Antiplasmodial Lanostanes from the *Ganoderma lucidum* Mushroom

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In a screen of 880 extracts from plants and fungi for antiplasmodial, antitrypanosomal, and leishmanicidal activity, an ethyl acetate extract of the mushroom *Ganoderma lucidum* showed antiplasmodial activity with 79% inhibition at 4.9 μg/mL. HPLC-based activity profiling and subsequent isolation of the antiplasmodial compounds yielded seven lanostanes (**1**−**7**), of which three (**2**, **3**, and **7**) were new. A new benzofuran derivative (**8**) of the farnesyl hydroquinone ganomycin B was also identified. The structures and relative configurations of the new compounds were elucidated by comprehensive spectroscopic analysis and by comparison of their NMR data with those of related compounds. The lanostanes exhibited in vitro antiplasmodial activity with IC_{50} values from 6 to greater than 20 μM.

Lingzhe has been used in traditional Chinese medicine (TCM) for thousands of years and is one of the best studied mushrooms in the world. Of the 365 remedies listed in the epochal 2200-year-old Shen Nong Ben Cao—a foundation of TCM—lingzhe lists first among the "superior herbs", that is, the class of remedies that may be taken every day for a long period of time. It used to be called the "ten thousand year mushroom" because it was so scarce,[1] but since methods of cultivation were developed in Japan, Taiwan, and China in the 1970s and 1980s, trade with this mushroom has developed into a million dollar business.[2] This abundant source also fueled scientific interest, which really took off in the past few years. A recent search for "Ganoderma" in SciFinder Scholar retrieved more than 6500 publications, of which roughly half were written in Chinese, and indicates the mushroom's significance there. Over the years medicinal qualities such as anticancer, antiaging, and anti-HIV properties have been attributed to it. The most commonly traded and studied remedy referred to as "lingzhe" consists of the fruiting bodies of *Ganoderma lucidum* (Curtis) P. Karst (Polyporaceae) and various kinds of extracts made from them, as well as fungal products obtained in submerged culture. A number of other species are also used.[3,4] A large number of natural products have been described from these taxonomically ill-defined sources. Most prominent are the ganoderic acids, a class of lanostane triterpenoids of which more than 200 have been reported.[3] We recently established an HPLC-based activity profiling protocol enabling efficient localization of antiplasmodial, antitrypanosomal, and leishmanicidal activity.[5,6] Complex extracts can be effectively separated and tested by applying just 350 μg of sample to analytical HPLC separation with automated one-minute microfractionation in microwell plates. We have previously developed and successfully applied HPLC-based profiling protocols for the discovery of COX-2, 5-LOX, MAO-B, and iNOS inhibitors and $GABA_A$-receptor modulators.[7−11]

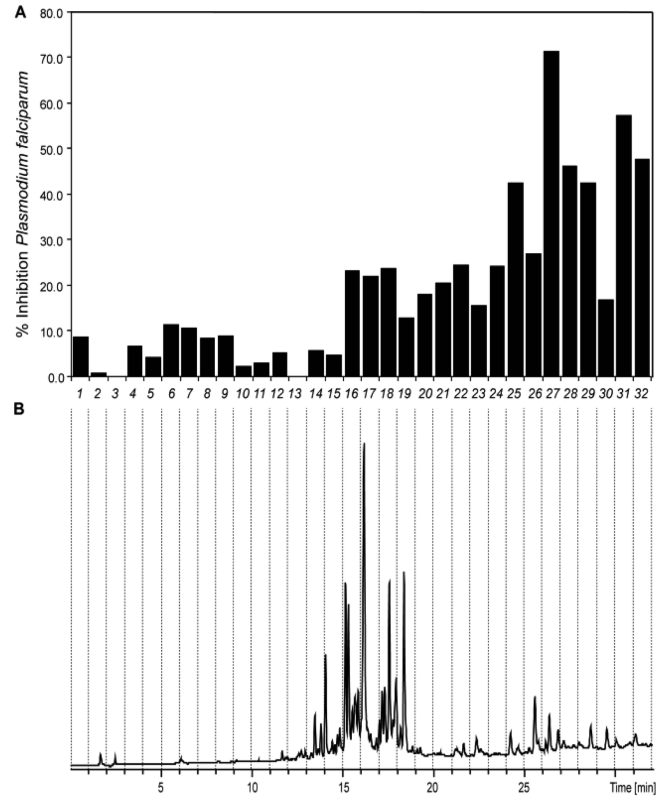

Figure 1. HPLC-MS trace (ESI positive, TIC *m*/*z* 200−1500) of the EtOAc extract of *Ganoderma lucidum* and the activity of the one-minute microfractions tested against *Plasmodium falciparum.*

Results and Discussion

In a recent screen of an in-house library of 880 plant and fungal extracts an ethyl acetate extract of lingzhe mushrooms showed antiplasmodial activity with 79% inhibition at 4.9 μg/mL.[5] The extract was microfractioned, and one-minute fractions were retested. Alongside the fractionation, online spectroscopic data (PDA, low- and high-resolution MS) were collected. Many of the substances in the very complex chromatogram were identified by analysis of data and comparison with literature and natural product databank searches. The distribution of activity is shown in Figure 1 fitted over the chromatogram (UV 245 nm). Antiplasmodial activity was quite dispersed over the chromatogram, but the activity was not so much in the highly oxygenated (water extractable) ganoderic acids eluted in minutes 13−18 (identified by LCMS, data not shown), but rather in the more lipophilic lanostane derivatives in minutes 27 and 31. Molecular formulas derived from LC-TOFMS data showed that these compounds contained only three or four oxygen atoms. Substances from the two most active one-minute microfractions (27 and 31) were subsequently isolated.

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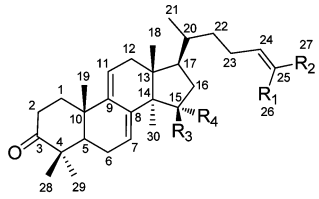
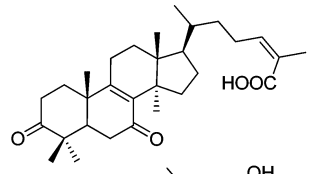


	R_1	R_2	R_3	R_4
1	COOH	CH_3	H	OH
2	CH_3	COOH	OH	H
3	CHO	CH_3	H	OH
4	COOH	CH_3	H	H



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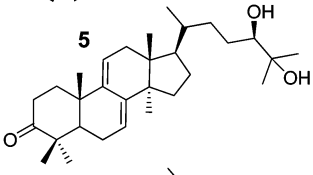

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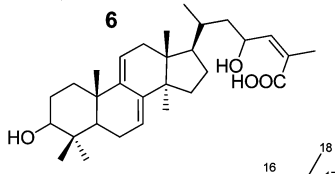

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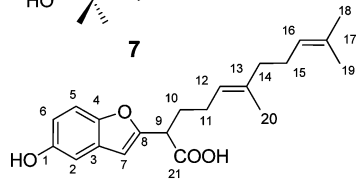

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Structure elucidations of lanostanes **1**−**7** were achieved by HR-MS-TOF data, MS-MS experiments, and NMR spectroscopy. ^{1}H and ^{13}C shifts are shown in Table 1 and in the Supporting Information. Relative configurations of the stereocenters were established by NOESY spectra. Structural differences between the lanostanes concerned the number and positions of double bonds and the state and positions of oxygenation. A structurally unrelated compound (**8**) was isolated because it raised our interest when we could not identify it online with our usual dereplication tools. It proved to also be a new natural product and substance class for *G. lucidum.*

Interpretation of the ^{1}H and ^{13}C NMR spectra and HSQC correlations (see Supporting Information) and comparison with literature data[12,13] led to the identification of **1** as ganoderic acid TR.

The molecular formula of **2** ($C_{30}H_{44}O_4$) and the UV spectra were comparable to those of **1**. ^{1}H and ^{13}C NMR spectra (Table 1) combined with HSQC correlations (see Supporting Information) showed the presence of one ketone, one carboxyl, six olefinic carbons, and four further quaternary carbons, as well as seven methyl, seven methylene, and four methine groups. Signals of a conjugated diene group at δ_C 116.4 (δ_H 5.31) (C-11), 120.4 (δ_H 5.83) (C-7), 140.5 (C-8), and 144.5 (C-9) were seen in the ^{13}C NMR spectrum. HMBC correlations confirmed a 7,9(11)-diene lanostane skeleton, as seen in **1**. Differences between the NMR spectra of compounds **1** and **2** were observed in the signals of the side chain. The ^{13}C chemical shift of the methyl carbon (δ_C 20.6, C-26) in **2** was significantly higher than in **1** (δ_C 12.1, C-27). Significant differences were also seen for the ^{1}H NMR shifts of the olefinic proton at C-24 (δ_H 6.84 in **1** compared to δ_H 5.99 in **2**). H-24 showed COSY coupling to the methyl at δ_H 1.84 (C-26). Altogether this indicated that in **2** the double bond of the side chain was *E*-configured. Another difference was seen in the ^{13}C chemical shift of C-30 (δ_C 25.18) from δ_C 17.02 in **1** which was α-oriented, suggesting β-configuration of the OH group in **2**. Substance **2** is therefore is the *E*-isomer of ganoderic acid TR (**1**) concerning the double bond in the side chain bearing a β-oriented hydroxy group at C-15. Given the close structural relationship to **1**, we named this new natural product ganoderic acid TR 1.

The molecular formula of compound **3** calculated from the high-resolution mass spectrum was $C_{30}H_{44}O_3$. Interpretation of the ^{1}H, ^{13}C, HSQC, and HMBC NMR spectra of **3** (Table 1 and Supporting Information) led to a structure closely related to compound **1**. However, C-26 had a shift of δ_C 195.0 (δ_H 9.42), which was indicative of an aldehyde. Thus, compound **3** was the aldehyde derivative of ganoderic acid TR (**1**), and we named this new compound ganoderic aldehyde TR.

The molecular formula of compound **4** was $C_{30}H_{44}O_3$. Interpretation of the ^{1}H, ^{13}C, HSQC, and HMBC NMR spectra (Supporting Information) showed that this was ganoderic acid S.[14]

By using HR-MS, ^{1}H, ^{13}C, HSQC, and HMBC and comparing with literature data,[15,16] compound **5** was identified as ganoderic acid DM, and **6** as ganodermanondiol, which had been previously reported from *G. lucidum*.

23-Hydroxyganoderic acid S (**7**) had a molecular formula of $C_{30}H_{44}O_4$. ^{13}C NMR chemical shifts of C-1 to C-21, and HSQC and HMBC correlations indicated that the compound had the same skeleton as **4**, with the difference being an OH group at C-3 (δ_C 79.0) instead of a carbonyl group. Methyl carbon C-27 (δ_C 13.6) and the olefinic proton H-24 (δ_H 5.42) indicated an *E*-configuration as in **1**. A hydroxyl moiety at C-23 (δ_H 4.0, δ_C 68.0) was deduced from its chemical shift and from HMBC correlation of HC-23 with C-24 (δ_C 127.1) and a cross-peak with H-24 (δ_H 5.42) in the COSY spectrum. The compound was thus a hitherto unknown derivative of ganoderic acid S (**4**). The configuration at C-23 was not assigned.

Compound **8** had a molecular formula of $C_{21}H_{23}O_4$. ^{1}H and ^{13}C NMR spectra and a DEPT edited HSQC spectrum showed the presence of one carboxyl and six olefinic quaternary carbons and three methyl, four methylene, and six methine groups. HMBC correlations suggested a hydroxylated benzofuran bearing an isoprenoid side chain with a carboxyl moiety at C-9. Proton H-9 (δ 6.14) and the adjacent protons at C-10 (2H, δ_H 2.35, t, J = 6.9 Hz) showed HMBC correlations to the furan ring as well as to the prenyl side chain. They both correlated with C-7 (δ_C 131.3) and C-8 (δ_C 148.9) from the benzofuran. Additionally, H-9 showed correlation to C-3 (δ_C147.8). The side chain was identified by comparing its NMR data to those of other prenylated natural products[17] and structurally related compounds.[18−20] This substance showed no optical activity. Given the biogenetic relationship of this new compound **8** to ganomycin B,[18] compound **8** was named ganofuran B.

Compounds **1**−**8** were tested for their in vitro antiplasmodial activity. The most active of these was compound **3**—the only aldehyde—with an IC_{50} of 6 μM, followed by **4** and **7** with IC_{50} values of 11 μM. In contrast to **4**, compound **5**, lacking the conjugated 7.9(11)-diene, showed no activity at 20 μM. 24,25-Diol **6** had an IC_{50} of 13 μM. The isomers **1** and **2** had similar IC_{50} values of 20 and 18 μM, respectively, while benzofuran **8** was inactive at 20 μM.

This work on the well-studied mushroom *G. lucidum* shows the suitability of the HPLC activity profiling approach to identify active minor constituents in very complex extracts. To our knowledge this is the first report of the antiplasmodial activity of lanostanes from *G. lucidum*. This study also demonstrates, by the discovery of ganofuran B (**8**), that with the right tools for dereplication one can selectively target new substances for the sake of studying the chemical diversity of an organism. To our knowledge there had

Table 1. ^{13}C (125 MHz) and ^{1}H (500 MHz, $CDCl_3$) NMR Data of Compounds **2**, **3**, and **7**

	ganoderic acid TR 1 (**2**)		ganoderic aldehyde TR (**3**)		23-hydroxyganoderic acid S (**7**)	
position	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)
1	35.5, CH_2	1.70, m 2.19, m	36.6, CH_2	1.54, m 2.04, m	36.0, CH_2	1.70, m 2.19, m
2	34.4, CH_2	2.68, m 2.17, m	34.6, CH_2	2.53, m 2.14, m	27.6, CH_2	2.68, m 2.17, m
3	216.9, qC		216.0, qC		79.0, CH	
4	47.5, qC		47.4, qC		47.5, qC	
5	50.51, CH	1.48 dd (3.7,12.1)	50.7, CH	1.33 dd (3.7, 12.0)	49.6, CH	1.11, dd (3.1, 12.8)
6	23.5, CH_2	2.04, m 2.11, m	23.9, CH_2	1.91 m 1.89 m	23.0, CH_2	2.10, m 2.11, m
7	120.4, CH	5.83, d (6.1)	120.8, CH	5.92 d (6.5)	120.4, CH	5.52, d (6.1)
8	140.5, qC		143.0, qC		143.1, qC	
9	144.5, qC		145.2, qC		146.1, qC	
10	37.2, qC		37.6, qC		37.4, qC	
11	116.4, CH	5.31, d (5.4)	117.2, CH	5.40, d (5.5)	116.4, CH	5.31, d (5.5)
12	38.4, CH_2	2.01, dd 2.24, dd	38.8, CH_2	2.08, dd 1.86, dd	37.9, CH_2	2.25, dd 2.31, dd
13	44.0, qC		43.1, qC		43.2, qC	
14	51.9, qC		52.0, qC		50.8, qC	
15	76.6, CH	4.2, dd (5.8, 9.8)	74.7, CH	4.31, dd (5.6, 14.0)	37.8, CH_2	2.05, dd 1.74, dd
16	39.5, CH_2	1.70, m 1.89, m	40.7, CH_2	1.52, m 1.74, m	27.9, CH_2	1.41, m 1.66, m
17	48.6, CH	1.61, m	48.8, CH	1.47, m	51.1, CH	0.61, s
18	15.9, CH_3	0.58, s	16.2, CH_3	0.43, s	15.5, CH_3	1.10, s
19	22.1, CH_3	1.11, s	22.5, CH_3	0.96, s	23.2, CH_3	1.48, m
20	35.7, CH	1.34, m	35.7,CH	1.19, m	36.5, CH	
21	18.4, CH_3	0.834, d (6.5)	18.30, CH_3	0.71, d (6.7)	18.4, CH_3	0.94 d (6.7)
22	35.6, CH_2	1.43, m 1.09, m	34.2, CH_2	1.35, m 0.99, m	36.0, CH_2	1.11 m 1.51 m
23	26.4, CH_2	2.51, m 2.35, m	26.1, CH_2	2.18, m 2.06, m	68.0, CH	4.00, m
24	146.4, CH	5.99, t (5.8)	154.6, CH	6.56, t (7.6)	127.1, qC	5.42, d
25	125.6, qC		139.0, qC		135.0, qC	
26	20.6, CH_3	1.84, s	195.0,CH	9.42, s	172.1, qC	1.68 s
27	172.0, qC		10.01, CH_3	1.20, s	13.6, CH_3	1.04, s
28	25.4, CH_3	1.01, s	25.4, CH_3	1.11, s	31.4, CH_3	1.62, m
29	22.0, CH_3	1.05 s	22.2, CH_3	1.07, s	28.4, CH_3	0.91, s
30	25.2, CH_3	0.9, s	17.23, CH_3	0.87, s	25.4, CH_3	0.93, s

been no report of similar prenylated phenolics from *G. lucidum*. However, farnesyl hydroquinones have been reported from *Ganoderma pfeifferi,*[18] *G. fornicatum*,[19] and, very recently, *G. colossum*.[20] Compound **8** is a furan derivative of ganomycin B[18] and is likely formed by a nucleophilic attack of OH-4 at C-8.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter equipped with a 1 dm microcell. The optical rotation for the Na D-line (589) was extrapolated from the lines of a mercury lamp (546 and 579 nm) using a Drude equation. NMR data were measured at room temperature on a Bruker Avance III 500 MHz spectrometer (Bruker, Fällanden, Switzerland). ^{1}H and ^{13}C experiments were performed as previously described.[6] Topspin 2.0 was used as software for data processing and evaluation. Analytical HPLC separations were carried out on a system consisting of a 1100 series binary high-pressure mixing pump with degasser module, column oven, and a 1100 series PDA detector (all Agilent, Waldbronn, Germany). A Gilson 215 liquid handler with a Gilson 819 injection module and 50 μL loop was used as the autosampler. The HPLC was coupled to an Esquire 3000 Plus ion trap mass spectrometer equipped with an electrospray (ESI) interface (Bruker Daltonics, Bremen, Germany). Data acquisition and processing was performed using HyStar 3.0 software (Bruker Daltonics). Semipreparative HPLC separations were done on an Agilent 1100 series HPLC system consisting of a 1100 series quaternary low-pressure mixing pump with degasser module, column oven, and a 1100 series PDA detector with a 1000 μL loop. Medium-pressure liquid chromatography (MPLC) was done on a Sepacore system (Büchi, Flawil, Switzerland) consisting of a C-620 control unit, a C-660 fraction collector, a C-635 UV photometer, and two C-605 pump modules. The MPLC unit was controlled with SepacoreControl software (version 1.0.3000.1). High-resolution mass spectra were recorded with a micrOTOF ESIMS system (Bruker Daltonics) connected to an Agilent 1100 series HPLC. HyStar 3.0 software (Bruker Daltonics) was used for data acquisition and processing. Conditions for LC-TOF ESIMS were as follows: A reference solution of sodium formate 0.1% in 2-propanol/water (1:1) containing 5 mM NaOH was used for calibration of the MS instrument. The LC conditions were the same as described for ion trap LCMS. The spectra were recorded in negative and positive modes in the range *m*/*z* 150−1500. Typical mass accuracy was ±3 ppm. HPLC grade solvents for HPLC analysis and analytical grade solvents for extraction and medium-pressure chromatography were procured from Scharlau (Barcelona, Spain). HPLC grade water was obtained by an EASY-pure II (Barnstead, Dubuque, IA) water purification system. Sigma-Aldrich (Buchs, Switzerland) was the source for the formic acid (98.0−100.0%). The preliminary screen and microfractionation were done as previously described.[5]

Fungal Material. The material used for the initial screening was purchased from Peter Weinfurth GmbH (Bochum, Germany). A voucher specimen has been deposited at the Institute of Pharmaceutical Biology, University of Basel (MTS No. 206). More starting material was needed for the isolation work. Thus, 1000 g of dried fruiting bodies of *Ganoderma lucidum* was purchased from QUAN GmbH (58256 Ennepeta, Germany). A voucher specimen has been deposited at the Institute of Pharmaceutical Biology, University of Basel (MTS No. 335). The substances reported here from the active minutes were present in both batches, as was seen by LC-MS analysis (data not shown).

Extraction and Isolation. *G. lucidum* fruiting bodies were finely ground andpercolated three times with petrol ether for at least five hours

in a glass column (yield 3.7 g). The fungal material was then dried and percolated three more times with ethyl acetate (yield 9.0 g). All fractionation steps were monitored by LC-MS analysis to localize the desired compounds. Separation conditions: SunFire RP-18 column (3.5 μm, 3 × 150 mm; Waters GmbH, Eschborn, Germany), H_2O in MeCN (both +0.1% formic acid) 90%−0% in 30 min, 100% MeCN (+0.1% formic acid) for 5 min. Flow rate was 0.5 mL/min. The ethyl acetate extract was washed by boiling it for one hour in 500 mL of water. After filtration, the water-insoluble portion was dissolved in ethyl acetate. This fraction (3.4 g) was applied dry to normal-phase medium-pressure column chromatography. Separation conditions: glass column (480 × 50 mm, Büchi) packed with silica gel (Kieselgel 60, 40−60 μm, Merck Darmstadt, Germany) in petrol ether. As a mobile phase we used petrol ether with an increasing amount of ethyl acetate: 96−60% petrol ether in 6 h and 52 min at a flow rate of 15 mL/min. Fractions were collected every 60 s and compared using TLC (silica gel 60 F254, Merck, Darmstadt, Germany). Mobile phase was *n*-hexane/ethyl acetate (3:7). Spots were observed under UV at 254 and 366 nm, and similar fractions were pooled, leading to 14 larger fractions. The next step in the isolation process was semipreparative HPLC using a SunFire Prep RP-18 column (5 μm, 10 × 150 mm; Waters GmbH, Eschborn, Germany). The mobile phase was water (+0.1% formic acid) and MeOH (+0.1% formic acid) with a gradient of 50−100% MeOH in 30 min, followed by flushing for 5 min with 100% MeOH. The flow rate was 5 mL/min. Combined fractions 8−11 yielded compounds **2** (2.0 mg), **3** (4.1 mg), **4** (16.5 mg}, **5** (18 mg), **6** (8.2 mg), **7** (2.8 mg), and **8** (8.2 mg). Fraction 12 yielded **1** (1.9 mg).

The spectroscopic data of the known compounds **1**, **4**, **5**, and **6** were identical to those in the literature.[12−15] For ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) of these substances see the Supporting Information. Concentrating the samples **2** and **3** in aqueous solution gave very fine needles, which could not be used for determination of their melting points.

Ganoderic Acid TR 1 (2): very fine, colorless needles ($CHCl_3$); UV (MeOH) λ_{max} (log ε) 235(3.6), 243(3.9), 252(3.5) nm; $[\alpha]^{20}_D$ +5.0 (*c* 0.2, $CHCl_3$); for ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) see Table 1; positive HRESIMS *m*/*z* 469.3274 (calcd for $C_{30}H_{44}O_4$, $[M + H]^+$, 469.3319); negative HRESIMS *m*/*z* 467.3112 (calcd for $C_{30}H_{44}O_4$, $[M - H]^-$, 467.3162).

Ganoderic Aldehyde TR (3): amorphous, white solid ($CHCl_3$); UV (MeOH) λ_{max} (log ε) 235(3,5), 243(3.8), 252(3.5) nm; $[\alpha]^{20}_D$ +0.0 (*c* 1, $CHCl_3$); for ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}CNMR ($CDCl_3$, 125 MHz) see Table 1; negative HRESIMS *m*/*z* 451.3272 (calcd for $C_{30}H_{44}O_3$, $[M - H]^-$, 451.3162).

23-Hydroxyganoderic Acid S (7): very fine, white needles ($CHCl_3$); UV/vis (MeOH) λ_{max} (log ε) 235(3.6), 243(3.9) nm; $[\alpha]^{20}_D$ + 20.2 (*c* 1, $CHCl_3$); for ^{1}HNMR ($CDCl_3$, 500 MHz) and ^{13}CNMR ($CDCl_3$, 125 MHz) see Table 1; negative HRESIMS *m*/*z* 453.3424 (calcd for $C_{30}H_{46}O_4$, $[M - OH]^-$, 453.3323).

Ganofuran B (8): yellow oil; UV (MeOH) λ_{max} (log ε) 226(4.6), 300(4.4) nm; $[\alpha]^{20}_D$ 0.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) 7.24 (1H, s, H-2), 6.99 (1H, s, H-7), 6.71 (1H, d, J = 8.5 Hz, H-5), 6.64 (1H, dd, J = 8.5, 3 Hz, H-6), 6.19 (1H, s, H-9), 5.11 (1H, t, J = 7.1, H-12), 5.07 t (1H, t, J = 6.8, H-16), 2.35 (1H, t, J = 6.9 H-10), 2.27 (2H, m, H-11), 2.05 (2H, t, J = 6.8, H-15), 1.99 (2H, m, H-14), 1.67 (3H, s, H-19), 1.58 (3H, s, H-20), 1.54 (3H, s, H-18); ^{13}C NMR ($CDCl_3$, 125 MHz) 173.20 (C-21), 150. 44 (C-1), 148.96 (C-8), 147.81 (C-2), 147.17 (C-4), 146.14 (C-9), 136.50 (C-13), 131.34 (C-7), 131.00 (C-17), 123.81 (C-16), 122.15 (C-12), 121.69 (C-3), 115.95 (C-5), 113.02 (C-6), 78.93 (C-10), 39.23 (C-14), 26.62 (C-15), 25.75 (C-18), 25.21 (C-11), 17.54 (C-19), 15.92 (C-20); negative HRESIMS *m*/*z* 341.1467 (calcd for $C_{21}H_{23}O_4$, $[M - H]^-$, 341.1752).

Antiplasmodial Assay. Screening of extracts, HPLC-based activity profiling, and testing of pure substances were done as previously described.[5] IC_{50} values were estimated by linear interpolation. Tests were done in two independent experiments in duplicate.

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Supporting Information Available: ^{13}C and ^{1}H NMR shifts of compounds **1**−**7** alongside relevant COSY and HMBC correlations are shown (S1). ^{1}H, HSQC, and HMBC spectra of the new compounds **2**, **3**, **7**, and **8** are provided (S2−S13). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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