001(F_o)^2]^{-1}$, $\sigma(F_o)$ based on counting statistics; isotropic extinction parameter $X = 0{\cdot}0025$. In the last cycle $(\Delta/\sigma)_{\max} = 0{\cdot}15$; $\Delta\rho$ from $-0{\cdot}16$ to $+0{\cdot}14$ e Å^{-3}; $S = 1{\cdot}09$; final $R = 0{\cdot}039$, $wR = 0{\cdot}046$; scattering factors from *International Tables for X-ray Crystallography* (1974). All computations performed on a Nova 4S computer and plots drawn on a Tektronix plotter with the *SHELXTL* system of programs.

Discussion. Atomic coordinates are in Table 1.‡ Fig. 1 shows the conformation of the title compound. The bond lengths for non-H atoms are listed in Table 2.

The X-ray analysis confirms formula (2) and establishes the configuration as 12*R* and the *A*/*B* ring fusion to be *cis*.

The cyclohexadiene ring exhibits a 1,3-diplanar conformation. The γ-lactone and cyclohexane rings are fused *trans*–*cis* with torsion angles of −35·0 (4), 20·5 (3)° and 46·8 (3), 54·5 (3)°.§ The lactone ring has a half-chair conformation. Δ and φ_m (Altona, Geise

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‡ Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates, bond angles and mean-plane calculations have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43793 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

§ Torsion angles C(3)—C(4)—C(5)—C(10), C(18)—C(4)—C(5)—C(19), C(4)—C(5)—C(10)—C(1), C(6)—C(5)—C(10)—C(9), respectively.

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Table 1. *Atomic coordinates* (× 10^4) *and equivalent isotropic temperature factors* ($Å^2 \times 10^3$)

$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$.

	x	y	z	U_{eq}
O(1)	15382 (3)	8524 (2)	2672 (2)	56 (1)
O(2)	14363 (4)	10016 (2)	2481 (2)	71 (1)
O(3)	14694 (5)	7566 (3)	5215 (2)	93 (1)
O(4)	7354 (3)	8919 (2)	567 (2)	63 (1)
O(5)	7699 (4)	9585 (2)	−731 (2)	66 (1)
C(1)	13249 (4)	8451 (3)	743 (2)	41 (1)
C(2)	13154 (4)	8960 (3)	12 (2)	48 (1)
C(3)	11490 (5)	9183 (3)	−357 (2)	45 (1)
C(4)	10137 (4)	9104 (2)	144 (2)	38 (1)
C(5)	10250 (4)	8816 (2)	1084 (2)	35 (1)
C(6)	10574 (5)	9750 (2)	1632 (2)	47 (1)
C(7)	10883 (5)	9499 (3)	2581 (2)	52 (1)
C(8)	12284 (4)	8734 (2)	2724 (2)	41 (1)
C(9)	12027 (4)	7785 (2)	2183 (2)	39 (1)
C(10)	11694 (4)	8067 (2)	1217 (2)	35 (1)
C(11)	13623 (5)	7117 (3)	2258 (2)	52 (1)
C(12)	15014 (5)	7486 (3)	2848 (2)	51 (1)
C(13)	14759 (4)	7338 (3)	3798 (2)	47 (1)
C(14)	14363 (6)	6431 (3)	4211 (2)	63 (2)
C(15)	14335 (6)	6597 (3)	5050 (3)	78 (2)
C(16)	14963 (6)	7986 (3)	4435 (3)	74 (2)
C(17)	14051 (5)	9159 (3)	2609 (2)	48 (1)
C(18)	8328 (5)	9244 (3)	−88 (3)	50 (1)
C(19)	8403 (4)	8438 (3)	1213 (2)	53 (1)
C(20)	10494 (5)	7216 (3)	2549 (2)	61 (1)

Table 2. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

O(1)–C(12)	1·462 (5)	O(1)–C(17)	1·355 (5)
O(2)–C(17)	1·204 (4)	O(3)–C(15)	1·367 (6)
O(3)–C(16)	1·353 (5)	O(4)–C(18)	1·344 (5)
O(4)–C(19)	1·450 (4)	O(5)–C(18)	1·205 (5)
C(1)–C(2)	1·329 (5)	C(1)–C(10)	1·514 (5)
C(2)–C(3)	1·454 (5)	C(3)–C(4)	1·318 (5)
C(4)–C(5)	1·512 (4)	C(4)–C(18)	1·472 (5)
C(5)–C(6)	1·546 (4)	C(5)–C(10)	1·533 (4)
C(5)–C(19)	1·546 (5)	C(6)–C(7)	1·529 (5)
C(7)–C(8)	1·526 (5)	C(8)–C(9)	1·549 (4)
C(8)–C(17)	1·508 (5)	C(9)–C(10)	1·568 (4)
C(9)–C(11)	1·547 (5)	C(9)–C(20)	1·534 (5)
C(11)–C(12)	1·507 (5)	C(12)–C(13)	1·501 (5)
C(13)–C(14)	1·419 (5)	C(13)–C(16)	1·331 (5)
C(14)–C(15)	1·321 (6)		

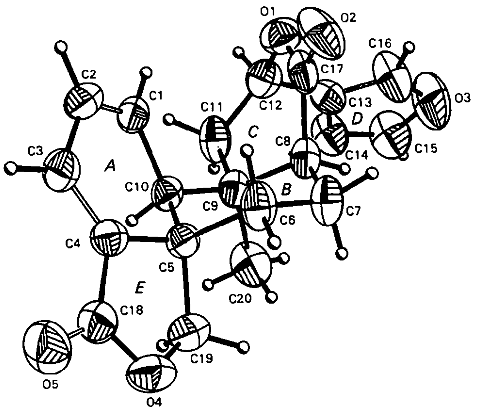

Fig. 1. The conformation of the title compound, showing atom numbering. The thermal ellipsoids are drawn at the 50% probability level.

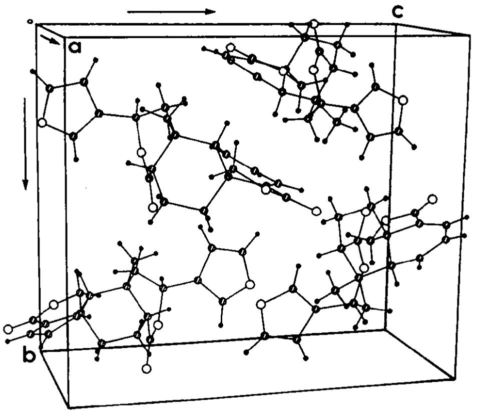

Fig. 2. A perspective drawing of the contents of one unit cell.

& Romers, 1968) are 3·2 (4) and 24·4 (4)° for the five-membered lactone ring. The cyclohexane ring exhibits a distorted chair conformation. The average bond length and angle, 1·542 (5) Å and 112·2 (3)°, respectively, agree with those obtained for cyclohexane (Kahn, Fourme, André & Renaud, 1973). The average value of the ring torsion angle is 52·6 (4)°. The methyl substituent at C(9) is axial. The *C* ring adopts a 1,4-diplanar conformation. The fusion to the cyclohexane ring is *cis* with torsion angles C(17)—C(8)—C(9)—C(11) = 43·4 (3) and C(7)—C(8)—C(9)—C(10) = 50·0 (4)°. The 13(16*H*)-furanone ring is almost planar; the maximum deviation is 0·028 (4) Å for C(13). It is almost perpendicular to ring *C* [dihedral angle 96·2 (4)°].

The three-dimensional packing of the molecules in the unit cell is shown in Fig. 2. There are five intramolecular C—H···O interactions involving O(1), O(2), O(2), O(4) and O(5) which are at 2·848 (5), 3·264 (5), 2·816 (5), 3·217 (4) and 3·071 (5) Å from C(16), C(6), C(7), C(6) and C(3), respectively. There are also seven intermolecular C—H···O contacts <3·4 Å: C(19)···O(1) (−1+*x*,*y*,*z*); C(1)···O(4), C(2)···O(4) (1+*x*,*y*,*z*); C(11)···O(5) (0·5+*x*, 1·5−*y*, −*z*); C(11)···O(2), C(14)···O(2) (3−*x*, −0·5+*y*, 0·5−*z*); and C(15)···O(5) (2−*x*, −0·5+*y*, 0·5−*z*) with values of 3·274 (4), 3·285 (4), 3·397 (4), 3·384 (4), 3·280 (4), 3·400 (5) and 3·330 (5) Å respectively.

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Conformation and Structure of a Blocked Gla Residue: *N*-Benzyloxycarbonyl-(γ,γ-di-*tert*-butyl)-L-carboxyglutamic Acid α-Methyl Ester

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Abstract. γ,γ-Di-*tert*-butyl α-methyl *N*-benzyloxycarbonyl-L-carboxyglutamate, $C_{23}H_{33}NO_8$, M_r = 451·4, orthorhombic, $P2_12_12_1$, $a = 14{\cdot}234\,(3)$, $b = 19{\cdot}671\,(5)$, $c = 8{\cdot}929\,(5)$ Å, $V = 2500\,(2)$ Å^3, $Z = 4$, $D_x = 1{\cdot}200$, D_m (flotation in aqueous NaBr) = 1·16 (3) Mg m^{-3}, Mo $K\alpha$ radiation ($\lambda K\alpha_1 = 0{\cdot}70926$, $\lambda K\alpha_2 = 0{\cdot}71354$ Å), $\mu = 0{\cdot}0975$ mm^{-1}, $F(000) = 968$, $T = 295$ K, $R = 0{\cdot}042$, $wR = 0{\cdot}043$ for 1348 observations. The molecule is extended, with C′ *trans* to Cγ and Cα *trans* to C^{δ}_{1}. There is an intermolecular hydrogen bond between the NH group and the carboxyl oxygen of a neighboring benzyloxycarbonyl group.

Introduction. The presence of γ-carboxyglutamic acid (Gla) residues in a variety of proteins is well established (Stenflo, Fernlund, Egan & Roepstorff, 1974; Hauschka, Lian & Gallop, 1975; Price, Otsuka, Poser, Kristaponis & Raman, 1976; Jackson & Nemerson, 1980). Both low- and high-resolution crystal structures of fragment 1 of prothrombin, which contains ten Gla residues, have been published, but unfortunately the extensive disorder in the metal-binding region of the protein leaves the Gla residues unresolved (Olsson, Andersen, Lindqvist, Sjolin, Magnusson, Petersen & Sottrup-Jensen, 1982; Park & Tulinsky, 1986). In view of the biological significance of species containing Gla residues, it is surprising that the only crystallographic studies reported to date are those of the free amino acid (Satyshur & Rao, 1979), its ammonium salt (Satyshur, Rao, Stenflo & Suttie, 1979), and our own study of a blocked Gla-Gly dipeptide, Z-Gla(O-^{t}Bu)$_2$-GlyOEt (Valente, Hiskey & Hodgson, 1979) (Z = benzyloxycarbonyl). The present study of Z-Gla(O-^{t}Bu)$_2$OMe was undertaken in order to compare the conformation of this fully blocked Gla residue with the structures of both the unblocked and blocked residues noted above, and with those unblocked glutamyl (Glu) peptides (Eggleston & Hodgson, 1983, and references therein) and their blocked analogues (Benedetti, DiBlasio, Pavone, Pedone, Germain & Goodman, 1979; Eggleston & Hodgson, 1984).

Experimental. Colorless rods by slow evaporation of an aqueous methanol solution at room temperature. Crystal 0·3 × 0·3 × 0·9 mm. Enraf–Nonius CAD-4 diffractometer. Systematic absences $h00$ for h odd, $0k0$ for k odd, $00l$ for l odd. Cell constants by least squares using 25 reflections with $23 \leq 2\theta(\text{Mo}) \leq 32°$ measured on the diffractometer. Intensity data collected in an ω–2θ scan mode, as suggested by peak-shape analysis. 1975 independent reflections, $2\theta \leq 44°$, $0 \leq h \leq 15$, $0 \leq k \leq 20$, $0 \leq l \leq 9$. Lorentz–polarization correction, no absorption correction. No systematic fluctuations in $\bar{9}\bar{9}1$, $\bar{5}\bar{7}3$, 275 monitored at the beginning and every 3 h of exposure time (20 times). Programs in CAD-4 *Structure Determination Package* (Enraf–Nonius, 1979); atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

Structure determined using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). E map revealed a 26-atom fragment of the molecule after several trials; remainder of the non-hydrogen atoms located from a difference Fourier synthesis after three cycles of least-squares refinement on the initial fragment. Anisotropic full-matrix least-squares refinement (on F) of all 32 non-hydrogen atoms led to $wR = 0{\cdot}148$; weights $4F_o^2/\sigma^2(I)$. Subsequent difference Fourier maps revealed positions for all 33 H atoms; however, because of the paucity of data all H atoms were fixed at calculated positions (with C—H = 0·95 and N—H = 0·87 Å) with fixed isotropic

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