molecule with all of its population in a ground state with spin S, a plot of $M/N\beta$ versus H/T would follow a Brillouin function[18] and approach a maximum (saturation) value of 2S at large values of H/T. The fact that the three isofield lines for complex **1** do not superimpose reflects the presence of zero-field splitting in the ground state.

Least-squares fitting of the $M/N\beta$ versus H/T data for **1** were carried out. At high fields and low temperatures, a true powder average of the theoretically calculated magnetization for all orientations must be made[19,20] using eq 1. In eq 1, θ and ϕ are

$$\bar{M} = \frac{-N}{4\pi}\int_{\theta=0}^{\pi}\int_{\phi=0}^{2\pi}\left[\sum_{i=1}^{p}\left(\frac{\delta E_i}{\delta H}\right)\exp(-E_i/kT)/\sum_{i=1}^{p}\exp(-E_i/kT)\right]\sin\theta\,d\theta\,d\phi \quad (1)$$

the polar angle orientations of the field with respect to the molecular principal axis system and $\delta E_i/\delta H$ is the change in the energy of the ith level in response to a change in a magnetic field. The energies of the various sublevels of the ground state are obtained by diagonalization of the $(2S + 1) \times (2S + 1)$ Hamiltonian matrix which includes the Zeeman terms. The derivatives $\delta E_i/\delta H$ were calculated from the corresponding eigenvectors with the Hellman-Feynman theorem.[19,20] The integral in eq 1 was evaluated numerically.

Thus, the magnetization data for **1** were least-squares fit with the spin Hamiltonian for $S = 14$ including axial ($D\hat{S}^2_z$) and rhombic [$E(\hat{S}^2_x - \hat{S}^2_y)$] zero-field interactions. TIP was assumed to be 2400×10^{-6} cgsu per complex **1**. For each setting of the parameters (g, D, and E) a powder-average of $M/N\beta$ versus H/T is calculated, and per the simplex approach a least-squares fitting was carried out for the $S = 14$ case which required ~35 h of cpu time on a VAX/780 computer. The fitting parameters for $S = 14$ were found to be $g = 1.974$, $D = -0.16$ cm^{-1}, and $E = 0.033$ cm^{-1}. The solid lines in Figure 3 show that these parameters fit the data well.

In a similar fashion the magnetization data for **1** were fit with the Hamiltonian for either $S = 13$ or $S = 15$. The parameters resulting from these fits are in the format (g, D, E) = (2.121, −0.18, 0.037) and (1.846, −0.138, 0.029), respectively. All three fits are of comparable quality with only the parameter g varying appreciably. The g value for the ground state of a $Mn^{IV}_4Mn^{III}_8$ complex should be $2.0 \geq g \geq 1.9$. We conclude that complex **1** has a $S = 14$ ground state and the largest spin ground state yet observed.

The present results indicate that polynuclear manganese complexes are good candidates to exhibit *intra*molecular ferromagnetic interactions. In fact, very recently we reported[21] that a distorted cubane $Mn^{IV}Mn^{III}_3$ complex has a $S = 9/2$ ground state. Clearly a strategy to prepare molecular ferromagnets would be to chemically link together these ferromagnetic molecular building blocks.

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Supplementary Material Available: Fully labeled figure of $[Mn_{12}O_{12}(O_2CPh)_{16}(H_2O)_4]$ and tables of fractional coordinates, isotropic and anisotropic thermal parameters, and bond distances and angles (10 pages). Ordering information is given on any current masthead page.

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Isolation and Structure of Combretastatin D-1: A Cell Growth Inhibitory Macrocyclic Lactone from *Combretum caffrum*[1a]

George R. Pettit,* Sheo Bux Singh, and Margaret L. Niven[1b]

Cancer Research Institute and Department of Chemistry, Arizona State University Tempe, Arizona 85287-1604

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The South African tree *Combretum caffrum* (Combretaceae) has been found to contain a series of biosynthetically related substances that significantly inhibit growth of the U.S. National Cancer Institute's murine P-388 lymphocytic leukemia cell line (PS system). Some of these dihydrostilbenes, *cis*-stilbenes, phenanthrenes, and dihydrophenanthrenes, especially combretastatin A-1 and A-4, were also found to strongly inhibit tubulin polymerization.[2] We now report the isolation and structural elucidation of an unexpected and unusual macrocyclic lactone designated combretastatin D-1 (**1**) with PS cell line activity corresponding to ED_{50} 3.3 μg/mL.

The methylene chloride–methanol extract obtained from 77 kg of *Combretum caffrum* stem wood was initially separated as previously described,[2a,b] and the fraction that led to combretastatin A-2 was further separated guided by PS bioassay with a sequence of gel permeation, partition (Sephadex LH-20, hexane–toluene–methanol, 3:1:1), and silica gel flash chromatography employing hexane–chloroform–acetone (3:2:0.25) as eluent to afford combretastatin D-1 (**1**) in 2.3×10^{-4}% yield: 180 mg as needles from acetone–hexane: mp 180–181 °C, R_f 0.44 (SiO_2 plate; 1:1 hexane–ethyl acetate); $[\alpha]_D$ −100° (*c* 0.015, $CHCl_3$), HREIMS (*m/z*) 312.0998 (M^+, 100%, for $C_{18}H_{16}O_5$, calcd 312.0998), 267.1015 (M^+, $-CO_2H$, 22%), 253.0862 ($M^+ - CH_3CO_2$, 42%), 227.0712 ($M^+ - C_4H_5O_2$, 66%), 131.0496 (15%), 122.0368 (6%), and 119.0497 (10%). UV ($CHCl_3$) λ_{max} 224 (ε 15215), 278 (3068) nm; IR (NaCl) ν_{max} 3439, 3431, 3422, 3415, 1735, 1518, 1507, 1438, 1362, 1288, 1216, 1159, and 1142 cm^{-1}. Consult ref 3 for the ^{13}C NMR and ^1H NMR assignments.

Mass spectral analysis of lactone **1** revealed molecular formula $C_{18}H_{16}O_5$ with eleven double bond equivalents. Because of the absence of any isolated or conjugated double bonds, with the exception of two aromatic rings, it became apparent that this molecule possessed two additional rings and a lactone (IR: 1735 cm^{-1}). One ring was located as an epoxide, while the other formed the skeletal cyclic system. The ^1H NMR spectrum was assigned by using $^1H,^1H$ COSY techniques. Four isolated coupling patterns were observed. Long-range (five bonds) coupling was observed between H-16 (both α and β) and H-13. All the protons were further assigned on the basis of NOE experiments (cf. **1**; magnitude of observed NOE's were 1 → 6%). Proton-20 (δ 4.940) was correlated to δ 112.24 in the carbon spectrum ($^1H,^{13}C$ COSY).

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(3) ^{13}C NMR (100 MHz, δ, $CDCl_3$) 26.97 (C-15), 31.24 (C-16), 52.99 (C-3), 55.84 (C-4), 62.56 (C-2), 112.24 (C-20), 115.38 (C-12), 122.03 (C-13), 123.14 (C-19), 123.95 (C-7), 126.34 (C-18), 128.83 (C-6), 131.90 (C-5), 132.44 (C-14), 142.62 (C-11), 149.09 (C-10), 156.01 (C-8), and 172.53 (C-17) ppm; ^1H NMR (400 MHz, δ, $CDCl_3$) 2.134 (1 H, ddd, J = 17.5, 12.5, 1.5 Hz, H-16α), 2.398 (1 H, ddd, J = 17.5, 6.0, 1.50 Hz, H-16β), 2.583 (1 H, dd, J = 16.8, 6.0 Hz, H-15α), 3.112 (1 H, dd, J = 16.8, 12.5 Hz, H-15β), 3.483 (1 H, ddd, J = 9.2, 4.5, 4.5 Hz, H-3), 3.871 (1 H, dd, J = 12.0, 9.2 Hz, H-2α), 4.264 (1 H, dd, J = 12.0, 4.5 Hz, H-2β), 4.355 (1 H, d, J = 4.5 Hz, H-4), 4.940 (1 H, d, J = 1.8 Hz, H-20), 5.486 (1 H, br s, OH), 6.617 (1 H, ddd, J = 8.2, 1.8, 1.5 Hz, H-13), 6.836 (1 H, d, J = 8.0 Hz, H-12), 7.081 (1 H, dd, J = 8.0, 2.0 Hz, H-19), 7.104 (1 H, dd, J = 8.0, 2.0 Hz, H-7), 7.362 (1 H, dd, J = 8.0, 2.0 Hz, H-18), 7.549 (1 H, dd, J = 8.0, 2.0 Hz, H-6).

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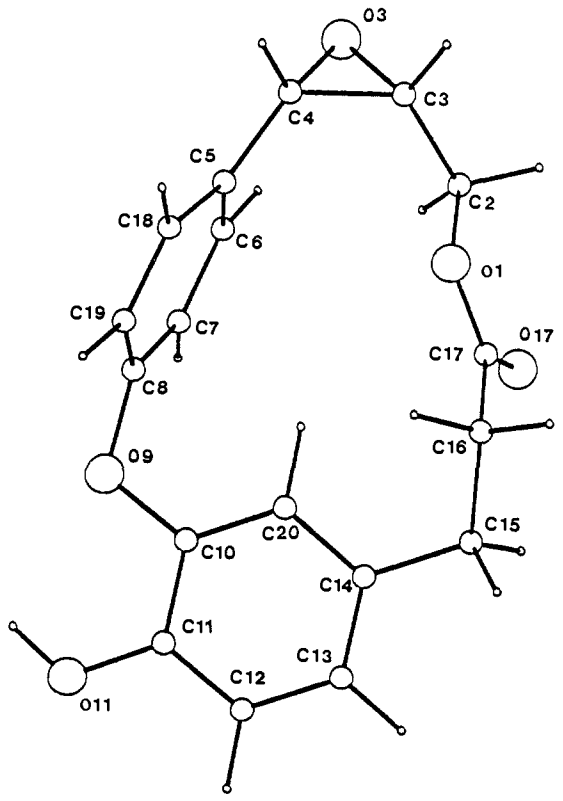
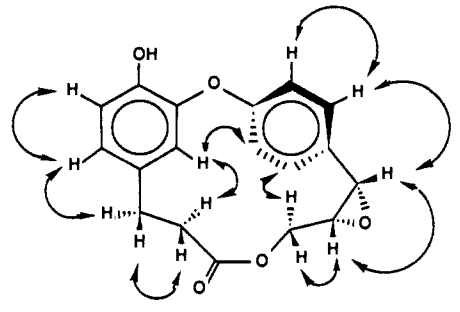


Figure 1. A PLUTO representation of combretastatin D-1 (**1**).



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Combretastatin D-1 with NOE

Figure 2. Combretastatin D-1 with NOE.

Such exceptional shielding of an aromatic proton was attributed to its entrance into the shielding cone of the other aromatic ring. Support for this assumption and the structure of combretastatin D-1 was obtained by an X-ray crystal structure determination (cf. Figure 1[4]) and examining the Dreiding model of this lactone. Restricted rotation between the two aromatic rings was apparent in the model. NOE experiments suggested that in solution the most stable conformation of the macrocycle also exists as presented in structure **1**, i.e., the carbonyl groups of the lactone must face away from the ring.

Attempts to determine the absolute configuration of combretastatin D-1 (**1**) on the basis of crystallographic data were unsuccessful. However, the absolute configuration of the epoxide ring was assigned (3*R*,4*S*) by comparing the sign of the Cotton effect curves in the CD spectrum[5] of epoxide **1** with the Cotton effect curves of (1*R*,2*R*)-(+)-1-phenylpropylene oxide and (1*S*,2*S*)-(−)-1-phenylpropylene oxide.

Combretastatin D-1 may originate biosynthetically from two units of tyrosine or equivalent *via ortho* phenol coupling, deamination, partial reduction, epoxidation, and lactonization. The significance of this new biosynthetic product in respect to antineoplastic and other biological properties is presently under study.

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Supplementary Material Available: Tables of bond distances and angles and positional parameters for combretastatin D-1 (6 pages); table of observed and calculated structure factors (14 pages). Ordering information is given on any current masthead page.

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(5) CD spectra (CH_3OH): **1**, ϵ (nm) 0 (308), +13.4 (285), 0 (275), +5.9 (267), −34.2 (247), 0 (240); (1*R*,2*R*)-(+)-1-phenylpropylene oxide, ϵ (nm) 0 (278), +0.15 (271), +0.07 (267), +0.16 (263), +0.09 (259), +0.11 (257), 0 (235); (1*S*,2*S*)-(−)-1-phenylpropylene oxide, ϵ (nm) 0 (278), −0.15 (271), −0.07 (267), −0.16 (263), −0.09 (259), −0.11 (257), 0 (235).

Epoxidation of Olefins on Silver: Conversion of Norbornene to Norbornene Oxide by Atomic Oxygen on Ag(110)

Jeffrey T. Roberts and Robert J. Madix*

Department of Chemical Engineering
Stanford University, Stanford, California 94303

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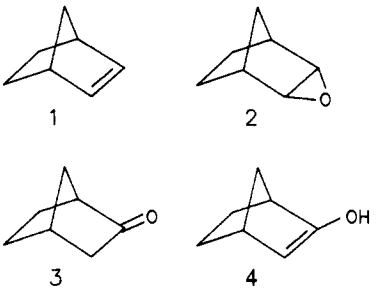
The nature of the reactive oxygen in olefin epoxidation is a subject of much debate.[1] We wish to report the epoxidation of an olefin by atomic oxygen on silver under ultrahigh vacuum. Norbornene (**1**) reacts with atomic oxygen on Ag(110) to form



1 **2** **3** **4**

norbornene oxide (**2**) at 310 K during temperature-programmed reaction. The importance of this observation is 3-fold. First, the role of atomic oxygen in the epoxidation of olefins is a subject of substantial controversy.[1] In this work, atomic oxygen is proved to easily epoxidize an olefin on a silver surface. Second, ethylene and atomic oxygen do not react when coadsorbed on silver under ultrahigh vacuum.[2] As a consequence of the present work, this fact is attributed to an activation energy for ethylene desorption that is lower than that for reaction between ethylene and atomic oxygen. Finally, the epoxidation of olefins on silver is shown to be facilitated by the absence of an acidic hydrogen on the olefin.

We chose norbornene as a candidate for epoxidation on Ag(110) for two reasons. The high molecular weight of norbornene compared to ethylene leads to a greater binding energy between norbornene and the surface and, consequently, to a higher desorption temperature. Thus norbornene and atomic oxygen remain coadsorbed to nearly 300 K, making it possible to observe reactions with activation energies up to approximately 15 kcal/mol.

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