EtOAc/hexanes) gave the alcohol **32** (5.5 mg, 77%) as a clear oil: ^{1}H NMR (selected data for major isomer) δ 5.72 (1 H, m, C*H*=CH_2), 5.42 (1 H, d, J = 8 Hz, C*H*=C(Me)CH(OH)), 5.20 (1 H, d, J = 6 Hz, C*H*CO_2*t*Bu), 5.02-4.92 (3 H, m, CH=CH_2 and C*H*=C(Me)CH_2), 4.38 (1 H, bd, J = 8 Hz, TIPSOC*H*CH(Me)), 4.26 (1 H, s, C*H*(OH)), 3.88 (2 H, m, TBSOC*H*CH(OMe) and OH), 3.68 (1 H, bd, J = 10 Hz, NC*H*H), 3.55 (2 H, m, TIPSOC*H*CH(OMe) and TBSOC*H*CH_2), 3.45 (3 H, s, MeO), 3.42 (3 H, s, MeO), 3.37 (1 H, m, NC*H*H), 3.33 (3 H, s, MeO), 3.29 (1 H, d, J = 9 Hz, MeOC*H*CH_2CH(Me)C(S)$_2$), 3.21 (1 H, m, MeOC*H*CH_2CH(Me)-CH_2), 2.99 (3 H, m), 2.67 (3 H, m), 2.45 (1 H, m, C*H*CH=C-(Me)CH_2), 1.59 (6 H, s, CH=C(*Me*) and CH=C(*Me*)), 1.49 (9 H, s, CO_2*t*Bu), 1.21 (3 H, d, J = 8 Hz), 1.11 (s, (Me_2CH)$_3$Si), 1.10 (s, (Me_2CH)$_3$Si), 0.94 (s, *t*BuSi), 0.91 (s, *t*BuSi), 0.82 (d, J = 7 Hz), 0.78 (d, J = 7 Hz), 0.13-0.06 (12 H, m, Me_2Si and Me_2Si).

[1*R*-[1α[1(*S),2*R**,4*S**,5*R**,6*S**,8*S**,10*E*,12*R**,13*R**,15*S**,16*S**,17*S**,18*E*],3α,4β]]-1-[[2-[5,13-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-17-hydroxy-4,6-dimethoxy-19-[3-methoxy-4-[[tris(1-methylethyl)silyl]oxy]cyclohexyl]-2,8,10,16,18-pentamethyl-12-(2-propenyl)-15-[[tris(1-methylethyl)silyl]oxy]-10,18-nonadecadienyl]-1,3-dithian-2-yl]oxoacetyl]-2-piperidinecarboxylic acid (33).** *tert*-Butyl ester **32** (5.5 mg, 3.6 μmol) was dissolved in THF (300 μL) at room temperature. 2,6-Lutidine (18 μL, 150 μmol) and trimethylsilyl triflate (21 μL, 109 μmol) were added successively. After 0.5 h at room temperature the mixture was heated to reflux. After 1 h further amounts of 2,6-lutidine (10 μL, 83 μmol) and TMSOTf (10 μL, 52 μmol) were added. After a further 1 h at reflux the reaction mixture was allowed to cool to room temperaure and 1 N aqueous hydrochloric acid was added followed by EtOAc. The organic layer was separated, and the aqueous layer was reextracted with EtOAc (2×). The combined organic extracts were washed with 1 N aqueous hydrochloric acid, then brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by chromatography (EtOAc → 5% MeOH/EtOAc) on 4% KH_2PO_4 impregnated silica gel gave the carboxylic acid **33** (4.8 mg, 87%) as a clear oil: ^{1}H NMR (selected data for major rotamer) δ 5.71 (1 H, m, C*H*=CH_2), 5.41 (1 H, d, J = 8 Hz, C*H*=C(Me)CH(OH)), 5.37 (1 H, bs, C*H*CO_2H), 5.00 (1 H, d, J = 15 Hz, *cis*-C*H*=CH_2), 4.95 (1 H, d, J = 9 Hz, *trans*-C*H*=CH_2), 4.90 (1 H, d, J = 12 Hz, C*H*=C(Me)CH_2), 4.38 (1 H, bd, J = 10 Hz, TIPSOC*H*CH(Me)), 4.28 (1 H, s, C*H*(OH)), 3.79 (1 H, d, J = 7 Hz, TBSOC*H*CH(OMe)), 3.75 (1 H, bd, J = 15 Hz, NC*H*H), 3.61 (1 H, m, TIPSOC*H*CH(OMe)), 3.50-3.33 (m, including 3.43, s, MeO), 3.29 (3 H, s, MeO), 3.25-3.13 (m), 3.07 (1 H, m, MeOC*H*CH(OTIPS)), 3.02-2.81 (m), 2.70-2.61 (m), 1.61 (s, CH=C(*Me*) and CH=C-(*Me*)), 1.21 (d, J = 7 Hz, CH(*Me*)), 0.83 (d, J = 8 Hz, CH(*M*)), 0.75 (d, J = 8 Hz, CH(*Me*)); IR (CH_2Cl_2 solution) 3500 (br), 2928, 2862, 1739, 1694, 1642, 1461, 1385, 1251, 1190, 1105, 1001, 881, 834, 775 cm^{-1}.

Acknowledgment. This research was supported by PHS Grant AI 16943. A PHS Fellowship (Grant GM 11747) to A.V. is gratefully acknowledged. An SERC Fellowship to A.B.J. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We wish to thank Drs. I. Shinkai and R. P. Volante of Merke Sharpe & Dohme for graciously providing us with comparison spectra of various synthetic intermediates.

Supplementary Material Available: Experimental procedures for **5**, **29**, **36**, **37**, **38**, and **39**, and ^{1}H NMR spectra for **24**, **26**, **30**, **31**, **33**, **36**, **37**, **38**, **39** (16 pages). Ordering information is given on any current masthead page.

Antineoplastic Agents. 206. Structure of the Cytostatic Macrocyclic Lactone Combretastatin D-2[1]

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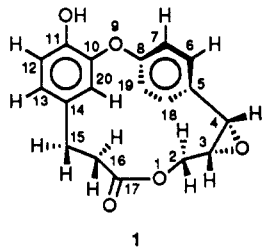
The South African tree *Combretum caffrum* (Combretaceae) has been found to contain two new and cytostatic (P388 lymphocytic leukemia) macrocyclic lactones designated combretastatin D-1 (**1**, ED_{50} 3.3 μg/mL) and D-2 (**2**, ED_{50} 5.2 μg/mL). With the X-ray crystal structure of combretastatin D-1 (**1**) serving as an unequivocal reference point ^{13}C NMR and high field (400 MHz) ^{1}H NMR spectral techniques were employed to assign structure **2** to combretastatin D-2.

The South African tree *Combretum caffrum* (Combretaceae) has been found to produce two *cis*-stilbenes, combretastatins A-1 and A-4, that strongly inhibit growth of the P-388 lymphocytic leukemia cell line (PS system) and tubulin polymerization.[2] Recently, we reported[3] the isolation and structure determination of an unexpected 17-membered macrocyclic lactone designated combretastatin D-1 (**1**) from the same plant. We now summarize the



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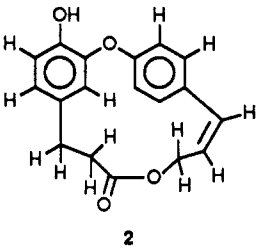

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isolation and structural elucidation of another PS cell line inhibitory member of this unusual series of macrocyclic lactones named combretastatin D-2 (**2**) along with chemical

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Table I. ^{1}H NMR Assignments for Combretastatin D-2 (2) and Derivatives 5a–c in Deuteriochloroform Solution in δ Value (ppm) with Chloroform as Internal Standard

position	2	5a[a]	5b	5c
2α	4.64, d, 6.8	4.64, d, 6.9	3.91, d, 11.4	4.05, d, 11.9
2β	4.64, d, 6.8	4.26, m	4.31, dd, 11.4, 7.0	4.56, dd, 12, 7.6
3	6.06, dt, 10.6, 6.8	2.09, 2.38, m	4.24, m	4.27, m
4	7.11, d, 10.6	3.72, m	2.81, dd, 12.9, 8.4	2.93, dd, 13.2, 11.4
		4.06, m	3.26, dd, 12.9, 5.1	3.60, dd, 13.2, 5.3
6	7.33, d, 8.4	7.33, br d, 9.7	7.35, dd, 8.3, 2.3	7.35, dd, 8.3, 2.1
7	7.09, d, 8.4	7.09, dd, 8.0, 1.7	7.05, dd, 8.4, 2.5	7.10, dd, 8.3, 2.5
12	6.85, d, 8.0	6.83, d, 8.2	6.84, d, 8.2	6.84, d, 8.2
13	6.63, ddd, 8, 1.8, 1.7	6.61, dd, 8.4, 1.7	6.61, dd, 8.3, 1.6	6.61, dd, 8.3, 1.8
15α	2.87, t, 5.0	2.82, m	2.72, br dd, 17.1, 8	2.61, br dd, 17.1, 7.2
15β	2.87, t, 5.0	2.85, m	2.96, br dd, 16.4, 9.9	3.05, br dd, 16.6, 10.6
16α	2.29, dt, 5.0, 1.7	2.25, m	2.23, ddd, 17, 10.5, 1.7	2.15, ddd, 15.2, 12, 1.4
16β	2.29, dt, 5.0, 1.7	2.30, m	2.35, ddd, 17, 8.2, 1.8	2.40, ddd, 16.8, 7.4, 1.4
18	7.33, d, 8.4	7.31, dd, 8.0, 1.9	7.31, dd, 8.0, 2.5	7.31, dd, 8.1, 2.2
19	7.09, d, 8.4	7.02, dd, 8.3, 2.0	7.02, dd, 8.2, 2.5	7.00, dd, 8.1, 2.5
20	5.07, d, 1.8	5.30, d, 2.0	5.23, d, 1.8	5.21, d, 1.8
11-OH	5.47, s	5.51, br s	5.50, br s	5.48, s
3-OH			2.07, d, 6.1	

[a] Two major conformers; the chemical shift of the major conformer is reported.

transformations of combretastatin D-1 undertaken as part of the original structural elucidation.[3]

A methylene chloride–methanol (1:1) extract of *Combretum caffrum* stem wood was initially fractionated and separated as described.[2a,b] The fraction that previously yielded[2b] combretastatin A-2 was subjected to a similar PS bioassay guided chromatographic separation sequence (a series of Sephadex LH-20 partition chromatograms using hexane–toluene–methanol, 3:1:1, and silica gel column chromatographic procedures employing various combinations of hexane–ethyl acetate as eluant) afforded combretastatin D-2 (**2**, 5.8 mg from 77 kg of wood), which exhibited PS ED_{50} 5.2 μg/mL.

As with combretastatin D-1 (**1**) mass spectral analysis of combretastatin D-2 indicated a molecular formula ($C_{18}H_{16}O_4$) with 11 double-bond equivalents. The infrared spectrum of lactone **2** showed absorption due to a lactone or an ester carbonyl (at 1728 cm^{-1}), hydroxyl group (3436, 3429 cm^{-1}), and aromatic rings. The ^{1}H NMR spectrum contained signals corresponding to methylene adjacent to carbonyl, a benzylic methylene, an oxymethylene, eight olefinic and/or aromatic protons, and a shielded aromatic proton (Table I). The proton NMR spectrum was assigned on the basis of 2D ^{1}H NMR and ^{1}H-COSY techniques.[4] The spin systems were (a) $ArCH_2CH_2CO$-; (b) -OCH_2CH=CH-; (c) a *para*-substituted aromatic ring; and (d) an ortho,ortho,meta-substituted aromatic ring. On the assumption that combretastatin D-2 had a lactone ring, all the double-bond equivalents were thereby accounted for. The ^{13}C NMR spectrum of olefin **2** was consistent with this deduction. The ^{1}H NMR spin systems were assembled[3] on the basis of NOEDS experiments.

Comparison of the ^{13}C NMR spectrum (Table II) of combretastatin D-2 with the spectrum of combretastatin D-1 (**1**, confirmed by X-ray crystal structure determination) provided unequivocal support for the proposed structure. The carbon-13 spectrum of lactone **2** was found to be essentially identical with that of combretastatin D-1, except for the olefinic carbon signals. Since the original ^{13}C assignments for combretastatin D-1 were based on direct one-bond ^{1}H, ^{13}C correlation using the ^{1}H, ^{13}C-COSY[5] experiment (ambiguous for the quaternary carbons), it became necessary to assign the carbon resonances of the more abundant combretastatin D-1. Therefore, all

Table II. ^{13}C NMR Assignments for Combretastatin D-1 (1 with HMBC Correlations) and Combretastatin D-2 (2) in Deuteriochloroform

position	1	2	1 (HMBC)
2	62.56	59.06	C-2 → H-3
3	52.99	137.74	C-3 → H-2α, H-2β, H-4
4	55.84	135.45	C-4 → H-2α, H-2β, H-6
5	132.44	132.01	C-5 → H-4, H-7, H-19
6	128.83	129.09	C-6 → H-4, H-18
7	123.95	123.89	C-7 → H-19
8	156.01	155.6	C-8 → H-7, H-19
10	149.09[a]	149.32[a]	C-10 → H-12, 11-OH, H-20
11	142.62[a]	142.48[a]	C-11 → H-12, 11-OH, H-20
12	115.38	115.39	C-12 → H-13, 11-OH
13	122.03	121.89	C-13 → H-15α, H-12, H-20
14	131.90	131.14	C-14 → H-12, H-15α,β, H-16α,β
15	26.97	26.89	C-15 → H-16α,β, H-20
16	31.24	32.42	C-16 → H-15α,β
17	172.53	173.30	C-17 → H-2α,β, H-15β, H-16α,β
18	126.34	125.68	C-18 → H-4, H-6
19	123.14	123.89	C-19 → H-7
20	112.24	112.58	C-20 → H-12, H-13, H-15α

[a] Assignments with identical superscripts in vertical columns may be interchanged.

the carbon resonances of epoxide **1** were assigned by heteronuclear multiple bond connectivity (HMBC) experiments.[6] The observed connectivities are recorded in Table II. The previous assignments[3] remain unchanged except for reversal of the quaternary carbon signals at C-5 and C-14. Both protons at C-2 gave a strong cross correlation with the carbonyl group, clearly confirming presence of the lactone. Similarly, assignment of the chemical shift of C-8 was confirmed by correlation with H-7 and H-19. Definite assignment of C-10 and C-11 remains uncertain because of common correlation cross peaks but this is of little consequence. Combretastatin D-2 must have structure **2** and this was further corroborated by the mass spectral fragmentation pattern (structure **4**).

Attempts to convert combretastatin D-1 (**1**) into D-2 (**2**) and thereby provide further support for the D-2 structure were unsuccessful. For example, reaction of combretastatin D-1 with Zn/Cu couple[7] gave hydrocarbon derivative **5a** and alcohol **5b**. Several other reagents such as P_2I_4[8]

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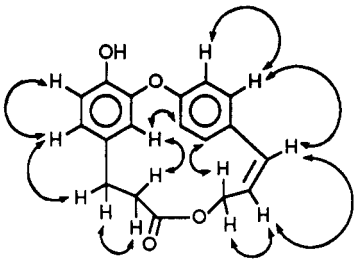
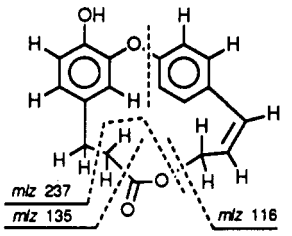
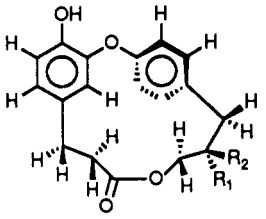


3 NOE



4 MS

or sodium iodide with acetonitrile and trifluoroacetic anhydride[9] were either unreactive under the conditions studied or caused decomposition. When the epoxide group of combretastatin D-1 was hydrogenated to give alcohol **5b**, subsequent treatment with thionyl chloride in pyridine yielded 3,4-deoxy-3-chlorocombretastatin D-1 (**5c**).



5a: $R_1 = R_2 = H$
5b: $R_1 = OH$, $R_2 = H$
5c: $R_1 = H$, $R_2 = Cl$

Combretastatins D-1 and D-2 both contain a new oxygen heterocyclic ring (17-membered exterior and 15-atom interior). We propose the designation caffrane for this new macrocyclic ring system. Combretastatin D-2 is probably a penultimate biosynthetic precursor of combretastatin D-1 and may originate biosynthethically as noted earlier[3] from two units of tyrosine or equivalent via *o*-phenol coupling, deamination, partial reduction, and lactonization. When additional quantities of combretastatins D-1 and D-2 become available, the biological properties of these biosynthetic products will be further ascertained.

Experimental Section

Synthetic intermediates were used as received from Sigma-Aldrich Co. All chromatographic solvents were redistilled. Sephadex LH-20 (particle size 25–100 μm) was obtained from Pharmacia Fine Chemicals AB (Uppsala, Sweden) and silica gel 60 (70–230 mesh) was supplied by E. Merck, (Darmstadt, Germany). Analtech, Inc. (Newark, DE) silica gel GHLF U (0.25-mm layer thickness) was employed for thin layer chromatograms. Development was performed with ceric sulfate–sulfuric acid spray reagent (heated at approximately 150 °C for 5–10 min) and/or by use of ultraviolet light. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate.

All melting points are uncorrected and were observed with a Kofler-type hot-stage apparatus. Ultraviolet spectra were obtained on a Hewlett-Packard Model 8540A UV/VIS spectrophotometer. Infrared spectra were measured with a Nicolet FT-IR Model MX-1 unit. Nuclear magnetic resonance spectra were obtained with a Bruker AM-400 instrument using deuteriochloroform as solvent and the residual chloroform signal as an internal standard (δ 7.256). The ^{13}C NMR multiplicities were determined by using the APT sequence. Mass spectral measurements were performed with a MS-50 instrument at the NSF Regional Facility, University of Nebraska, Lincoln, NE.

Isolation of Combretastatins D-1 (1) and D-2 (2). Fraction A (28.6 g),[2a-c] obtained after extraction of *Combretum caffrum* (77 kg) stem wood, was further separated on a column of Sephadex LH-20 (2.5 kg) by partition chromatography using hexane–toluene–methanol (3:1:1) to afford two active fractions (1.97 g, PS ED_{50} 1.8×10^{-2} μg/mL, and 0.54 g, PS ED_{50} 1.9 μg/mL). The latter fraction (0.54 g) was chromatographed on a silica gel (0.04–0.063 μm) flash column (3.0 × 20.0 cm). The column was packed and eluted with hexane–chloroform–acetone (3:2:0.25) to give combretastatin D-1 (**1**, 180 mg, (2.3×10^{-4})% yield). For the physical data, consult ref 3.

The fraction weighing 1.97 g was dissolved in hexane–toluene–methanol (3:1:1, 20 mL) and the solution was filtered. The filtrate was chromatographed on a Sephadex LH-20 (200 g) column using the same solvent system. The resulting active fraction (1.35 g, PS ED_{50} 2.4×10^{-2} μg/mL) was dissolved in hexane–ethyl acetate (1:1, 5 mL) and chromatographed on a column (60 × 2.5 cm) of silica gel (60 g). Gradient elution from 4:1 → 1:1 hexane–ethyl acetate afforded in a 3:1 fraction the PS-active (0.7 g, ED_{50} 1.0×10^{-2} μg/mL) material. Rechromatography in acetone (2 mL) over a long silica gel column (100 × 1.2 cm, 45 g) and gradient elution with hexane–ethyl acetate (9:1 → 4:1) furnished in the 4:1 fraction pure combretastatin D-2 (**2**, 5.8 mg, (7.5×10^{-6})% yield based on dried plant material), needles from acetone–hexane: mp 148–51 °C; PS ED_{50} 5.2 μg/mL; UV λ_{max} (nm) 235 (ε 7300), 274 (2260), 339 (1050); IR (NaCl) ν_{max} 3436, 3429, 1728, 1519, 1503, 1440, 1215, 1186, 1159, 1110 cm^{-1}; HREIMS *m/z* 296.1052 (M^+, 100, calcd for $C_{18}H_{16}O_4$ 296.1049), 237.0916 (20, calcd for $C_{16}H_{13}O_2$ 237.0916), 180.0426 (5, calcd for $C_9H_8O_4$ 180.0423), 138.0321 (46, calcd for $C_7H_6O_3$ 138.0317), 135.0450 (50 calcd for $C_8H_7O_2$ 135.0446), 116.0620 (30, calcd for C_9H_8 116.0626), 91.0545 (35, calcd for C_7H_7 91.0548); for ^1H and ^{13}C NMR data see Tables I and II, respectively.

Benzyl Bond Hydrogenolysis of Combretastatin D-1 (1 → 5b). Method A. To a solution of combretastatin D-1 (1, 10 mg) in a mixture of ethyl acetate–methanol (5:3, 10 mL) was added 5% Pd/C (10 mg). The mixture was hydrogenated under ambient temperature and pressure for 72 h. Catalyst was removed (filtration) and the filtrate was concentrated to give pure alcohol **5b** (10 mg, quantitative yield) as needles from ethyl acetate–hexane: mp 191–93 °C; $[\alpha]^{30}_D$ – 12.6° (*c* 0.95, $CHCl_3/CH_3OH$, 1:1); IR (KBr) ν_{max} 3200, 1740, 1719, 1521, 1504, 1285, 1220, 1163, 1155, 1142, 1103 cm^{-1}; HREIMS *m/z* 314.1153 (M^+, 100, calcd for $C_{18}H_{18}O_5$ 314.1154), 271.0966 (69, calcd for $C_{16}H_{15}O_4$ 271.0970), 226.0995 (55, calcd for $C_{15}H_{14}O_2$ 226.0994); for ^1H NMR data see Table I.

Method B. Combretastatin D-1 (5.0 mg) in ethanol (2 mL) was treated with freshly prepared[7] zinc/copper couple (100 mg) for 10 days. The solution was filtered and the filtrate concentrated to give a mixture of unreacted starting material and two products. Separation on a preparative silica gel plate using hexane–acetone (7:3) as solvent afforded the less polar hydrocarbon product (**5a**, 0.8 mg) as a viscous oil (for ^1H NMR data see Table I): HREIMS *m/z* 298 (M^+, 6), 135 (10), 115 (60), 107 (65), 91 (100). Unreacted combretastatin D-1 (1.0 mg) was recovered, and the most polar product (2.0 mg) was identified as alcohol **5b** by direct comparison (TLC, ^1H NMR) with the product of method A.

Chlorination of Alcohol 5b. To a cooled (0 °C) solution of alcohol **5b** (1.0 mg) in pyridine (0.2 mL) was added thionyl chloride (0.1 mL), and the solution was stirred for 1 h at 0 °C and overnight at room temperature. The solvent was evaporated under a stream of nitrogen and the residue was chromatographed by using a pipet filled with silica gel. Elution of the pipet column with hexane–acetone (3:1) gave 3-chloro-3,4-deoxycombretastatin D-1 (**5c**, 1.0 mg) as an amorphous powder from acetone–hexane: mp 170–172 °C; IR (NaCl) ν_{max} 3450, 1740, 1597, 1520, 1506, 1205 cm^{-1}; HREIMS *m/z* 332.0812 (M^+, 100, calcd for $C_{18}H_{17}O_4{}^{35}Cl$ 332.0816), 334.0798 (31, calcd for $C_{18}H_{17}O_4{}^{37}Cl$ 334.0786), 297.1132 (29, calcd for $C_{18}H_{17}O_4$ 297.1127); for ^1H NMR data see Table I.

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Total Synthesis of (−)-Denticulatins A and B: Marine Polypropionates from *Siphonaria denticulata*

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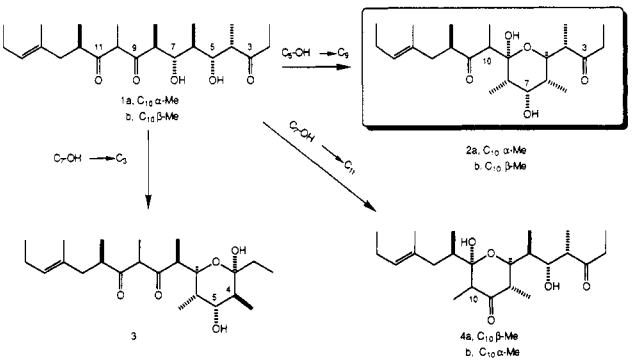
A synthesis of the marine polypropionates (−)-denticulatin A (**2a**) and B (**2b**) is described. The targets, which are β-hydroxy ketones wherein the hydroxyl group is also a tertiary hemiketal, are sensitive to acid dehydration. An open-chain form (**26**) of the denticulatins, having the 1,3-diol functionality protected as its *p*-methoxyacetophenylidene derivative, is prepared and is demonstrated to undergo only one of three possible modes of hemiketalization upon acid hydrolysis. The open-chain structure is constructed by an aldol condensation between ketone **5** and keto aldehyde **25**, which is synthesized by the 3-methyl-γ-butyrolactone strategy.

The genus *Siphonaria*, air-breathing mollusks of the subclass Pulmonata, produces numerable, structurally intriguing polypropionate metabolites.[1] In particular, denticulatin A (**2a**) and denticulatin B (**2b**) have been isolated from *Siphonaria denticulata*, which was collected in the intertidal zone of the coast of New South Wales, Australia.[2] Through a combination of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and a single-crystal X-ray analysis of denticulatin B, the structures were determined. The absolute stereochemistry was established by the isolation of (*R*)-ketone **5** upon exposure of denticulatin A or B to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Interconversion of the denticulatins was achieved upon brief treatment with DBU through retrohemiketalization via the β-diketone enolate.

Although the denticulatins have been shown to arise via propionate biosynthesis,[3] the actual timing of the hemiketalization is an intriguing question. One possibility is that an open-chain C_9 monoketone undergoes cyclization followed by subsequent oxidation at C_3 and C_{11}. The prospect that the open-chain C_3, C_9, C_{11} trione **1** can be formed in Nature prior to any intermediates suffering cyclization is unlikely. However, the very challenge of generating trione **1** in the laboratory to assess its fate offered itself as a formidable challenge.

Three modes of hemiketalization are available to the two diasteromers of trione **1**. First, the C_7-OH may add to the C_3-carbonyl to give hemiketal **3** that would most likely have the hydroxyl group axial in accord with the anomeric effect. The C_4-methyl and the C_5-hydroxyl groups are axial

Scheme I



to the tetrahydropyran ring while the remaining alkyl substituents are equatorial. A second mode of cyclization has the C_7-OH adding to the C_{11}-carbonyl. In this instance, open-form **1a** affords **4a** that has all the carbon substituents about the ring equatorial except for the C_{10}-methyl group that is axial. On the other hand, open-form **1b** gives rise to **4b** that has all of the carbon substituents of the ring equatorial. Lastly, cyclization of the C_5-OH group with the C_9-carbonyl provides the denticulatins **2** having all the carbon substituents equatorial and the C_7-OH axial and hydrogen bonded to the anomeric hydroxyl. If the cyclization were to be thermodynamically controlled and mediated by steric interactions about the ring, the formation of pyranone **4b** and the denticulatins would be the expected products. The denticulatins have the advantage of hydrogen bonding between the axial hydroxyl groups.

Precedent for the proposed modes of cyclization was found in earlier work wherein the diol **6**, which is chiral by virtue of the stereochemistry of a single methyl group, underwent ozonolysis and cyclization to give only the anomeric acetals **7** and not those of structure **8**.[4] Acetals

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