Novel Cytotoxic, Alkylated Hydroquinones from *Lannea welwitschii*

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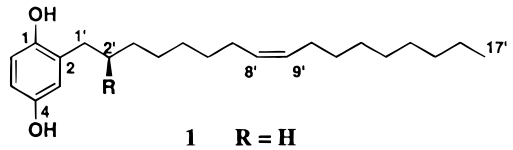
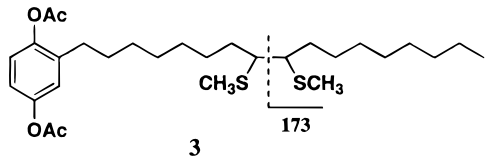
Two novel natural products, lanneaquinol (**1**) and 2′(*R*)-hydroxylanneaquinol (**2**), were isolated from the organic extract of the plant *Lannea welwitschii* (Hiern) Engl. Their structures were solved by spectroanalytical methods and confirmed by comparison to synthetic models. The absolute configuration of **2** was determined by the modified Mosher method. Both compounds exhibited modest cytotoxicity against the NCI panel of 60 human tumor cell lines. The structures of two isomeric 4,5-dihydroxy-5-alkyl-2-cyclohexenones (**7** and **8**), which appear to be biogenetic precursors of **1** and **2**, were also elucidated.

An organic extract of the plant *Lannea welwitschii* (Hiern) Engl. (family Anacardiaceae) was selected for bioassay-guided fractionation based upon modest potency and preliminary indications of an unusual pattern of differential cytotoxicity in the NCI 60-cell line, human disease oriented, in vitro tumor screen.[1,2] The crude CH_2Cl_2−CH_3OH (1:1) extract was subjected to a solvent−solvent partitioning protocol, which concentrated the antitumor activity in the CCl_4-soluble fraction. Sequential bioassay-guided chromatography on Sephadex LH-20 and Si gel gave two novel metabolites, lanneaquinol (**1**) and 2′(*R*)-hydroxylanneaquinol (**2**), in 1.0% and 0.2% of the crude organic extract, respectively.



1 R = H

2 R = OH



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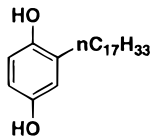
Results and Discussion

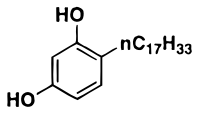
The molecular composition of lanneaquinol, $C_{23}H_{38}O_2$, was determined by HREIMS (*m*/*z* 346.2867), a composition also confirmed by CIMS and in accord with five degrees of unsaturation. The structure was elucidated mainly by interpretation of the spectral data, especially the ^{1}H- and ^{13}C-NMR and 2D-NMR spectra, and by spectral comparisons with synthetic analogues.

The UV absorption at λ_{max} 294 nm was indicative of a phenolic moiety. Examination of the ^{13}C NMR revealed an aromatic ring containing three protons, while the other substituents were two oxygen atoms (δ_C 149.2 and 147.3 ppm) and a carbon atom (δ_c 130.1 ppm). Further interpretation led to the conclusion that the ring was substituted by two phenol groups and by a linear alkyl chain of 17 carbons. This chain contained the remaining (disubstituted) double bond. In order to complete the structure elucidation, two points had to be solved: the substitution pattern of the aromatic ring and the location and geometry of the double bond in the alkyl side chain.

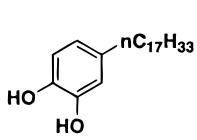
The ^{1}H NMR spectrum revealed that the three aromatic protons (a proton at δ 6.53 coupled ortho and meta, respectively, to protons resonating at δ 6.62 and 6.60) comprised a 1,2,4-trisubstituted system, which could be presented by three possible geometrical isomers (**1a**−**c**). A comparison of the spectral data of lanneaquinol and a synthetic analogue, 4-*n*-hexyl-1,3-dihydroxybenzene, quickly eliminated the possibility of **1b**. There were many chemical shift differences, especially in the ^{13}C-NMR spectrum, between the natural product and this 1,3-dihydroxybenzene ("resorcinol") derivative, for example, the resonances at δ_C 107.6 and 102.8 ppm, which had no corresponding signals in lanneaquinol (Table 1). On the other hand, spectral data alone could not readily differentiate between 2-alkyl-hydroquinone **1a** and the catechol derivative **1c** (4-alkyl-1,2-dihydroxybenzene).



1a



1b



1c

The first evidence that favored isomer **1a** over **1c** came from the HMBC experiment. All the correlations in isomer **1a** lay within the expected two and three bonds, while for **1c** some crucial connectivities could only be explained by less acceptable four-bond correlations. Two important examples were the correlations between one of the phenolic carbons (δ_C 149.2) and the

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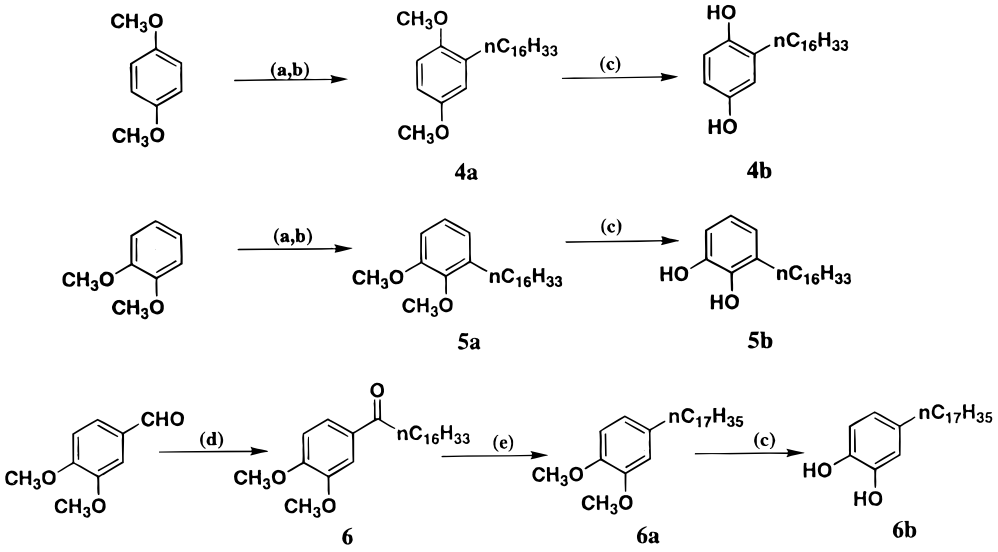
Table 1. NMR Data for Compounds **1** and **2**[a]

	^{13}C-NMR data			^{1}H-NMR data				
C#	δ (ppm)	mult.	HMBC	δ (ppm)	mult.	J (Hz)	COSY	NOE
			Lanneaquinol (**1**)					
4	149.2	C	6.62, 6.60, 6.53					
1	147.3	C	6.62, 6.53, 2.52					
2	130.1	C	6.62, 6.60, 2.52					
8′ & 9′	129.9, 129.8	CH		5.33	m, 2H		1.99	
3	116.8	CH	6.53, 2.52	6.60	d	2.9	6.53	2.52
6	116.0	CH		6.62	d	8.3	6.53	
5	113.3	CH	6.60	6.53	dd	8.3, 2.9	6.62, 6.60	
1′	30.1	CH_2	6.60	2.52	m, 2H	7.8	1.56	6.60, 1.56
7′ & 10′	27.3	2, CH_2	5.33	1.99	m, 4H		5.33, 1.2	
16′	22.7	CH_2		1.25	br s, 22H			
17′	14.2	CH_3		0.86	t, 3H	7.3	1.2	
			2′-Hydroxy-lanneaquinol (**2**)					
1	149.2	C	6.59, 6.52, 2.75, 2.69					
4	148.9	C	6.75					
8′ & 9′	130.2, 129.4	CH		5.33	m, 2H		1.99	
2	126.5	C	6.75, 3.94, 2.75, 2.69					
3	118.0	CH	6.53, 2.52	6.52	d	2.9	6.59	2.75, 2.69
6	117.8	CH	6.59	6.75	d	8.8	6.59	
5	114.7	CH	6.75, 6.52	6.59	dd	8.8, 2.9	6.75, 6.52	6.75
2′	74.5	CH	2.75, 2.69, 1.49	3.94	dddd	10.4, 7.3 6.5, 2.9	2.75, 2.69 1.49	
1′	38.9	CH_2	6.52, 3.94	2.75, 2.69	dd	14.5, 2.9	3.94	6.52, 3.94
					dd	14.5, 7.3		1.94
3′	36.9	CH_2	2.75, 2.69	1.49	m, 2H		3.94, 1.2	
7′ & 10′	27.3, 27.1	2, CH_2	5.33	1.99, 1.2	t, 4H	7.8	5.33, 1.2	
16′	22.7	CH_2	0.86	1.25	br s, 18H			
17′	14.1	CH_3		0.86	t, 3H	7.3	1.2	

[a] Recorded in $CDCl_3$.

Scheme 1[a]



[a] Key: (a) *n*-BuLi, THF; (b) *n*-$C_{16}H_{33}Br$; (c) BBr_3, CH_2Cl_2; (d) Mg, *n*-$C_{16}H_{33}Br$, THF; (e) NH_2NH_2, KOH.

benzylic protons (δ_H 2.52) and the aromatic proton at δ_H 6.53. These correlations could best be explained by **1a**.

Additional evidence favoring the hydroquinone came from difference NOE experiments. Irradiation of the signal of the benzylic protons at δ 2.52 enhanced only the signal of the proton at δ 6.60. This correlation would be expected for structure **1a**, while in **1c** it could be argued that an NOE to the aromatic proton at δ 6.53 might also be observed. However, this argument provided no discriminating evidence; therefore, in order to distinguish between the two possible isomers, the synthesis of analogues was undertaken.

Compound **4b**, the model for **1a**, was prepared using methodology developed for the synthesis of urushiol-related compounds[3] (see Scheme 1). 1,4-Dimethoxybenzene was alkylated under standard conditions (*n*-BuLi, *n*-$C_{16}H_{33}Br$). The resulting intermediate (**4a**) was then treated with BBr_3 to cleave the methyl ethers to provide the alkylhydroquinone **4b**. The catechol analogue **5b** was prepared in an analogous manner. For the synthesis of **6b**, however, a different approach was required. The starting material, 3,4-dimethoxybenzaldehyde, was treated with hexadecyl magnesium bromide under the conditions of the Grignard reaction in an attempt to produce the appropriate benzyl alcohol.[3] Quite unexpectedly, the main product was the alkyl aryl ketone **6** rather than the expected alcohol. The mass spectrum of **6**, which had a molecular ion at *m*/*z* 390 ($C_{25}H_{42}O_3$), also showed strong fragment ions at *m*/*z* 180 (100%) and 225 ($C_{16}H_{33}$), which could be attributed to a McLafferty rearrangement and cleavage α to the car-

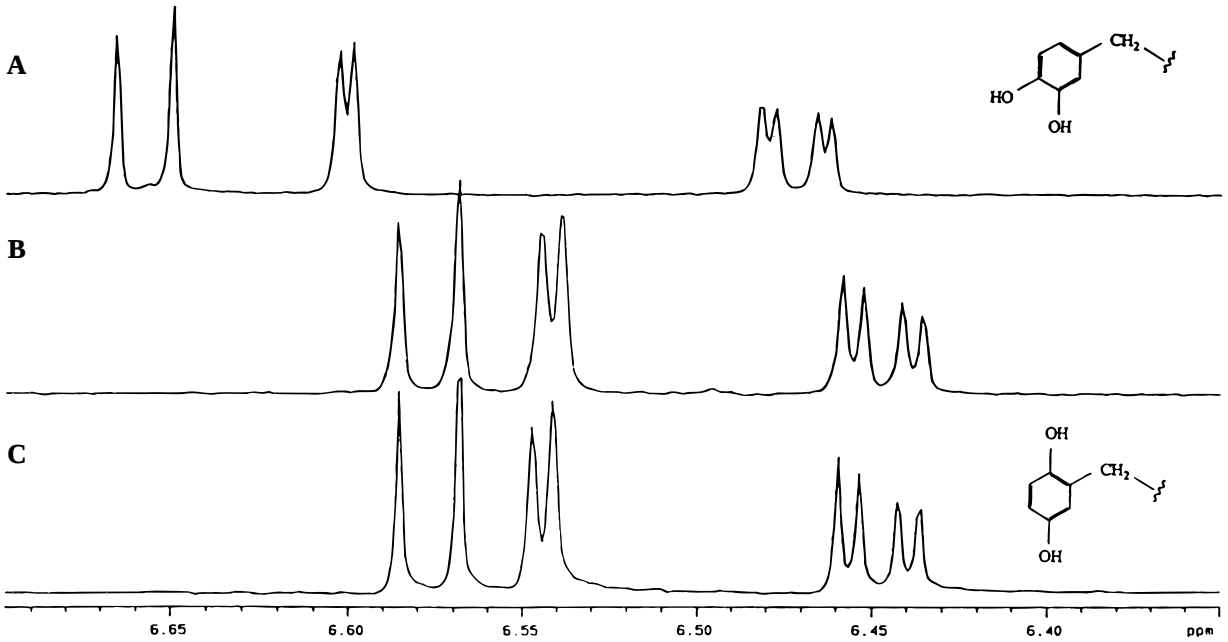


Figure 1. Comparison of the 1H-NMR spectra (aromatic region) of (A) 6b, (B) 4b, and (C) natural 1.

bonyl, respectively. The IR spectrum and the ^{13}C NMR (δ_C 199.2) were also indicative of the presence of a ketone. Therefore, Wolff−Kishner reduction of the carbonyl to **6a** and cleavage of the methoxy groups by reaction with BBr_3 completed the synthesis of the desired 4-heptadecyl-1,2-dihydroxybenzene (**6b**) (Scheme 1). The NMR spectra of **4b** and **6b** showed many similar chemical shifts, and only careful comparison between the ^1H- and the ^{13}C-NMR spectra of both compounds with lanneaquinol (see Figure 1 and Experimental Section) finally confirmed that the natural product indeed had the hydroquinone regiochemistry, as in structure **1a**.

The location of the extra double bond on the linear alkyl side chain was determined as $\Delta^{8',9'}$ by mass spectrometric techniques. The FABMS (negative ion) of **1** gave intense peaks at *m/z* 345 (M − H), 259 (M − H − C_6H_{14}), and 191 (M − H − $C_{11}H_{22}$). These latter two fragmentations, namely the cleavage of a saturated six-carbon unit and an unsaturated C_{11} fragment, revealed that the double bond was located between C7′ and C11′ of the side chain.

Lanneaquinol was then acetylated and treated with dimethyl disulfide, which added to the double bond to give compound **3**.[4−6] The EIMS of the latter molecule (*m/z* 524, M^+, $C_{29}H_{48}O_4S_2$) showed an intense fragment ion corresponding to cleavage of $C_{10}H_{21}S$. This clearly revealed that the double bond was originally located between the tenth and eleventh carbons from the terminal methyl group, namely at C8′−C9′.

The second isolated cytotoxic compound was slightly more polar than lanneaquinol; its composition, $C_{23}H_{38}O_3$, was established by HREIMS. Comparing the spectral data of **2** with **1** clearly showed that both compounds were very similar with respect to the aromatic ring and the alkyl moiety with only one exception, the presence of secondary hydroxyl group on the alkyl side chain. The data for the latter group included an IR absorption at 3592 cm^{-1} a proton chemical shift at δ 3.94 and a D_2O exchangeable proton (δ 7.75), and the observed δ_C 74.9 in the ^{13}C-NMR spectrum. The COSY spectrum (Table 1) showed distinct correlations between the signal at δ 3.94 and the two benzylic protons (δ 2.75 and 2.69), and, most importantly, the HMBC spectrum showed a three-bond correlation to one of the aromatic carbons (δ_C 126.5), thereby confirming that the OH group was located in the homobenzylic position (C2′). The absolute configuration at this carbon was determined to be *R* by a modified Mosher method.[7]

The natural products **1** and **2** and their synthetic analogues were all evaluated in the NCI primary antitumor screen.[1,2,8] The mean panel GI_{50} value [2] for **1** and **2** was approximately 1 μM. The range of differential sensitivity of the panel cell lines was 5−10-fold; the mean-graph profiles were otherwise unremarkable. None of the *O*-methyl compounds (**4a**, **5a**, **6**, and **6a**) had any significant differential cytotoxicity.

The most active compound among the three geometrical isomers **4b**, **5b**, and **6b** was indeed the 2-alkyl-1,4-dihydroxybenzene (**4b**), and the activity of **4b** was virtually identical to that of lanneaquinol. The biological testing suggested that the activities of **1** and **2** resulted from the 2-alkyl-1,4-dihydroxybenzene framework and that the actual length of the side chain or the presence of a double bond therein was less important. Alkylated phenols have previously been shown to be cytotoxic. In a study of natural antimutagenic agents, Wall reported that cymopol (2-bromo-5-geranyl hydroquinone) was quite toxic,[9] while the Hecht group has reported the DNA-cleaving activity of 5-alkyl resorcinols.[10,11]

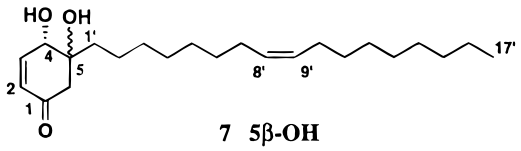
Another Sephadex LH-20 fraction from the CCl_4-soluble portion, which showed moderate activity in the antitumor screen, was further separated by several consecutive column chromatographies on Si gel and flash chromatography on cyano-bonded phase bulk packing. This separation led to the isolation of two diastereomers, **7** and **8**, which were similar in several aspects to lanneaquinol and 2′-hydroxylanneaquinol and may be their biosynthetic precursors. The molecular composition of both compounds, $C_{23}H_{40}O_3$, was determined by high-resolution mass spectrometry. The four

Table 2. NMR Data for Compounds **7** and **8**

	^{13}C-NMR data			^{1}H-NMR data				
C#	δ (ppm)	mult.	HMBC	δ (ppm)	mult.	J (Hz)	COSY	NOE
			Dihydroxyketone **7**					
1	197.7	C	6.82, 2.78, 2.41					
3	149.2	CH	4.50	6.82	dd	10.3, 2.9	6.01, 4.50	6.01, 4.50
2	129.7	CH	4.50	6.01	ddd	10.3, 2.2 0.9	6.82, 4.50	6.82
8′ & 9′	130.0, 129.7	CH	1.98	5.31	m, 2H		1.98	
5	77.1	C	6.82, 4.50, 2.78, 2.41, 1.66, 1.52					
4	74.2	CH	6.01, 2.78, 2.41, 1.66, 1.52	4.50	br s		6.62, 6.01 2.41	6.82, 2.41
6	47.6	CH_2	1.66	2.78	d	15.9	2.41	2.41
				2.41	dd	15.9,0.9	4.50, 2.78	4.50, 2.78
1′	32.9	CH_2	4.50, 2.41, 1.66, 1.52	1.66	m	16, 12, 6	1.52, 1.26	4.50
				1.52	m	16, 10, 7	1.66, 1.26	no NOE
16′	31.9	CH_2	0.86	1.26	m, 22H			
17′	14.1	CH_3		0.86	t, 3H	7	1.26	
			Dihydroxyketone **8**					
1	197.3	C	6.72, 2.66, 2.47					
3	149.0	CH	4.34	6.72	dd	10.3, 2.4	6.03, 4.34	6.03, 4.34
2	129.3	CH	4.34, 2.66	6.03	dd	10.3, 1	6.72, 4.34	6.72
8′ & 9′	130.0, 129.7	CH	1.98	5.32	m, 2H		1.98	
5	76.5	C	6.72, 2.66, 2.47 w					
4	70.5	CH	6.03, 2.66, 2.47 w	4.34	t	2.4	6.72, 6.03	6.72, 2.47
6	46.8	CH_2	6.03	2.66	dd	16.3, 1	2.47	2.47
				2.47	d	16.3	2.66	4.34, 2.66
1′	38.8	CH_2	4.34, 2.66	1.65	m		1.26	4.34, 2.66, 2.47
				1.50	m		1.26	no NOE
16′	31.9	CH_2	0.86	1.26	br m, 22H			
17′	14.1	CH_3		0.86	t, 3H	7	1.26	

[a] Recorded in $CDCl_3$.

degrees of unsaturation were in agreement with the ^{1}H- and ^{13}C-NMR spectra, which showed only two double bonds and a carbonyl group, and, therefore, lacked the aromatic ring of **1** and **2**. The structure elucidation was based on the interpretation of the spectral data, especially the 1D and 2D NMR. A comparison between lanneaquinol and **7** revealed that the side chain was similar in both compounds, and the difference lay only in the six-membered ring. This ring in **7** is composed of an α,β-unsaturated ketone (carbonyl at δ_C 197.7 ppm, two coupled olefinic protons at δ 6.82 and 6.01), a secondary hydroxy group (δ 4.50, coupled in the HMQC experiment to the carbon at δ 74.2), and a tertiary alcohol (δ_C 77.1). Besides these functional groups, there was a ring methylene carbon (δ_C 47.6 ppm), which was coupled (HMQC) to two protons at δ 2.78 and 2.41. The structure and substitution of the cyclohexenone moiety were established by COSY and HMBC experiments (see Table 2). The former experiment established that the secondary alcohol was allylic, while all the HMBC connectivities, including the highly important one between the protons α to the carbonyl (δ 2.78 and 2.41) and one of the side-chain methylenes (δ_C 32.9 ppm), established the structure as **7**. The position and geometry of the olefinic bond in the side chain were determined as described for **1** and **2**.



7 5β-OH
8 5α-OH

Compound **8** was a diastereomer of **7** and differed only in the stereochemistry at C5. The main changes in the ^{13}C-NMR spectra were found at the region of C4 ($\Delta\delta$ = δ_C**7** − δ_C**8** = 3.7 ppm), C5 ($\Delta\delta$ = 0.6 ppm), C6 ($\Delta\delta$ = 0.8 ppm), and C1′ ($\Delta\delta$ = −5.9 ppm), while the chemical shift differences for all the other carbon pairs were ≤0.4 ppm.

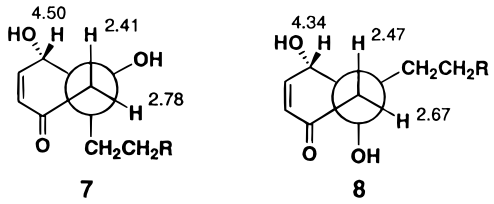


Figure 2. Relative stereochemistry of 7 and 8.

The relative stereochemistry of the two isomers was established by difference NOE experiments. In both **7** and **8**, an NOE was observed between H-4 and one of the H-6 protons (e.g., δ 2.41 in **7**), indicating a pseudo-axial disposition of H-4. In **8**, an additional NOE was detected between one of the C-1′ methylene protons (δ 1.65) and both H-6 protons (δ 2.66 and 2.47), revealing that the alkyl ring substituent was equatorial. Thus, the hydroxyl groups were *cis*-oriented in **8** (4*S**, 5*R** relative stereochemistry) and, by inference, *trans*-oriented in **7** (4*S**, 5*S**), as shown in Figure 2. The absolute configurations of **7** and **8** have not been defined.

Dihydroxy ketone **8** is a potential biogenetic precursor of lanneaquinol (**1**). The *trans*-anti-parallel configuration of H-4 and OH-5 in **8** suggests an easy elimination of water; subsequent keto−enol tautomerism at C-1 would lead to the aromatic product **1**. This phenomenon was indeed observed when compound **8** was left for several weeks in an NMR tube (in $CDCl_3$); **8** was partially transformed to lanneaquinol. This transformation also occurred, but to a much lesser extent, with **7**; after 1 year, only a small fraction of the compound was transformed to **1**. This observation may explain

the moderate cytotoxicity of **7** and **8**, the result of partial *in situ* transformation into the more potent lanneaquinol.

Experimental Section

General. Experimental Procedures: NMR spectra were recorded on a Varian VXR-500 spectrometer using $CDCl_3$ and CD_3OD as solvents and internal standards. IR spectra were measured on a Perkin-Elmer 267 and Nicolet 5MX spectrometers; UV spectra were obtained with a Beckman 34 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. MS were recorded on VG Micromass ZAB 2F and JEOL SX-102 mass spectrometers. Elemental analyses were carried out on a Carlo-Erba NA-1500 analyzer.

Plant Material. Fruits, leaves, stems, and twigs of *L. welwitschii* (Hiern) Engl. were collected by D. Thomas, under contract to the National Cancer Institute, near Mundemba, Cameroon, in March 1987. The plant was identified by L. Aké Assi; a voucher specimen (Q66P-6785) is maintained at the Missouri Botanical Garden. Extraction of 558 g of dried, ground plant material with CH_2Cl_2−MeOH (1:1) and MeOH yielded 18.22 g of crude extract.

Isolation of Compounds 1 and 2. The crude organic extract (14.04 g) of *L. welwitschii* was partitioned by the following protocol: distribution between 90% aqueous MeOH and hexane (affording 5.89 g), 80% aqueous MeOH and CCl_4 (1.91 g), and 70% MeOH−H_2O and $CHCl_3$ (1.00 g). The MeOH was then removed from the aqueous phase, which was subsequently extracted with EtOAc to give 1.11 g; finally, lyophilization of the H_2O phase gave a residue of 2.07 g. Cytotoxic activity was concentrated primarily in the CCl_4 fraction. This fraction was subjected to gel permeation through a Sephadex LH-20 column (elution with 2:1:1 CH_2Cl_2−MeOH−hexane), followed by Si gel column chromatography of the most active fraction (109 mg; elution with a mixture of hexane−EtOAc). This chromatography gave pure **1** (59 mg) and **2** (19 mg) as amorphous solids.

Lanneaquinol (1): UV (MeOH) λ_{max} nm (log ϵ) 294 (3.52), 218 (3.71), and 205 (4.00); IR (CH_2Cl_2) ν_{max} 3589, 2928, 1503, 1260, 1174, 750 cm^{-1}; HREIMS *m/z* 346.2867 (M^+, calcd for $C_{23}H_{38}O_2$, 346.2872); EIMS *m/z* (rel abundance): 346 (M^+, 96), 163 (10), 151 (10), 123 (100); ^{13}C NMR ($CDCl_3$) δ 149.2, 147.3, 130.1, 129.9, 129.8, 116.8, 116.0, 113.3, 31.9, 30.1, 29.8 (× 2), 29.7, 29.55, 29.50, 29.46, 29.36, 29.34, 29.28, 27.3 (× 2), 22.7, 14.2; for ^1H NMR, see Table 1.

2′-*R*-Hydroxylanneaquinol (2): $[\alpha]_D$ + 0.8° (*c* 1.24, $CHCl_3$); UV (MeOH) λ_{max} nm (log ϵ) 295 (3.46), 227 (3.57), 218 (3.68), 204 (4.10); IR (CH_2Cl_2) ν_{max} 3592, 2928, 2856, 1499, 1239, 1174, 750 cm^{-1}; HREIMS *m/z* 362.2824 (M^+, calcd for $C_{23}H_{38}O_3$, 362.2821); EIMS *m/z* (rel abundance) 362 (M^+, 20), 344 (22), 124 (96), 123 (40), 69 (100); ^{13}C NMR ($CDCl_3$) δ 149.2, 148.9, 130.2, 129.4, 126.5, 118.0, 117.8, 114.7, 74.5, 38.9, 36.9, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 29.1, 27.3, 27.1, 25.6, 22.7, 14.1; for ^1H NMR, see Table 1.

Isolation of Compounds 7 and 8. Several fractions from the Sephadex LH-20 chromatography of the CCl_4 fraction showed moderate in vitro activity in the antitumor screen. These fractions (a total of 1.03 g) were combined and subjected to a flash chromatography over Si gel and subsequent column chromatography on cyano-bonded phase (elution with hexane−*i*-PrOH), leading to the isolation of two additional compounds, **7** (16 mg) and **8** (9 mg). Both compounds were obtained as colorless, viscous oils.

Compound 7: $[\alpha]_D$ −51.5° (*c* 0.54,$CHCl_3$); UV (MeOH) λ_{max} nm (log ϵ) 294 (2.81), 215 (3.82), 204 (3.88); IR (neat) ν_{max} 3418 (br), 2924, 2854, 1674, 1456, 1259, 1075 cm^{-1}; HREIMS *m/z* 364.2930 (M^+, calcd for $C_{23}H_{40}O_3$, 364.2977); EIMS *m/z* (rel abundance) 364 (M^+, 20), 346 (44), 328 (M^+− 2 H_2O, 5), 265 (13), 123 (25), 111 (37), 84 (100), 69 (22), 55 (33); ^{13}C NMR ($CDCl_3$) δ 197.7, 149.2, 130.0, 129.73, 129.66, 77.1, 74.2, 47.6, 32.9, 31.9, 30.0, 29.75, 29.70, 29.50, 29.44, 29.30, 29.29, 29.20, 27.21, 27.16, 22.7, 22.4, 14.1; for ^1H NMR, see Table 2.

Compound 8: $[\alpha]_D$ +23° (*c* 0.9,$CHCl_3$); UV(MeOH) λ_{max} nm (log ϵ) 290 (3.21), 217 (3.82), 204 (3.83); IR (neat) ν_{max} 3408 (br), 2928, 2854, 1674, 1466, 1378, 1258, 1157, 1069, 833, 723 cm^{-1}; HREIMS *m/z* 364.2978 (M^+, calcd for $C_{23}H_{40}O_3$, 364.2977); EIMS *m/z* (rel abundance) 364 (M^+, 19), 346 (41), 328 (9), 265 (13), 123 (22), 111 (41), 84 (100), 69 (22), 55 (34); ^{13}C NMR ($CDCl_3$) δ 197.3, 149.0, 130.0, 129.7, 129.3, 76.5, 70.5, 46.8, 38.8, 31.9, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3 (× 2), 29.2, 27.20, 27.18, 23.6, 22.7, 14.1; for ^1H NMR, see Table 2.

2-Hexadecyl-1,4-dimethoxybenzene (4a). All the reactions were done solely to prepare small samples of the products and therefore were not optimized. The reactions were run under N_2 with magnetic stirring.

A 100-mL three-necked, round-bottomed flask, equipped with a reflux condenser and a funnel for addition of reagents, was charged with 2.33 g (16.9 mmol) of 1,4-dimethoxybenzene and 30 mL of dry THF. The solution was cooled to 0 °C, and 8 mL of 1.6 M *n*-BuLi (in hexane, 12.8 mmol) was added dropwise over 10 min. The reaction mixture was stirred for 30 min and then refluxed for 90 min. Then the flask was cooled to room temperature, a mixture of *n*-hexadecyl bromide (2.585 g, 8.5 mmol) in dry THF (7 mL) was added slowly over 15 min, and the reaction mixture was refluxed for another 90 min. The solvents were evaporated, and the white solid residue was dissolved in Et_2O−H_2O (1:1, 100 mL). The phases were separated, the aqueous residue was extracted with Et_2O (2 × 80 mL), and the organic fractions were combined, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting product (2.93 g) contained a mixture of **4a** and 1,4-dimethoxybenzene. Crystallization from 95% EtOH (with a few drops of Et_2O) gave 2.46 g of **4a** (> 95% purity) in the first crop of crystals (80% yield). Compound **4a**: mp 45 °C; HREIMS *m/z* 362.3175 (calcd for $C_{27}H_{42}O_2$, 362.3185); ^1H NMR ($CDCl_3$) δ 6.74 (d, J = 8.8 Hz), 6.71 (d, 2.9), 6.66 (dd, 8.8,2.9), 3.76 (s, 3H), 3.74 (s, 3H), 2.54 (m, 2H), 1.52 (m, 2H), 1.26 (m, 26H), 0.86 (t, 3H, 7); ^{13}C NMR ($CDCl_3$) δ 153.4 (× 2), 132.7, 116.2, 111.2, 110.5, 56.0, 55.6, 31.9, 30.2−29.4 (13C), 22.7, 14.1.

2-Hexadecyl-1,4-hydroquinone (4b). Compound **4a** (1.45 g, 4.0 mmol) was dissolved in CH_2Cl_2 (30 mL) in a three-necked flask under N_2. The solution was cooled to 0 °C and 8 mL of BBr_3 (in CH_2Cl_2) was added dropwise over 15 min. The reaction mixture was stirred for 45 min at 0 °C and 4 h at room temperature. The reaction was quenched with H_2O, the phases were separated, and the organic portion was washed with H_2O (2 × 100 mL), then with 10% Na_2CO_3 (100 mL),

and finally with H_2O. The CH_2Cl_2 phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. Only 300 mg of **4b** were obtained in a pure form as a tan solid: mp 114 °C; HREIMS *m/z* 334.2866 (calcd for $C_{22}H_{38}O_2$, 334.2872); ^{1}H NMR (1:1 $CDCl_3$−CD_3OD) δ 6.28 (d, J = 8.3 Hz), 6.24 (d, 2.9), 6.15 (dd, 8.3,2.9), 2.19 (m, 2H), 1.23 (m, 2H), 0.92 (m, 26H), 0.54 (t, 3H, J = 7); ^{13}C NMR (1:1 $CDCl_3$−CD_3OD) δ 149.0, 147.1, 129.9, 116.0, 115.0, 112.2, 31.3, 29.6−28.7 (13C), 22.0, 13.2; *anal.* C 79.10%, H 11.40% (calcd C 78.99%, H 11.45%).

3-Hexadecyl-1,2-dihydroxybenzene (5b). The same procedures used for preparation of **4a** and **4b** were applied. 1,2-Dimethoxybenzene (veratrole, 2.36 g) was reacted with *n*-BuLi and then with 1.80 g of *n*-hexadecylbromide to give a mixture of **5a** and starting material (3.12 g). This fraction was separated by column chromatography to give 1.1 g of 3-hexadecyl-1,2−dimethoxybenzene (**5a**): mp 36 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (t, J = 8 Hz), 6.80 (d, 8), 6.79 (d, 8), 3.88 (s, 3H), 3.86 (s, 3H), 2.66 (t, 8, 2H), 1.62 (m, 2H), 1.28 (m, 22H), 0.92 (t, 3H, 7); ^{13}C NMR ($CDCl_3$) δ 151.6, 146.0, 135.7, 122.6, 120.8, 108.8, 59.5, 54.5, 30.9, 29.8, 28.8−28.3 (12C), 21.7, 13.1; *anal.* found C 79.65%, H 11.03% (calcd C 79.50%, H 11.68%).

3-Hexadecyl-1,2-dimethoxybenzene (226 mg, 0.62 mmol) was then dissolved in CH_2Cl_2 and treated with BBr_3 as described for **4b**. 3-Hexadecylcatechol (**5b**, 207 mg) was obtained as a solid: mp 44−45 °C; ^{1}H NMR ($CDCl_3$) δ 6.72 (3H, m), 5.37 and 5.26 (br s, OH), 2.61 (t, 8, 2H), 1.62 (m, 2H), 1.27 (m, 26H), 0.90 (t, 3H, J = 7); ^{13}C NMR ($CDCl_3$) δ 143.0, 141.8, 129.4, 122.1, 120.1, 112.9, 31.9, 29.8−29.4 (13C), 22.7, 14.1; IR (KBr) ν_{max} 3368 (br), 2917, 2845, 1468, 1282, 1192, 959, and 726 cm^{-1}; *anal.* found C 79.01%, H 11.13%, (calcd for C 78.99%, H 11.45%).

3,4-Dimethoxyphenyl *n*-Heptadecyl Ketone (6). A 250-mL three-necked flask, equipped with a reflux condenser and a funnel for the addition of reagents, was charged with 0.24 g of magnesium turnings, 15 mL of dry THF, a few crystals of I_2. and a magnetic stirring bar. A solution of *n*-hexadecyl bromide (3.05 g, 10 mmol) in dry THF (15 mL) was introduced into the funnel, and about one quarter of this solution was added into the reactor under a stream of N_2. The reaction was initiated by heating the mixture gently with a heat gun. The rest of the alkyl bromide solution was added dropwise, and the reaction advanced very slowly, as observed by the consumption of the Mg turnings (ca. 4 h). Then a mixture of 3,4-dimethoxybenzaldehyde (1.66 g, 10.0 mmol) in dry THF (15 mL) was added gradually over 20 min, and the reaction mixture was refluxed gently for 20 h. The reaction was quenched by the addition of 1 M HCl (5 mL); the THF was evaporated, $CHCl_3$ was added, and the phases were separated. The organic phase was washed with 1 M HCl and then H_2O, dried over anhydrous Na_2SO_4, and then evaporated to dryness. The resulting product, which solidified upon standing, was separated by column chromatography to give 1.52 g (39%) of the unexpected product **6**. All the fractions were examined by NMR, and none contained the expected Grignard product. The only other product isolated was 3,4-dimethoxybenzyl alcohol (**6**): ^{1}H NMR ($CDCl_3$) δ 7.57 (dd, J = 8.3,2 Hz), 7.52 (d, 2), 6.87 (d, 8.3), 3.93 (s, 3H), 3.92 (s, 3H), 2.90 (m, 2H), 1.70 (m, 2H), 1.24 (m, 26H), 0.86 (t, 3H, 7); ^{13}C NMR ($CDCl_3$) δ 199.2, 153.0, 148.9, 130.3, 122.6, 110.1, 109.9, 56.0, 55.9, 38.1, 31.9, 29.6−29.3 (11C), 24.7, 22.6, 14.1; EIMS *m/z* 390 (M^+, $C_{25}H_{42}O_3$), 180 (100), 165.

Wolff−Kishner Reduction of 6. Compound **6** (450 mg) and KOH (250 mg) were dissolved in diethylene glycol (10 mL) in a 100-mL flask. The temperature was raised to 80 °C, and hydrazine hydrate (400 μL) was added. Then the temperature was raised to 175 °C. After 75 min, when TLC indicated total consumption of **6**, the reaction was cooled to room temperature, H_2O (10 mL) was added, and the organic materials were extracted with $CHCl_3$. The $CHCl_3$ fraction, containing most of the diethylene glycol, was dried over anhydrous Na_2SO_4 and evaporated to give 1.43 g of oily product. This material was subjected to flash chromatography on Si gel. Elution with hexane−EtOAc (19:1) afforded 123 mg (28% yield) of pure 4-heptadecyl-1,2-dimethoxybenzene (**6a**): ^{1}H NMR($CDCl_3$) δ 6.80 (d J = 8 Hz), 6.71 (d, 8), 6.70 (s), 3.87 (s, 3H), 3.86 (s, 3H), 2.55 (m, 2H), 1.60 (m, 2H), 1.25 (m, 28H), 0.88 (t, 3H,7); ^{13}C NMR ($CDCl_3$) δ 148.7, 146.9, 135.6, 120.1, 111.7, 111.1, 55.9, 55.7, 35.6, 31.9, 31.7, 29.7−29.3 (12C), 22.7, 14.1.

4-Heptadecyl-1,2-dihydroxybenzene (6b). Compound **6a** (112 mg, 0.3 mmol) was converted to **6b** by reaction with excess of BBr_3 (1 mmol) in CH_2Cl_2 as described above for **4b**. After the usual workup, 98 mg (95% yield) of **6b** were obtained as a white crystalline material. Crude **6b** was recrystallized from EtOAc−hexane to give 82 mg of highly purified product (**6b**): mp 95−96 °C; IR (KBr) ν_{max} 3452, 3349 (br), 2945, 2847, 1518, 1470, 1276, 979, 931, 813 and 716 cm^{-1}; HREIMS *m/z* 348.3016 (M^+, calcd for $C_{23}H_{40}O_2$, 348.3028); ^{1}H NMR (1:1 $CDCl_3$−CD_3OD) δ 6.66 (d, J = 8 Hz), 6.60 (d, 2), 6.47 (dd, 8, 2), 2.42 (m, 2H), 1.50 (m, 2H), 1.25 (m, 28H), 0.83 (t, 3H, 7); ^{13}C NMR (1:1 $CDCl_3$−CD_3OD, partial) δ 145.1, 143.1, 135.5, 120.3, 116.0, 115.7, 112.2; *anal.* found C 78.72%, H 11.69%, calcd C 79.25%, H 11.57%).

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