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Andalusol, a New Diterpenoid from a *Sideritis arborescens* Salzm. Subspecie. Chemical and X-Ray Structure Determination[1]

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Continuing our studies[2] on diterpenoids from a subspecie of *Sideritis arborescens* Salzm. (family Labiatae) we have now isolated a new compound, andalusol (1, $C_{20}H_{34}O_3$), the UV spectrum of which showed characteristic absorption (λ_{max} 224 nm, ϵ 11 000) for a monosubstituted conjugated diene grouping.[3] Treatment of compound 1 with acetic anhydride in pyridine solution gave the diacetate 2 plus a minor triacetyl derivative (3), thus establishing the hydroxylic nature of the three oxygen atoms of the molecule of andalusol. The ^1H NMR spectrum of 3 showed signals for an exocyclic methylene (δ 4.98, 2 H, broad singlet) and a vinyl group (δ_X 6.34, 1 H, quartet, and δ_A, δ_B 5.00–5.54, 2 H, multiplet), responsible for the UV diene absorption.

Hydroxylation of the diacetate 2 with osmium tetroxide gave a product which without further characterization was treated with HIO_4 to yield the lactone 4.

With the preceding information a single-crystal x-ray determination of the structure of 4 was undertaken in order to establish the structure and relative stereochemistry of andalusol. A computer-generated drawing of the final x-ray model is shown in Figure 1. This model shows that the hydroxyl groups in andalusol are at C-6 (eq), C-8 (eq), and C-18 on a labdane skeleton. The lactone ring presents approximately an envelope conformation, being C-8, C-11, and C-9 at −0.12, 0.08, and 0.70 Å, respectively, out of the plane defined by C-12, C-13, O-25, and O-26. This envelope conformation is related to the special geometry displayed by the planar group: C-11–C-12 = 1.50, C-12–C-13 = 1.49, C-13–O-26 = 1.19, C-13–O-25 = 1.33, O-25–C-8 = 1.48 Å, C-11–C-12–C-13 = 119.8, C-12–C-13–O-26 = 121.7, C-12–C-13–O-25 = 119.7, O-25–C-13–O-26 = 118.6, C-13–O-25–C-8 = 122.2°. Both acetyl groups are coplanar with the carbon atoms at which they are bonded (C-6, C-18), the carbonyl oxygen atoms being at the cis positions. Electronic repulsion between all three methyl groups causes a bending effect on the main plane of the molecule. Distances between these groups follow: C-19–C-20 = 3.33 and C-17–C-20 = 3.24 Å. (For most details on x-ray structure determination see Experimental Section.)

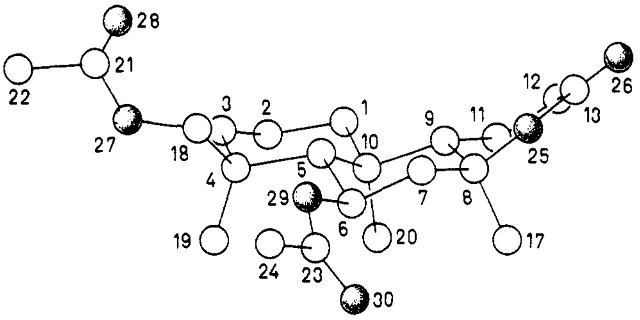
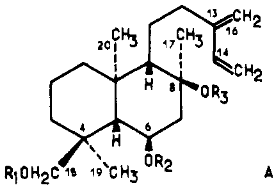


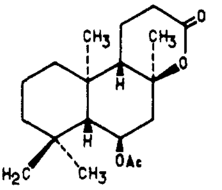
Figure 1. Computer-generated perspective drawing of *ent*-6 α,18-diacetoxy-14,15,16-trinorlabdan-13,8α-olide (4).

The absolute stereochemistry of the diterpenoid was established as follows. Treatment of compound 1 with benzoyl chloride in pyridine solution under controlled conditions yielded the monobenzoate 5. Horeau's method[4] of partial resolution applied to product 5 afforded (+)-α-phenylbutyric acid, defining as 6*R* the absolute configuration of this center. On the other hand, application of Brewster's "benzoate rule"[5] to compounds 5 and 6 confirmed the above assignation.

Therefore andalusol is *ent*-13(16),14-labdadiene-6α,8α,18-triol (1).



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = R_2 = Ac$; $R_3 = H$
3, $R_1 = R_2 = R_3 = Ac$
5, $R_1 = COPh$; $R_2 = R_3 = H$
6, $R_1 = R_2 = COPh$; $R_3 = H$



4

Experimental Section

All melting points were determined in a Kofler apparatus and are uncorrected. The optical rotations were measured with a Perkin-Elmer 141 polarimeter with 1-dm cells; the UV spectra were recorded on a Perkin-Elmer 402 spectrophotometer and the IR spectra on a Perkin-Elmer 257 spectrometer. The ^1H NMR spectra were obtained on a 60-MHz Perkin-Elmer R-12 or a 100-MHz Varian XL-100 apparatus with Me_4Si as an internal standard. The mass spectra were determined on an Hitachi Perkin-Elmer RMU 6MG apparatus. Elemental analyses were carried out in this laboratory with the help of an automatic analyzer.

Isolation of Andalusol (1). Dried and finely powdered *S. arborescens* Salzm. subspecie plants (5 kg), collected near Barbate (Cádiz), were extracted with light petroleum (16 L) in a Soxhlet apparatus during 120 h. The extract was concentrated under vacuum to 2 L and repeatedly extracted with 90% aqueous methanol (6 × 200 mL). The methanolic extracts were concentrated to 0.5 L, diluted with water (3 L), and extracted with chloroform (6 × 200 mL). The chloroform extracts were dried, filtered, and concentrated under vacuum to leave a residue (52 g) which was chromatographed on an Al_2O_3 (1.5 kg) (grade III) column with C_6H_6–EtOAc (19:1) as eluent, yielding the following compounds in order of elution: siderol[6] (320 mg), barbatol[2] (136 mg), and andalusol 1 (7.3 g) [mp 167–170 °C (acetone–*n*-hexane); $[\alpha]^{20}_D$ −38.2° (*c* 0.69, EtOH); UV (EtOH) λ_{max} 224 nm (ϵ 11 000); IR (KBr) 3270, 3200, 3090, 3020, 1640, 1600, 1047, 920, 895 cm^{-1}; mass spectrum M^+ *m/e* 322]. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.17; H, 10.51.

Acetylation of 1. Compounds 2 and 3. Acetic anhydride (5 mL) was added to a solution of 1 (300 mg) in pyridine (2.5 mL) and the mixture placed for 24 h at room temperature, poured into ice-water, and extracted with chloroform. Vacuum distillation of the solvent left a residue (308 mg) which was separated by PLC on SiO_2 plates (C_6H_6–EtOAc, 9:1, as eluent) into two components, **2** (most polar, 270 mg) and **3** (35 mg).

Compound **2** is a syrup: IR (film) 3550, 3100, 1735, 1600, 1250, 940, 895 cm^{-1}; NMR)100 MHz, $CDCl_3$) δ 6.34 (1 H, q, $J_{XA} = 18$, $J_{XB} = 10$ Hz, H-14), 5.36–4.88 (3 H, m, H-6 and H-15 protons), 4.99 (2 H, s, H-16), 3.86 (2 H, AB system, $J = 11$ Hz, H-18), 2.06 and 2.01 (3 H each, s, two -OAc), 1.26 (3 H, s, H-17), 0.92 and 0.85 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum M^+ m/e 406.

Compound **3**: mp 118–120 °C (aqueous EtOH); $[\alpha]^{20}{}_D$ −31° (c 0.18, $CHCl_3$); IR (KBr) no -OH absorption, 3100, 1745, 1600, 1255, 920, 900 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.34 (1 H, q, $J_{XA} = 18$, $J_{XB} = 10$ Hz, H-14), 5.54–4.90 (3 H, m, H-6 and H-15 protons), 4.99 (2 H, s, H-16), 3.83 (2 H, AB system, $J = 11$ Hz, H-18), 2.13, 2.07, and 2.00 (3 H each, s, three -OAc), 1.58 (3 H, s, H-17), 0.96 and 0.85 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum $[M - 60]^+$ m/e 388. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.73; H, 8.89.

Lactone 4. The diacetate **2** (250 mg) was treated with an excess of osmium tetroxide in Et_2O–dioxane (1:1) solution yielding quantitatively a product which without further characterization was treated with HIO_4 in aqueous ethanol solution affording 210 mg of **4**: mp 145–147 °C (aqueous EtOH); $[\alpha]^{20}{}_D$ −88.7° (c 0.40, $CHCl_3$); IR (KBr) 1740, 1720, 1235 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 5.07 (1 H, sextet, $J_{aa'} = J_{aa''} = 11$, $J_{ae'} = 4$ Hz, H-6), 3.86 (2 H, AB system, $J = 11$ Hz, H-18), 2.60 (2 H, m, H-12), 2.26 (1 H, q, $J_{gem} = 12$, $J_{ea'} = 4$ Hz, equatorial H-7), 2.06 and 2.03 (3 H each, s, two -OAc), 1.49 (3 H, s, H-17), 0.98 and 0.87 (3 H each, s, H-20 and H-19 protons, respectively); mass spectrum $[M - 60]^+$ m/e 320. Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.42; H, 8.57.

X-Ray Structure Determination of 4. $C_{21}H_{32}O_6$ (**4**) crystallizes in the space group $P2_1$ with two molecules in a cell of dimensions $a = 10.790$ (1), $b = 10.055$ (1), $c = 9.458$ (1) Å, and $\beta = 93.95$ (1)°. The molecular weight is 380 g mol^{-1} and the calculated density is 1.23 g cm^{-3}. The intensity of 3144 independent reflections with $\theta \leq 30°$ were measured on a computer-controlled diffractometer using graphite-monochromated Mo Kα radiation (0.7107 Å). No crystal decomposition was observed during the data collection. After correction for Lorentz and polarization effects, 1707 reflections were considered observed with the criterion $I > 2\sigma(I)$. The structure was solved by using the multisolution tangent formula.[7] It was necessary to take into account the amplitude error[8] to obtain a substantial fragment of the molecule among several E-map solutions. The rest of the molecule was found on a difference map after a "hard" least-squares correction ($\sin \theta/\lambda < 0.4$) of the first fragment. The hydrogen atoms, found on a difference map, were included in the last weighted anisotropic least-squares refinements (isotropic for H atoms). Final unweighted and weighted disagreement indices are $R = 0.051$ and $Rw = 0.066$, respectively.[9]

Monobenzoate 5. Benzoyl chloride (200 mg) was added to a solution of **1** (300 mg) in dry pyridine (5 mL) and the mixture kept for 2 h at 0 °C, poured into water, and extracted with chloroform. Vacuum distillation of the solvent left a residue from which the compound **5** (280 mg) was chromatographically isolated [PLC on SiO_2, C_6H_6–EtOAc (9:1)]: mp 139–143 °C (aqueous EtOH); $[\alpha]^{20}{}_D$ −16.6° (c 0.58, $CHCl_3$); IR (KBr) 3540, 3500, 3300, 3100, 3080, 1700, 1600, 1285, 915, 890, 715 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 8.40–7.30 (5 H, m, phenyl protons), 4.20 (2 H, AB system, $J = 11$ Hz, H-18), 3.85 (1 H, m, H-6). Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.90; H, 8.89.

Application of Horeau's Method[4] to 5. A mixture of (±)-α-phenylbutyric anhydride (0.37 mmol) and **5** (36 mg) in pyridine solution (2 mL) was kept at room temperature during 20 h: $\alpha_1 = -0.106$, $\alpha_2 = -0.201$; $\alpha_1 - (1.1\alpha_2) = +0.115$. Configuration: 6$R$.

Dibenzoate 6. Reaction of a pyridine solution of compound **1** with a large excess of benzoyl chloride for 24 h at room temperature yielded **6**: mp 62–65 °C (EtOH); $[\alpha]^{20}{}_D$ −13.8° (c 0.53, $CHCl_3$); IR (KBr) 3520, 3100, 3080, 1720, 1600, 1275, 940, 890, 710 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 8.40–7.20 (10 H, m, phenyl protons), 4.20 (2 H, s, H-18), no signal at 4.00–3.00. Anal. Calcd for $C_{34}H_{42}O_5$: C, 76.95; H, 7.98. Found: C, 77.01; H, 7.94.

Application of the "Benzoate Rule":[5] 6, $[M]_D$ −73.6° **5**, $[M]_D$ −70.7°; $\Delta [M]_D = -2.9$. Absolute stereochemistry: 6R.

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Registry No.—**1**, 62279-93-0; **2**, 62264-72-6; **3**, 62264-73-7; **4**, 62264-74-8; **5**, 62264-75-9; **6**, 62264-76-0; benzoyl chloride, 98-88-4.

Supplementary Material Available. A list of atomic parameters, bond distances, and angles (3 pages). Ordering information is given on any current masthead page.

References and Notes

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Structure, Chemistry, and Absolute Configuration of 1(*S*)-Bromo-4(*R*)-hydroxy-(−)-selin-7-ene from a Marine Red Alga *Laurencia* Sp.

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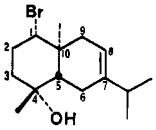
As part of a program aimed at assessing the diversity of halogen-based terpene synthesis in the red seaweed *Laurencia* (Rhodomelaceae), we have investigated the metabolites from a number of unrecorded species from this genus indigenous to the Gulf of California.[1-3] One collection of an apparently unrecorded *Laurencia*[4] has now yielded a bromine-containing derivative of the selinane type (**1**), which is a previously unknown ring system from this source.



1

1(*S*)-Bromo-4(*R*)-hydroxy-(−)-selin-7-ene (**1**), an oil, $[\alpha]^{22}{}_D$ +52.6° (c 4.62, $CHCl_3$), was obtained in high yield (10% extract) from silica gel chromatography of the chloroform–methanol extract of the fresh alga. High-resolution mass spectral analysis of **1** established a molecular formula of $C_{15}H_{25}OBr$ and illustrated a facile loss of water. Intense infrared absorption at 3450 cm^{-1} further confirmed that **1** was an alcohol. The lack of acetylation upon treatment with acetic anhydride in pyridine (25 °C), the presence of a quaternary carbon resonance at 70.4 ppm in the ^{13}C NMR (relative to $Me_4Si = 0$), and a singlet at δ 1.16 in the ^1H NMR spectrum indicated the hydroxyl to be tertiary and located at a methyl-bearing carbon. The ^{13}C NMR spectrum of **1** further indicated a secondary bromine-containing carbon (doublet at 68.5 ppm) and a single trisubstituted olefin (singlet at 142.0 and doublet at 116.4 ppm) to be present in the molecule, which indicated that **1** is bicyclic. The ^1H NMR spectrum gave considerable insight into the structure of **1**. A symmetrical one-proton heptet at δ 2.16 and a six-proton doublet at δ 1.0 indicated that **1** contained an isopropyl group. Also, a complex signal at δ 2.43, appearing as a double quartet (actually a dddd