Biomimetic Transformation and Biological Activities of Globiferin, a Terpenoid Benzoquinone from *Cordia globifera*

Suppamit Dettrakul,[†] Sanya Surerum,[‡] Shuleewan Rajviroongit,[†] and Prasat Kittakoop*[,‡,§]

Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand, Chulabhorn Research Institute, Vibhavadi-Rangsit Highway, Laksi, Bangkok 10210, Thailand, and Chemical Biology Program, Chulabhorn Graduate Institute, and the Center for Environmental Health, Toxicology and Management of Chemicals (ETM), Vibhavadi-Rangsit Highway, Laksi, Bangkok 10210, Thailand

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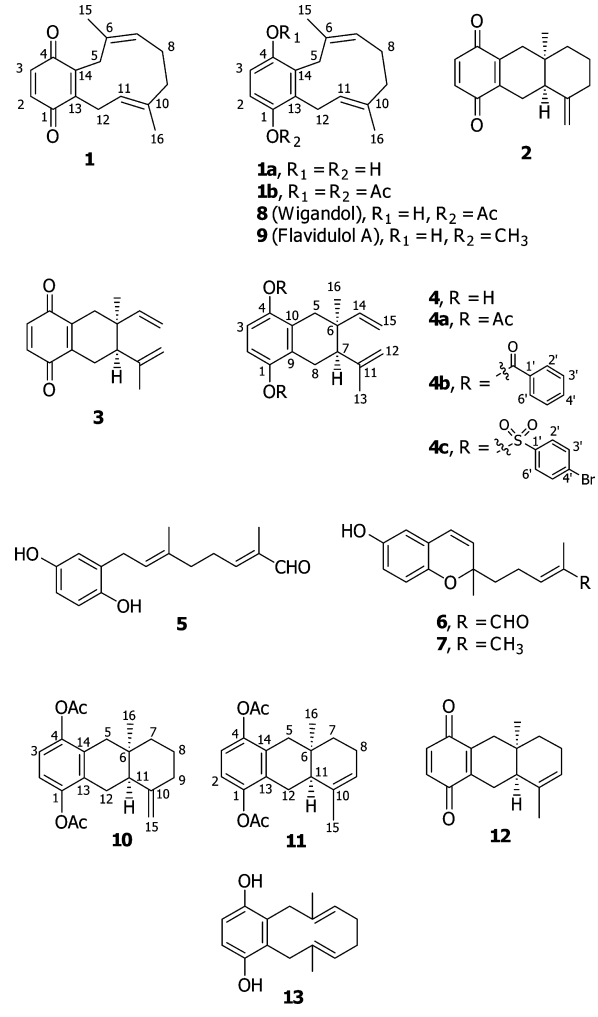
A new 10-membered ring meroterpene (**1**), named globiferin, was isolated from root extracts of *Cordia globifera*. Biomimetic transformations of **1** and its derivatives, either by acid cyclization or by Cope rearrangement, provided information relating to the biogenesis of cordiachromes A−C. Globiferin (**1**) underwent Cope rearrangement upon refluxing in xylene and DMSO-d_6 to yield cordiachrome C (**3**) and cordiaquinol C (**4**), respectively. Heating in DMSO-d_6 resulted in an unexpected reduction of a quinone moiety. Globiferin diacetate (**1b**) cyclized under acidic conditions to give compounds **10** and **11**, respective derivatives of natural cordiachromes B (**2**) and A (**12**). The present study indicates that globiferin (**1**) is a genuine intermediate for the biosynthesis of cordiachromes in *Cordia* species. Compounds **1** and **3** exhibited significant antimycobacterial activity, with MIC values of 6.2 and 1.5 μg/mL, respectively. Antimalarial, antifungal, and cytotoxic activities of **1** and its derivatives were also evaluated.

Plants of the genus *Cordia*, family Boraginaceae, are native to tropical America, Africa, and Asia, and they are recognized for their durability in marine use and general construction, as well as in traditional folk medicine.[1] Compounds isolated from the genus *Cordia* have displayed a broad range of biological activities, including antiandrogenic,[2] anti-inflamatory,[3] antifungal,[4,5] and larvacidal properties.[5] A number of plants of the genus *Cordia*, including *C. alba, C. alliodora,*[4,6] *C. globosa,*[7] *C. millenii,*[1] and *C. trichotoma*,[8] have been chemically examined and yielded sesquiterpenes,[8] triterpenes,[2,9,10] flavanoids,[11] chromens, quinones, and hydroquinones.[5,12−14] *C. globifera* W. W. Smith (Boraginaceae), known in Thai as "Sak Hin", is found in many parts of Thailand. Our preliminary study showed that the root extract of *C. globifera* possessed antimalarial activity. Chemical exploration of root extracts of *C. globifera* led to the identification of several bioactive compounds, including a new 10-membered terpenoid benzoquinone, named globiferin (**1**), and six known compounds, cordiachrome B (**2**),[1,6] cordiachrome C (**3**),[1,8] cordiaquinol C (**4**),[6] alliodorin (**5**),[6,15] elaeagin (**6**),[12] and cordiachromene (**7**).[3] We found that globiferin (**1**) and its derivatives could be biomimetically transformed to other related natural products, thus providing information relating to the possible biogenesis of cordiachromes. Antimalarial, antimycobacterial, antifungal, and cytotoxic activities of the isolated substances are also reported.



Results and Discussion

Chromatography of a hexane-soluble extract of *C. globifera* roots on silica gel yielded **1**, cordiachrome B (**2**),[1,6] and cordiachrome C (**3**).[1,8] The MeOH-soluble extract was separated by column chromatography (on Sephadex LH-20 and silica gel) and semi-preparative HPLC (reversed-phase C_{18} column) to afford cordiaquinol C (**4**),[6] alliodorin (**5**),[6,15] elaeagin (**6**),[12] and cordiachromene (**7**).[3] The known compounds were identified by analysis of NMR data and by comparison of spectroscopic data with those in the literature.

Globiferin (**1**) possessed a molecular formula of $C_{16}H_{18}O_2$, as revealed by the ESITOF MS spectrum, showing the accurate mass at *m/z* 265.1203 $[M + Na]^+$. The IR absorption band at 1650 cm^{-1} and the ^{13}C NMR resonances at δ_C 188.2 and 187.9 indicated the presence of a 1,4-benzoquinone unit in **1**. Analysis of ^{13}C and DEPT NMR data of **1** revealed the presence of two methyl, four methylene, four methine, and six nonprotonated carbons. The ^1H NMR spectrum of **1** demonstrated resonances of benzoquinone protons,

* To whom correspondence should be addressed. Tel: +66-86-9755777. Fax: +662-5740622, ext. 1513. E-mail: prasatkittakoop@yahoo.com.
[†] Department of Chemistry, Mahidol University.
[‡] Chulabhorn Research Institute.
[§] Chulabhorn Graduate Institute.

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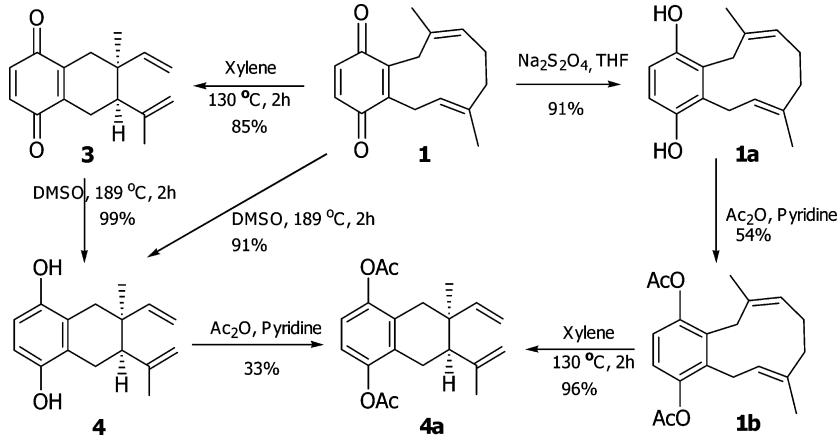
Scheme 1. Transformations of Globiferin (**1**) and Its Derivatives



H-2 (δ_H 6.80) and H-3 (δ_H 6.76); two olefinic protons of H-7 (δ_H 5.13) and H-11 methines (δ_H 5.09); four nonequivalent methylene groups (δ_H 1.56−3.65); and two methyl groups (δ_H 1.49 and 1.74). It should be noted that broad signals of methylene protons were observed on the ^{1}H NMR spectrum of **1** (see Supporting Information). The ^{1}H−^{1}H COSY spectrum of **1** established a partial structure from H-7 to H-9 and from H-11 to H-12 and also showed allylic couplings between H-7 and H-15 as well as between H-11 and H-16. The HMBC spectrum of **1** displayed correlations from H-2 to C-4 and C-13; H-3 to C-1 and C-14; H-7 to C-5 and C-15; H-11 to C-9, C-12, and C-16; H-15 to C-5, C-6, and C-7; and H-16 to C-9, C-10, and C-11. Unfortunately, no methylene protons showed HMBC correlations to any carbon; therefore, available NMR data could not conclusively establish the structure of **1**, particularly of the linkage between the 1,4-benzoquinone unit and the aliphatic part. Compound **1** was reduced by $Na_2S_2O_4$ to its corresponding 1,4-quinol derivative (**1a**), whose ^{1}H NMR spectrum exhibited, unlike that of **1**, sharp methylene signals. The IR absorption peak at 3318 cm^{-1} (OH) and the replacement of the quinone carbonyls (δ_C 188.2 and 187.9) with oxygenated sp^2 carbons (δ_C 149.1 and 150.3) suggested that the 1,4-benzoquinone unit in **1** was transformed to a 1,4-quinol moiety in **1a**. Acetylation of **1a** gave *O*-diacetate **1b**. Analysis of the HMBC spectrum allowed construction of the gross structure of **1a**. The linkage between a 1,4-quinol unit and an aliphatic part was established by the following key HMBC correlations: from H-5 to C-4, C-13, and C-14; from H-12 to C-1, C-13, and C-14. Other important HMBC correlations were observed from H-2 to C-13; H-3 to C-14; H-7 to C-5 and C-15; H-9 to C-10 and C-11; H-11 to C-9, C-13, and C-16; H-15 to C-6 and C-7; and H-16 to C-10 and C-11. On the basis of these spectroscopic data, the structure of **1a** was assigned as shown, and therefore the structure of globiferin (**1**) was established accordingly. The NOESY spectra of **1** and **1a** showed the correlation between H-7 and H-15, suggesting *cis*-geometry of the C-6/C-7 double bond, while the NOESY correlation between H-12 and H-16 implied *trans*-geometry of the C-9/C-10 double bond. Globiferin (**1**) was a derivative of wigandol (**8**), a meroterpenoid previously isolated from the plant *Wigandia kunthii*.[16] Wigandol (**8**) was previously proposed to possess *trans*,*trans*-geometry;[16] however, its ring system was revised to *cis*,*trans*-configuration by a single-crystal X-ray analysis.[17] It should be noted that flavidulols (i.e., **9**), geranylphenols isolated from the mushroom *Lactarius flavidulus*, also had a structural feature similar to that of globiferin (**1**).[18]

The chemistry of globiferin (**1**) and its derivatives provides insight into the biosynthesis of cordiachromes A−C. Upon heating, compounds **1** and **1b** easily underwent Cope rearrangement. Refluxing **1** in xylene provided cordiachrome C (**3**) in 85% yield, whereas heating **1** in DMSO-d_6, in an NMR tube, gave cordiaquinol C (**4**) in 91% yield (Scheme 1). Similar rearrangement was also observed for *O*-diacetate **1b**, and **4a** was obtained in 96% yield after refluxing **1b** in xylene (Scheme 1). NMR data of derivative **4a** obtained from Cope rearrangement of **1b** were identical to those from an acetylation of cordiaquinol C (**4**) (Scheme 1). Previous studies had demonstrated that *trans*,*trans*-cyclodeca-1,5-dienes underwent Cope rearrangement to give *trans*-1,2-divinylcyclohexane derivatives, while *cis*,*trans*-cyclodeca-1,5-dienes provided *cis*-1,2-divinylcyclohexane derivatives.[19−21] In the present work, globiferin (**1**) and its derivatives adopted *cis*,*trans*-cyclodeca-1,5-diene systems, and their Cope rearrangement yielded *cis* derivatives. Previously, wigandol acetate (**1b**) was found to undergo Cope rearrangement by pyrolysis to give compound **4a**.[16] It was interesting to note that Cope rearrangement of **1** in DMSO-d_6 gave cordiaquinol C (**4**), which was a reduced form of cordiachrome C (**3**), and that significant reduction (99%) of **3** to **4** was observed upon heating in DMSO-d_6 (in an NMR tube) (Scheme 1). Cordiaquinol C (**4**) obtained from chemical transformation was derivatized to **4b** and **4c**.

Interestingly, the diacetate **1b** could be cyclized under acidic conditions to give compounds **10** and **11**. The mechanistic transformation from **1b** to compounds **10** and **11** possibly involved protonation of a *cis*-double bond to provide a tertiary-carbocation, cyclization of an *E*-double bond to a tertiary-carbocation while generating a new tertiary-carbocation, and deprotonation of a tertiary-carbocation giving rise to exo- and endo-products **10** and **11**, respectively. Compounds **10** and **11** are respective derivatives of cordiachromes B (**2**) and A (**12**), which were isolated from *Cordia millenii*.[1]

Transformations of globiferin (**1**) and its derivatives either by acid cyclization or by Cope rearrangement provide substantial information on the biogenesis of cordiachromes A−C. In 1973, Moir and Thomson proposed a biosynthetic pathway to cordiachromes A−C via a *trans*,*trans*-cyclodecatriene intermediate (i.e., **13**),[1] whose structure was coincidently similar to that of globiferin (**1**), except for diene geometry. It should be noted that at that time when Moir and Thomson proposed the biogenesis a natural product with a cyclodecatriene ring system had not been isolated from *Cordia* species. Moir and Thomson proposed that acid cyclization of a *trans*,*trans*-cyclodecatriene intermediate led to the formation of cordiachromes B (**2**) and A (**12**) with *cis*-stereochemistry, while a "biogenetic Cope rearrangement" would produce the skeleton of cordiachrome C (**3**).[1] In the past, it was mistakenly perceived that Cope rearrangement of a *trans*,*trans*-cyclodecatriene would lead to the formation of a *cis*-ring junction,[1,16] but in fact, a *cis*,*trans*-isomer gave a *cis*-ring junction.[19−21] Interestingly, the quinones (e.g., cordiachromes A−C) isolated from the *Cordia* species were obtained as racemic mixtures,[1,22] and in the present study, cordiachrome B (**2**), cordiachrome C (**3**), and cordiaquinol C (**4**) exhibited small values of specific rotation, suggesting that they were likely to be racemates. Previous work suggested that the optically inactive intermediate (e.g., compound **1**) explained why these

Table 1. Antimycobacterial, Antimalarial, and Cytotoxic Activities of the Isolated Compounds and Derivatives

	antimycobacterial activity[a]	antimalarial activity[b]	antifungal activity[c]	cytotoxic activity (IC_{50}, μg/mL)			
	(MIC, μg/mL)	(IC_{50}, μg/mL)	(IC_{50}, μg/mL)	Vero[d]	KB[d]	BC-1[d]	NCI-H187[d]
1	6.2	2.1 ± 0.5	>20	>50	>20	>20	0.5 ± 0.04
2	12.5	1.5 ± 0.2	7.7 ± 0.1	1.7 ± 0.6	6.0 ± 0.5	6.4 ± 0.8	0.4 ± 0.09
3	1.5	0.2 ± 0.1	4.6 ± 0.2	1.4 ± 0.4	1.5 ± 0.1	1.8 ± 0.1	0.2 ± 0.06
4	25.0	0.3 ± 0.0	>20	1.6 ± 0.7	6.9 ± 0.1	3.2 ± 0.2	1.9 ± 0.1
4a	25.0	0.4 ± 0.1	>20	7.3 ± 0.5	8.5 ± 0.6	9.2 ± 0.6	5.1 ± 0.9
4b	200	>20	>20	>50	>20	>20	>20
4c	>200	>20	>20	>50	>20	>20	>20
5	12.5	3.1 ± 0.1	>20	14.1 ± 1.4	12.0 ± 0.2	10.3 ± 0.2	2.2 ± 0.8
6	12.5	3.6 ± 0.1	>20	20.0 ± 0.7	>20	>20	6.1 ± 1.1
7	12.5	>20	11.2 ± 0.8	>50	>20	>20	>20

[a] Standard drugs were rifampicin, isoniazid, and kanamycin, exhibiting respective MIC values of 0.0047, 0.05, and 2.5 μg/mL. [b] The IC_{50} value of the reference drug, dihydroartemisinin, was 0.0012 μg/mL. [c] Amphotericin B was the reference compound, exhibiting an IC_{50} value of 0.08 μg/mL. [d] The standard drug, ellipticine, exhibited IC_{50} values toward Vero, KB, BC-1, and NCI-H187 cell lines of 0.4, 0.2, 0.2, and 0.3 μg/mL, respectively.

quinones were racemates.[1,22] Although previous reports,[1,22] as well as the present work, employed mild conditions for extraction and isolation, racemic cordiachromes were obtained. Accordingly, we propose that cordiachromes A−C in *Cordia* species might alternatively be formed via a nonenzymatic pathway as guided by the biomimetic transformations proposed here. The present study indicates that globiferin (**1**) is a genuine intermediate for the biosynthesis of cordiachromes in *Cordia* species. It should be noted that the content of globiferin (**1**) in *C. globifera* root is relatively high (0.6 g/2 kg).

The compounds isolated from the root extract of *C. globifera*, as well as derivatives, were evaluated for their antimycobacterial, antimalarial, antifungal, and cytotoxic activities (Table 1). Compounds **1** and **3** exhibited significant antimycobacterial activity, with respective MIC values of 6.2 and 1.5 μg/mL, while other compounds (**2**, **4**, **4a**, **5**, **6**, and **7**) showed weak activity (Table 1). Compounds **1**−**4**, **4a**, **5**, and **6** exhibited antimalarial activity against *Plasmodium falciparum* with IC_{50} values ranging from 0.2 to 3.6 μg/mL. Compounds **2**, **3**, and **7** displayed weak antifungal activity against the fungus *Candida albicans* with IC_{50} ranges of 4.6−11.2 μg/mL. Compounds **2**−**4**, **4a**, and **5** showed cytotoxic activity toward all cell lines tested, while **1** and **6** exhibited activity against some cell lines. Derivatives **4b** and **4c** did not show any biological activity in these tests. It is interesting to note that the products **3** and **4** obtained from Cope rearrangement exhibited better activities than globiferin (**1**). While antimycobacterial activity of **3** was slightly more potent than **1** (6.2 μg/mL for **1** and 1.5 μg/mL for **3**), antimalarial activity of **3** and **4** was significantly improved, 1 order of magnitude more potent than **1** (Table 1). Compound **3** was active against the fungus *C. albicans* (IC_{50} 4.6 μg/mL), whereas **1** was inactive. Both **3** and **4** were more cytotoxic than **1**. Previously, metabolites of *Cordia* species were reported to exhibit antifungal,[4,5] antiandrogenic,[2] anti-inflamatory,[3] larvacidal,[5] and antileishmanial[22] activities.

Experimental Section

General Experimental Procedures. Melting points were measured with a digital melting point apparatus and are uncorrected. IR spectra and optical rotations were measured on a Vector 22 (Bruker) spectrometer and Jasco P-1030 polarimeter, respectively. UV spectra were recorded on a Cary 1E UV−vis spectrophotometer. ^{1}H, ^{13}C, ^{1}H−^{1}H COSY, HMQC, HMBC, NOESY, and DEPT spectra were recorded on a Bruker Advance 500 D NMR spectrometer, operating at 500 MHz for ^{1}H spectra and at 125 MHz for ^{13}C spectra. ESITOF-MS were obtained using a Micromass LCT mass spectrometer. Column chromatography and preparative TLC were carried out using 60−230 mesh silica gel.

Plant Material. Roots of *C. globifera* were collected from Nakhon Sawan Province, Thailand, in August 2002. The plant material was authenticated by Dr. Nijsiri Ruangrungsi (Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Chulalongkorn University). A voucher specimen (no. CRI 566) was deposited at the Laboratory of Natural Products, Chulabhorn Research Institute.

Extraction and Isolation. The air-dried roots of *C. globifera* (2 kg) were chopped, ground, and extracted with CH_2Cl_2 for three days at room temperature. The extract was evaporated to yield a brown, sticky residue (450 g). The CH_2Cl_2 extract was then partitioned between hexane and MeOH, yielding a hexane-soluble extract (150 g) and a MeOH-soluble extract (250 g). A portion of the hexane-soluble extract (1.7 g) was first subjected to silica gel column chromatography eluted with a gradient of EtOAc−hexane (2 to 10% EtOAc), providing 11 fractions, designated as CA−CL. Fraction CB was chromatographed on a silica gel flash column, eluted with 2% EtOAc in hexane to afford 15 subfractions (CB_1−CB_{15}). Subfractions CB_1−CB_5 were combined to afford globiferin (**1**; 614 mg). Fraction CD was subjected to a silica gel column, eluted with a gradient system of EtOAc in hexane (2 to 20%), to give **1** (45 mg), cordiachrome B (**2**) (40 mg), and cordiachrome C (**3**) (370 mg).

A portion of the MeOH-soluble extract (11.8 g) was separated on a Sephadex LH-20 column eluted with MeOH to yield 10 fractions, designated as MA−MJ. Fraction MD was chromatographed on Sephadex LH-20 (MeOH eluent) to obtain fractions MD_1−MD_{15}. Fraction MD_5 was fractionated by HPLC (reversed-phase C_{18} column, MeCN−H_2O, 55:45), furnishing cordiachromene (**7**) (8.3 mg). Fraction MD_8 was separated on a silica gel column, eluted with 10% EtOAc in CH_2Cl_2, to yield 10 fractions (MD_{801}−MD_{810}). Fraction MD_{805} was separated on a Sephadex LH-20 column (MeOH eluent) to afford cordiaquinol C (**4**; 6.3 mg). Fraction MD_{12} was chromatographed on a silica gel column, eluted with 10% EtOAc in CH_2Cl_2, yielding alliodorin (**5**; 11.6 mg) and elaeagin (**6**; 15.3 mg).

Globiferin (1): yellow oil; UV ($CHCl_3$) λ_{max} (log ε) 252 (4.1) nm; IR (KBr) ν_{max} 2930, 2858, 1650, 1287, 1444, 846, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80 (1H, d, J = 9.9 Hz, H-2), 6.76 (1H, d, J = 9.9 Hz, H-3), 5.13 (1H, dd, J = 8.3, 8.3 Hz, H-7), 5.09 (1H, dd, J = 7.3, 9.5 Hz, H-11), 3.64 (1H, br signal, H-12b), 3.32 (1H, br signal, H-5b), 3.13 (1H, br signal, H-12a), 2.99 (1H, br signal, H-5a), 2.18 (1H, br signal, H-9b), 2.02, (2H, br signal, H-8), 1.74 (1H, br signal, H-9a), 1.74 (3H, s, H-16), 1.49 (3H, s, H-15); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 188.2 (C, C-1), 187.9 (C, C-4), 144.2 (C, C-13), 143.3 (C, C-14), 137.8 (C, C-6), 136.5 (CH, C-2), 136.2 (CH, C-3), 133.0 (C, C-10), 122.8 (CH, C-7), 121.2 (CH, C-11), 38.2 (CH_2, C-9), 27.7 (CH_2, C-12), 27.3 (CH_2, C-5), 24.5 (CH_2, C-8), 23.5 (CH_3, C-15), and 16.9 (CH_3, C-16); ESITOFMS m/z 265.1203 [M + Na]$^+$ (calcd for $C_{16}H_{18}O_2Na$, 265.1204).

Cordiachrome B (2): brown oil; $[\alpha]^{25}_D$ +12.5 (c 0.13, $CHCl_3$); ESITOFMS m/z, 243.1387 [M + H]$^+$ (calcd for $C_{16}H_{19}O_2$, 243.1385). Spectroscopic data of **2** were identical in all respects to literature data.[1,6]

Cordiachrome C (3): brown oil; $[\alpha]^{26}_D$ +1.13 (c 0.25, $CHCl_3$); ESITOFMS m/z 243.1388 [M + H]$^+$ (calcd for $C_{16}H_{19}O_2$, 243.1385). Spectroscopic data of **3** were identical in all respects to literature data.[1,8]

Cordiaquinol C (4): off-white solid; mp 264−266 °C; $[\alpha]^{26}_D$ +2.1 (c 0.12, acetone); ESITOFMS m/z 243.1391 [M − H]$^-$ (calcd for $C_{16}H_{19}O_2$, 243.1385). Spectroscopic data of **4** were identical in all respects to literature data.[6]

Alliodorin (5): off-white, amorphous solid; ESITOFMS *m/z* 238.1308 $[M + Na]^+$ (calcd for $C_{16}H_{20}O_3Na$, 283.1310). Spectroscopic data of **5** were identical in all respects to literature data.[6,15]

Elaeagin (6): brown oil: $[\alpha]^{26}_D$ +3.7 (*c* 0.18, $CHCl_3$); ESITOFMS *m/z* 259.1331 $[M + H]^+$ (calcd for $C_{16}H_{19}O_3$, 259.1334). Spectroscopic data of **6** were identical in all respects to literature data.[12]

Cordiachromene (7): brown oil; $[\alpha]^{26}_D$ −10.9 (*c* 0.095, acetone); ESITOFMS *m/z* 245.1534 $[M + H]^+$ (calcd for $C_{16}H_{21}O_2$, 245.1541). Spectroscopic data of **7** were identical in all respects to literature data.[3]

Preparation of 1a. An aliquot of **1** (123 mg, 0.50 mmol) in THF (4 mL) was added to a solution of $Na_2S_2O_4$ (8.5 mg, 0.05 mmol) in H_2O (1 mL), and the reaction mixture was stirred vigorously for 30 min until colorless. Aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc (10 mL × 3). The EtOAc layers were combined, evaporated, and separated on Sephadex LH-20 (MeOH eluent) to give **1a** (111 mg, 91%): off-white, amorphous solid; λ_{max} (log ε) 204 (4.4) and 291 (3.7) nm; IR (KBr) ν_{max} 3318, 2964, 2927, 2861, 1617, 1376, 1288, 1183, 798, 747 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 7.61 (1H, br s, 1-OH), 7.63 (1H, br s, 4-OH), 6.59 (1H, d, J = 8.6 Hz, H-2), 6.57 (1H, d, J = 8.7 Hz, H-3), 5.23 (1H, dd, J = 1.8, 13.8 Hz, H-11), 5.06 (1H, dd, J = 7.2, 8.4 Hz, H-7), 3.87 (1H, br d, J = 16.7 Hz, H-12b), 3.42 (1H, d, J = 13.8 Hz, H-5b), 3.21 (1H, dd, J = 13.8 and 16.7 Hz, H-12a), 3.20 (1H, d, J = 13.8 Hz, H-5a), 2.13 (1H, dd, J = 5.2, 11.6 Hz, H-9b), 1.96 (2H, m, H-8), 1.79 (3H, s, H-16), 1.70 (1H, t, J = 11.9 Hz, H-9a), 1.59, (3H, s, H-15); ^{13}C NMR (acetone-d_6, 125 MHz) δ 150.3 (C, C-1), 149.1 (C, C-4), 141.1 (C, C-10), 130.9 (C, C-6), 127.6 (C, C-13), 126.5 (C, C-14), 125.1 (CH, C-11), 121.8 (CH, C-7), 113.6 (CH, C-2), 113.4 (CH, C-3), 39.1 (CH_2, C-9), 28.7 (CH_2, C-5), 27.8 (CH_2, C-12), 25.3 (CH_2, C-8), 22.7 (CH_3, C-16), 17.0 (CH_3, C-15); ESITOFMS *m/z* 245.1541 $[M + H]^+$ (calcd for $C_{16}H_{21}O_2$, 245.1531).

Preparation of 1b. Acetic anhydride (0.5 mL) was added to a solution of **1a** (15.4 mg, 0.06 mmol) in pyridine (1.5 mL). The mixture was stirred at room temperature for 12 h, and the solvent was removed under reduced pressure. The residue was separated by preparative TLC (10% EtOAc in hexane) to yield a yellow liquid (**1b**, 11.1 mg, 54%); λ_{max} (log ε) 204 (4.4) and 291(3.7) nm; IR (KBr) ν_{max} 2925, 1764, 1469, 1370, 1186, 1041, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.94 (1H, d, J = 8.7 Hz, H-3), 6.90 (1H, d, J = 8.7 Hz, H-2), 5.18 (1H, d, J = 13.2 Hz, H-11), 5.12 (1H, br dd, J = 7.9 and 8.6 Hz, H-7), 3.45 (1H, br d, J = 16.4 Hz, H-12b), 3.33 (1H, dd, J = 13.2 and 16.4 Hz, H-12a), 3.31 (1H, d, J = 15.3 Hz, H-5b), 2.98 (1H, d, J = 15.3 Hz, H-5a), 2.29 (3H, s, CH_3 of acetate), 2.28 (3H, s, CH_3 of acetate), 2.13 (1H, dd, J = 5.7 and 11.5 Hz, H-9b), 2.02 (1H, m, H-8b), 1.92 (1H, dd, J = 10.7, 11.4 Hz, H-8a), 1.72 (2H, s, H-16), and 1.52 (3H, s, H-15); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3 (C, C═O of acetate), 169.2 (C, C═O of acetate), 148.3 (C, C-4), 146.9 (C, C-1), 132.6 (C, C-14), 138.0 (C, C-6), 132.2 (C, C-13), 132.1 (C, C-10), 122.7 (CH, C-7), 122.2 (CH, C-11), 120.6 (2 × CH, C-2 and C-3), 38.1 (CH_2, C-9), 29.3 (CH_2, C-5), 28.0 (CH_2, C-12), 24.7 (CH_2, C-8), 22.8 (CH_3, C-15), 21.1 (CH_3 of acetate), 20.9 (CH_3 of acetate), and 17.0 (CH_3, C-16); ESITOFMS *m/z* 351.1564 $[M + Na]^+$ (calcd for $C_{22}H_{24}O_4Na$, 351.1572).

Preparation of Ester 4a. Acetic anhydride (0.5 mL) was added to a solution of **4** (31.1 mg, 0.13 mmol) in dry pyridine (2 mL), and the mixture was stirred for 12 h at room temperature. Solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (5 mL) and subsequently washed twice with water. The organic layer was evaporated to dryness and separated on silica gel eluting with 5% EtOAc in hexane to provide **4a** (13.8 mg, 33%): yellow oil; UV ($CHCl_3$) λ_{max} (log ε) 241 (3.1) and 260 (2.8) nm; IR (KBr) ν_{max} 3082, 2927, 2855, 1764, 1639, 1470, 1185, 1017, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.88 (2 × 1H, s, H-2 and H-3), 5.93 (1H, dd, J = 10.9, 17.5 Hz, H-14), 4.97 (1H, dd, J = 1.2, 10.9 Hz, H-15b), 4.90 (1H, dd, J = 15.0, 17.5 Hz, H-15a), 4.88 (1H, s, H-12b), 4.77 (1H, s, H-12a), 2.64 (1H, d, J = 17.1 Hz, H-5b), 2.62 (1H, d, J = 7.9 Hz, H-8), 2.44 (1H, d, J = 7.2 Hz, H-5a), 2.33 (1H, dd, J = 7.3, 7.3 Hz, H-7), 2.30 (3H, s, H-18), 2.29 (3H, s, H-20), 1.76 (3H, s, H-13), 1.12 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2 (2 × C, C-17 and C-19), 146.4 (C, C-1), 146.3 (C, C-4), 146.2 (C, C-11), 141.7 (CH, C-14), 130.4 (C, C-10), 129.9 (C, C-9), 119.7 (C, C-3), 113.7 (CH_2, C-15), 113.4 (CH_2, C-12), 49.9 (CH, C-7), 37.9 (C, C-6), 37.8 (CH_2, C-5), 27.4 (CH_2, C-8), 26.2 (CH_3, C-16), 23.3 (CH_3, C-13), and 20.9 (2 × CH_3, C-18 and C-20); ESITOFMS *m/z* 315.1569 $[M + Na]^+$ (calcd for $C_{20}H_{24}O_4Na$, 351.1572).

Preparation of Ester 4b. A solution of **4** (40.4 mg, 0.16 mmol) in dry pyridine (2 mL) was treated with 0.5 mL of benzoyl chloride, and the solution was stirred at room temperature overnight. Solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (5 mL) and washed twice with water. The organic layer was evaporated to dryness and subjected to a Sephadex LH-20 column (eluting with MeOH) followed by silica gel column (eluting with 5% EtOAc in hexane) chromatography to give **4b** (25.3 mg, 33.8%): white needles; mp 171−172 °C; UV ($CHCl_3$) λ_{max} (log ε) 241 (4.2) nm; IR (KBr) ν_{max} 2924, 1732, 1638, 1469, 1450, 1314, 1266, 1211, 1083, 1063, 1025, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.23 (4 × 1H, m, overlapping signals of H-2′, H-2″, H-6′, and H-6″), 7.66 (2 × 1H, m, overlapping signals of H-4′ and H-4″), 7.53 (4 × 1H, m, overlapping signals of H-3′, H-3″, H-5′, and H-5″), 7.08 (2 × 1H, s, H-6 and H-7), 5.99 (1H, dd, J = 11.0, 17.5 Hz, H-14), 5.00 (1H, d, J = 11.0 Hz, H-15b), 4.95 (1H, dd, J = 0.95, 17.3 Hz, H-15a), 4.84 (1H, s, H-12b), 4.75 (1H, s, H-12a), 2.77 (1H, d, J = 17.3 Hz, H-5b), 2.75 (2H, d, J = 8.8 Hz, H-8), 2.56 (1H, d, J = 17.1 Hz, H-5a), 2.38 (1H, d, J = 8.5 Hz, H-7), 1.72 (3H, s, H-13), and 1.10 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.8 (2 × C, C-17 and C-17′), 146.7 (C, C-1), 146.6 (C, C-4), 146.1 (C, C-11), 141.9 (CH, C-14), 133.7 (2 × CH, C-4′ and C-4″), 130.8 (2 × C, C-1′ and C-1″), 130.3 (4 × CH, C-2′, C-2″, C-6′, and C-6″), 129.5 (C, C-10), 129.4 (C, C-9), 128.7 (4 × CH, C-3′, C-3″, C-5′, and C-5″), 120.0 (CH, C-2), 119.9 (CH, C-3), 113.7 (CH_2, C-15), 113.4 (CH_2, C-12), 50.0 (CH, C-7), 37.9 (C, C-6), 37.8 (CH_2, C-5), 27.5 (CH_2, C-8), 26.2 (CH_3, C-16), and 23.2 (CH_3, C-13); ESITOFMS *m/z* 475.1878 $[M + Na]^+$ (calcd for $C_{30}H_{28}O_4Na$, 475.1885).

Preparation of Ester 4c. To a solution of **4** (35.4 mg, 0.14 mmol) in dry pyridine (2 mL) was added 4-bromobenzenesulfonyl chloride (178.8 mg, 0.7 mmol), and the solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, then the residue was dissolved in 5 mL of EtOAc and subsequently washed twice with water. The residue was subjected to Sephadex LH-20 column chromatography (MeOH eluent) to remove traces of 4-bromobenzenesulfonyl chloride and 4-bromobenzenesulfonic acid and was then purified over silica gel, eluting with 4% EtOAc in hexane to obtain **4c** (38.8 mg, 39.4%): pale pink, amorphous solid; UV ($CHCl_3$) λ_{max} (log ε) 242 (4.6) nm; IR (KBr) ν_{max} 3087, 2924, 1575, 1460, 1380, 1091, 822, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71 (4 × 1H, m, aromatic protons of 4-bromobenzenesulfonyl group), 7.64 (4 × 1H, m, aromatic protons of 4-bromobenzenesulfonyl group), 7.03 (1H, d, J = 8.9 Hz, H-2), 6.89 (1H, d, J = 8.9 Hz, H-3), 5.48 (1H, dd, J = 10.9, 17.5 Hz, H-14), 4.86 (1H, d, J = 10.9, H-15b), 4.81 (1H, s, H-12b), 4.65 (1H, d, J = 17.5 Hz, H-15a), 4.51 (1H, s, H-12a), 2.60 (1H, d, J = 17.6 Hz, H-5b), 2.50 (1H, dt, J = 10.2, 10.3 Hz, H-8b), 2.24 (1H, d, J = 17.5 Hz, H-5a), 2.00 (1H, dd, J = 10.3, 10.7 Hz, H-8a), 1.61 (3H, s, H-13), and 0.97 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0 (C, C-1), 145.7 (C, C-4), 145.2 (C, C-11), 140.9 (CH, C-14), 134.9 (C, C-1′), 134.8 (C, C-1″), 132.7 (4 × C, C-3′, C-3″, C-5′, and C-5″), 132.5 (C, C-9), 132.0 (C, C-10), 129.9 (2 × C, C-4′ and C-4″), 129.7 (4 × C, C-2′, C-2″, C-6′, and C-6″), 120.3 (CH, C-2), 120.0 (CH, C-3), 113.7 (CH_2, C-15), 113.5 (CH_2, C-12), 49.2 (CH, C-7), 37.6 (C, C-6), 37.5 (CH_2, C-5), 27.3 (CH_2, C-8), 26.0 (CH_3, C-16), and 23.1 (CH_3, C-13); ESITOFMS *m/z* 702.9434 $[M + Na]^+$ (calcd for $C_{28}H_{26}O_6S_2Br_2Na$, 702.9435).

Cope Rearrangement of 1 to 4a. A solution of globiferin (**1**) (17.7 mg) in xylene (2 mL) was heated under reflux for 2 h. After removing solvent, the residue was separated on a silica gel column (eluting with 2% EtOAc in hexane) to provide cordiachrome C (**3**) (15.6 mg, 85%).

Cope Rearrangement of 1 to 4. Globiferin (**1**) (81.9 mg) was dissolved in DMSO-d_6 (1.5 mL) in an NMR tube and then heated at reflux (189 °C) for 2 h. Progress of the reaction was monitored by ^1H NMR. Water (5 mL) was added to precipitate, and the resulting solid was dissolved in acetone and filtered through charcoal. The filtrate was evaporated to dryness and separated on a Sephadex LH-20 column (MeOH as eluent) to obtain **4** (75.2 mg, 91%).

Cope Rearrangement of 1b to 4a. A solution of compound **1b** (11.0 mg) in xylene (2 mL) was heated under reflux for 2 h. Solvent was removed, and the residue was separated on a Sephadex LH-20 column eluted with MeOH to yield **4a** (10.6 mg, 96%).

Transformation of 3 to 4. Cordiachrome C (**3**) (ca. 25 mg) was dissolved in DMSO-d_6 (0.5 mL) in an NMR tube and then heated at reflux (189 °C) for 2 h. Progress of the conversion was monitored by ^1H NMR, and it was found that 99% of cordiachrome C (**3**) was converted to cordiaquinol C (**4**) after heating for 2 h.

Acid-Catalyzed Cyclization of 1b. To a solution of compound **1b** (26.5 mg, 0.08 mmol) in MeOH (2 mL) was added 25% dilute HCl (3 drops). The reaction mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with saturated NaCl solution and water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by HPLC (reversed-phase C_{18} column, MeCN−H_2O, 40:60), furnishing compounds **10** (10.8 mg, 40.7%) and **11** (2.0 mg, 7.6%).

Compound 10: Yellow oil; $[\alpha]^{26}_D$ +2.1 (*c* 0.12, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (2 × 1H, s, overlapping signals of H-2 and H-3), 4.68 (1H, s, H-15b), 4.42 (1H, s, H-15a), 2.79 (1H, dd, J = 18.1, 4.1 Hz, H-12b), 2.70 (1H, dd, J = 18.1, 6.4 Hz, H-12a), 2.53 (1H, d, J = 16.9 Hz, H-5b), 2.31 (3H, s, CH_3COO), 2.29 (3H, s, CH_3COO), 2.27 (1H, dd, J = 13.6 and 5.2 Hz, H-9b), 2.18 (1H, br t, J = 4.4 Hz, H-11), 2.07 (1H, d, J = 16.9 Hz, H-5a), 2.01 (1H, ddd, J = 13.6, 8.0, 5.2 Hz, H-9a), 1.66 (2H, m, H-8), 1.58 (1H, m, H-7b), 1.39 (1H, ddd, J = 14.9, 10.2, 4.9 Hz, H-7a), and 0.96 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3 (C, CH_3*C*OO), 169.1 (C, CH_3*C*OO), 148.8 (C, C-10), 146.9 (C, C-4), 146.3 (C, C-1), 129.6 (C, C-14), 128.8 (C, C-13), 119.5 (CH, C-3), 119.3 (CH, C-2), 107.9 (CH_2, C-15), 45.1 (CH, C-11), 36.9 (CH_2, C-7), 34.4 (CH_2, C-9), 33.8 (C, C-6), 31.5 (CH_2, C-5), 27.3 (CH_3, C-16), 24.2 (CH_2, C-12), 23.6 (CH_2, C-8), 20.9 (*C*H_3COO), and 20.8 (*C*H_3COO); ESITOFMS *m*/*z* 329.1748 $[M + H]^+$ (calcd for $C_{20}H_{25}O_4$, 329.1753).

Compound 11: Yellow oil; $[\alpha]^{26}_D$ +5.5 (*c* 0.08, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.88 (2 × 1H, s, H-2 and H-3), 5.23 (1H, d, J = 2.9 Hz, H-9), 2.91 (1H, dd, J = 17.6 and 6.4 Hz, H-12b), 2.47 (1H, d, J = 16.4 Hz, H-5b), 2.34 (1H, d, J = 16.4 Hz, H-5a), 2.31 (1H, s, H-18), 2.30 (2 × 1H, s, H-12a and H-20), 2.03 (2H, m, H-8), 1.85 (1H, br t, J = 7.7 Hz, H-11), 1.70 (3H, s, H-15), 1.51 (1H, dd, J = 13.5 and 7.8 Hz, H-7b), 1.07 (1H, m, H-7a), and 0.99 (3H, s, H-16); ^{13}C NMR data could not be recorded due to a limited amount of the material; ESITOFMS *m*/*z* 351.1578 $[M + Na]^+$ (calcd for $C_{20}H_{24}O_4Na$, 351.1572).

Antimycobacterial Assay. Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H_{37}Ra using the Microplate Alamar Blue Assay (MABA).[23] Standard drugs rifampicin, isoniazid, and kanamycin sulfate were use as the reference compounds (MIC 0.0047, 0.05, and 2.5 μg/mL, respectively.).

Antimalarial Assay. Antimalarial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain), which was cultured continuously according to the method of Trager and Jensen.[24] Quantitative assessment of malarial activity in vitro was determined by means of microculture radioisotope technique based upon the method described by Desjardins et al.[25] An IC_{50} value of 0.0012 μg/mL was observed for the standard compound dihydroartemisinin in the same test system.

Antifungal Assay. The isolated compounds were tested for their antifungal activity against *Candida albicans* using a method modified from the soluble formazan assay.[26] The IC_{50} value of the standard drug amphotericin B was 0.08 μg/mL.

Cytotoxicity Assay. The cytotoxicity assays against the KB (human epidermoid carcinoma of the mouth), BC (human breast cancer cells), NCI-H187 (human small cell lung cancer), and Vero cell lines (African green monkey kidney fibroblast cells) were evaluated using the colorimetric method as described by Skehan and co-workers.[27] The reference substance was ellipticine (Table 1).

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Supporting Information Available: ^{1}H and ^{13}C spectra of **1**, **1a**, **4b**, **4c**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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