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MAGNOLIALIDE: A NOVEL EUDESMANOLIDE FROM THE ROOT BARK OF *MAGNOLIA GRANDIFLORA*

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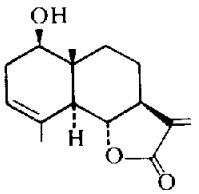
Key Word Index—*Magnolia grandiflora*; Magnoliaceae; costunolide-1,10-epoxide; cyclization; santamarine; reynosin; sesquiterpene lactones.

Abstract—The hitherto unknown γ-isomer of the two eudasmanolides santamarine and reynosin was found to occur naturally in the root bark of *M. grandiflora* L. Its identity was established by studying its spectral data and by synthesis by cyclizing costunolide-1,10-epoxide. It was named magnolialide.

INTRODUCTION

The two eudesmanolides santamarine (**1**) and reynosin (**2**) were previously reported [1] to occur in the root bark of *M. grandiflora* L. It was speculated that they could have been derived from the cyclization of the highly unstable costunolide-1,10-epoxide (**3**). The latter was synthesized from costunolide (**4**) by different authors by three different procedures [1–3] and, indeed, was found to cyclize spontaneously, even in the crystalline state to produce **1** and **2**.

Careful chromatography of a root bark fraction of *M. grandiflora* L. furnished in addition to **1** and **2**, their γ-isomer, which was named magnolialide (**5**). The structure elucidation of this novel compound is the subject of this publication.



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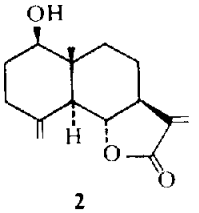

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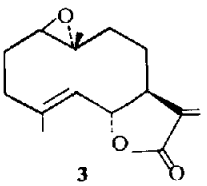

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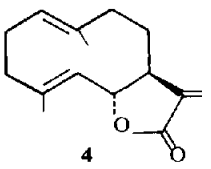

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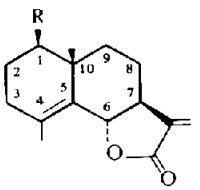

5 R = OH
6 R = H

RESULTS AND DISCUSSION

The root bark of *M. grandiflora* L. was extracted by percolation with chloroform at room temperature. The extract was then evaporated *in vacuo* to leave an oily residue which was partitioned between *n*-hexane and 10% aqueous methanol. The latter fraction was chromatographed on silica gel 60 using chloroform to yield costunolide (**4**) as the principal constituent [1].

The composition of the other column fractions was monitored by TLC analysis on silica gel G impregnated with 10% $AgNO_3$ and using 10% acetonitrile in chloroform. While many fractions were found to be mixtures of santamarine (**1**), R_f 0.45 and reynosin (**2**), R_f 0.35, a group of earlier fractions showed a third spot due to the less polar magnolialide (**5**), R_f 0.50.

Magnolialide (**5**) was separated by PLC and was obtained as colourless prisms, mp 152–153°, $[\alpha]_D^{25}$ +74° (*c*, 0.23 EtOH), and analysed for the formula $C_{15}H_{20}O_3$. The IR spectrum (chloroform) showed a sharp peak at 3600 cm^{-1} and a broad one at 3500 cm^{-1} (OH). It also exhibited a single carbonyl band at 1775 cm^{-1} (α,β′-unsaturated-γ-lactone). The ^1H NMR spectrum ($CDCl_3$) was very similar to that of γ-cyclocostunolide (**6**) [4] except for the presence of an overlapping pair of doublets, centered at δ 3.60, J = 7.0 Hz, due to the proton on C-1. The C-1 proton in santamarine (**1**) couples with the two vicinal protons in a similar but not identical manner, giving rise to a pair of doublets with the close coupling constants of J = 6.6 and 8.8 Hz. This peculiar coupling pattern is due to the distortion in the conformation of ring A of magnolialide (**5**) and santamarine (**1**), brought about by the presence of an endocyclic double bond. This distortion does not take place in the case of reynosin (**2**), as the double bond there is exocyclic. Therefore, the coupling constants of the C-1 proton of reynosin with the two vicinal protons are 4.0 and 10.5 Hz [5], as would be expected for an axial proton coupling with a pair of protons, one axial and one equatorial.

Other signals in the ^1H NMR spectrum were consistent with the assigned structure (**5**) and included a three-proton singlet at δ 1.13 (methyl on C-10), another three-proton but broad singlet at δ 1.90 (methyl on C-4), a broad doublet at δ 4.61, J = 11.0 Hz due to the proton on C-6 and a pair of doublets at δ 5.50, J = 3.0 Hz and δ 6.17, J = 3.0 Hz due to the olefinic protons on C-12.

The ^{13}C NMR spectrum* taken in $CDCl_3$ was consistent with the assigned structure showing two methyl signals at δ 19.6 and 18.5, 4 methylenes at δ 38.3, 33.3, 27.1 and 23.1, three methine signals at δ 83.2, 77.6 and 49.8, an aliphatic quaternary carbon signal at δ 42.1 and three olefinic ones at δ 139.2, 129.3 and 126.2, an olefinic exocyclic methylene signal at δ 118.4, and a carbonyl signal at δ 170.3.

The structure and the stereochemical assignments at all chiral centers of magnolialide (**5**) were confirmed by synthesizing it by cyclization of costunolide-1,10-epoxide (**3**). Boron trifluoride, phosphorus pentachloride, HCl-saturated chloroform, Amberlite IR-120H C.P. and thionyl chloride were attempted as cyclizing catalysts. Thionyl chloride [4] produced more of **5** than any of the other reagents. In addition to **5**, santamarine (**1**) and reynosin (**2**) were also produced, and the mixture was separated by PLC on silver nitrate impregnated silica gel G. The synthetic product was identical with the natural material in all regards.

EXPERIMENTAL

All mps were taken in capillaries and are uncorr. Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter, ^1H NMR spectra were recorded at 60 MHz operating at room temp. with $CDCl_3$ as solvent and TMS as internal standard with chemical shifts reported as δ(ppm) values; the ^{13}C NMR spectra were recorded on JNM-Fx 60 Fourier Transform NMR spectrometer at 15.06 MHz using $CDCl_3$ as solvent and TMS as internal standard. Elemental analyses were done by Scandinavian Microanalytical Laboratory in Herlev, Denmark. Spot detection on TLC plates was achieved by spraying with 0.5% aq. $KMnO_4$ or by viewing under UV light.

Ground root bark of *Magnolia grandiflora* L. collected in June 1976 in Tupelo, MS, was used in this study. A voucher specimen is kept at the herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi.

Isolation of magnolialide (**5**). The powdered root bark of *M. grandiflora* L. (1 kg) was extracted by cold percolation using $CHCl_3$ as solvent. The extract was evapd *in vacuo* to leave 86 g of an oily residue. This residue was partitioned between *n*-hexane (4 × 100 ml) and 10% aq. MeOH (400 ml). Evapn of the MeOH *in vacuo* left 50 g of a dark residue which was chromatographed on 1200 g of Si gel 60, using $CHCl_3$ as solvent.

The composition of each fraction was monitored by TLC. Costunolide (**4**) (5.5 g) was first eluted from the column followed by a group of fractions, which when examined by TLC on 10% $AgNO_3$ impregnated Si gel G plates using 10% acetonitrile in $CHCl_3$, revealed the presence of 3 spots, R_f values 0.50 (magnolialide), 0.45 (santamarine) and 0.35 (reynosin). These fractions were pooled together then evapd to leave 100 mg of a crystalline residue. All 3 compounds were separated by preparative TLC using the same conditions as before, to yield 50 mg of santamarine (**1**), 20 mg of reynosin (**2**) and 15 mg of magnolialide (**5**).

Magnolialide (**5**) was crystallized from *n*-hexane–Et_2O to give colourless prisms, mp 152–153°, $[\alpha]_D^{25}$ +74° (*c*, 0.23, EtOH); UV λ_{max}^{MeOH} 213 nm (log ε 3.95); major IR bands ($CHCl_3$) at 3600, 3500, 2930, 2850 and 1775 cm^{-1}; MS $M^{\cdot+}$ at *m/e* 248 (37%); (Found: C, 72.70; H, 8.12. $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%).

Cyclization of costunolide-1,10-epoxide (**3**). Costunolide-1,10-epoxide (**3**) (1.013 g) obtained as previously reported [1] was dissolved in 200 ml of $CHCl_3$ and 1.0 ml of $SOCl_2$ was added. The reaction mixture was allowed to stand at room temp. for 5 min then evapd. The residue, which consisted of a mixture of santamarine (**1**), reynosin (**2**) and magnolialide (**5**), was separated by preparative TLC to yield 103 mg of pure magnolialide (**5**) in addition to 232 mg of pure santamarine (**1**) and 78 mg of pure reynosin (**2**). Synthetic magnolialide (**5**) was identical in all regards with the isolated material.

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* Complete assignments of the signals of the ^{13}C NMR spectrum of magnolialide and many other eudesmanolides will be reported elsewhere.