Brominated Sesquiterpenes from the Red Alga *Laurencia obtusa*

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Four new sesquiterpenes, (8*R**)-8-bromo-10-*epi*-*β*-snyderol (**1**), (8S*)-8-bromo-*β*-snyderol (**2**), 5-bromo-3-(3′-hydroxy-3′-methylpent-4′-enylidene)-2,4,4-trimethylcyclohexanone (**3**), and the epoxide **4**, have been isolated from the chloroform−methanol extract of *Laurencia obtusa*, together with the three known compounds α-snyderol (**5**), α-snyderol acetate (**6**), and stigmasterol. The structures of the isolated compounds were elucidated through spectroscopic analyses. Compound **1** showed antimalarial activity, with IC_{50} values of 2700 and 4000 ng/mL against the D6 and W2 clones of *Plasmodium falciparum*, respectively.

The red algae of the genus *Laurencia* (Rhodomelaceae) are known as a rich source of halogenated sesquiterpenes, diterpenes, and acetylenes.[1,2] In our continuing research on secondary metabolites of the alga *Laurencia obtusa* Lamouroux, which has different colors in different regions of Turkey and at different times, we have obtained several halogenated sesquiterpenoids. These include *β*-snyderol,[3] obtusenol,[4] and C_{15} acetogenins of many different structural types such as obtusenyne,[5] epoxy-*trans*-isodihydrorhodophytin,[6] bromoallenes,[7] obtusallene I,[8] and kasallene.[9] In a very recent study on *L. obtusa* collected from southeastern Greece, the isolation of four new C_{15} acetogenins has been reported.[10] In the present study, we describe the isolation and elucidation of six sesquiterpenes, four of which are new and one of which is active against the malaria parasite, *Plasmodium falciparum*.

A sample of *L. obtusa* was extracted and the extract chromatographed on a silica gel column followed by preparative TLC to give compounds **1**−**6**. The HRMS of compound **1** gave a molecular ion peak at *m*/*z* 378.0176, corresponding to the molecular formula $C_{15}H_{24}OBr_2$, with three degrees of unsaturation; the presence of double bonds was indicated by IR bands at 1653, 920, and 758 cm^{-1}. The ^1H NMR spectrum (Table 1) of compound **1** exhibited three methyl singlets at *δ* 0.77, 1.17, and 1.29. The signals of a characteristic terminal vinyl moiety were observed at *δ* 5.90 (1H, dd, *J* = 10.5 and 17.5 Hz, H-2), 5.22 (1H, dd, *J* = 1.2 and 17.5 Hz, H-1a), and 5.08 (1H, dd, *J* = 1.2 and 10.5 Hz, H-1b). The presence of an exocyclic methylene group was indicated by signals at *δ* 5.11 (1H, brs, H-14a) and 4.73 (narrow triplet, *J* = 1.5 Hz, H-14b). In the ^1H NMR spectrum, two other downfield signals were observed at *δ* 4.28 and 4.49, attributed to protons on oxygen or halogen-bearing carbons.

The basic skeleton of **1**, which is very similar to that of *β*-snyderol isolated from *L. obtusa* and other *Laurencia* species,[11,12] was established by NMR and mass spectroscopy, including COSY, HMQC, and HMBC experiments. The ^{13}C NMR spectrum (Table 2) exhibited 15 carbon signals, consisting of three quaternary, five methylene, three methyl, and four methine carbons, as determined by an APT experiment. Two olefinic carbon pairs were observed at *δ* 147.5 and 144.7, and their methylene carbons at *δ* 112.0 and 111.9. A quaternary carbon signal at *δ* 73.6 indicated the presence of an oxygenated carbon, and the presence of a hydroxyl group was supported by the IR spectrum with an absorption band at 3410 cm.$^{-1}$ The location of the oxygenated carbon was shown to be adjacent to a vinyl moiety by the observation of HMBC correlations between the protons at *δ* 5.90, 5.22, and 5.08 and the carbon at *δ* 73.6 (C-3). Three-bond correlations between the C-15 methyl protons (*δ* 1.29) and C-2 at *δ* 144.7 and C-4 at *δ* 40.8 verified this assignment, as did a two-bond correlation between the C-15 methyl proton and C-3. The presence of a similar tertiary hydroxyl group has been previously observed in the snyderols.[2,11,12] A COSY experiment indicated the presence of two spin systems, assigned to the H-4−H-6 and H-8−H-10 protons, respectively. In an HMBC experiment, the signal at *δ* 4.28, part of the second spin system, showed a three-bond coupling with the carbon signal at *δ* 63.0, which was assigned to C-10 by an HMQC experiment. Additional assignments came from the HMBC experiment by the observation of correlations between both

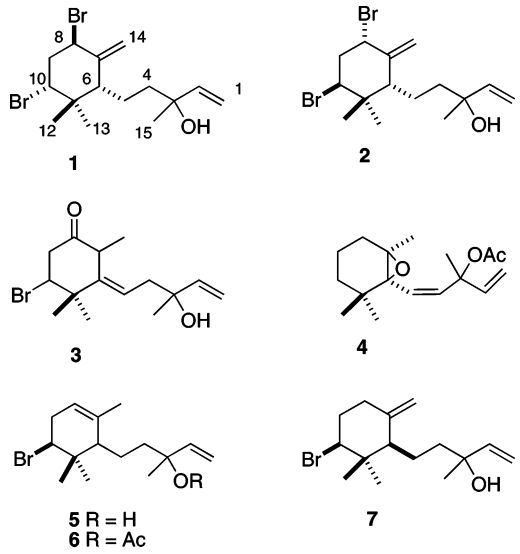

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Table 1. ^{1}H NMR Data of Compounds **1**−**4** and **7** (in $CDCl_3$)[a]

C	**1**	**2**	**3**	**4**	β-snyderol (**7**)
1	5.22 (dd 17.5, 1.2)	5.25 (brd, 17.5)	5.11 (dd, 17.5,1.5)	5.29 (brd, 17)	5.21 (brd, 17.5)
	5.08 (dd 10.5, 1.2)	5.17 (dd 10.5, 1.2)	5.02 (dd, 10.5, 1.5)	5.17 (brd, 10)	5.06 (brd, 10.5)
2	5.90 (dd 17.5, 10.5)	5.91 (dd 17.5, 10.5)	5.95 (dd, 17.5, 10.5)	5.97 (dd 17, 10)	5.90 (dd, 17.5, 10.5)
4	1.72 (m)	1.75 (m)		6.72 (d, 10)	1.63 (m)
	1.33 (m)	1.34 (m)			1.75 (m)
5	1.21 (m)	1.28 (m)	5.33 (d, 2)	6.18 (d, 10)	1.28 (m)
					1.55 (m)
6	2.35 (brd, 10.5)	2.20 (m)			1.71 (m)
7			2.35 (m)		
8	4.28 (t, 3)	4.27 (dd, 13, 5)	-	1.91 (m)	2.02 (m)
				2.08 (m)	2.32 (m)
9	2.13 (ddd, 3, 12.5, 12)	2.51 (m)	1.88 (dd, 3.5, 13)	1.78 (m)	2.01 (m)
	2.45 (ddd, 3, 5, 12)		2.01 (dd, 3.5, 13)	1.60 (m)	2.23 (m)
10	4.49 (dd, 12.5, 5)	4.43 (t, 3)	4.43 (t, 3.5)	0.85 (m)	4.12 (dd, 11.5, 4.5)
				1.23 (m)	
12	1.17 (s)	1.13 (s)	1.24 (s)	1.24 (s)	0.82 (s)
13	0.77 (s)	0.75 (s)	1.22 (s)	1.22 (s)	1.16 (s)
14	5.11 (brs)	5.29 (brs)	0.89 (d, 7)	1.37 (s)	4.91 (brs)
	4.73 (t, 1.5)	4.90 (brs)			4.60 (brs)
15	1.29 (s)	1.28 (s)	1.31 (s)	1.62 (s)	1.27 (s)
OAc				1.89 (s)	

[a] These assignments were based on HMQC and HMBC experiments for compounds **1**−**4**.

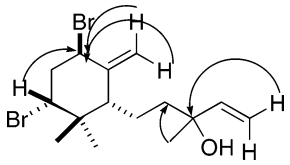

Figure 1. Selected HMBC correlations of compound **1**.

Table 2. ^{13}C NMR Data of Compounds **1**−**4** and **7** (125 Mz) (in $CDCl_3$)

C	**1**	**2**	**3**	**4**	β-snyderol (**7**)
1	112.0	112.4	111.7	112.6	111.8
2	144.7	143.7	148.1	144.2	144.9
3	73.6	70.1	72.2	74.4	73.3
4	40.8	39.2	40.8	125.8	41.3
5	31.2	29.8	120.1	136.9	35.9
6	47.6	46.9	136.8	58.2	53.1
7	147.5	149.2	43.5	62.3	145.6
8	74.6	71.5	203.0	30.2	37.4
9	42.3	42.7	53.5	25.8	20.6
10	63.0	62.9	66.3	35.0	67.1
11	40.3	42.7	40.8	40.0	41.9
12	16.5	16.8	19.7	16.5	16.4
13	29.2	29.5	29.5	28.1	28.4
14	111.9	114.6	31.0	26.3	109.0
15	28.1	28.1	31.0	29.7	27.8
OCO*CH*$_3$				23.9	
O*CO*CH$_3$				171.6	

exocyclic methylene signals at δ 4.73 and 5.11 (H-14a, H-14b) and the carbon signals at δ 74.6 (C-8) and 47.6 (C-6). Further, the C-12 and C-13 methyl proton signals (δ 1.17 and 0.77) showed three-bond correlations with C-6 and C-10. These HMBC correlations determined the locations of the brominated carbons unambiguously. All protonated carbons were assigned by an HMQC experiment, and nonprotonated carbons and the CH_2 groups were assigned by an HMBC experiment (Figure 1).

The EI mass spectrum did not give a molecular ion peak. The base peak was at *m*/*z* 71, consistent with cleavage α to the hydroxyl group with concomitant formation of the $C_4H_7O^+$ ion. Fragment ions at *m*/*z* 299/301 were consistent with the loss of a bromine atom, while the ions at *m*/*z* 279/281/283 (M − $C_6H_{11}O$) revealed the loss of the side chain $C_6H_{11}O$ (99) from the (unobserved) molecular ion at *m*/*z* 378/380/382; a fragment ion at *m*/*z* 99 supported this conclusion. The loss of a second bromine was also observed, with a fragment ion at *m*/*z* 219. On the basis of all the above spectral data, the structure of compound **1** was elucidated as a dibromo snyderol derivative.

The stereochemistry of the two bromines was assigned on the basis of the coupling constants observed for their neighboring protons. The signal at δ 4.49 (H-10) showed one large (12.5 Hz) and one small (5 Hz) coupling to H_2-9, indicating an axial orientation for the C-10 proton and thus an equatorial orientation for the bromine. The stereochemistry of the methine proton of the second brominated carbon at δ 4.28 (H-8) was assigned as equatorial on the basis of its coupling constants (t, J = 3.0 Hz), thus assigning the C-8 bromine as axial. The stereochemistry at C-6 was deduced by the observation of an NOE interaction between H-10 (4.49 ppm) and H-6 (2.35 ppm), indicating that H-6 is axial. The structure of **1** was thus assigned as (8*R**)-8-bromo-10-*epi*-β-snyderol, or [(1′*R**,3′*R**,5′*R**)-5-(3′,5′-dibromo-2′,2′-dimethyl-6′-methylenecyclo hexyl)-3-methylpent-1-en-3-ol], with an undetermined stereochemistry at the C-3 position.

The second compound (**2**) was a stereoisomer of compound **1** that showed spectral properties very similar to those of **1**. Its ^{1}H NMR spectrum (Table 1) revealed three methyl singlets at δ 0.75, 1.13, and 1.28. It was assigned as a snyderol derivative by the signals at δ 5.91 (1H, dd, J = 10.5 and 17.5 Hz, H-2), 5.25 (1H, brd, J = 17.5 Hz, H-1a), and 5.17 (1H, dd, J = 1.2 and 10.5 Hz, H-1b) and two broadened singlets at δ 4.90 and 5.29 assigned to an exocyclic double bond as in compound **1**. There were also two downfield signals with chemical shifts very similar to those of **1** at δ 4.27 (1H, dd, J = 5 and 13 Hz) and 4.43 (1H, t, J = 3 Hz), probably located on hydroxyl- or halogen-bearing carbons. Their locations were deduced to be on the same carbon atoms as in compound **1**, but their J values were reversed as compared with those of compound **1**, indicating that their stereochemistry should be reversed. The ^{13}C NMR spectrum (Table 2) was also similar to that of compound **1**, giving 15 carbon signals consisting of three quaternary, four methine, five methylene, and three methyl carbons. The signals at δ 143.7 (C-2) and 112.4 (C-1) were assigned to the terminal vinyl carbons of the side chain, while the carbons of the exocyclic double bond were at δ 114.6 (C-14) and 149.2 (C-7). The brominated carbons were observed at δ 71.5 and 62.9 (C-8 and C-10), and the hydroxylated carbon was at δ 70.2 (C-3); the resonances of

the other carbons were similar to those of **1** (Table 1). Compound **2** did not give a molecular ion peak in its EIMS, as also observed with **1**, but the same fragment ions were observed as with **1**. All the spectral data thus confirmed the structure of compound **2** as an epimer of **1**, either (8*S**)-8-bromo-*β*-snyderol [(1′*R**,3′*S**,5′*S**)-5-(3′,5′-dibromo-2′,2′-dimethyl-6′-methylenecyclohexyl)-3-methylpent-1-en-3-ol] or its enantiomer.

The third compound had spectral properties similar to those of both compounds **1** and **2**. Its IR spectrum had absorption bands at 3455, 1720, and 1660 cm^{-1}, indicating the presence of hydroxyl, a cyclic keto, and double-bond moieties, respectively. The UV spectrum exhibited weak maxima at 234 and 244 nm. There were four methyl signals in the ^1H NMR spectrum (Table 1), one of which appeared as a doublet at δ 0.89 and was assigned to Me-14; the other three signals were observed as singlets at δ 1.22, 1.24, and 1.31 ppm. The signals of the characteristic vinyl group of the side chain were observed at δ 5.95 (1H, dd, J = 10.5 and 17.5 Hz, H-2), 5.11 (1H, dd, J = 1.5 and 17.5 Hz, H-1a), and 5.02 (1H, dd, J = 10.5 and 1.5 Hz, H-1b), and an additional olefinic proton signal was observed at δ 5.33 (d, J = 2 Hz). A narrow triplet signal appeared at δ 4.43, and its chemical shift and multiplicity resembled those observed for the C-10 proton of compound **2**. The keto group indicated by the IR spectrum could in principle be located at C-4, C-8, or C-9. The C-4 location was excluded by the lack of UV absorption for a conjugated ketone and the absence of a downfield signal for the C-5 proton as a singlet around 5.7−5.9 ppm. The ^{13}C NMR spectrum (Table 2) was also inconsistent with a C-4 location for the carbonyl group. The C-9 location was also excluded by the chemical shift of H-10 at δ 4.43 and its appearance as a triplet rather than a singlet predicted for a C-9 carbonyl compound. A characteristic pair of doublet of doublets at δ 1.88 and 2.01 with J couplings of 3.5 and 13 Hz were assigned to the C-9 protons. A COSY experiment showed that they were adjacent to the brominated methine carbon at δ 4.43, and these data confirmed the presence of the keto group at C-8.

The EI mass spectrum did not give a molecular ion peak, but it gave fragment ion peaks at *m/z* 296/298 from the loss of one molecule of H_2O. Other key fragment ion peaks were observed at *m/z* 219 [M − H_2O − Br], 97, 85, and 71. The peaks at *m/z* 99 ($C_6H_{11}O^+$) and 85 ($C_5H_9O^+$) confirmed that the oxo group could not be located on the side chain. All these data confirmed that the structure of compound **3** is 5-bromo-3-(3′-hydroxy-3′-methylpent-4′-enylidene)-2,4,4-trimethylcyclohexanone, with the stereochemistries at C-3, C-7, and C-10 undefined.

The fourth compound was also a sesquiterpene, but no bromine was present in the molecule. In the ^1H NMR spectrum (Table 1), four methyl signals were observed, one being an acetoxy methyl at δ 1.89. The other methyl signals were observed as singlets at δ 1.24, 1.22 (Me-12 and Me-13), 1.62 (Me-15), and 1.37 (Me-14). A terminal vinyl moiety with signals at δ 5.97, 5.29, and 5.17 was seen as in the previous compounds. A new feature as compared with compounds **1**−**3** was the observation of two doublets for vinyl protons at δ 6.72 and 6.18 (J = 10 Hz). The double bond was assigned the *Z* configuration and to the C-4 and C-5 positions based on the coupling constants and multiplicity of its protons. The ^{13}C NMR (500 MHz) spectrum revealed signals for 17 carbons (Table 2). Signals for two quaternary carbons at δ 62.3 and 58.2 were attributed to the presence of an epoxy group, which must be located between C-6 and C-7 and should be in a pseudoaxial position. $^1H-^1H$ COSY experiments revealed an H-8 to-H-10 spin system and a terminal vinyl group. The protonated carbons were assigned by an HMQC experiment. The EI mass spectrum gave a molecular ion peak at *m/z* 278 and significant fragment ions at *m/z* 113 $[C_6H_9O_2]^+$ and 165 [M − $C_6H_9O_2]^+$, which were indicative for the location of the acetoxyl group at C-3. On the basis of these spectral data, the epoxide **4** was identified as acetic acid 1-methyl-3-(2,2,6-trimethyl-7-oxa-bicyclo[4.1.0]hept-1-yl)-1-vinyl-allyl ester.

Compounds **5** and **6** were identified as α-snyderol and α-snyderol acetate, respectively, by comparison of their spectroscopic properties with literature data.[11,13]

Compounds **1**−**5** were tested for their antimalarial potential, using a single dose against the chloroquine-sensitive D6 strain of *Plasmodium falciparum*. Only compound **1** inhibited a high percentage (90%) of parasite growth, and so a dose−response assay was carried out with this compound on the chloroquine-sensitive clone D6 and chloroquine-resistant clone W2 of *P. falciparum*. Compound **1** showed moderate activity, with IC_{50} values of 2700 and 4000 ng/mL against the D6 and W2 clones, respectively. The IC_{50} values of artemisinin (as a control) were 2.8 ng/mL for D6 and 1.1 ng/mL for W2. The compounds were also tested for cytotoxicity against a panel of cell lines, but none of them were found to be active.

Experimental Section

General Experimental Procedures. Optical rotations were measured with an Optical Activity polarimeter. IR spectra (NaCl) were obtained on a Perkin-Elmer 1600 FT-IR. ^1H NMR were recorded on either a Bruker AC 200L or a Varian 400 MHz spectrometer. ^{13}C NMR spectra and 2D experiments were recorded on a JEOL Eclipse 500 MHz spectrometer. ^{13}C NMR multiplicities were determined by using APT spectra. EIMS and HRMS were measured on a VG ZabSpec instrument.

Plant Material. *Laurencia obtusa* plant was collected in August 1999 at Bademli, north of Izmir. A dried voucher specimen is kept in the Department of Analytical Chemistry, Faculty of Pharmacy, Istanbul University, Istanbul.

Extraction and Isolation. Powdered and dried plant material (450 g) was macerated 10 times with $CHCl_3$−MeOH (2:1, v/v) at room temperature and evaporated under vacuum to give 15 g of extract. It was chromatographed on a silica gel column (35−70 mesh; 3.5 × 45 cm), using hexane with increasing amounts of EtOAc (v/v) as eluent, to afford 60 fractions, each of approximately 50 mL. Fractions 11−29 (hexane−EtOAc, 10:1) of extract were separated by preparative TLC on silica gel plates using a petroleum ether (50−70 °C)−ether (10:1) solvent system to give α-snyderol (**5**, 500 mg), α-snyderol acetate (**6**, 17 mg), and stigmasterol (3.6 mg). Fractions 30−43 (hexane−EtOAc, 5:1) were rechromatographed on a silica gel column (70−230 mesh; 1.5 × 20 cm) eluting with petroleum ether−ether (1:1) to afford a mixture of compounds **1** and **2**, which were purified by preparative TLC to give pure **1** (9 mg) and **2** (7 mg). Fractions 44−58 (hexane−EtOAc, 2:1) were separated by preparative TLC on silica gel using a CH_2Cl_2−acetone (9:1) solvent system to give compounds **3** (6 mg) and **4** (7 mg).

(8*R)-8-Bromo-10-*epi*-*β*-snyderol[(1′*R**,3′*R**,5′*R**)-5-(3,5′-dibromo-2′,2′-dimethyl-6′-methylenecyclohexyl)-3-methylpent-1-en-3-ol] (1):** $[\alpha]^{25}_D$ +137.5° (*c* 0.4, $CHCl_3$); IR (film) ν_{max} 3410, 2930, 1653, 1458, 1369, 1133, 996, 920, 758 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); (EIMS *m/z* (rel int) 299/301 $[M - Br]^+$ (1.9/1.3), 281 (11)/283 (6), 219 $[M - Br - HBr]^+$ (13.4), 201 $[M - Br - HBr - H_2O]^+$ (7.6), 149 (52.9), 121 $[M - 2\times Br - C_6H_{11}O]^+$ (27.7), 99 $[C_6H_{11}O]^+$ (72.1), 86 $[C_5H_{10}O^+]$ (87), 71 (100); HREIMS *m/z* 378.0176 (calcd for $C_{15}H_{24}Br_2O$ 378.0194).

(8*S)-8-Bromo-*β*-snyderol[(1′*R**,3′*S**,5′*S**)-5-(3′,5′-dibromo-2′,2′-dimethyl-6′-methylenecyclohexyl)-3-methylpent-1-en-3-ol] (2):** $[\alpha]^{25}_D$ +115.3° (*c* 0.2, $CHCl_3$); IR (film) ν_{max} 3418, 2923, 1647, 1458, 1363, 1128, 1010, 927, 743 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); (EIMS *m*/*z* (rel int) 299/301 $[M - Br]^+$ (1.7/1.0), 281 (12)/283 (7), 219 $[M - Br - HBr]^+$ (11.3), 217 (13.4), 201 $[M - Br - HBr - H_2O]^+$ (9.1), 149 (56), 121 $[M - 2\times Br - C_6H_{11}O]^+$ (26.3), 99 $[C_6H_{11}O]^+$ (76), 85 ($C_5H_9O^+$) (89), 71 (100).

5-Bromo-3-(3-hydroxy-3-methylpent-4-enylidene)-2,4,4-trimethylcyclohexanone (3): (optical rotation was not measured due to its small quantity); UV λ_{max} (ϵ) ($CHCl_3$) 234 (60) and 244 (242) nm; IR ν_{max} (KBr) 3455, 2940, 1720, 1660, 1375, 1270, 1120, 1080, 860 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); EIMS *m*/*z* (rel int) 296/298 $[M - H_2O]^+$ (1.3/1.2), 217 $[M - H_2O - HBr]^+$ (9.6), 177 (14), 163 (17.2), 149 (45.2), 107 (40.8), 99 $[C_6H_{11}O]^+$ (16), 97 (54), 95 (71.3), 85 $[C_5H_7O_2]^+$ (36), 81 (58.6), 77 (16), 71 (100).

Acetic acid 1-methyl-3-(2,2,6-trimethyl-7-oxa-bicyclo-[4.1.0]hept-1-yl)-1-vinyl-allyl ester (4): $[\alpha]^{25}_D$ −111.1° (*c* 0.03, $CHCl_3$); UV λ_{max} (ϵ) ($CHCl_3$) 247 (1470) and 261 (249); IR ν_{max} (KBr) 2940, 2910, 1735, 1660, 1620, 1460, 1400, 1380, 1245, 1100, 1055, 940, 845 cm^{-1}; ^1H NMR (see Table 1); ^{13}C NMR (see Table 2); EIMS *m*/*z* (rel int) 278 $[M]^+$ (22), 235 (25), 218 (56), 165 $[M - C_6H_9O_2]^+$ (52), 149 (52), 135 (47), 123 (69), 113 (73), 97 $[C_6H_9O]^+$ (80), 81 (100), 71 (93), 57 (84).

Antimalarial Assay. Antimalarial activity was evaluated against two *P. falciparum* clones (chloroquine-sensitive clone D6 derived from CDC Sierra Leone, and chloroquine-resistant clone W2 derived from CDC Indochina III), which were cultured continuously according to the method of Trager and Jensen.[14] Quantitative assessment of in vitro antimalarial activity was determined using the microculture radioisotope technique described previously.[15] Test compounds (Sigma, Chemical Co., St. Louis, MO) were dissolved in DMSO. Test compounds were assayed over a concentration range of 10 000−14 ng/mL, and artemisinin as a standard antimalarial agent was assayed over a concentration range of 63−0.09 ng/mL. *P. falciparum* cultures were added to the microtiter plate at a parasitemia of 0.5−1% and a hematocrit of 1%. Test plates were then incubated in a sealed chamber under an atmosphere of 5% O_2, 5% CO_2, and 90% N_2 at 37 °C for 24 h. Subsequently, 0.5 μCi $[^3H]$-hypoxanthine (NEN Research Products) was added to each well, and the plates were returned to the sealed chamber for an additional 18 h of incubation. The assay was terminated by harvesting the parasite culture onto a glass fiber filter (Wallac) using the Tomtec Mach III Harvestor (Wallac). The concentrations of test compounds and positive controls that inhibited parasite-specific $[^3H]$-hypoxanthine incorporation by 50% (IC_{50}) were determined using nonlinear regression analyses.

Cytotoxicity Assays. Isolated compounds were evaluated for their cytotoxic activity against a panel of cell lines [KB (human epidermoid carcinoma), LU1 (human lung carcinoma), Col 2 (human colon carcinoma), LNCaP (hormone dependent human prostate carcinoma)] as decribed previously;[16] ellipticine was used as a positive control.

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