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Synthesis and Revised Configuration of (+)-Combretastatin D-1

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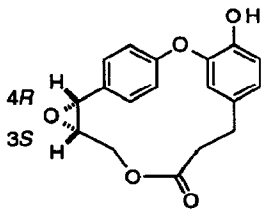
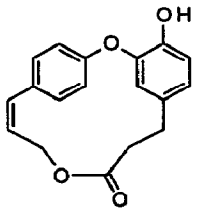
Abstract.: (+)-Combretastatin D-1 was prepared with modest enantioselectivity by Jacobsen epoxidation of combretastatin D-2 acetate. The configuration of (+)-combretastatin was shown to be (3*R*,4*S*) based on precedent from the Jacobsen epoxidation, and an advanced Mosher ester analysis of a derivative. The stereochemistry of natural (–)-combretastatin should be corrected to (3*S*,4*R*).

Combretastatins D-1 (**1**) and D-2 (**2**) are two 15-membered macrocyclic lactones isolated from the South African tree *Combretum caffrum* that have been found to inhibit PS cell line growth with ED_{50} values of 3.3 μg/mL and 5.2 μg/mL respectively.[1] Combretastatin D-2 has been a popular synthetic target,[2] and we recently described the first total synthesis of racemic combretastatin D-1.[3] We now report the synthesis of (+)-combretastatin D-1 and a correction of the previously assigned configuration of natural combretastatin D-1.



(–)-Combretastatin D-1 (1)

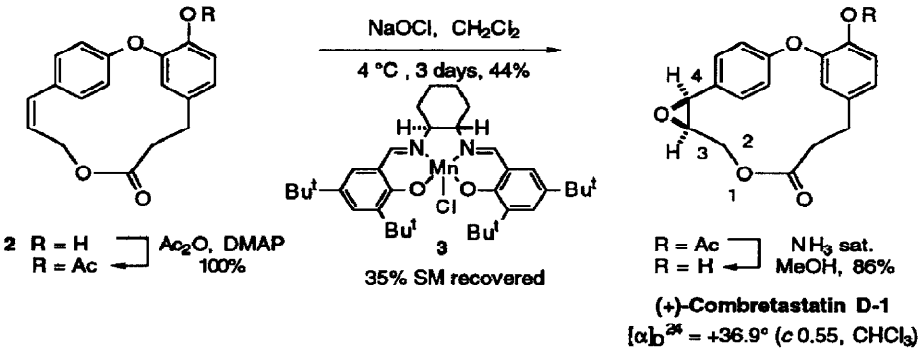


Combretastatin D-2 (2)

Figure 1. Structure of combretastatin D-2 and the revised structure of (–)-combretastatin D-1

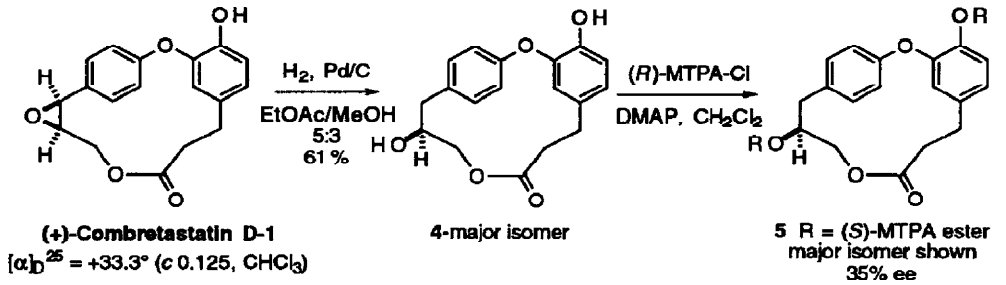
Enantioselective epoxidation of combretastatin D-2 should lead to optically active combretastatin D-1. Combretastatin D-2 is a (*Z*)-styrene, and Jacobsen has shown that (*Z*)-styrenes are epoxidized with good to excellent enantiomeric excess using his chiral (salen)Mn catalysts.[4] The combretastatin D-2 was protected as the acetate, and then oxidized using 4 mol % of Jacobsen's (*S*,*S*)-(salen)Mn catalyst **3** derived from 1,2-diaminocyclohexane.[5] The acetate was removed by treatment with NH_3-saturated methanol to give (+)-combretastatin D-1 with an optical rotation of $[\alpha]_D^{24}$ = +36.9° (*c* 0.55, $CHCl_3$). This outcome was

surprising on two counts: the enantioselectivity was modest,[6] and *the sign of the rotation was opposite that of the natural product* ($[\alpha]_D = -100°$ (*c* 0.015, $CHCl_3$)).[1a] Several attempts to improve the enantioselectivity by modifying the conditions were unsuccessful. Sharpless dihydroxylation of **2** with AD-mix-α, not unexpectedly, gave a racemic diol.[7]



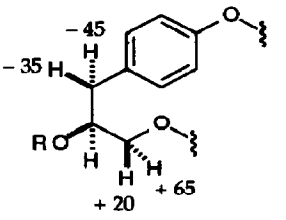
The (*S*,*S*)-(salen)Mn catalyst **3** was selected because Jacobsen has shown that it oxidizes a wide variety of (*Z*)-styrenes, including (*Z*)-1-phenylpropene, to the corresponding (1*S*,2*R*) epoxides with good enantioselectivity.[4] The configuration of natural (–)-combretastatin D-1 was assigned as (3*R*,4*S*) by comparison of its CD spectrum with (1*R*,2*R*)-(+)-1-phenylpropylene oxide and (1*S*,2*S*)-(–)-1-phenylpropylene oxide,[1a] so catalyst **3** should have given the natural configuration. To clarify the configuration of the synthetic material, (+)-combretastatin D-1 was hydrogenated over Pd/C as described by Pettit[1b] to give the expected secondary alcohol **4**.[8] Treatment of alcohol **4** with (*R*)-MTPA-Cl gave the (*S*,*S*)-bis Mosher ester **5** as a 2.1:1 mixture of major and minor isomers that were inseparable.[9] The ratio of isomers corresponds to an enantiomeric excess of 35%, which is consistent with the optical rotations observed for the synthetic and natural materials.

The configuration of the major isomer of alcohol **4** can be assigned using the advanced Mosher's method.[10] The $\Delta\delta_H$ values are defined as the chemical shift of the (*S*)-Mosher ester minus the chemical shift (*R*)-Mosher ester, and are listed for **5** in Figure 2.[11] Because alcohol **4** has a single chiral center, the (*S*,*S*)-bis Mosher ester of the minor isomer is the enantiomer of the (*R*,*R*)-bis Mosher ester of the major isomer, and ^1H



NMR chemical shifts are identical. The chemical shifts of (*S*,*S*)-bis Mosher ester of the minor isomer were used to calculate $\Delta\delta_H$ value for the major isomer. The $\Delta\delta_H$ values for the major isomer of **5** clearly indicate an *S* configuration at C-3, which would correspond to synthetic (3*R*,4*S*)-(+)-combretastatin. The (3*R*,4*S*) configuration of synthetic (+)-combretastatin is consistent with that expected of a Jacobsen epoxidation using the (*S*,*S*)-(salen)Mn catalyst **3**. The preponderance of evidence indicates that the original assignment of configuration is incorrect, and the correct configuration of natural (–)-combretastatin D-1 is (3*S*,4*R*) as shown in Figure 1.[12]

Figure 2. $\Delta\delta_H$ values (in Hz at 500 MHz) for selected protons[11] in **5**.



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5 The household bleach (NaOCl) used in the oxidation was adjusted to pH 11.3 by addition of 0.05 M Na_2HPO_4 and 1 N HCl.

6 The relatively low enantioselectivity may be due to the nearly orthogonal conformation of the aromatic ring and the alkene in **2**. Some of the best substrates for a Jacobsen epoxidation are planar.[4b]

7 Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

8 Synthetic **4**: $[\alpha]_D^{23} = +8.2°$ (*c* 0.25, $CHCl_3/CH_3OH$, 1:1). Alcohol **4** from natural (–)-combretastatin D-1: $[\alpha]_D^{30} = -12.6°$ (*c* 0.95, $CHCl_3/CH_3OH$, 1:1).[1b]

9 Compound **5**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 6.0, 3.0 Hz, 2 H); 7.55 (dd, *J* = 10.0, 6.5 Hz, 2 H); 7.52 (m, 7 H); 7.25 (m, 1 H); 7.10 (ddd, *J* = 8.5, 8.5, 2.5 Hz, 1 H); 7.00 (ddd, *J* = 8.5, 6.0, 2.5 Hz, 1 H); 6.89 (d, *J* = 8.0 Hz, 1 H); 6.70 (d, *J* = 8.0 Hz, 1 H); 5.39 (d, *J* = 2.0 Hz, 1 H); 5.32 (m, 1 H); 4.52 (dd, *J* = 12.5, 7.5 Hz, 2β-major, 0.67 H); 4.48 (dd, *J* = 12.0, 7.0 Hz, 2β-minor, 0.32 H); 3.85 (d, *J* = 12.0 Hz, 2α-major, 0.67 H); 3.76 (s, 3 H); 3.72 (d, *J* = 12.0 Hz, 2α-minor, 0.32 H); 3.58 (s, 3 H); 3.43 (dd, *J* = 13.0, 5.5 Hz, 4β-minor, 0.32 H); 3.36 (dd, *J* = 12.0, 5.5 Hz, 4β-major, 0.67 H); 3.05 (dd, *J* = 17.0, 11.5 Hz, 1 H); 2.84 (dd, *J* = 13.0, 10.5 Hz, 4α-minor, 0.32 H); 2.75 (dd, *J* = 13.0, 10.0 Hz, 4α-major, 0.67 H); 2.71 (dd, *J* = 16.5, 8.0 Hz, 1 H); 2.39 (m, 1 H); 2.22 (m, 1 H).

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11 The 4α and 4β proton assignments are tentative. Assignments are based on ^1H COSY analysis and predicted coupling constants using Macromodel 4.5 (Still, W. C., Columbia University).

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