

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

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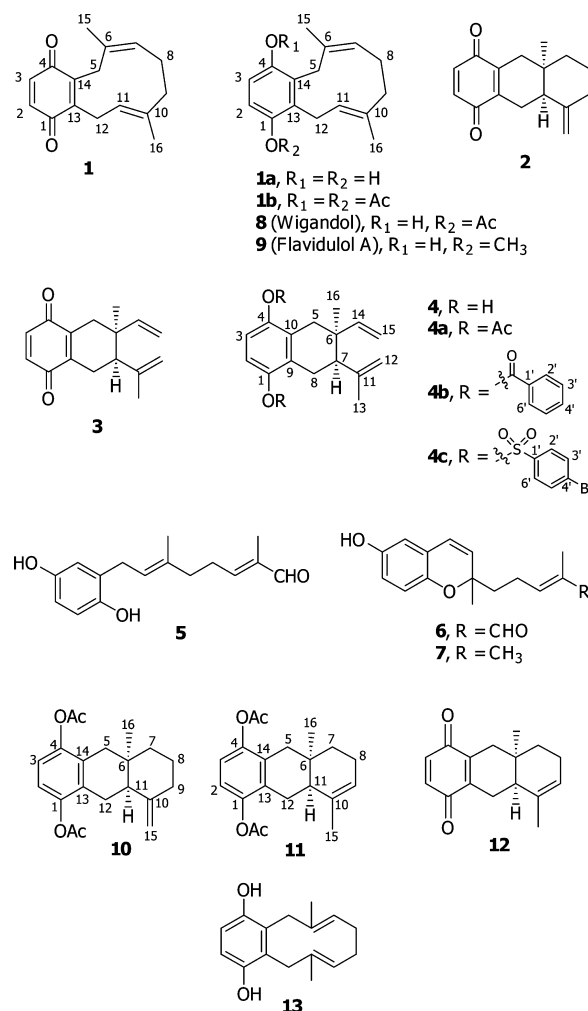
A new 10-membered ring meroterpene (**1**), named globiferin, was isolated from root extracts of *Cordia globifera*. Biomimetic transformations of **1** and its derivatives, either by acid cyclization or by Cope rearrangement, provided information relating to the biogenesis of cordiachromes A–C. Globiferin (**1**) underwent Cope rearrangement upon refluxing in xylene and DMSO-*d*<sub>6</sub> to yield cordiachrome C (**3**) and cordiaquinol C (**4**), respectively. Heating in DMSO-*d*<sub>6</sub> 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.<sup>1</sup> Compounds isolated from the genus *Cordia* have displayed a broad range of biological activities, including antiandrogenic,<sup>2</sup> anti-inflammatory,<sup>3</sup> antifungal,<sup>4,5</sup> and larvicidal properties.<sup>5</sup> A number of plants of the genus *Cordia*, including *C. alba*, *C. alliodora*,<sup>4,6</sup> *C. globosa*,<sup>7</sup> *C. millenii*,<sup>1</sup> and *C. trichotoma*,<sup>8</sup> have been chemically examined and yielded sesquiterpenes,<sup>8</sup> triterpenes,<sup>2,9,10</sup> flavanoids,<sup>11</sup> chromens, quinones, and hydroquinones.<sup>5,12–14</sup> *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**),<sup>1,6</sup> cordiachrome C (**3**),<sup>1,8</sup> cordiaquinol C (**4**),<sup>6</sup> alliodorin (**5**),<sup>6,15</sup> elaeagin (**6**),<sup>12</sup> and cordiachromene (**7**).<sup>3</sup> 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**),<sup>1,6</sup> and cordiachrome C (**3**).<sup>1,8</sup> The MeOH-soluble extract was separated by column chromatography (on Sephadex LH-20 and silica gel) and semi-preparative HPLC (reversed-phase C<sub>18</sub> column) to afford cordiaquinol C (**4**),<sup>6</sup> alliodorin (**5**),<sup>6,15</sup> elaeagin (**6**),<sup>12</sup> and cordiachromene (**7**).<sup>3</sup> 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<sub>16</sub>H<sub>18</sub>O<sub>2</sub>, as revealed by the ESITOF MS spectrum, showing the accurate mass



at *m/z* 265.1203 [M + Na]<sup>+</sup>. The IR absorption band at 1650 cm<sup>−1</sup> and the <sup>13</sup>C NMR resonances at δ<sub>C</sub> 188.2 and 187.9 indicated the presence of a 1,4-benzoquinone unit in **1**. Analysis of <sup>13</sup>C and DEPT NMR data of **1** revealed the presence of two methyl, four methylene, four methine, and six nonprotonated carbons. The <sup>1</sup>H NMR spectrum of **1** demonstrated resonances of benzoquinone protons,

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

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

<sup>a</sup> Standard drugs were rifampicin, isoniazid, and kanamycin, exhibiting respective MIC values of 0.0047, 0.05, and 2.5  $\mu$ g/mL. <sup>b</sup> The IC<sub>50</sub> value of the reference drug, dihydroartemisinin, was 0.0012  $\mu$ g/mL. <sup>c</sup> Amphotericin B was the reference compound, exhibiting an IC<sub>50</sub> value of 0.08  $\mu$ g/mL. <sup>d</sup> The standard drug, ellipticine, exhibited IC<sub>50</sub> values toward Vero, KB, BC-1, and NCI-H187 cell lines of 0.4, 0.2, 0.2, and 0.3  $\mu$ g/mL, respectively.

quinones were racemates.<sup>1,22</sup> Although previous reports,<sup>1,22</sup> 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  $\mu$ g/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<sub>50</sub> values ranging from 0.2 to 3.6  $\mu$ g/mL. Compounds **2**, **3**, and **7** displayed weak antifungal activity against the fungus *Candida albicans* with IC<sub>50</sub> ranges of 4.6–11.2  $\mu$ g/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  $\mu$ g/mL for **1** and 1.5  $\mu$ g/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<sub>50</sub> 4.6  $\mu$ g/mL), whereas **1** was inactive. Both **3** and **4** were more cytotoxic than **1**. Previously, metabolites of *Cordia* species were reported to exhibit antifungal,<sup>4,5</sup> antiandrogenic,<sup>2</sup> anti-inflammatory,<sup>3</sup> larvicidal,<sup>5</sup> and antileishmanial<sup>22</sup> 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. <sup>1</sup>H, <sup>13</sup>C, <sup>1</sup>H–<sup>1</sup>H COSY, HMQC, HMBC, NOESY, and DEPT spectra were recorded on a Bruker Avance 500 D NMR spectrometer, operating at 500 MHz for <sup>1</sup>H spectra and at 125 MHz for <sup>13</sup>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. Nijisiri Ruangrunsi (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<sub>2</sub>Cl<sub>2</sub> for three days at room temperature. The extract was evaporated to yield a brown, sticky residue (450 g). The CH<sub>2</sub>Cl<sub>2</sub> 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<sub>1</sub>–CB<sub>15</sub>). Subfractions CB<sub>1</sub>–CB<sub>5</sub> 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<sub>1</sub>–MD<sub>15</sub>. Fraction MD<sub>5</sub> was fractionated by HPLC (reversed-phase C<sub>18</sub> column, MeCN–H<sub>2</sub>O, 55:45), furnishing cordiachromene (**7**) (8.3 mg). Fraction MD<sub>8</sub> was separated on a silica gel column, eluted with 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, to yield 10 fractions (MD<sub>801</sub>–MD<sub>810</sub>). Fraction MD<sub>805</sub> was separated on a Sephadex LH-20 column (MeOH eluent) to afford cordiaquinol C (**4**; 6.3 mg). Fraction MD<sub>12</sub> was chromatographed on a silica gel column, eluted with 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, yielding alliodorin (**5**; 11.6 mg) and elaeagin (**6**; 15.3 mg).

**Globiferin (1):** yellow oil; UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 252 (4.1) nm; IR (KBr)  $\nu_{\max}$  2930, 2858, 1650, 1287, 1444, 846, 755 cm<sup>−1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  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<sub>2</sub>, C-9), 27.7 (CH<sub>2</sub>, C-12), 27.3 (CH<sub>2</sub>, C-5), 24.5 (CH<sub>2</sub>, C-8), 23.5 (CH<sub>3</sub>, C-15), and 16.9 (CH<sub>3</sub>, C-16); ESITOFMS *m/z* 265.1203 [M + Na]<sup>+</sup> (calcd for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>Na, 265.1204).

**Cordiachrome B (2):** brown oil; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +12.5 (*c* 0.13, CHCl<sub>3</sub>); ESITOFMS *m/z*, 243.1387 [M + H]<sup>+</sup> (calcd for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub>, 243.1385). Spectroscopic data of **2** were identical in all respects to literature data.<sup>1,6</sup>

**Cordiachrome C (3):** brown oil; [ $\alpha$ ]<sub>D</sub><sup>26</sup> +1.13 (*c* 0.25, CHCl<sub>3</sub>); ESITOFMS *m/z* 243.1388 [M + H]<sup>+</sup> (calcd for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub>, 243.1385). Spectroscopic data of **3** were identical in all respects to literature data.<sup>1,8</sup>

**Cordiaquinol C (4):** off-white solid; mp 264–266 °C; [ $\alpha$ ]<sub>D</sub><sup>26</sup> +2.1 (*c* 0.12, acetone); ESITOFMS *m/z* 243.1391 [M + H]<sup>+</sup> (calcd for C<sub>16</sub>H<sub>19</sub>O<sub>2</sub>, 243.1385). Spectroscopic data of **4** were identical in all respects to literature data.<sup>6</sup>



**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.<sup>6,15</sup>

**Elaeagin (6):** brown oil;  $[\alpha]_D^{26} +3.7$  ( $c$  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.<sup>12</sup>

**Cordiachrome (7):** brown oil;  $[\alpha]_D^{26} -10.9$  ( $c$  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.<sup>3</sup>

**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  $\times$  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;  $\lambda_{max}$  (log  $\epsilon$ ) 204 (4.4) and 291 (3.7) nm; IR (KBr)  $\nu_{max}$  3318, 2964, 2927, 2861, 1617, 1376, 1288, 1183, 798, 747  $cm^{-1}$ ;  $^1H$  NMR (acetone- $d_6$ , 500 MHz)  $\delta$  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)  $\delta$  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<sub>2</sub>, C-9), 28.7 (CH<sub>2</sub>, C-5), 27.8 (CH<sub>2</sub>, C-12), 25.3 (CH<sub>2</sub>, C-8), 22.7 (CH<sub>3</sub>, C-16), 17.0 (CH<sub>3</sub>, 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%);  $\lambda_{max}$  (log  $\epsilon$ ) 204 (4.4) and 291 (3.7) nm; IR (KBr)  $\nu_{max}$  2925, 1764, 1469, 1370, 1186, 1041, 895  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  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)  $\delta$  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  $\times$  CH, C-2 and C-3), 38.1 (CH<sub>2</sub>, C-9), 29.3 (CH<sub>2</sub>, C-5), 28.0 (CH<sub>2</sub>, C-12), 24.7 (CH<sub>2</sub>, C-8), 22.8 (CH<sub>3</sub>, C-15), 21.1 (CH<sub>3</sub> of acetate), 20.9 (CH<sub>3</sub> of acetate), and 17.0 (CH<sub>3</sub>, 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 ( $CHCl_3$ )  $\lambda_{max}$  (log  $\epsilon$ ) 241 (3.1) and 260 (2.8) nm; IR (KBr)  $\nu_{max}$  3082, 2927, 2855, 1764, 1639, 1470, 1185, 1017, 895  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  6.88 (2  $\times$  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)  $\delta$  169.2 (2  $\times$  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<sub>2</sub>, C-15), 113.4 (CH<sub>2</sub>, C-12), 49.9 (CH, C-7), 37.9 (C, C-6), 37.8 (CH<sub>2</sub>, C-5), 27.4 (CH<sub>2</sub>, C-8), 26.2 (CH<sub>3</sub>, C-16), 23.3 (CH<sub>3</sub>, C-13), and 20.9 (2  $\times$  CH<sub>3</sub>, 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  $^{\circ}C$ ; UV ( $CHCl_3$ )  $\lambda_{max}$  (log  $\epsilon$ ) 241 (4.2) nm; IR (KBr)  $\nu_{max}$  2924, 1732, 1638, 1469, 1450, 1314, 1266, 1211, 1083, 1063, 1025, 709  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  8.23 (4  $\times$  1H, m, overlapping signals of H-2', H-2'', H-6', and H-6''), 7.66 (2  $\times$  1H, m, overlapping signals of H-4' and H-4''), 7.53 (4  $\times$  1H, m, overlapping signals of H-3', H-3'', H-5', and H-5''), 7.08 (2  $\times$  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)  $\delta$  164.8 (2  $\times$  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  $\times$  CH, C-4' and C-4''), 130.8 (2  $\times$  C, C-1' and C-1''), 130.3 (4  $\times$  CH, C-2', C-2'', C-6', and C-6''), 129.5 (C, C-10), 129.4 (C, C-9), 128.7 (4  $\times$  CH, C-3', C-3'', C-5', and C-5''), 120.0 (CH, C-2), 119.9 (CH, C-3), 113.7 (CH<sub>2</sub>, C-15), 113.4 (CH<sub>2</sub>, C-12), 50.0 (CH, C-7), 37.9 (C, C-6), 37.8 (CH<sub>2</sub>, C-5), 27.5 (CH<sub>2</sub>, C-8), 26.2 (CH<sub>3</sub>, C-16), and 23.2 (CH<sub>3</sub>, 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 ( $CHCl_3$ )  $\lambda_{max}$  (log  $\epsilon$ ) 242 (4.6) nm; IR (KBr)  $\nu_{max}$  3087, 2924, 1575, 1460, 1380, 1091, 822, 784  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 500 MHz)  $\delta$  7.71 (4  $\times$  1H, m, aromatic protons of 4-bromobenzenesulfonyl group), 7.64 (4  $\times$  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)  $\delta$  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  $\times$  C, C-3', C-3'', C-5', and C-5''), 132.5 (C, C-9), 132.0 (C, C-10), 129.9 (2  $\times$  C, C-4' and C-4''), 129.7 (4  $\times$  C, C-2', C-2'', C-6', and C-6''), 120.3 (CH, C-2), 120.0 (CH, C-3), 113.7 (CH<sub>2</sub>, C-15), 113.5 (CH<sub>2</sub>, C-12), 49.2 (CH, C-7), 37.6 (C, C-6), 37.5 (CH<sub>2</sub>, C-5), 27.3 (CH<sub>2</sub>, C-8), 26.0 (CH<sub>3</sub>, C-16), and 23.1 (CH<sub>3</sub>, 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  $^{\circ}C$ ) 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  $^{\circ}C$ ) 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<sub>3</sub> 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<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by HPLC (reversed-phase C<sub>18</sub> column, MeCN–H<sub>2</sub>O, 40:60), furnishing compounds **10** (10.8 mg, 40.7%) and **11** (2.0 mg, 7.6%).

**Compound 10:** Yellow oil;  $[\alpha]_D^{26} +2.1$  (c 0.12, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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<sub>3</sub>COO), 2.29 (3H, s, CH<sub>3</sub>COO), 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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 169.3 (C, CH<sub>3</sub>COO), 169.1 (C, CH<sub>3</sub>COO), 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<sub>2</sub>, C-15), 45.1 (CH, C-11), 36.9 (CH<sub>2</sub>, C-7), 34.4 (CH<sub>2</sub>, C-9), 33.8 (C, C-6), 31.5 (CH<sub>2</sub>, C-5), 27.3 (CH<sub>3</sub>, C-16), 24.2 (CH<sub>2</sub>, C-12), 23.6 (CH<sub>2</sub>, C-8), 20.9 (CH<sub>3</sub>COO), and 20.8 (CH<sub>3</sub>COO); ESITOFMS *m/z* 329.1748 [M + H]<sup>+</sup> (calcd for C<sub>20</sub>H<sub>25</sub>O<sub>4</sub>, 329.1753).

**Compound 11:** Yellow oil;  $[\alpha]_D^{26} +5.5$  (c 0.08, MeOH); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 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); <sup>13</sup>C NMR data could not be recorded due to a limited amount of the material; ESITOFMS *m/z* 351.1578 [M + Na]<sup>+</sup> (calcd for C<sub>20</sub>H<sub>24</sub>O<sub>4</sub>Na, 351.1572).

**Antimycobacterial Assay.** Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H<sub>37</sub>Ra using the Microplate Alamar Blue Assay (MABA).<sup>23</sup> Standard drugs rifampicin, isoniazid, and kanamycin sulfate were used 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.<sup>24</sup> Quantitative assessment of malarial activity in vitro was determined by means of microculture radioisotope technique based upon the method described by Desjardins et al.<sup>25</sup> An IC<sub>50</sub> 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.<sup>26</sup> The IC<sub>50</sub> 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.<sup>27</sup> The reference substance was ellipticine (Table 1).

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**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>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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