# 2-Substituted Furans from the Roots of *Polyalthia evecta*

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Four new 2-substituted furans, 19-(2-furyl)nonadeca-5,7-diynoic acid (**1**), 19-(2-furyl)nonadeca-5-ynoic acid (**2**), 1-(2-furyl)pentacosa-7,9-diyne (**3**), and ester 21-(2-furyl)heneicosa-14,16-diyne-19-(2-furyl)nonadeca-5,7-diynoate (**4**) have been isolated from the roots of *Polyalthia evecta*. Their structures were established by spectroscopic techniques. Compounds **1** and **1a** showed antiplasmodial activity. The acids **1** and **2** exhibited antiviral activity against *Herpes simplex* type 1. In addition, **5** also showed cytotoxicity against the NCI-H187 cell line.

*Polyalthia evecta* (Pierre) Finet & Gagnep (Annonaceae) is a small tree found in the northeastern part of Thailand. It is known as "Nam-tou-lang" or "Tong-lang" in Thai, and a water decoction of the roots is used traditionally as a galactagogue (inducing milk secretion in breastfeeding mothers).[1] Previous phytochemical investigations on *Polyalthia* species resulted in the isolation of various types of compounds such as clerodane diterpenes,[2−4] triterpenes,[5,6] benzopyran derivatives,[7] polyacetylenes,[8,9] and several types of alkaloids.[10−16] In a previous paper we reported the isolation and characterization of a new 21-furan-heneicosa-5,7-diynoic acid from roots of *P. evecta*.[8] In our continuing search for bioactive constituents from Thai plants, hexane and dichloromethane extracts of air-dried roots of *P. evecta* were shown to be active against *Plasmodium falciparum* ($IC_{50}$ 20 $\mu$g/mL for both extracts) and *Mycobacterium tuberculosis* (MIC 50 and 25 $\mu$g/mL, respectively). Further investigation of *P. evecta* by bioactivity guidance led to the isolation of four new 2-substituted furans, 19-(2-furyl)nonadeca-5,7-diynoic acid (**1**), 19-(2-furyl)nonadeca-5-ynoic acid (**2**), 1-(2-furyl)pentacosa-7,9-diyne (**3**), and an ester, 21-(2-furyl)heneicosa-14,16-diyne-19-(2-furyl)nonadeca-5,7-diynoate (**4**). Saponification of ester **4** was performed to confirm the structure of **4**. In addition, methyl ester derivatives of **1** and **2**, **1a** and **2a**, were also prepared for chemical investigation as well as biological evaluation.

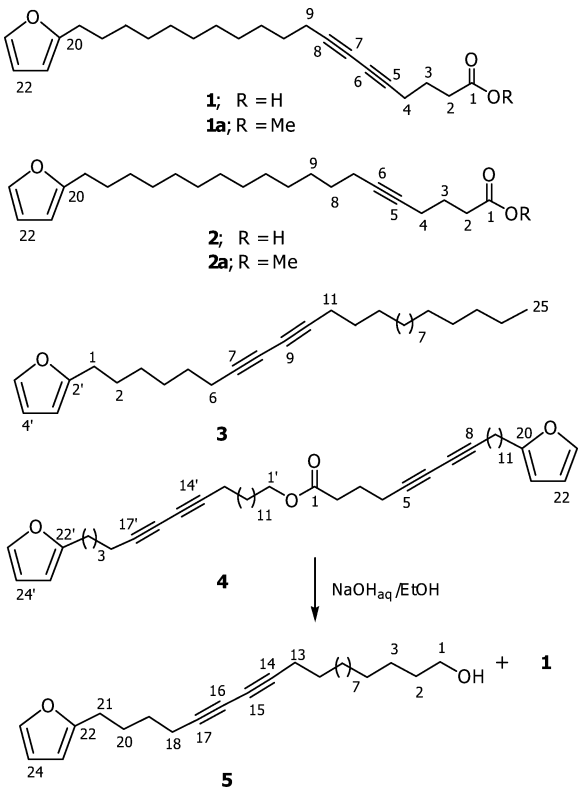


**Table 1.** $^1$H and $^{13}$C NMR Data of **1** and **2** ($CDCl_3$, 400 Mz)[a]

| | **1** | | **2** | |
|---|---|---|---|---|
| position | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ |
| 1 | | 178.7 | | 179.1 |
| 2 | 2.50 (2H, t, 7.4) | 32.6 | 2.42 (2H, t, 7.4) | 32.7 |
| 3 | 1.86 (2H, tt, 7.7, 6.9) | 23.3 | 1.74 (2H, tt, 7.4, 6.9) | 23.9 |
| 4 | 2.34 (2H, brt, 7.0) | 18.6 | 2.06 (2H, brt, 7.0) | 18.7 |
| 5 | | 75.7 | | 78.5 |
| 6 | | 66.4 | | 81.6 |
| 7 | | 65.1 | 2.17 (2H, t, 6.8) | 18.2 |
| 8 | | 78.2 | 1.40 (2H, quint, 7.0) | 28.9 |
| 9 | 2.24 (2H, t, 7.1) | 19.2 | 1.29 (2H, m) | 29.2 |
| 10 | 1.58 (2H, quint, 7.1) | 28.3 | *d* | *e* |
| 11 | 1.37 (2H, m) | *c* | *d* | *e* |
| 12−16 | *b* | *c* | *d* | *e* |
| 17 | 1.25 (2H, m) | *c* | *d* | *e* |
| 18 | 1.62 (2H, quint, 7.3) | 28.1 | 1.56 (2H, quint, 7.3) | 28.0 |
| 19 | 2.62 (2H, t, 7.6) | 27.9 | 2.53 (2H, t, 7.6) | 27.9 |
| 20 | | 156.6 | | 156.7 |
| 21 | 5.95 (1H, d, 3.2) | 104.5 | 5.94 (1H, d, 3.2) | 104.5 |
| 22 | 6.26 (1H, dd, 3.2, 1.9) | 110.0 | 6.25 (1H, dd, 3.2, 1.9) | 110.0 |
| 23 | 7.23 (1H, brs) | 140.6 | 7.22 (1H, brs) | 140.6 |

[a] Chemical shift values are in ppm, and *J* values (in Hz) are presented in parentheses. [b] 1.25 (10H, brs). [c] 28.9, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7. [d] 1.19 (16H, brs). [e] 28.9, 29.1, 29.4, 29.6, 29.6.

## Results and Discussion

Compound **1** was obtained as colorless plates, and it was assigned the molecular formula $C_{23}H_{32}O_3$ from the HRESITOFMS, *m*/*z* 379.2249 $[M + Na]^+$. The IR spectrum showed the presence of carboxylic acid (3500−2400 and 1690 $cm^{-1}$), conjugated acetylene (2180 and 2145 $cm^{-1}$), and furan (1595, 1500, 1140, 1005, and 880 $cm^{-1}$) groups. Esterification of **1** with MeOH in the presence of $SOCl_2$ yielded the monomethyl ester **1a** [$\delta_H$ 3.63, $\delta_C$ 51.6, 173.4 ($CO_2CH_3$)], which supported the presence of a carboxylic acid in **1**. The $^1$H and $^{13}$C NMR spectra (Table 1) showed a broad singlet signal observed at $\delta_H$ 1.25 (10H), which correlated to the overlapping signals between $\delta_C$ 28.9 and 29.6 in the HSQC spectrum and revealed a long methylene chain. The COSY spectrum indicated the partial structure of three $-CH_2CH_2CH_2-$ units and a 2-substituted furan (see Figure 1). The HMBC correlations of H-2 to

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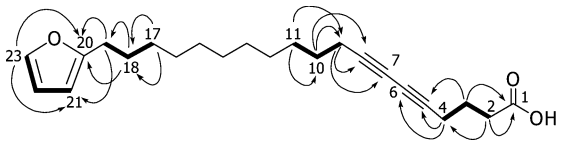

**Figure 1.** COSY (bold line) and HMBC (arrow, $^1H \rightarrow ^{13}C$) correlations obtained for **1**.

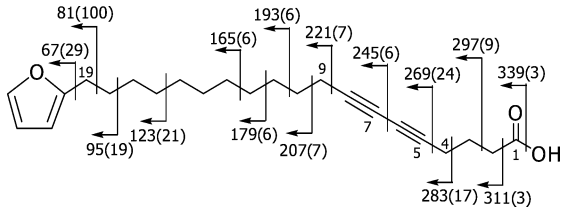

**Figure 2.** EIMS fragmentations of **1** with relative intensity values in parentheses.

C-1 ($\delta$ 178.7) and C-4; H-3 to C-1 and C-5 ($\delta$ 75.7); H-4 to C-2, C-5, and C-6 ($\delta$ 66.4); H-9 to C-7 ($\delta$ 65.1) and C-8 ($\delta$ 78.2); H-10 to C-8 and C-9; H-11 to C-10 and C-9; H-17 to C-18 and C-19; H-18 to C-19 and C-20; and H-19 to C-20 and C-21 revealed two partial structures C-1 through C-11 and a furan ring with a 2-substituted long methylene chain (see Figure 1). The $^1H$ and $^{13}C$ chemical shifts at C-1−C-8 of **1** were comparable to those reported for a related compound, 18-dibromooctadeca-9(*E*),17(*E*)-diene-5,7-diynoic acid.[17] These two parts were connected through the methylene chain (C-12−C-16). The complete structure of **1** was further established by the intensive examination of EIMS fragmentation (see Figure 2). The fragment at *m*/*z* 311 $[M - COOH]^+$ confirmed the carboxylic acid group. The conjugated acetylene unit was located between C-4 and C-9 on the basis of the ion peaks at *m*/*z* 269, 245, and 221. Finally, the peaks at *m*/*z* 67 and 81 [furfuryl, $C_5H_5O]^+$ supported that the furan ring was connected to C-19. From the above data, the structure of **1** was determined as 19-(2-furyl)-nonadeca-5,7-diynoic acid.

Compound **2** was obtained as colorless plates, and it was assigned the molecular formula $C_{23}H_{36}O_3$ from the HRESITOFMS, *m*/*z* 361.2654 $[M + H]^+$. The IR spectrum showed the presence of a carboxylic acid (3500−2400 and 1685 $cm^{-1}$), an acetylene (2200 $cm^{-1}$), and a furan (1595, 1505, 1150, 1010 and 887 $cm^{-1}$) group. Esterification of **2** with MeOH in the presence of $SOCl_2$ gave the monomethyl ester **2a** [$\delta_H$ 3.69, $\delta_C$ 51.9, 173.6 ($CO_2CH_3$)], supporting the presence of a carboxylic acid in **2**. The $^1H$ and $^{13}C$ NMR spectra (Table 1) displayed resonance patterns similar to those of **1** except for the appearance of two more methylene groups in the chain, and only one acetylenic unit at $\delta_C$ 78.5 (C-5) and 81.6 (C-6) has been found in **2**. The COSY spectrum exhibited the partial structure of three $-CH_2CH_2CH_2-$ units and 2-substituted furan as in **1**. Weak correlation observed between H-4 ($\delta$ 2.06) and H-7 ($\delta$ 2.17) suggested that these two methylenes were connected through an acetylene unit. The HMBC also confirmed the connection of C-1 through C-9 by showing correlations of H-2 to C-1 ($\delta$ 179.1) and C-4; H-3 to C-1 and C-5; H-4 to C-2, C-5, and C-6; H-7 to C-5, C-6, and C-9; H-8 to C-6 and C-7; and H-9 to C-7 and C-8. The $^1H$ and $^{13}C$ chemical shifts at C-1−C-6 of **2** were also comparable to those reported for the related compound, 16-bromohexadeca-7(*E*),11(*E*),15(*E*)-triene-5-ynoic acid.[17] The complete structure of **2** was further established by intensive examination of EIMS fragmentation (see Figure 3). The fragment at *m*/*z* 315 $[M - COOH]^+$ confirmed the carboxylic acid in **2**. The acetylenic unit was located between C-4 and C-7 on the basis of the ion peaks at *m*/*z* 273 and 249. The other ion peaks were similar to those of **1**. From the above data, the structure of **2** was determined as 19-(2-furyl)nonadeca-5-ynoic acid.

Compound **3** was isolated as a pale yellow oil, and it was assigned the molecular formula $C_{29}H_{46}O$ from the HRESITOFMS,

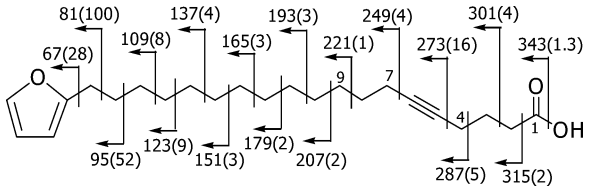

**Figure 3.** EIMS fragmentations of **2** with relative intensity values in parentheses.

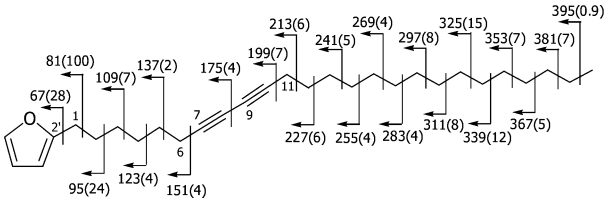

**Figure 4.** EIMS fragmentations of **3** with relative intensity values in parentheses.

*m*/*z* 411.3540 $[M + H]^+$. The most abundant ion, at *m*/*z* 81, from EIMS, due to a $[furfuryl]^+$ fragment unit suggested a partial structure of a furan ring connected to one methylene carbon ($-C_5H_5O$). The IR spectrum showed the presence of absorption bands of conjugated acetylene (2220 and 2150 $cm^{-1}$) and furan (1590, 1500, 1170, 1070, and 885 $cm^{-1}$) units. The $^1H$ NMR spectrum of **3** showed the presence of a 2-substituted furan at $\delta$ 7.31 (d, $J = 1.2$ Hz, H-5′), 6.29 (dd, $J = 2.3$, 1.2 Hz, H-4′), and 5.86 (d, $J = 2.3$ Hz, H-3′). The methylene group bearing the furan ring showed a triplet signal at $\delta$ 2.62 ($J = 7.6$ Hz, H-1), while the two methylene groups connected to the acetylene units appeared as a triplet signal at $\delta$ 2.26 ($J = 7.0$ Hz, $H_2$-6 and $H_2$-11). Two methylene protons, $H_2$-5 and $H_2$-12, showed overlapping signals at $\delta$ 1.53 (4H, quint, $J = 7.1$ Hz). The resonances at $\delta$ 1.28 (brs) and 0.90 (t, $J = 6.9$ Hz, H-25) supported the methylene chain with a terminal methyl group. The $^{13}C$ NMR spectrum provided strong support for the 2-substituted furan at $\delta$ 156.4 (C-2′), 140.6 (C-5′), 110.0 (C-4′), and 104.5 (C-3′). The conjugated acetylenic carbons were observed as two symmetrical signals at $\delta$ 77.6 (C-7 and C-10) and 65.2 (C-8 and C-9), which were comparable to those of $^{13}C$ NMR data of the most closely related compound, 1-(2-furyl)-pentacosa-16,18-diyne [$\delta$ 75.50 (C-16 or C-19), 75.51 (C-19 or C-16), and 65.25 (C-17 and C-18)].[9] The other connectivities were confirmed by COSY, HMQC, and HMBC correlations. The HMBC spectrum displayed correlations of H-1 to C-2′, C-3′, and C-2; H-2 to C-1and C-2′; H-5 to C-6 and C-7; H-6 to C-7 and C-8; H-11 to C-9 and C-10; H-12 to C-10; and H-25 to C-24 and C-23, which revealed the partial connection in the molecule. The complete structure of **3** was further established by intensive examination of EIMS fragmentation (see Figure 4). The conjugated acetylene unit was located between C-6 and C-11 on the basis of the ion peaks at *m*/*z* 199, 175, and 151, while the furan ring was connected to C-1 according to the peaks at *m*/*z* 67 and 81 $[furfuryl]^+$. From the above data, the structure of **3** was determined as 1-(2-furyl)pentacosa-7,9-diyne.

Compound **4** was obtained as white wax, and it was assigned the molecular formula $C_{48}H_{68}O_4$ from the ESITOFMS, *m*/*z* 709 $[M + H]^+$. The IR spectrum showed absorption bands of conjugated acetylene (2220 and 2140 $cm^{-1}$), carbonyl ester (1735 $cm^{-1}$), and furan (1590, 1500, 1070, 1000, and 880 $cm^{-1}$) groups. The $^1H$ NMR spectrum indicated resonances of two 2-substituted furan groups at $\delta$ 7.27 (brd, $J = 1.0$ Hz, H-23 and H-25′), 6.25 (dd, $J = 2.3$ and 1.0 Hz, H-22 and H-24′), and 5.95 (d, $J = 2.3$ Hz, H-21 and H-23′), an oxymethylene of an ester function at 4.04 (t, $J = 6.7$ Hz, H-1′), and a methylene adjacent to a carbonyl group at 2.41 ($J = 7.4$ Hz, H-2) with an integration ratio of 1:1:1:1:1, suggesting two symmetrical furan units in the structure. The overlapping signals at $\delta$ 2.59 (4H, t, $J = 6.7$ Hz) were assigned to the methylene groups

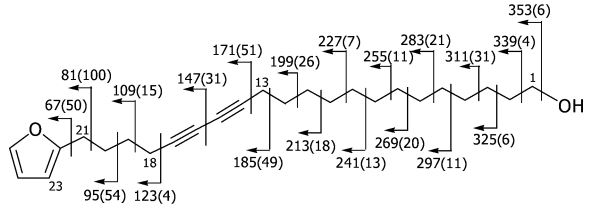


**Figure 5.** EIMS fragmentations of **5** with relative intensity values in parentheses.

($H_2$-19 and $H_2$-21′) adjacent to the furan rings. Resonances of four methylene groups ($H_2$-4, $H_2$-9, $H_2$-18′, and $H_2$-13′) connecting to acetylene units appeared as four triplet signals with the same coupling constant values (6.9 Hz) at $\delta$ 2.40, 2.31, 2.29, and 2.22, respectively. The $^{13}$C NMR and DEPT spectra of **4** exhibited eight resonances of acetylenic carbons at $\delta$ 78.4, 78.1, 77.6, 76.4, 66.6, 65.9, 65.6, and 65.5, revealing two sets of conjugated acetylene units. The EIMS spectrum showed a fragmentation ion of [furfuryl]$^+$ at *m*/*z* 81, which confirmed the furan unit. The two fragment ions due to the α-cleavage at *m*/*z* 339 and 397 suggested that **4** was the ester. Finally, saponification was performed to confirm the structure by cleaving the suspected ester **4**, with aqueous NaOH in EtOH, to yield a carboxylic acid and alcohol **5**. The acid product was identical to the diynoic acid **1** by comparison of the spectral data and physical properties with an authentic sample.

Alcohol **5** was obtained as a yellow oil, and it was assigned the molecular formula $C_{25}H_{38}O_2$ from the HRESITOFMS, *m*/*z* 371.2941 [M + H]$^+$. The IR spectrum showed the presence of hydroxyl (3500 cm$^{-1}$), conjugated acetylene (2232 and 2143 cm$^{-1}$), and furan (1597, 1506, 1175, 1074, 1007, and 885 cm$^{-1}$) groups. The $^1$H and $^1$C NMR spectra displayed signals of a 2-substituted furan similar to those of parent **4**. The signal of a methylene bearing the hydroxyl group appeared at $\delta_H/\delta_C$ 3.66 (2H, t, $J$ = 6.6 Hz, H-1)/63.3. The methylene group connecting to the furan ring appeared at $\delta_H$ 2.63 (t, $J$ = 7.4 Hz, H-21), while two methylene groups adjacent to acetylene units showed at $\delta_H$ 2.28 (t, $J$ = 6.7 Hz, H-18) and 2.26 (t, $J$ = 6.7 Hz, H-13). A broad singlet signal at $\delta_H$ 1.28 corresponded to the methylene chain (H-4−H-10). The conjugated acetylenic carbons appeared at $\delta$ 78.1 (overlapping signals of C-14 and C-17), 65.8 (C-16), and 65.6 (C-15). Other connectivities were confirmed by COSY, DEPT, HMQC, and HMBC correlations. The HMBC spectrum exhibited correlations of H-21 to C-19, C-20, C-22, and C-23; H-20 to C-18 and C-22; H-19 to C-17 and C-21; H-18 to C-16, C-17, C-19, and C-20; H-13 to C-14 and C-15; H-12 to C-13 and C-14; and H-2 to C-1 and C-3. The complete structure of **5** was further established by the intensive examination of EIMS fragmentation (see Figure 5). The fragment ions at *m*/*z* 369 [M − H]$^+$, 353 [M − OH]$^+$, and 352 [M − $H_2O$]$^+$ indicated the alcohol of **5**. The fragment ions at *m*/*z* 171, 147, and 123 confirmed that the acetylene units must be connected between C-13 and C-18. Finally, the furan ring was connected to C-1 according to the peaks at *m*/*z* 67 and 81 [furfuryl]$^+$. On the basis of the above evidence, the structure of **5** was established as 21-(2-furyl)heneicosa-14,16-diyne-1-ol.

Several of these compounds exhibited activities against *Mycobacterium tuberculosis*. Compound **2a** showed the most activity, followed by **5**, with MIC values of 3.1 and 6.25 μg/mL, respectively. The methyl ester derivative, **1a**, was more active against *Plasmodium falciparum* than its parent **1**, with $IC_{50}$ values of 3.7 and 50 μg/mL, respectively. Acids **1** and **2** showed weak antiviral activity against *Herpes simplex* type 1 (HSV-1) with $IC_{50}$ values of 47.0 and 19.4 μg/mL, respectively. In addition, only alcohol **5** exhibited cytotoxicity against the NCI-H187 cell line, with $IC_{50}$ values of 12.4 μg/mL.

## Experimental Section

**General Experimental Procedures.** Melting points (uncorrected) were determined using a Gallenkamp melting point apparatus. IR spectra were carried out on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 spectrometer, using residual $CHCl_3$ as an internal standard. HRESITOFMS were obtained using a Micromass LCT mass spectrometer, and the lock mass calibration was applied for the determination of accurate masses. EIMS spectra were measured on Finnigan Mat INCOS 50 and Bruker-HP ESQUIRE-LC mass spectrometers. Column chromatography and preparative TLC were carried out on silica gel 60 (230−400 mesh) and $PF_{254}$, respectively.

**Plant Materials.** Roots of *Polyalthia evecta* were collected from Sri-Than Village in front of Khon Kaen University, Khon Kaen Province, Thailand, in January 2000. The plant was identified by Prof. Pranom Chantaranothai, Department of Biology, Khon Kaen University. A plant specimen (voucher number SK94001) was deposited in the herbarium of the Department of Biology, Khon Kaen University.

**Extraction and Isolation.** Air-dried roots (3.5 kg) of *P. evecta* were ground and extracted successively with hexane (6 L × 3), $CH_2Cl_2$ (5 L × 3), and MeOH (5 L × 3) at room temperature. The filtered samples were combined, and the solvents were evaporated in vacuo to yield crude hexane (105.4 g), $CH_2Cl_2$ (114.5 g), and MeOH (148.3 g) extracts, respectively. Hexane (100 mL) was added to the hexane extract (105.4 g) and allowed to stand at room temperature for a day and then kept cool in the refrigerator overnight. The precipitate was filtered and washed with cool hexane to afford a white amorphous solid of **1** (19.6 g). The filtrate was evaporated to dryness to yield an oily brown residue (85.8 g). The residue (10.9 g) was then subjected to silica gel (320 g) column chromatography and eluted with increasing concentrations of EtOAc in hexane. Each fraction (100 mL) was monitored by TLC; fractions with similar TLC pattern were combined to yield five major fractions ($F_1$−$F_5$). Fraction $F_2$ (2.9 g) was rechromatographed on a silica gel column eluted with a gradient system of $CH_2Cl_2$−EtOAc to furnish five subfractions, designated as $F_{2/1}$−$F_{2/5}$. Subfraction $F_{2/3}$ (390 mg) was further separated by preparative TLC eluted with hexane to yield **3** ($R_f$ 0.44, 89.6 mg). Subfraction $F_{5/5}$ was purified by preparative TLC eluted with EtOAc−hexane (10:90) to yield **4** ($R_f$ 0.64, 92.3 mg). Fraction $F_4$ (4.67 g) was rechromatographed on a silica gel flash column, eluted with a gradient system of EtOAc−hexane, to give seven subfractions ($F_{4/1}$−$F_{4/7}$). Subfraction $F_{4/4}$ was purified by crystallization from hexane to yield colorless plates of **2** (189 mg). Subfraction $F_{4/5}$ was purified by crystallization from hexane to yield colorless plates of an additional amount of **1** (117 mg).

The $CH_2Cl_2$ extract (78.3 g) was subjected to silica gel column chromatography, eluted with the same gradient system as the hexane extract above, to give six fractions, $F'_1$−$F'_6$. Fraction $F'_2$ was dissolved in cool hexane to yield a white solid of **1** (2.73 g). The filtrate was evaporated and the residue (15.6 g) was further chromatographed on a silica gel column, eluted with a gradient system of EtOAc−hexane, to give six subfractions, designated as $F'_{2/1}$−$F'_{2/6}$. Subfraction $F'_{2/3}$ (30−40% EtOAc−hexane) was further separated by preparative TLC, eluted with $CH_2Cl_2$−hexane (40:60), to yield an additional amount of **3** ($R_f$ 0.98, 224.3 mg). The band with $R_f$ 0.8 was further purified by preparative TLC, eluted with $CH_2Cl_2$−hexane (30:70), to yield an additional amount of **4** ($R_f$ 0.61, 159.5 mg). Subfraction $F'_{2/6}$ (50−100% EtOAc−hexane) yielded an additional amount of **1** (7.54 g).

**Compound 1:** colorless plates; mp 60−61 °C; IR (KBr) $\nu_{max}$ 3500−2400, 2910, 2840, 2180, 2145, 1690, 1595, 1500, 1465, 1450, 1425, 1410, 1140, 1200, 1170, 1075, 1005, 880 cm$^{-1}$; $^1$H and $^{13}$C NMR, see Table 1; EIMS (70 eV) *m*/*z* 356 [M]$^+$ (see Figure 2); HRESITOFMS *m*/*z* 379.2249 [M + Na]$^+$ (calcd for $C_{23}H_{32}O_3$ + Na, 379.2351).

**Compound 2:** colorless plates; mp 63−64 °C; IR (KBr) $\nu_{max}$ 3500−2400, 2910, 2840, 2200, 1685, 1595, 1505, 1460, 1440, 1410, 1340, 1285, 1270, 1220, 1175, 1150, 1060, 1010, 887 cm$^{-1}$; $^1$H and $^{13}$C NMR, see Table 1; EIMS (70 eV) *m*/*z* 360 [M]$^+$ (see Figure 3); HRESITOFMS *m*/*z* 361.2654 [M + H]$^+$ (calcd for $C_{23}H_{36}O_3$ + H, 361.2664).

**Compound 3:** yellow oil; IR (neat) $\nu_{max}$ 3100, 2910, 2840, 2220, 2150, 1590, 1500, 1460, 1420, 1145, 1170, 1070, 1007, 885 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.31 (1H, d, $J$ = 1.2 Hz, H-5′), 6.29 (1H, dd, $J$ = 2.3, 1.2 Hz, H-4′), 5.86 (1H, d, $J$ = 2.3 Hz, H-3′), 2.62 (2H, t, $J$ = 7.6 Hz, H-1), 2.26 (4H, t, $J$ = 7.0 Hz, H-6 and H-11), 1.64 (2H, quint, $J$ = 7.4 Hz, H-2), 1.53 (4H, quint, $J$ = 7.1 Hz, H-5 and H-12), 1.40 and 1.39 (4H, m, H-4 and H-13), 1.28 (24H, brs, H-3 and H-14-H-24), 0.90 (3H, t, $J$ = 6.9 Hz, H-25); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 156.4 (C-2′), 140.6 (C-5′), 110.0 (C-4′), 104.5 (C-3′), 77.6 (C-7), 77.6 (C-10), 65.2 (C-8), 65.2 (C-9), 31.3, 29.6, 29.5, 29.4, 29.3, 29.2,

29.1, 28.8 (C-4 and C-13), 28.5 (C-2), 28.3 (C-1), 28.0, 27.9, 22.5, 19.2 (C-5 and C-12), 14.0 (C-25); EIMS (70 eV) *m/z* 410 $[M]^+$ (see Figure 4); HRESITOFMS *m/z* 411.3540 $[M + H]^+$ (calcd for $C_{29}H_{46}O$ + H, 411.3549).

**Compound 4:** white wax; IR (neat) $\nu_{max}$ 3100, 2910, 2840, 2220, 2140, 1735, 1590, 1500, 1460, 1420, 1175, 1140, 1070, 1000, 880 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.27 (2H, brd, $J$ = 1.0 Hz, H-23 and H-25′), 6.25 (2H, dd, $J$ = 2.3, 1.0 Hz, H-22 and H-24′), 5.95 (2H, d, $J$ = 2.3 Hz, H-21 and H-23′), 4.04 (2H, t, $J$ = 6.7 Hz, H-1′), 2.59 (4H, t, $J$ = 6.7 Hz, H-19 and H-21′), 2.41 (2H, t, $J$ = 7.4 Hz, H-2), 2.40 (2H, t, $J$ = 6.9 Hz, H-4), 2.31 (2H, t, $J$ = 6.9 Hz, H-9) 2.29 (2H, t, $J$ = 6.9 Hz, H-18′) and 2.22 (2H, t, $J$ = 6.9 Hz, H-13′), 1.82 (2H, quint, $J$ = 7.2 Hz), 1.60 (8H, quint, $J$ = 7.1 Hz), 1.49 (8H, quint, $J$ = 7.1 Hz), 1.40−1.20 (28H, m); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 173.4 (C-1), 157.0 (C-20 and C-22′), 141.0 (C-23 and C-25′), 110.4 (C-22 and C-24′), 104.9 (C-21 and C-23′), 78.4 (C-8), 78.1 (C-14′), 77.6 (C-5), 76.4 (C-17′), 66.6 (C-6), 65.9 (C-16′), 65.6 (C-15′), 65.5 (C-7), 64.9 (C-1′), 33.4, 30.0, 30.0, 29.9, 29.8, 29.3, 28.9, 28.8, 28.7, 28.6, 28.4, 25.9, 24.0, 19.6, 19.5, 19.1; EIMS (70 eV) *m/z* (rel int) *m/z* 708 (0.8) $[M]^+$, 397 (2), 353 (3), 339 (4), 325 (2), 311 (3), 297 (4), 283 (3), 269 (3), 255 (2), 245 (2), 241 (2), 227(3), 221 (3), 213 (3), 199 (4), 193 (3), 185 (5), 179 (3), 171 (7), 165 (2), 151 (2), 147 (8), 137 (4), 123 (7), 109 (9), 95 (29), 81 (100), 67 (24); ESITOFMS *m/z* 709 $[M + H]^+$ (calcd for $C_{48}H_{68}O_4$ + H, 709).

**Preparation of Ester 1a.** To a solution of **1** (300.6 mg) in absolute MeOH (5 mL) were added a few drops of $SOCl_2$. The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The product was purified by preparative TLC (EtOAc−hexane, 20:80) to give a yellow oil of **1a** (151.9 mg, 50.5%); IR (neat) $\nu_{max}$ 3115, 2928, 2855, 2233, 2164, 1738, 1597, 1508, 1462, 1456, 1435, 1211, 1157, 1148, 1074, 1007, 880 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.31 (1H, brs, H-23), 6.29 (1H, brs, H-22), 5.98 (1H, brs, H-21), 3.63 (3H, s, $CO_2CH_3$), 2.60 (2H, t, $J$ = 7.6 Hz, H-19), 2.45 (2H, t, $J$ = 7.2 Hz, H-2), 2.33 (2H, t, $J$ = 6.8 Hz, H-4), 2.22 (2H, t, $J$ = 7.0 Hz, H-9), 1.85 (2H, quint, $J$ = 7.0 Hz, H-3), 1.63 (2H, quint, $J$ = 7.0 Hz, H-18), 1.51 (2H, quint, $J$ = 6.8 Hz, H-8), 1.40−1.30 (m), 1.28 (brs), H-11-H-17; $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 173.4 (C-1), 156.6 (C-20), 140.6 (C-23), 110.0 (C-22), 104.5 (C-21), 78.1 (C-8), 75.9 (C-5), 66.3 (C-6), 65.1 (C-7), 51.6 ($OCH_3$), 32.7 (C-2), 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.3, 28.1 (C-12 − C-17), 28.8 (C-8), 28.3 (C-10), 28.1 (C-18) 27.9 (C-19), 24.1 (C-3), 19.2 (C-9), 18.5 (C-4); ESITOFMS *m/z* 371 $[M + H]^+$ (calcd for $C_{24}H_{34}O_3$ + H, 371).

**Preparation of Ester 2a.** To a solution of **2** (27.2 mg) in absolute MeOH (3 mL) were added a few drops of $SOCl_2$. The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed in vacuo. The product was purified by preparative TLC (EtOAc−hexane, 20:80) to give a yellow oil of **2a** (13.7 mg, 48.5%); IR (Neat) $\nu_{max}$ 3117, 2926, 2855, 2202, 1742, 1595, 1462, 1456, 1435, 1161, 1148, 1074, 1009, 880 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.31 (1H, s, H-23), 6.29 (1H, brs, H-22), 5.98 (1H, brs, H-21), 3.69 (3H, s, $OCH_3$), 2.58 (2H, t, $J$ = 7.6 Hz, H-19), 2.41 (2H, t, $J$ = 7.4, H-2), 2.20 (2H, t, $J$ = 7.0 Hz, H-7), 2.11 (2H, t, $J$ = 7.0 Hz, H-4), 1.77 (2H, quint, $J$ = 7.2 Hz, H-3), 1.59 (2H, quint, $J$ = 7.0 Hz, H-18), 1.44 (2H, quint, $J$ = 7.1, H-8), 1.30 (18H, brm, H-9−H-17); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 173.6 (C-1), 157.1 (C-20), 141.0 (C-23), 110.4 (C-22), 104.9 (C-21), 81.8 (C-6), 79.1 (C-5), 51.9 ($OCH_3$), 32.7 (C-2), 28.7 (C-8), 27.8 (C-18), 27.7 (C-19), 24.1 (C-3), 18.5 (C-4), 18.1 (C-7), 29.7, 29.5, 29.1, 29.0, 28.0, 28.4, 23.9, 18.7, 19.1 (C-9−C-17); ESITOFMS *m/z* 375 $[M + H]^+$ (calcd for $C_{24}H_{38}O_3$ + H, 375).

**Saponification of 4.** To a solution of **4** (194.9 mg) in EtOH (5 mL) was added 6 M NaOH (3 mL). The solution mixture was refluxed for 2.5 h, acidified with 3 M HCl, and then extracted with $CH_2Cl_2$ (15 mL × 2). The $CH_2Cl_2$ solution was dried over anhydrous $Na_2SO_4$, and the solvent was removed in vacuo. The residue was separated by preparative TLC ($CH_2Cl_2$) to yield an amorphous solid of **1** ($R_f$ 0.10, 47.4 mg, 24.4%) and a pale yellow oil of **5** ($R_f$ 0.51, 67.8 mg, 34.8%); IR (neat) $\nu_{max}$ 3500, 3115, 2920, 2851, 2232, 2143, 1597, 1506, 1470, 1441, 1175, 1148 1074, 1030, 1007, 885 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.31 (1H, brs, H-25), 6.29 (1H, brs, H-24), 5.99 (1H, d, $J$ = 2.3 Hz, H-23), 3.66 (2H, t, $J$ = 6.6 Hz, H-1), 2.63 (2H, t, $J$ = 7.4 Hz, H-21), 2.28 (2H, t, $J$ = 6.7 Hz, H-18), 2.26 (2H, t, $J$ = 6.7 Hz, H-13) 1.65 (2H, quint, $J$ = 6.8 Hz, H-20), 1.60 (2H, quint, $J$ = 6.8 Hz, H-2), 1.55 (2H, quint, $J$ = 6.8 Hz, H-19), 1.50 (2H, quint, $J$ = 6.8 Hz, H-12), 1.36 (2H, m, H-3) and 1.28 (brs, H-4-H-11); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 157.0 (C-22), 141.0 (C-25), 110.4 (C-24), 104.9 (C-23), 78.1 (C-14), 78.1 (C-17) 65.8 (C-16), 65.6 (C-15), 63.3 (C-1), 33.0 (C-2), 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.0 (C-4-C-12), 28.7 (C-19), 28.3 (C-21), 28.4 (C-20), 25.6 (C-3), 19.6 (C-13), 19.5 (C-18); EIMS (70 eV) *m/z* 370 $[M]^+$ (see Figure 5); HRESITOFMS *m/z* 371.2941 $[M + H]^+$ (calcd for $C_{25}H_{38}O_2$ + H, 371.2872).

**Antimalarial Assay.** Antimalarial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain), using the method of Trager and Jensen.[18] Quantitative assessment of malarial activity in vitro was determined by means of the microculture radioisotope technique based upon the method described by Desjardins et al.[19] The inhibitory concentration ($IC_{50}$) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of [$^3$H]-hypoxanthine by *P. falciparum*. The standard compound was artemisinin ($IC_{50}$ 0.001 $\mu$g/mL).

**Antimycobacterial Assay.** Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the Microplate Alamar Blue Assay (MABA).[20] Standard drugs, isoniazid and kanamycin sulfate, were used as the reference compounds (MIC 0.04−0.09 and 2.0−5.0 $\mu$g/mL, respectively).

**Cytotoxicity and Antiviral Assay.** Antiviral activity against *Herpes simplex* type 1 and cytotoxic assays against human epidermoid carcinoma (KB), human breast cancer (BC), and human small cell lung cancer (NCI-H187) cell lines were performed employing the colorimetric method as described by Skehan and co-workers.[21] The reference substances were acyclovir ($IC_{50}$ 1.1 $\mu$g/mL) for antiviral and ellipticine for anticancer cell lines ($IC_{50}$ 0.36, 0.32, and 0.26 $\mu$g/mL, respectively).

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**Supporting Information Available:** EIMS spectra of compounds **1**, **2**, **3**, and **5** are available free of charge via the Internet at http://pubs.acs.org.

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