

X-RAY STRUCTURE AND SYNTHESIS OF ISOGALLICADIOL

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38206 Tenerife, Canary Islands, SpainABSTRACT.—Isogallicadiol [**2**], a new *cis*-eudesmanolide from *Artemisia maritima* ssp. *gallica*, was characterized by spectral means, X-ray diffraction studies, and a partial synthesis.

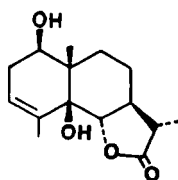
Isogallicadiol [**2**], a new *cis*-(10 β ,5 β)-eudesmanolide, was obtained as a very minor constituent of *Artemisia maritima* ssp. *gallica* Willd. (Compositae) and proved to be an isomer of gallicadiol [**1**] (1). Its structure, absolute configuration as determined by X-ray diffraction analysis, and partial synthesis are described below.

Isogallicadiol [**2**] was isolated as a crystalline compound. Its structure was determined by comparing its ¹H- and ¹³C-nmr data with those of its epimer **3** (2,3) and dihydroreynosin [**4**] (4). Comparison of the H-1 chemical shifts in **2** and **3** and the mean breadth (4.5 Hz) of the H-1 signal, which ruled out an axial-axial coupling (5), indicated the axial disposition (1*R*, β -OH) of the secondary hydroxy. The *cis*-(10 β -Me, 5 β -OH) stereochemistry of the A/B-ring junction was assigned on the basis of the H-6 and H-14 chemical shifts in **2**, compared with those in **1** and **3** (1).

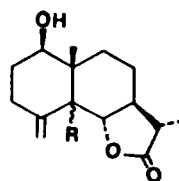
The chemical shifts of the C-1 in **2** and **3**, compared with the ¹³C-nmr spectrum for **4**, agree with this assignment, because $\Delta\delta = \delta_4 - \delta_2 = +0.90$ ppm in **2** while $\Delta\delta = \delta_4 - \delta_3 = +6.42$ ppm in **3**, showing the γ effect, which occurs in **3** but not in **2** (6). The configuration 1*1S*

(α -Me) can be assigned to C-11 on the basis of the C-13 chemical shift in the ¹³C-nmr spectrum, in accordance with the data of Pregosin *et al.* (7).

The determination of the molecular structure of **2** by X-ray diffraction confirms the above results and establishes the absolute configuration as 1*R*,5*S*,6*S*,7*S*,10*S*,11*S*. Figure 1 is a molecular perspective of the correct enantiomer for **2** produced by the PLUTO program. The six-membered rings A and B are *cis*-fused, with hydroxy groups on C-1 and C-5 and a 1,3-diaxial disposition. Ring A is in the ¹C₄ chair conformation, differing from the half-chair ¹H₁₀ found for the equivalent ring in gallicadiol [**1**] (1). The interisomer variance in conformation for this ring is associated with the change of the exocyclic double bond in **2** to an endocyclic double bond in **1**. However, both the six-membered Ring B and the lactonic ring have the same conformation in the two isomers, ⁸C₅ in Ring B and (C₃) with C-7 out of plane in the lactonic ring. The crystal structure of **2** is built on hydrogen bonds, one of which is intramolecular, H-01 . . . O-4 with distance equal to 2.765 (5) Å and angle 122° and the other intermolecular, H-



1



2 R = β -OH
3 R = α -OH
4 R = α -H

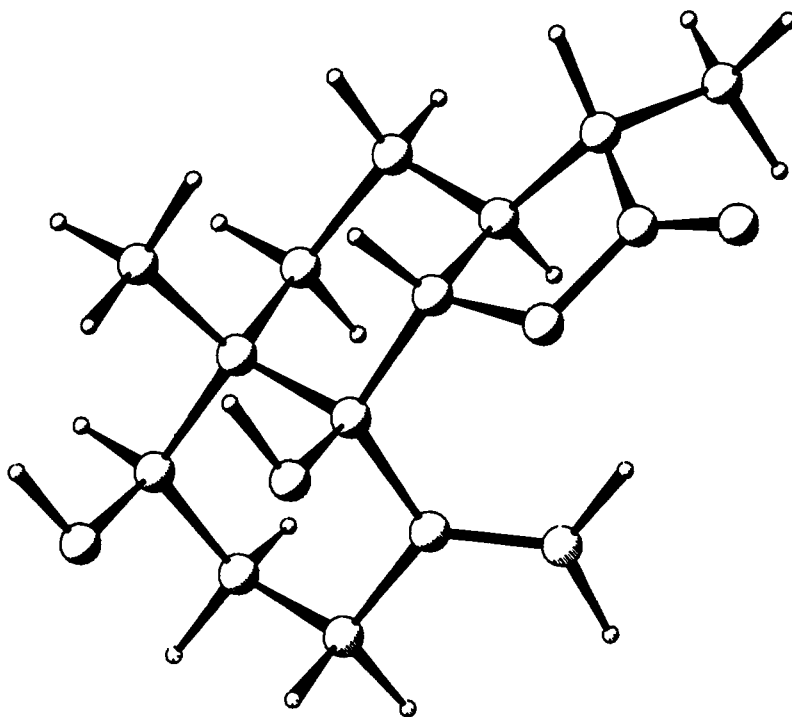


FIGURE 1. The molecule of isogallicadiol [2].

04 . . . O-1 with distance 2.775 (5) Å and angle 135°.

The synthesis of isogallicadiol [2] was carried out in three stages from **5**, a compound prepared from vulgarin (1). Treatment of **5** with NaBH₄ in DMF at 80° (**8**) gave **6** (63%) which, when treated with lithium diethylamide in anhydrous Et₂O (**9**), afforded **7** (51%) (Scheme 1). Deprotection of **7** then led to a compound identical to the natural compound.

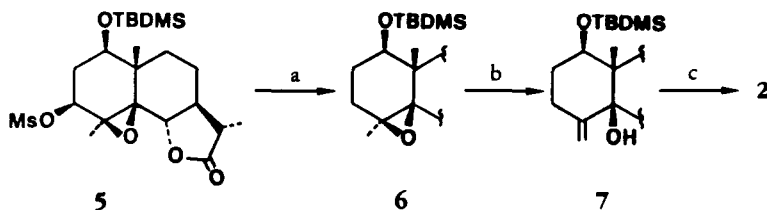
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's, determined on a Kofler-type block, are uncorrected. Ir spectra were taken in CHCl₃ on a Perkin-Elmer spectrophotometer, model 257. The ¹H and ¹³C nmr were collected on a Bruker WP-200SY at 200 MHz with CDCl₃ as solvent. The ms spectra were recorded on a VG Micromass ZAB-2F. The optical rotations were measured on a Perkin-Elmer polarimeter, model 241, at 20–30° in CHCl₃ in 0.2–0.4% concentrations. Cc, except when specified otherwise, used Merck Si gel (0.065–0.2 mm).

TABLE 1. ¹H-nmr Data for Compounds **2**, **3**, and **4**.^a

Proton	Compound		
	2	3	4
H-1	3.45 complex	4.14 dd (4.9, 5.0)	3.46 dd (4.7, 4.7)
H-6	4.36 d (11.5)	4.23 d (10.6)	4.02 dd (10.4, 10.4)
H-13	1.23 d (6.4)	1.21 d (6.6)	1.19 d (6.9)
H-14	1.34 s	0.86 s	0.79 s
H-15	5.07 s, 5.36 d (2.2)	5.00 s, 4.94 d (1.8)	4.93 d (1.3), 4.78 d (1.4)

^aChemical shifts in ppm. Spectra were taken in CDCl₃ at 200 MHz. Coupling constants (*J*) are given in Hz.

SCHEME 1. (a) NaBH₄/DMF; (b) Et₂NLi/Et₂O; (c) HOAc/THF aqueous.

ISOLATION OF ISOGALLICADIOL [2].—*A. maritima* ssp. *gallica* (12 kg), gathered at Cabo Corbera, Valencia, Spain, in May–July (voucher specimen on file in the Department of Botany, University of Valencia) was chopped and extracted with hot EtOH. The EtOH extract was concentrated in vacuo, yielding a syrupy liquid which was dissolved in EtOH–H₂O (1:2) 3 liters containing Pb(OAc)₂ (10 g). It was left to settle for 24 h and filtered, and the greater part of the EtOH was eliminated. The resulting crude extract was chromatographed on 5 kg Si gel. It was eluted with hexane and hexane/EtOAc mixtures, and 900-ml fractions were collected. By repeated chromatography of fractions 116–188 [hexane–EtOAc (4:6)] and subsequent fractionated crystallization, artemin [3] and isogallicadiol [2] (25 mg) were obtained. Isogallicadiol [2] was crystallized in CH₂Cl₂/hexane: mp 187–189°; [α]_D –94.2 (*c* = 0.2, CHCl₃); ir ν max cm⁻¹ 3750, 3600, 1765; ms *m/z* [M]⁺ 266.1528 (C₁₅H₂₂O₄), 248.1425 (C₁₅H₂₀O₃), 230.1307 (C₁₅H₁₈O₂), 202.1332 (C₁₄H₁₈O).

CRYSTALLINE STRUCTURE DETERMINATION

TABLE 2. ¹³C-nmr Data for Compounds 2, 3, and 4.^a

Carbon	Compound		
	2	3	4
C-1	77.31	71.79	78.21
C-2	27.62 ^b	29.77 ^b	33.61 ^b
C-3	29.06 ^b	29.95 ^b	36.04 ^b
C-4	144.16	145.21	142.99
C-5	76.65	76.74	52.55 ^c
C-6	85.38	81.96	79.46
C-7	47.08	45.50	52.39 ^c
C-8	24.00	22.90	23.06
C-9	33.06	30.36 ^b	31.28 ^b
C-10	44.72	44.69	42.92
C-11	42.09	41.31	41.24
C-12	178.51	179.61	179.55
C-13	12.80	12.53	12.54
C-14	18.24	13.34	11.70
C-15	115.57	112.35	110.24

^aChemical shifts are given in ppm, and CDCl₃ was used as solvent.

^{b,c}Values in the same column with the same superscript are interchangeable.

TABLE 3. Atomic Positional Parameters.

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
O-1	0.8926 (5)	0.6807 (5)	0.2408 (2)
O-2	0.7325 (5)	1.2809 (4)	0.4772 (3)
O-3	0.7851 (4)	1.1932 (4)	0.3994 (2)
O-4	0.8524 (4)	0.9848 (4)	0.2780 (3)
C-1	0.8472 (7)	0.6443 (7)	0.3134 (3)
C-2	0.6696 (7)	0.6142 (7)	0.3137 (3)
C-3	0.5806 (5)	0.7598 (7)	0.2937 (3)
C-4	0.6228 (6)	0.8934 (6)	0.3407 (3)
C-5	0.8032 (6)	0.9256 (6)	0.3472 (3)
C-6	0.8522 (6)	1.0385 (6)	0.4048 (3)
C-7	0.8110 (6)	0.9870 (6)	0.4804 (2)
C-8	0.9063 (6)	0.8456 (6)	0.4994 (3)
C-9	0.8688 (6)	0.7226 (6)	0.4432 (2)
C-10	0.8990 (6)	0.7734 (6)	0.3649 (2)
C-11	0.8321 (7)	1.1362 (6)	0.5219 (3)
C-12	0.7790 (6)	1.2522 (6)	0.4669 (3)
C-13	0.7419 (9)	1.1489 (7)	0.5924 (3)
C-14	1.0806 (6)	0.7989 (7)	0.3542 (3)
C-15	0.5104 (6)	0.9807 (7)	0.3687 (3)
H-01	0.8330 (–)	0.7761 (–)	0.2242 (–)
H-02	0.9691 (–)	1.0060 (–)	0.2822 (–)

OF ISOGALLICADIOL [2].¹—Isogallicadiol, C₁₅H₂₂O₄, crystallizes in the orthorhombic *P2₁2₁2₁* space group, *a* = 8.458 (1), *b* = 8.731 (1), *c* = 18.677 (2) Å, *V* = 1379 Å³, *Z* = 4, *D_c* = 1.28 g·cm⁻³, *F*(0,0,0) = 576, *μ* = 7.1 cm⁻¹. A total of 1218 independent reflections up to *θ* = 60° were measured in a four-circle computer-controlled Siemens AED diffractometer, using CuKα (*λ* = 1.5418 Å) radiation and *ω*:*θ* scan mode. After correction for Lorentz and polarization factors, 1157 reflections with *I* > 3σ(*I*) were considered as observed. The structure was solved by direct methods (10). All the hydrogen atoms were found on an electronic den-

¹Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

sity difference map. Final full-matrix least-squares refinement (11), with anisotropic temperature factors for non-hydrogen atoms and fixed isotropic contribution for hydrogen atoms, using unit weights, has converged to a standard crystallographic residual of $R = 0.05$. The absolute configuration (12) was established by using 38 Bijvoet pairs with $F_o > 10\sigma(F_o)$ in the ranges $5 < F_o < 50$ and $0.15 < \sin\theta/\lambda < 0.40$. The averaged Bijvoet differences are 0.21 for the correct enantiomer vs. 0.24 for the wrong one.

REDUCTION OF COMPOUND 5.— NaBH_4 (114 mg) was added to **5** (450 mg) dissolved in DMF (5 ml) and stirred for 3 h at 80° . It was cooled to room temperature, poured over an aqueous solution of NaCl, extracted with Et_2O , and dried on anhydrous Na_2SO_4 . The solvent was eliminated at reduced pressure and chromatographed with hexane-EtOAc (9:1), affording **6** (228 mg) (63%): mp $144\text{--}145^\circ$ (hexane/ CH_2Cl_2); $[\alpha]_D - 11.9$ ($c = 0.4$; CHCl_3); ir ν max cm^{-1} 1770; ms m/z $[M]^+$ 380.2377 ($\text{C}_{21}\text{H}_{36}\text{O}_4\text{Si}$), 365.2125 ($\text{C}_{20}\text{H}_{33}\text{O}_4\text{Si}$), 323.1671 ($\text{C}_{17}\text{H}_{27}\text{O}_4\text{Si}$), 305.1583 ($\text{C}_{17}\text{H}_{25}\text{O}_3\text{Si}$); ^1H nmr δ 0.017 (3H, s), 0.026 (3H, s), 0.87 (9H, s), 1.11 (3H, s, H-14), 1.24 (3H, d, $J = 6.9$ Hz, H-13), 1.57 (3H, s, H-15), 3.21 (1H, dd, $J = 3.3, 3, 3$ Hz, H-1), 4.37 (1H, d, $J = 11.6$ Hz, H-6).

PREPARATION OF COMPOUND 7.—A hexane solution (1.4 M) of *n*-BuLi (0.43 ml) was added slowly to anhydrous Et_2NH (0.5 mmol) in anhydrous Et_2O (2 ml) at 0° under argon atmosphere. The epoxide **6** (0.42 mmol) in anhydrous Et_2O (5 ml) was then added drop by drop for 5 min. After refluxing for 6 h, the mixture was cooled, poured over H_2O , extracted with Et_2O , dried on anhydrous Na_2SO_4 , concentrated in vacuo, and chromatographed with hexane-EtOAc (8:2) as eluent; this afforded alcohol **7** (82 mg) (51%): mp $159\text{--}161^\circ$ (hexane/EtOAc); $[\alpha]_D - 67.9$ ($c = 0.3$; CHCl_3); ir ν max cm^{-1} 3450, 1770; ms m/z $[M + 1]^+$ 381.2599 ($\text{C}_{21}\text{H}_{37}\text{O}_4\text{Si}$), 362.2272 ($\text{C}_{21}\text{H}_{34}\text{O}_3\text{Si}$), 323.1688 ($\text{C}_{17}\text{H}_{27}\text{O}_4\text{Si}$), 305.1191 ($\text{C}_{17}\text{H}_{25}\text{O}_3\text{Si}$); ^1H nmr δ 0.026 (3H, s), 0.087 (3H, s), 0.82 (9H, s), 1.10 (3H, d, $J = 6.5$ Hz, H-13), 1.13 (3H, s, H-14), 3.47 (1H, complex, H-1), 4.21 (1H, d, $J = 11.6$ Hz, H-6), 4.98 (2H, complex, H-15).

DEPROTECTION OF COMPOUND 7.—Glacial

HOAc (2 ml) and H_2O (0.5 ml) were added to a solution of **7** (18 mg) in THF (1 ml) and stirred for 24 h at 60° . The mixture was cooled, an NaHCO_3 -saturated solution was added; it was washed with H_2O , extracted with CH_2Cl_2 , dried on anhydrous Na_2SO_4 , concentrated, and chromatographed to yield **2** quantitatively.

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