Antitumor Activity of Novel Deoxoartemisinin Monomers, Dimers, and Trimer

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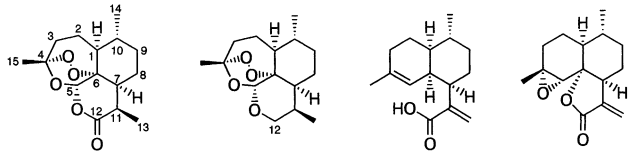
The first primary amines **9** and bromoalkyl analogues **7** of deoxoartemisinin with nonacetal functionality at C-12 are prepared as versatile intermediates for the synthesis of various derivatives. Eight C-12 nonacetal type dimers and one trimer of deoxoartemisinin were prepared using novel chemistry. Dimers, particularly **12a**, **18a**,**b**, and trimer **17**, were especially potent and selective at inhibiting the growth of certain human cancer cell lines and were comparable to that of clinically used anticancer drugs. The linker with one amide- or one sulfur-centered two ethylene groups of the dimers is essential for high anticancer activity. Trimer **17** shows very potent activity against most of the human cancer cell lines tested.

Introduction

Artemisinin (Qinghaosu) **1**, a sesquiterpene lactone endoperoxide, is the first natural trioxane isolated from *Artemisia annua*, L. (Scheme 1). This compound is of special biological interest because of its outstanding antimalarial activity[1] and in vitro activity against *Pneumocystis carinii*[2] and *Toxoplasma gondii*.[3] The anti-human immunodeficiency virus (HIV) activity of artemisinin-related trioxanes was also first reported by our group.[4] Artemisinin has been subjected to a number of reviews[5−14] because of its novel structure and outstanding antimalarial activity. Most first generation C-12 acetal type derivatives are hydrolytically unstable, and most semisyntheses have involved replacing the C-12 acetal functionality in ether derivatives by less hydrolytically prone functional groups. Deoxoartemisinin **1a**, prepared from either artemisinin or artemisinic acid **2** by Jung et al.,[15] is the first nonacetal type analogue of artemisinin and shows more antimalarial activity than that of artemisinin both in vitro and in vivo.[16] Nonacetal type analogues of deoxoartemisinin recently drew attention due to better bioavailability, such as acid stability, than acetal type analogues. Furthermore, evidence that analogues not possessing exo-oxygen at C-12 are less neurotoxic in animal studies than acetal type artemisinin is also emerging and may thus in the future bypass the current clinically used acetal type analogues (artemether, arteether, artesunate, and artelinic acid).[17] After the preparation of 12-*n*-butyldeoxoartemisinin as the first hydrolytically stable nonacetal type analogue[18] containing a C−C bond at C-12 was reported, a series of nonacetal type derivatives including a few heteroaryl and unsaturated substituents at C-12 have been prepared.[19−27] Although most studies have focused on antimalarial activities, a few research groups have recently reported on cytotoxicity of artemisinin and its related derivatives.[28−33] We first reported that artemsinin-related sesquiterpene, arteannuin B **2a**, shows good in vitro antineoplastic activity ($IC_{50} = 12\ \mu M$ against L-1210).[34] Because of their higher rate of cell division, most cancer cells express a higher surface concentration of transferrin receptors than normal cells[35,36] and have high rates of iron intake.[37,38] A unique structure bearing endoperoxide could be a trigger for the generation of active oxygen radicals via homolytic cleavage of the weak oxygen peroxide bond accelerated by higher ferrous ion concentration of cancer cells,[38] which may mediate for the selective and preferable damage to vital cellular structures of the relatively active cancer cells. This concept, coupled with preliminary results, prompted us to prepare deoxoartemisinin-related compounds and evaluate their in vitro cytotoxicity. Some dimeric chemical structures showed especially high biological activities. Although some dimers of acetal type derivatives of artemisinin have been prepared[39] and show antitumor activities,[40,41] yields are low and most of them possess either aromatic linkers or still acetal types at the C-12 position, which are neurotoxic, acid unstable, and show low antitumor activities. In this paper, we report a novel preparation of C-12 nonacetal type derivatives of deoxartemisinin as monomers, dimers, and one trimer and their exceptionally high antitumor activities.

Scheme 1



Results and Discussion

Chemistry. We designed nonacetal type analogues for increasing bioavailability such as acid stability or water solubility of the lead compound artemisinin **1**. Because artemisinin is much more expensive than artemisinic acid **2** and because the direct introduction of a C−C bond at C-12 of artemisinin for the preparation

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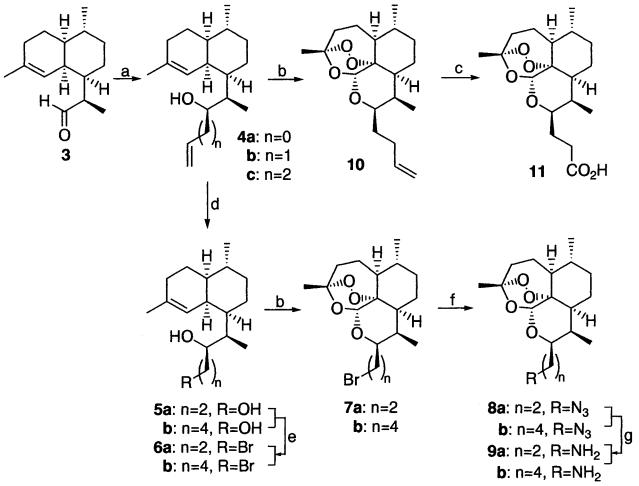
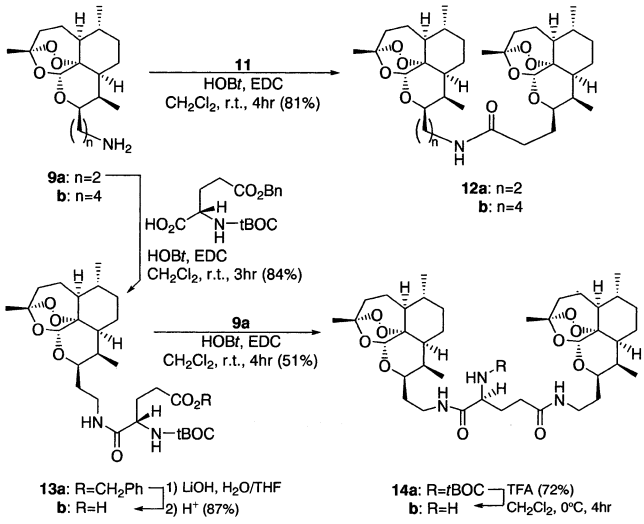
Scheme 2[a]



[a] Regents and conditions: (a) Mg, $Br(CH_2)_nCHCH_2$ (n = 0, 1, 2), Et_2O, 0 °C (80−97%). (b) (i) O_2, Rose Bengal, 500 W tungsten lamp, CH_2Cl_2/CH_3CN (1/1), −23 °C for 4 h; (ii) TFA, O_2, CH_2Cl_2/CH_3CN (1/9), room temperature for 12 h (25−40%). (c) $KMnO_4$, $NaHCO_3$, acetone, room temperature for 1 h, 1 M HCl, room temperature for 5 h (73%). (d) 9-BBN, 3 M NaOH, H_2O_2, room temperature for 1 h (73−97%). (e) TPP, CBr_4, CH_2Cl_2, 0 °C (91%). (f) NaN_3, DMF, room temperature for 5 h (92%). (g) LAH, THF, −10 °C for 4 h (79%).

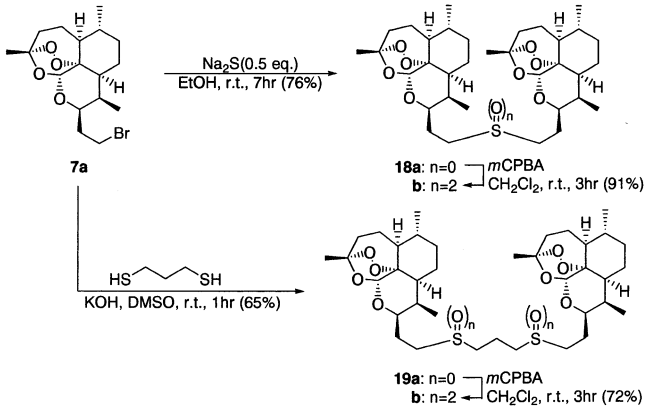
Scheme 3



of a series of novel analogues may cause destruction of the biologically essential endoperoxide, we applied our photooxygenative cyclization[15,16,18] of more abundant artemisinic acid **2** as a key step. A series of novel analogues have been prepared from artemisinic acid as useful chiral synthons, as outlined in Schemes 2−5.

(a) Monomer. Reaction of dihydroartemisinyl aldehyde **3**, prepared from artemisinic acid **2** by a known procedure,[18] with vinyl-, 1-propenyl-, and 1-butenylmagnesium chlorides gave homologated alcohols **4a**−**c** (80−97% yield), respectively. As previously mentioned,[15,16,18] photooxygenative cyclization of alcohol **4c** provided analogue **10** (41% yield) and a C−C bond introduced at C-12. Water soluble 12-carboxyethyldeoxoartemisinin **11** (as sodium salt) was also prepared from the olefinic deoxoartemisinin **10** by a known procedure[42] in a single step by direct oxidation ($KMnO_4$) of the terminal olefin in 73% yield. Direct hydroborative oxidation (9BBN followed by $NaOH/H_2O_2$) of the terminal olefin of the olefinic alcohols **4a**,**c** afforded the dialcohols **5a**,**b** in 73−97% yield, respectively. Treatment of **5a**,**b** with CBr_4/PPh_3 in methylene chloride (0 °C, 1 h) gave the new bromo alcohols **6a**,**b** (91% yield). As previously mentioned,[15,16,18] photooxygenative cyclization of bromo alcohols **6a**,**b** provided new bromoalkyl deoxoartemisinins **7a**,**b** (40% yield). Direct bromination (CBr_4, PPh_3, CH_2Cl_2, room temperature) of hydroxyalkyldeoxoartemisinin[19] did not provide **7a**,**b**. Treatment of **7a**,**b** with sodium azide in dimethyl formamide (DMF; 92% yield) and subsequent reduction of **8a**,**b** finally afforded novel aminoalkyl deoxoartemisinins **9a**,**b** (79% yield), respectively (Scheme 2). In the preparation of compounds **7**−**11**, β-epimer was obtained

Scheme 4



Scheme 5

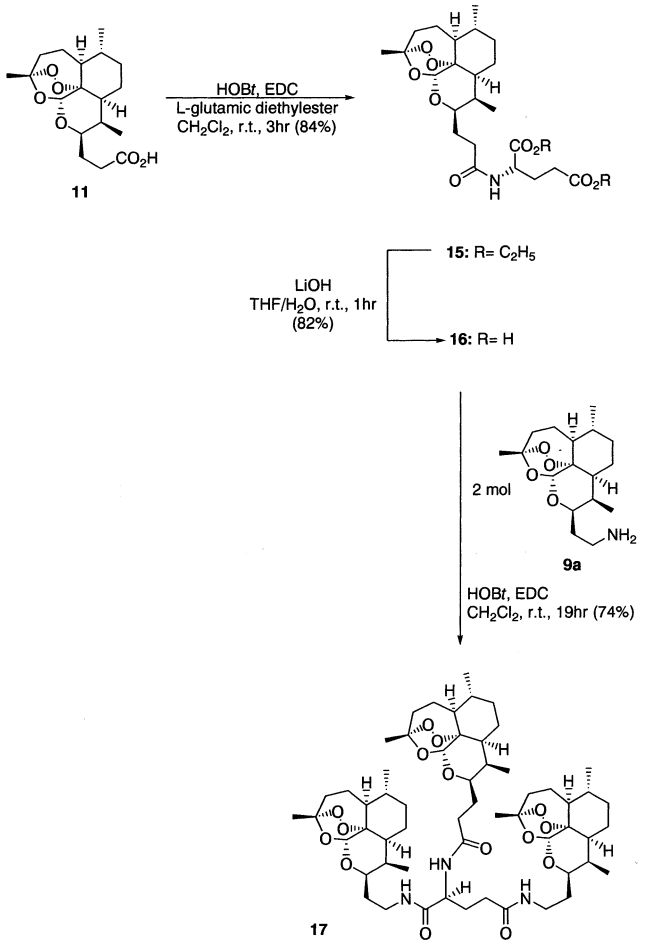


Table 1. In Vitro Cytotoxicities of Deoxoartemisinin-Related Trioxane Monomers, Dimers, and Trimers on Murine and Human Cancer Cell Lines[a]

	IC_{50} (μg/mL)												
cell line	**8b**	**9b**	**12b**	**12a**	**18a**	**18b**	**19b**	**16**	**14b**	**17**	**20**	**21**	**22**
P388	10.30	6.18	>20	10.40	0.40	5.60	8.40	>20	15.60	0.12	0.39	1.50	2.27
EL4	1.61	5.63	>20	6.29	0.23	0.54	10.00	>20	16.50	1.07	0.67	3.94	1.34
Bewo	>20	>20	>20	7.50	14.20	1.04	8.50	>20	>20	18.30	6.24	0.85	7.39
HT-29	2.76	2.20	20.20	0.69	0.24	0.38	0.38	8.60	6.50	0.09	0.10	0.02	0.01
MCF7	11.6	0.02	>20	0.005	0.017	0.025	5.6	13.4	15.3	0.017	0.12	0.93	0.0001

[a] Compound **20**, adriamycin; **21**, mitomycin; **22**, taxol; P388, mouse fibroblast, leukemia; EL4, mouse thymoma; Bewo, human choriocarcinoma; HT-29, human colorectal adenocarcinoma; and MCF7, human breast cancer.

exclusively ($J_{11,12} = 9.8$ Hz). No 12α-isomer was isolated. We found bromo- and amino-alkyldeoxoartemisins **7**, **9**, and **11** to be versatile intermediates for the preparation of dimers and the trimer, as shown below.

(b) Dimers. Dimeric deoxoartemisinin derivatives with alkylamide and sulfur linkers of various lengths and flexibility were obtained in good yields from amino-, bromo-, and carboxyl-deoxoartemisinin monomers (Schemes 3 and 4). Coupling of **9** with **11** in the presence of EDC and HOBt (methylene chloride, room temperature, 4 h) gave **12** in 81% yield. Direct coupling of **9a** with the protected glutarate afforded **13a** in 84% yield. Removal of the benzyl group of the ester of **13a** (LiOH, H_2O/tetrahydrofuran (THF)) to the acid **13b** (87% yield) and subsequent coupling with **9a** in EDC/HOBt afforded **14a** (51% yield). Deprotection of *t*BOC of the amino group of **14a** with trifluoroacetic acid (TFA) (methylene chloride, 0 °C, 4 h) gave **14b** (yield 72%). The dimeric amine **14b** is five times more water soluble (5.21 mg/mL) than artemisinin. Dimeric deoxoartemisinin derivatives **18** and **19** with alkyl-sulfide or -sulfone linkers of various lengths and flexibility were obtained via a bis-nucleophilic coupling reaction in good yields from bromoalkyldeoxoartemisinin monomer **7a** (Scheme 4). Treatment of **7a** with sodium sulfide in ethanol afforded **18a** (76% yield). Oxidation of **18a** with *m*CPBA gave the dimeric sulfone **18b** (91% yield). In a similar fashion, bis-nucleophilic reaction (KOH/dimethyl sulfoxide (DMSO), room temperature, 1 h) of 2 mol of **7a** with 1,3-propanedithiol gave **19a** (65% yield), and subsequent oxidation of **19a** with *m*CPBA gave **19b** in 72% yield.

(c) Trimer. Coupling of carboxyethyl deoxoartemisinin **11** with L-glutamic diethylester as a linker in the presence of EDC/HOBt gave **15** (84% yield) (Scheme 5). Hydrolysis of two ester groups of **15** with LiOH in aqueous THF and subsequent acidification provided the diacid **16** (82% yield). Finally, double coupling of **16** with 2 mol of aminoethyldeoxoartemisinin **9a** in the presence of EDC/HOBt at room temperature afforded the tris adduct trimer **17** as a colorless solid in 74% yield.

All new monomers **7**−**11**, dimers **12**, **14**, **18**, and **19**, and trimer **17** and their stereochemistries were fully and satisfactorily characterized by spectral data, as shown in the Schemes 2−5. Most analogues in this paper possess increased bioavailability in terms of stability or water solubility with retention of biologically essential endoperoxide. Compounds **7a**,**b** and **9a**,**b** are the first primary amines and bromo analogues of deoxoartemisinin with C-12 nonacetal functionality and are versatile intermediates for the synthesis of various derivatives. Because all deoxoartemisinin-derived analogues prepared in this paper lack the carbonyl function and exo C−O bond at C-12, they are projected to possess increased stability in simulated stomach acid, as experimentally proven,[43] and longer half-life in the body, pointing the way to potential next-generation anticancer analogues.

Antitumor Activity

The in vitro cytotoxicity of artemisinin and its related trioxanes against murine and human cancer cells was defined by the microculture tetrazolium assay as previously described.[44] The IC_{50} values are presented in Table 1. Sulfide dimer **18a** is active comparable to adriamycin and four times more active than mitomycin against mouse fibroblast leukemia (P388). Trimer **17** is three times more active than adriamycin, 12 times more active than mitomycin, and 20 times more active than taxol against P388. Sulfur-linked dimers **18a**,**b** and trimer **17** are also comparable to adriamycin against mouse thymoma cells (EL4). Most are inactive, although sulfone-linked dimer **18b** is active comparable to mitomycin and six times more active than adriamycin and taxol against human placental choriocarcinoma cells (Bewo). The free azide **8b** is inactive against most cancer cell lines. Trimer **17** is comparable to adriamycin against human colorectal adenocarcinoma cell line (HT29) and is twice as active than taxol ($IC_{50} = 5.76$ μg/mL) against human pancreas epitheloid carcinoma cells (PANC-1). While most compounds are inactive against human ovarian carcinoma (SKOV3), aminobutyldeoxoartemisinin **9b**, amide-linked dimer **12a**, and trimer **17** are comparable to taxol ($IC_{50} = 12.30$ μg/mL). Aminobutyldeoxoartemisinin **9b**, amide-linked dimer **12a**, sulfide-linked dimer **18a**, sulfone-linked dimer **18b**, and trimer **17** are highly active against human breast carcinoma (MCF7). Dimer **12a**, particularly, is 24 times more active than adriamycin and 200 times more active than mitomycin but 50 times less active than taxol. While most compounds tested are inactive against human lung cancer (A549), trimer **17** is comparable to mitomycin ($IC_{50} = 1.85$ μg/mL). Most compounds are inactive against mouse melanoma (B16), human gastric cancer cell line (AGS), PANC-1, human brain tumor cells (A172), SKOV3, and A549. Trimer **17** shows very potent activity against most of the murine and human cancer cell lines tested. Analogous to *n*-butyldeoxoartemisinin,[18] 12-(4′-aminobutyl)deoxoartemisinin **9b** shows good antitumor activity, thus suggesting that the *n*-butyl group is crucial for both anti-HIV[4] and antitumor activities. Generally, the dimers and the trimer of deoxoartemisinin are shown to have much more potent antitumor activity than monomers. It is noteworthy to say that the anticancer activities of the dimers are dependent on the length of the linker between two

deoxoartemisinins. The linker with one amide- or one sulfur-centered two ethylene groups of the dimers is essential for high anticancer activity, as shown in dimers **12a** and **18a**,**b**. The longer linker of one amide- or one sulfur-centered two ethylene groups of the dimers dramatically decreases most anticancer activity, as shown in dimers **12b**, **14a**,**b**, and **19b**. Lipophilicity may play an important role here. Increased lipophilicity due to the aminobutyl side chains (**12b**) or the methylene groups located between two amides or two sulfides of the dimers (**14b** and **19b**) may decrease cytotoxicity.[28,45]

Conclusion

In conclusion, this structure−activity relationship of deoxoartemisinin may be used as a lead for the possible development of new, hydrolytically stable and orally active anticancer agents related to virtually nontoxic artemisinin (LD_{50} = 4228 mg/kg orally administered to mice). The linker with one amide- or one sulfur-centered two ethylene groups of the dimers is essential for high anticancer activity. Monomer **9b**, dimers **12a** and **18a**,**b**, and trimer **17** are comparable to or more active than in vitro anticancer activities of clinically used adriamycin, mitomycin, and taxol. Trimer **17**, in particular, shows very potent activity against most human cancer cell lines tested and should receive more attention as a possible anticancer drug candidate.

Experimental Section

Chemistry. Merck Kieselgel 60 F 254 precoated silica plates for thin-layer chromatography (TLC) were obtained from BDH, Poole, Dorset, U.K. Column chromatography was carried out on Merck Kieselgel 60 (230−400 mesh). Melting points were determined using a Meltemp apparatus (Laboratory Devices, Holliston, MA). Infrared spectra were recorded in the range of 4000−600 cm^{-1} using a Nicolet Impact 400 spectrometer. Spectra of liquids were taken as films. Sodium chloride plates (Nujol mull) and KBr disks were used as indicated. Nuclear magnetic resonance (NMR) spectra were obtained on Bruker AC250 or DRX500 spectrometers using Me_4Si as an internal standard. Gas chromatography−mass spectrometry (GC−MS) spectra were operated on an HP 5980II GC-HP 5988 (Hewlett-Packard) in the EI mode. High-resolution mass spetrometry (HRMS) was obtained on a Trio2000 (VG-Biotec) and a JMS-700 Mstation (JEOL) spectrometer in fast atom bombardment (FAB) mode. Specific rotations were recorded on a Rudolph AP III-589 polarimeter.

Preparation of 12-(2′-Hydroxyethyl)dihydroartemisinyl Alcohol (5a) from Olefinic Dihydroartemisinyl Alcohol (4a). Under a nitrogen atmosphere, 12-vinyldihydroartemisinyl alcohol (**4a**) (568 mg, 2.290 mmol) was slowly mixed with THF solution of 0.5 M 9BBN (9.1 mL, 4.58 mmol). The mixture was stirred at room temperature for 30 min and then was treated with 30% H_2O_2/3 N NaOH(1/1, 2 mL). This solution was stirred at room temperature for 1 h. The reaction mixture was extracted with ether (40 mL × 2) and was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/1 as eluent) to obtain 12-(2′-hydroxyethyl)dihydroartemisinyl alcohol (**5a**) (591.8 mg) in 97% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.15 (s, 1H, H-5), 4.14 (d, 1H, J = 9.8 Hz, H-12), 3.89−3.80 (m, 2H, H-2′), 2.47 (s, 1H), 1.94−1.72 (m, 6H), 1.54 (s, 3H, CH_3-15), 1.53−1.25 (m, 9H), 0.84 (d, 3H, J = 7.3 Hz, CH_3-13), 0.87 (d, 3H, J = 6.6 Hz, CH_3-14). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 135.5, 120.9, 72.0, 62.6, 42.6, 42.5, 39.7, 37.8, 37.6, 36.0, 28.1, 27.0, 26.4, 26.2, 24.1, 20.1, 10.4. IR (neat): υ_{max} 3435 (OH), 2921, 1647, 1622, 1386, 1124, 1088, 1016 cm^{-1}. MS (EI): m/z 266 ([M^+]), 248 ([M^+] − H_2O), 203 ([M^+] − C_2H_5O).

Preparation of 12-(2′-Bromoethyl)dihydroartemisinyl Alcohol (6a) from Diol (5a). A solution of 12-(2′-hydroxyethyl)dihydroartemisinyl diol (**5a**) (399 mg, 1.503 mmol) in dry CH_2Cl_2 (20 mL) was stirred with TPP (393 mg, 1.503 mmol) at 0 °C for 30 min. The reaction mixture was warmed to room temperature, and CBr_4 (498 mg, 1.503 mmol) was slowly added. The reaction mixture was stirred at room temperature for 30 min and then was quenched with methanol (10 mL). The mixture was extracted with ethyl acetate (20 mL × 3) and washed with brine (20 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 5/2 as eluent) to obtain 12-(2′-bromoethyl)dihydroartemisinyl alcohol (**6a**) (470 mg) in 95% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.14 (s, 1H, H-5), 4.1 (d, 1H, J = 7.5 Hz, H-12), 3.57−3.52 (t, 2H, J = 7.5 Hz), 2.31 (s, 1H), 1.94−1.71 (m, 6H), 1.54 (s, 3H, CH_3-15), 1.53−1.25 (m, 9H), 0.84 (d, 6H, J = 5.0 Hz, CH_3-13, 14). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 135.5, 120.7, 69.8, 42.8, 42.4, 39.1, 38.9, 37.8, 36.0, 31.9, 28.0, 27.0, 26.4, 26.1, 24.1, 20.1, 10.2. IR (neat): υ_{max} 3427 (OH), 2910, 1726, 1447, 1378, 1259, 992, 908, 734 cm^{-1}. MS (EI): m/z 328 ([M^+]), 310 ([M^+] − H_2O), 249 ([M^+] − Br).

Preparation of 12-(2′-Bromoethyl)deoxoartemisinin (7a) from Bromoethyl Diol (6a). A solution of 12-(2′-bromoethyl)dihydroartemisinyl diol (**6a**) (250 mg, 0.665 mmol) in CH_3CN/CH_2Cl_2 (1/1) (60 mL), containing catalytic Rose Bengal, was irradiated with white light (500 W tungsten lamp) at −23 °C for 4 h under oxygen. TLC analysis indicated the disappearance of the majority of the starting material. The mixture was poured onto saturated $NaHCO_3$ solution (50 mL), and products were extracted into diethyl ether (20 mL × 3). The Rose Bengal remained in the aqueous phase. The combined ether extracts were washed with brine (20 mL × 3) and dried with $MgSO_4$. Removal of solvent under reduced pressure left a colorless foam. This was dissolved in CH_3CN/CH_2Cl_2 (9/1) (10 mL), and the resultant solution was cooled to −40 °C and was followed by in situ treatment of acidic catalyst TFA. The mixture was stirred at this temperature under an oxygen atmosphere for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL), and the products were extracted with diethyl ether (30 mL × 3). The extract was washed with water (30 mL × 2) and brine (30 mL × 2) and dried with $MgSO_4$. The extract was concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 5/1 as eluent) to obtain 12-(2′-bromoethyl)-deoxoartemisinin (**7a**) (99 mg) in 40% yield as white solid; $[\alpha]_D^{18}$ = +96.3° (c 0.1 $CHCl_3$); mp 94 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.26 (s, 1H, H-5), 4.33−4.27 (m, 1H, H-12), 3.56−3.51 (m, 2H, H-2′), 2.60−2.45 (m, 2H), 2.30 (ddd, 1H, J = 4.1, 3.8, 4.1 Hz), 2.05−1.89 (m, 4H), 1.83−1.48 (m, 4H), 1.39 (s, 3H, CH_3-15), 1.28−1.22 (m, 2H), 0.94 (d, 3H, J = 4.8 Hz, CH_3-13), 0.87 (d, 3H, J = 7.4 Hz, CH_3-14), 0.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 103.4, 89.5, 81.2, 73.2, 52.4, 44.4, 37.7, 37.3, 35.8, 34.8, 33.7, 31.6, 30.3, 26.3, 25.0, 20.4, 13.1. IR (KBr): υ_{max} 2950, 1451, 1377, 1272, 1117, 1042, 1010, 880 (O−O), 756 cm^{-1}. MS (EI): m/z 376 (M^{+2}), 342 ([M^+] − O_2).

1.1. Synthesis of Azide Derivatives (8). A solution of bromo alkyldeoxoartemisinin derivatives **7** in DMF (5 mL) was stirred at room temperature with sodium azide (45.7 mg, 0.704 mmol) for 5 h. The mixture was poured onto water (30 mL) and then was extracted with ethyl acetate (50 mL × 2) and washed with brine (40 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 5/2 as eluent) to obtain azide derivatives **8**.

Preparation of 12-(2′-Ethyl azide)deoxoartemisinin (8a) from 12-(2′-Bromoethyl)deoxoartemisinin (7a). This compound was prepared from 12-(2′-bromoethyl)deoxoartemisinin (**7a**) (128 mg, 0.352 mmol) using the general procedure in section 1.1 to give the azide (**8a**) (109 mg) in 92% yield as a colorless oil; $[\alpha]_D^{23}$ = +64.2° (c 0.47 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.28 (s, 1H, H-5), 4.31−4.27 (m, 1H, H-12), 3.56−3.53 (m, 1H), 3.44−3.38 (m, 1H), 2.69−2.64 (m, 1H), 2.31 (ddd,

1H, J = 4.1, 3.8, 4.1 Hz), 2.03−1.75 (m, 5H), 1.67−1.60 (m, 3H), 1.40 (s, 3H, CH_3-15), 1.33−1.27 (m, 3H), 0.96 (d, 3H, J = 5.6 Hz, CH_3-13), 0.87 (d, 3H, J = 7.5 Hz, CH_3-14), 0.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 103.5, 89.5, 81.3, 72.3, 52.5, 49.8, 44.5, 37.8, 36.9, 34.7, 30.4, 29.5, 26.3, 25.1, 25.1, 20.4, 13.1. IR (neat): υ_{max} 2927, 2875, 2095 (N_3), 1733, 1454, 1377, 1277, 1098, 1011, 880 (O−O), 756 cm^{-1}. MS (EI): m/z 337 [M^+], 305 ([M^+] − O_2).

Preparation of 12-(4′-Butyl azide)deoxoartemisinin (8b) from 12-(Bromoethyl)deoxo-artemisinin (7b). This compound was prepared from 12-(4′-bromoethyl)deoxoartemisinin (**7b**) (137.9 mg, 0.352 mmol) using the general procedure in section 1.1 to give azide (**8b**) (116.9 mg) in 92% yield as a colorless oil; $[\alpha]_D^{24}$ = +71.3° (c 0.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.29 (s, 1H, H-5), 4.19−4.12 (m, 1H, H-12), 3.26 (t, 2H, J = 6.6 Hz, H-4′), 2.64−2.62 (m, 1H), 2.31 (ddd, 1H, J = 4.1, 3.8, 4.1 Hz), 2.04−1.89 (m, 2H), 1.68−1.65 (m, 2H), 1.63−1.58 (m, 7H), 1.40 (s, 3H, CH_3-15), 1.34−1.22 (m, 4H), 0.96 (d, 3H, J = 5.7 Hz, CH_3-13), 0.86 (d, 3H, J = 7.5 Hz), 0.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 103.4, 89.4, 81.4, 75.3, 52.6, 51.7, 44.6, 37.7, 36.9, 34.7, 30.6,29.3,29.0, 26.4, 25.2, 25.0, 25.0, 20.5, 13.2. IR (neat): υ_{max} 2927, 2876, 2095 (N_3), 1597, 1454, 1379, 1255, 1097, 1012, 946, 881 (O−O), 643 cm^{-1}. MS (FAB): 366.4 ([M + H]$^+$).

1.2. Synthesis of Amine Derivatives (9). A solution of azide derivatives **8** in dry THF (10 mL) was cooled at −78 °C. The mixture was treated with LAH (35.1 mg, 0.925 mmol) at −78 °C, was stirred for 1 h, then was slowly warmed to −10 °C, and was further stirred at −10 °C for 1 h. The mixture was extracted with ethyl acetate (50 mL × 2) and washed with brine (40 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (100% methanol as eluent) to obtain amine derivatives **9**.

Preparation of 12-(Aminoethyl)deoxoartemisinin (9a) from 12-(2′-Ethyl azide)deoxo-artemisinin (8a). This compound was prepared from 12-(2′-ethyl azide)deoxoartemisinin (**8a**) (137.9 mg, 0.352 mmol) using the general procedure in section 1.2 to give amine (**9a**) (85.4 mg) in 78% yield as a white solid; $[\alpha]_D^{23}$ = +38.7° (c 0.1, $CHCl_3$); mp 103 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.32 (s, 1H, H-5), 4.29−4.21 (m, 1H, H-12), 2.93−2.84 (m, 3H), 2.69−2.64 (m, 1H), 2.32 (ddd, 1H, J = 4.0, 3.7, 4.0 Hz), 2.05−1.82 (m, 3H), 1.80−1.74 (m, 2H), 1.62−1.50 (m, 2H), 1.40 (s, 3H, CH_3-15), 1.32−1.26 (m, 4H), 0.96 (d, 3H, J = 5.7 Hz, CH_3-13), 0.87 (d, 3H, J = 7.5 Hz, CH_3-14), 0.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 103.5, 89.4, 81.5, 74.2, 52.7, 44.7, 41.0, 37.8, 36.9, 34.8, 33.2, 30.6, 26.5, 25.1, 25.0, 20.5, 13.4. IR (KBr): υ_{max} 3365 (NH), 2924, 2874, 1663, 1570, 1455, 1377, 1114, 1054, 1011, 944, 877 (O−O), 753 cm^{-1}. HRMS (FAB): m/z 312.2175 ([M + H]$^+$, obsd), 311.2097 (calcd for $C_{17}H_{29}NO_4$). Anal. ($C_{17}H_{29}NO_4$) C, H, N.

Preparation of 12-(Aminobutyl)deoxoartemisinin (9b) from 12-(4′-Butyl azide)deoxoartemisinin (8b). This compound was prepared from 12-(4′-butyl azide)deoxoartemisinin (**8b**) (128.8 mg, 0.352 mmol) using the general procedure in section 1.2 to give the amine (**9b**) (94.3 mg) in 79% yield as a white solid; $[\alpha]_D^{25}$ = +49.4° (c 0.1, $CHCl_3$); mp 105 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.29 (s, 1H, H-5), 4.16−4.09 (m, 1H, H-12), 2.71−2.66 (m, 3H), 2.32 (ddd, 1H, J = 4.1, 3.8, 4.1 Hz), 2.08−2.04 (m, 2H), 1.87−1.72 (m, 3H), 1.66−1.53 (m, 4H), 1.51−1.45 (m, 4H), 1.41 (s, 3H, CH_3-15), 1.36−1.24 (m, 4H), 0.96 (d, 3H, J = 4.3 Hz), 0.86 (d, 3H, J = 7.5 Hz), 0.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 103.5, 89.4, 81.5, 76.0, 52.6, 51.8, 44.8, 38.4, 36.9, 34.8, 31.2,29.4, 29.0, 26.5, 25.3, 25.2, 25.1, 20.5, 13.3. IR (KBr): υ_{max} 3378 (NH), 2925, 1591, 1454, 1379, 1117, 1038, 1005, 887 (O−O), 748 cm^{-1}. HRMS (FAB): m/z 340.2402 ([M + H]$^+$, obsd), 339.2410 (calcd for $C_{19}H_{33}NO_4$). Anal. ($C_{19}H_{33}NO_4$) C, H, N.

Preparation of 12-(3′-Butenyl)deoxoartemisinin (10) from Homologated Alcohol (4c). This compound was prepared from the homologated alcohol **4c** (250 mg, 0.776 mmol) using the same procedure for the preparation of **7a** from **6a** to give **10** (50 mg) in 25% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.78 (m, 1H, H-3′), 5.27 (s, 1H, H-5), 4.92−5.07 (m, 2H, H-4′), 4.05−4.13 (m, 1H, H-12), 1.50 (s, 3H, CH_3-15). IR (neat): υ_{max} 3074, 2877, 1453, 1382, 1210, 1141, 1100 cm^{-1}. MS (EI): m/z 306 ([M^+] − 16). Anal. ($C_{19}H_{30}O_4$) C, H.

Preparation of 12-Carboxyethyldeoxoartemisinin (11) from 12-(3′-Butenyl)deoxoartemisinin (10). This compound was prepared from the 12-(3′-butenyl)deoxoartemisinin (**10**) (200 mg, 0.621 mmol) using the known procedure[39] to give **11** (155 mg) in 73% yield as a colorless oil; $[\alpha]_D^{24}$ = +41.4° (c 0.2 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.29 (s, 1H, H-5), 4.14 (m, 1H, H-12), 2.30 (m, 2H, H-2′), 1.39 (s, 3H, CH_3-15), 0.95 (d, J = 5.4 Hz, 3H, CH_3-13), 0.89 (d, J = 7 Hz, 3H, CH_3-14). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 178.7, 103.4, 89.3, 81.1, 75.2, 52.7, 44.6, 36.9, 34.8, 33.2, 32.2, 30.6, 26.4, 25.4, 25.3, 25.1, 20.6, 13.3. IR (neat): υ_{max} 3341, 2930, 1710, 1210 cm^{-1}. MS (EI): m/z 342 ([M + 2]). Anal. ($C_{18}H_{28}O_6$) C, H.

1.3. Synthesis of Amide-Linkered Dimers (12). A solution of carboxylethyl deoxoartemisinin (**11**) in dry CH_2Cl_2 (3 mL) was treated with HOBt (38 mg, 0.256 mmol) and EDC (47 mg, 0.256 mmol). The reaction mixture was stirred at room temperature for 30 min, and then, aminoalkyl deoxoartemisinin (**9**) was added and further stirred at room temperature for 4 h. The mixture was extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain dimer **12**.

Preparation of 12-(2′-Aminoethyl)deoxoartemisinin Dimer (12a) from 12-(Aminoethyl)deoxoartemisinin (9a). This compound was prepared from 12-(carboxylethyl)deoxoartemisinin (**11**) (32 mg, 0.086 mmol) and 12-(2′-aminoethyl)-deoxoartemisinin (**9a**) (30 mg, 0.096 mmol) using the general procedure in section 1.3 to give dimer **12a** (44 mg) in 81% yield as a colorless oil; $[\alpha]_D^{23}$ = +111.3° (c 0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.28 (s, 1H, NH), 5.30 (s, 1H, H-5), 5.29 (s, 1H, H-5), 4.33−4.31 (m, 1H, H-12), 4.06−4.04 (m, 1H, H-12), 3.58−3.56 (m, 1H, H-2′), 3.28−3.26 (m, 1H, H-2′), 2.73−2.69 (m, 1H), 2.65−2.62 (m, 1H), 2.51−2.44 (m, 1H), 2.35−2.32 (t, 2H, J = 13.5 Hz), 2.24−2.15 (m, 1H), 2.04−1.98 (m, 2H), 1.95−1.89 (m, 3H), 1.78−1.71 (m, 4H), 1.66−1.64 (m, 4H), 1.40 (s, 6H, CH_3-15), 1.37−1.24 (m, 9H), 0.96 (d, 3H, J = 5.3 Hz, CH_3-13), 0.95 (d, 3H, J = 5.7 Hz, CH_3-13), 0.88 (d, 3H, J = 7.5 Hz, CH_3-14), 0.86 (d, 3H, J = 7.5 Hz, CH_3-14), 0.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 173.8, 126.8, 126.1, 118.0, 111.2, 103.7, 103.5, 89.6, 89.0, 81.5, 81.4, 76.4, 74.7, 52.8, 52.5, 44.8, 44.3, 37.8, 37.6, 36.8, 35.1, 34.8, 34.7, 30.7, 30.5, 26.5, 26.4, 25.4, 25.1, 25.0, 20.5, 20.4, 13.7, 13.6. IR (neat): υ_{max} 3380 (NH), 2941, 2877, 1653 (C═O), 1545, 1446 (C−N), 1379, 1097, 1051, 1013, 915, 878 (O−O), 733 cm^{-1}. HRMS (FAB): m/z 634.3995 ([M + H] $^+$, obsd), 633.3877 (calcd for $C_{35}H_{55}NO_9$). Anal. ($C_{35}H_{55}NO_9$) C, H, N.

Preparation of 12-(4′-Aminobutyl)deoxoartemisinin Dimer (12b) from 12-(Aminobutyl)deoxoartemisinin (9b). This compound was prepared from 12-(carboxyethyl)deoxoartemisinin (**11**) (32 mg, 0.086 mmol) and 12-(4′-aminobutyl)-deoxoartemisinin (**9b**) (28 mg, 0.096 mmol) using the general procedure in section 1.3 to give the dimer **12b** (46 mg) in 81% yield as a colorless oil; $[\alpha]_D^{23}$ = +104.2° (c 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.68 (s, 1H, NH), 5.28 (s, 2H, H-5), 4.13−4.03 (m, 2H, H-12), 3.25−3.21 (m, 2H, H-4′), 2.72−2.65 (m, 2H), 2.39−2.21 (m, 4H), 2.11−1.67 (m, 9H), 1.61−1.46 (m, 10H), 1.40 (s, 6H, CH_3-15), 1.36−1.22 (m, 7H), 0.96 (d, 6H, J = 4.6 Hz, CH_3-13), 0.89 (d, 3H, J = 7.4 Hz, CH_3-14), 0.86 (d, 3H, J = 7.4 Hz, CH_3-14), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 173.3, 126.5, 126.3, 118.2, 112.5, 103.7, 103.6, 89.4, 89.1, 81.5, 76.9, 76.4, 75.9, 52.8, 52.5, 44.8, 44.3, 37.8, 37.0, 36.4, 36.1, 35.2, 35.1, 34.8, 34.3, 30.6, 30.6, 26.6, 26.4, 25.2, 25.1, 25.1, 25.1, 20.6, 20.5, 13.7, 13.6. IR (neat): υ_{max} 3388 (NH), 2936, 2875, 1650 (C═O), 1539, 1452 (C−N), 1379, 1216, 1097, 1051, 1005, 873 (O−O), 753 cm^{-1}. HRMS (FAB): m/z 662.4173 ([M + H]$^+$, obsd), 661.4190 (calcd for $C_{37}H_{59}NO_9$). Anal. ($C_{37}H_{59}NO_9$) C, H, N.

Preparation of 12-[2′-(*N*-*t*BOC-glutamic-γ-benzylester)-α-amide]deoxoartemisinin (13a) from 12-(Aminoethyl)-

deoxoartemisinin (9a). A solution of *N*-*t*-BOC-L-glutamic acid γ-benzyl ester (35 mg, 0.11 mmol) in dry CH_2Cl_2 (5 mL) was treated with HOBt (52 mg, 0.342 mmol) and EDC (63 mg, 0.342 mmol). The reaction mixture was stirred at room temperature for 30 min, and then, 12-(2′-aminoethyl)deoxoartemisinin (**9a**) (42 mg, 0.135 mmol) was added and further stirred at room temperature for 3 h. The mixture was extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain compound (**13a**) (71.5 mg) in 84% yield as a colorless oil; $[\alpha]_D^{25}$ = +73.6° (c 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.36 (s, 5H, aromatic H), 7.02 (br, 1H, NH), 5.33 (s, 1H, H-5), 5.11 (s, 2H, benzyl), 4.40−4.39 (m, 1H, H-12), 4.29−4.27 (m, 1H), 4.15−4.13 (m, 1H), 3.58−3.56 (m, 1H, H-2′), 3.28−3.24 (m, 1H, H-2′), 2.61−2.43 (m, 3H), 2.36−2.14 (m, 3H), 2.12−1.98 (m, 4H), 1.91−1.65 (m, 4H), 1.44 (s, 9H, *t*-BOC), 1.42 (s, 3H, CH_3-15), 1.35−1.26 (m, 3H), 0.96 (d, 3H, *J* = 5.6 Hz, CH_3-13), 0.85 (d, 3H, *J* = 7.6 Hz, CH_3-14), 0.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 173.2, 171.5, 155.2, 136.1, 128.8, 128.8, 128.5, 128.5, 128.4, 128.4, 103.8, 89.9, 81.3, 74.4, 66.6, 61.2, 53.1, 52.3, 44.0, 39.4, 37.7, 36.7, 34.6, 30.8, 28.6, 28.5, 28.5, 26.2, 25.1, 25.0, 20.4, 12.6. IR (neat): υ_{max} 3364 (NH), 2932, 2876, 1736 (C═O), 1663 (C═O), 1538, 1453, 1393, 1249, 1163, 1051, 880 (O−O), 702, 610 cm^{-1}. HRMS (FAB): *m*/*z* 631.3507 ([M + H]$^+$, obsd), 630.3516 (calcd for $C_{34}H_{50}N_2O_9$).

Preparation of 12-[2′-(*N*-*t*BOC-glutamic acid)-α-amide]-deoxoartemisinin (13b) from 12-[2′-(*N*-*t*BOC-glutamic-γ-benzylester)-α-amide]deoxoartemisinin (13a). A solution of 12-[2′-(*N*-*t*BOC-glutamic-γ-benzylester)-α-amide]deoxoartemisinin (**13a**) (36 mg, 0.057 mmol) in dry THF/H_2O(1/1, 5 mL) was treated with 1 N LiOH (1 mL) and then was stirred at room temperature for 2 h. The reaction mixture was poured onto 1 N HCl (1 mL) for acidification, and then extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain compound **13b** (26.8 mg) in 87% yield as a colorless oil; $[\alpha]_D^{25}$ = +66.4° (c 0.34, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.60 (d, 1H, *J* = 7.9 Hz, NH), 5.33 (s, 1H, H-5), 4.34−4.32 (m, 1H, H-12), 4.20−4.15 (m, 1H), 3.49−3.47 (m, 1H, H-2′), 3.33−3.31 (m, 1H, H-2′), 2.66−2.58 (m, 1H), 2.48−2.40 (m, 2H), 2.30 (ddd, 1H, *J* = 2.2, 1.9, 3.7 Hz), 2.03−1.73 (m, 5H), 1.67−1.61 (m, 6H), 1.41 (s, 9H, *t*-BOC), 1.38 (s, 3H, CH_3-15), 1.33−1.21 (m, 3H), 0.95 (d, 3H, *J* = 5.1 Hz, CH_3-13), 0.84 (d, 3H, *J* = 7.4 Hz, CH_3-14), 0.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 176.6, 172.2, 103.7, 89.7, 81.4, 76.9, 74.7, 53.4, 52.5, 44.3, 39.1, 37.8, 36.8, 34.7, 30.7, 30.6, 29.8, 28.7, 28.7, 28.7, 28.7, 26.2, 25.2, 25.0, 20.5, 13.0. IR (neat): υ_{max} 3352 (CO_2H and NH), 2933, 2879, 1714 (C═O), 1657 (C═O), 1533, 1459, 1379, 1275, 1170, 1053, 914, 882 (O−O), 733 cm^{-1}. LCMS (ESI): *m*/*z* 540 ([M$^+$]).

Preparation of 12-[2′-(*N*-*t*BOC-glutamic)-α,β-amide]-deoxoartemisinin Dimer (14a) from 12-[2′-(*N*-*t*BOC-glutamic-γ-carboxylic acid)-α-amide]deoxoartemisinin (13b). A solution of 12-[2′-(*N*-*t*BOC-glutamic-γ-carboxylic acid)-α-amide]deoxoartemisinin (**13b**) (21 mg, 0.039 mmol) in dry CH_2Cl_2 (2 mL) was treated with HOBt (22 mg, 0.119 mmol) and EDC (29 mg, 0.119 mmol). The reaction mixture was stirred at room temperature for 30 min, and then, 12-(2′-aminoethyl)deoxoartemisinin (**9a**) (18 mg, 0.058 mmol) was added and further stirred at room temperature for 3 h. The mixture was extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain dimer **14a** (16.6 mg) in 51% yield as a colorless oil: $[\alpha]_D^{25}$ = +114.6° (c 0.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.71 (s, 1H, NH), 5.87 (s, 1H, NH), 5.34 (s, 1H, H-5), 5.33 (s, 1H, H-5), 4.34−4.31 (m, 2H, H-12), 4.13−4.10 (m, 1H), 3.53−3.48 (m, 2H), 3.25−3.23 (m, 2H), 2.62−2.60 (m, 2H), 2.39−2.29 (m, 6H), 2.05−1.88 (m, 8H), 1.86−1.62 (m, 12H), 1.43 (s, 9H, *t*-BOC), 1.39 (s, 6H, CH_3-15), 1.28−1.25 (m, 5H), 0.96 (d, 6H, *J* = 5.3 Hz, CH_3-13), 0.86 (d, 6H, *J* = 7.5 Hz, CH_3-14), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 173.3, 173.2, 171.5, 171.4, 103.5, 103.4, 89.8, 89.6, 81.4, 81.4, 76.9, 74.3, 52.5, 52.5, 44.4, 44.3, 39.3, 37.8, 36.8, 34.7, 30.8, 28.9, 28.7, 26.4, 25.2, 25.1, 20.5, 14.5, 13.0, 12.8. IR (neat): υ_{max} 3379 (NH), 2877, 1713 (C═O), 1656 (C═O), 1545, 1451, 1379, 1268, 1030, 917, 880 (O−O), 732 cm^{-1}. LCMS (ESI): *m*/*z* 834 ([M + H]).

Preparation of 12-[2′-(*N*-Glutamic)-α,β-amide]deoxoartemisinin Dimer (14b) from Dimer 14a. To a stirred solution of dimer **14a** (28 mg, 0.036 mmol) in dry CH_2Cl_2 (2 mL at 0 °C for 30 min, TFA (4.92 mg, 1.2 equiv) was slowly dropped. The reaction mixture was stirred at 0 °C for 4 h and was extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain dimer **14b** (19 mg) in 72% yield as a colorless oil: $[\alpha]_D^{25}$ = +120.8° (c 0.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.83 (s, 1H, NH), 5.74 (s, 1H, NH), 5.34 (s, 1H, h-5), 5.31 (s, 1H, H-5), 4.35−4.33 (m, 2H, H-12), 4.15−4.12 (m, 1H), 3.53−3.49 (m, 2H), 3.27−3.24 (m, 2H), 2.64−2.62 (m, 2H), 2.32-2.30 (m, 2H), 2.15−1.58 (m, 12H), 1.53−1.41 (m, 10H), 1.39 (s, 6H, CH_3-15), 1.34−1.28 (m, 6H), 0.97 (d, 6H, *J* = 5.3 Hz, CH_3-14), 0.86 (d, 6H, *J* = 7.5 Hz, CH_3-14), 0.82 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 173.4, 173.3, 171.5, 171.3, 103.6, 103.4, 89.8, 89.7, 84.4, 84.3, 76.9, 74.3, 52.6, 52.4, 44.5, 44.3, 39.3, 37.9, 36.7, 34.6, 30.9, 30.8, 28.7, 26.4, 25.2, 25.1, 20.5, 20.4, 14.5, 13.3, 12.7. IR (neat): υ_{max} 3367 (NH), 3098 (NH), 2956, 2868, 1689 (C═O), 1558, 1446, 1380, 1209, 1137, 998, 887 (O−O), 847, 757, 729 cm^{-1}. HRMS (FAB): *m*/*z* 734.4592 ([M + H]$^+$, obsd), 733.4513 (calcd for $C_{39}H_{63}N_3O_{10}$). Anal. ($C_{39}H_{63}N_3O_{10}$) C, H, N.

Preparation of 12-(2′-Ethylsulfur)deoxoartemisinin Dimer (18a) from 12-(Ethylbromo)deoxoartemisinin (7a). A solution of 12-(2′-bromoethyl)deoxoartemisinin (**7a**) (45 mg, 0.124 mmol) in absolute ethanol (4 mL) was stirred at room temperature for 10 min, and then, Na_2S (4.8 mg, 0.5 equiv) was slowly added. The reaction mixture was stirred at room temperature for 7 h, then was extracted with ethyl acetate (10 mL × 3), and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 5/1 as eluent) to obtain dimer **18a** (58.7 mg) in 76% yield as a colorless oil; $[\alpha]_D^{25}$ = +58.7° (c 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.29 (s, 2H, H-5), 4.24−4.19 (m, 2H, H-12), 2.91−2.84 (m, 2H), 2.71−2.70 (m, 2H), 2.55−2.49 (m, 2H), 2.33 (ddd, 2H, *J* = 3.1, 3.5, 4.0 Hz), 2.03−1.78 (m, 8H), 1.67−1.55 (m, 10H), 1.41 (s, 6H, CH_3-15), 1.36−1.26 (m, 4H), 0.96 (d, 6H, *J* = 5.8 Hz, CH_3-13), 0.88 (d, 6H, *J* = 7.4 Hz, CH_3-14), 0.83 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 103.6, 89.2, 81.4, 76.8, 75.5, 52.7, 44.8, 37.7, 36.9, 34.8, 30.5, 30.1, 26.5, 25.2, 25.0, 20.6, 13.5. IR (neat): υ_{max} 2925, 2876, 1617, 1459, 1379, 1119, 1054, 1011, 887 (O−O), 735 cm^{-1}. HRMS (FAB): *m*/*z* 645.3541 ([M + Na]$^+$, obsd), 622.3539 (calcd for $C_{34}H_{54}O_8S$). Anal. ($C_{34}H_{54}O_8S$) C, H, S.

Preparation of *S*,*S*′-[12-(2′-Ethyl)deoxoartemisinin]-dithiopropane (19a) from 12-(2′-Bromoethyl)deoxoartemisinin (7a). After the powdered KOH (12.36 mg, 0.22 mmol) was stirred at room temperature in DMSO (2 mL) for 1 h, this solution was treated with 1,3-propanedithiol (6.46 μ, 0.054 mmol) and 12-(2′-bromoethyl)deoxoartemisinin (**7a**) (41 mg, 0.112 mmol) and then further stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (30 mL × 3) and washed with brine (20 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 5/2 as eluent) to obtain dimer **19a** (50.7 mg) in 65% yield as a colorless oil: $[\alpha]_D^{24}$ = +112.3° (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.29 (s, 2H, H-5), 4.22−4.17 (m, 2H, H-12), 2.83−2.66 (m, 10H), 2.41−2.29 (m, 2H), 2.05−1.76 (m, 10H), 1.66−1.53 (m, 10H), 1.41 (s, 6H, CH_3−15), 1.33−1.26 (m, 4H), 0.96 (d, 6H, *J* = 5.7 Hz, CH_3-13), 0.88 (d, 3H, *J* = 7.5 Hz, CH_3-14), 0.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 103.6,

89.3, 81.4, 75.3, 52.7, 44.7, 38.8, 37.8, 36.9, 34.8, 32.2, 30.5, 30.2, 29.1, 26.5, 25.2, 25.0, 20.5, 13.4. IR (neat): υ_{max} 2928, 2873, 1655, 1719, 1452, 1378, 1215, 1120, 1036, 877 (O−O), 755 cm^{-1}. HRMS (FAB): *m/z* 719.3701 ([M + Na]$^+$, obsd), 696.3730 (calcd for $C_{37}H_{60}O_8S_2$). Anal. ($C_{37}H_{60}O_8S_2$) C, H, S.

1.4. Oxidation of Sulfur-Linked Dimers (18a and 19a). A solution of sulfide deoxoartemisinin dimer **18a** or **19a** in dry CH_2Cl_2 (2 mL) was stirred at room temperature for 10 min, and then, *m*-CPBA (2.2 eq) was slowly added. The reaction mixture was stirred at room temperature for 3 h and then was poured onto saturated $NaHCO_3$ solution (3 mL). The mixture was extracted with ethyl acetate (10 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 2/1 as eluent) to obtain sulfone dimer **18b** or **19b**.

Preparation of 12-(2′-Ethyl sulfone)deoxoartemisinin Dimer (18b) from Sulfide 18a. This compound was prepared from 12-(2′-ethyl sulfide)deoxoartemisinin dimer (**18a**) (28 mg, 0.041 mmol) and *m*-CPBA (15.7 mg, 0.091 mmol) using the general procedure in section 1.4 to give the dimer **18b** (24.6 mg) in 91% yield as a white solid; $[\alpha]_D^{20}$ = +84.2° (c 0.44, $CHCl_3$); mp 98 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.30 (s, 2H, H-5), 4.25−4.18 (m, 2H, H-12), 3.53−3.41 (m, 2H, H-2′), 3.05−2.93 (m, 2H, H-2′), 2.79−2.71 (m, 2H), 2.36 (ddd, 2H, *J* = 3.2, 3.5, 4.1 Hz), 2.17−1.92 (m, 6H), 1.88−1.78 (m, 4H), 1.69−1.49 (m, 8H), 1.39 (s, 6H, CH_3-15), 0.97 (d, 6H, *J* = 5.7 Hz, CH_3-13), 0.92 (d, 6H, *J* = 7.6 Hz, CH_3-14), 0.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 134.1, 130.6, 130.1, 128.6, 103.6, 89.4, 81.4, 74.1, 52.5, 44.4, 36.8, 30.5, 26.4, 25.2, 22.4, 20.4, 13.2. IR (KBr): υ_{max} 2928, 2876, 1723, 1575, 1449, 1380, 1280, 1123, 1052, 880 (O−O), 734 cm^{-1}. HRMS (FAB): *m/z* 677.3335 ([M + Na]$^+$, obsd), 654.3438 (calcd for $C_{34}H_{64}O_{10}S$). Anal. ($C_{34}H_{64}O_{10}S$) C, H, S.

Preparation of *S,S′*-[12-(2′-Ethyl)deoxoartemisinin]-disulfonyl Propane (19b) from Dimer 19a. This compound was prepared from *S,S′*-[12-(2′-ethyl)deoxoartemisinin]dithiopropane (**19a**) (29 mg, 0.041 mmol) and *m*-CPBA (31.1 mg, 0.18 mmol) using the general procedure in section 1.4 to give the dimer **19b** (22.6 mg) in 72% yield as a white solid; $[\alpha]_D^{25}$ = +110.4° (c 0.47, $CHCl_3$); mp 138 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.30 (s, 2H, H-5), 4.25−4.21 (m, 2H, H-12), 3.49−3.43 (m, 2H), 3.26 (t, 2H, *J* = 7.1 Hz), 3.04−2.92 (m, 2H), 2.74−2.62 (m, 2H), 2.49−2.43 (m, 2H), 2.41−2.29 (m, 2H), 2.08−1.94 (m, 8H), 1.89−1.75 (m, 4H), 1.69−1.59 (m, 8H), 1.39 (s, 6H, CH_3-15), 1.34−1.27 (m, 4H), 0.97 (d, 6H, *J* = 5.7 Hz, CH_3-13), 0.91 (d, 6H, *J* = 7.6 Hz, CH_3-14), 0.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 134.2, 130.6, 130.1, 128.4, 103.6, 89.5, 81.4, 74.1, 52.5, 44.3, 37.7, 36.8, 34.7, 31.3, 30.5, 26.4, 25.2, 20.4, 13.5. IR (KBr): υ_{max} 2926, 2875, 1720, 1584, 1495, 1387, 1310, 1130, 1052, 877 (O−O), 756, 465 cm^{-1}. HRMS (FAB): *m/z* 783.3538 ([M + Na]$^+$, obsd), 760.3526 (calcd for $C_{37}H_{60}O_{12}S_2$). Anal. ($C_{37}H_{60}O_{12}S_2$) C, H, S.

Preparation of *N*-[12-(*β*-Deoxoartemisinin)propionyl]-L-glutamic Diethyl Ester (15) from 12-(Carboxyethyl)-deoxoartemisinin (11). A solution of 12-(carboxylethyl)-deoxoartemisinin (**11**) (32 mg, 0.086 mmol) in dry CH_2Cl_2 (3 mL) was treated with HOBt (38 mg, 0.256 mmol) and EDC (47 mg, 0.256 mmol). The reaction mixture was stirred at room temperature for 30 min, and after L-glutamic diethyl ester (36 mg, 0.171 mmol) was added, the solution was further stirred at room temperature for 3 h. The mixture was extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain compound **15** (37.9 mg) in 84% yield as a colorless oil; $[\alpha]_D^{25}$ = +44.5° (c 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.31 (d, 1H, *J* = 7.5 Hz, NH), 5.29 (s, 1H, H-5), 4.63−4.56 (m, 1H), 4.23−4.08 (m, 5H), 2.75−2.71 (m, 1H), 2.50−2.18 (m, 7H), 2.04−1.65 (m, 9H), 1.40 (s, 3H, CH_3-15), 1.31 (s, 3H), 1.28 (s, 3H), 1.22−1.15 (m, 2H), 0.96 (d, 3H, *J* = 5.8 Hz, CH_3-13), 0.88 (d, 3H, *J* = 7.5 Hz, CH_3-14), 0.85 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 173.2, 172.3, 103.7, 89.1, 81.5, 76.8, 76.3, 61.9, 61.0, 52.7, 52.0, 44.8, 37.7, 36.8, 34.8, 34.8, 31.2, 30.7, 30.5, 27.8, 26.4, 25.2, 25.0, 20.5, 14.5, 13.5. IR (neat): υ_{max} 3370 (NH), 2939, 2878, 1737 (C═O), 1669 (C═O), 1533, 1446, 1372, 1054, 1012, 880 (O−O), 742 cm^{-1}. MS (FAB): *m/z* 526.5 ([M + H]$^+$). Anal. ($C_{27}H_{43}NO_9$) C, H, N.

Preparation of *N*-[12-(*β*-Deoxoartemisinin)propionyl]-L-glutamic Diacid (16) from Ester 15. A solution of *N*-[12-(*β*-deoxoartemisinin)propionyl]-L-glutamic diethyl ester (**15**) (2 mg, 0.08 mmol) in dry THF/H_2O (1/1, 5 mL) was treated with 1 N LiOH (1 mL) and then was stirred at room temperature for 2 h. The reaction mixture was poured onto 1 N HCl (1 mL) for acidification and then extracted with ethyl acetate (20 mL × 3) and washed with brine (10 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain compound **16** (30.8 mg) in 82% yield as a colorless solid; $[\alpha]_D^{26}$ = +76.8° (c 0.22, $CHCl_3$); mp 106 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.96 (br, 2H, CO_2H), 7.08 (d, 1H, *J* = 6.5 Hz, NH), 5.34 (s, 1H, H-5), 4.62−4.60 (m, 1H), 4.12−4.04 (m, 1H, H-12), 2.72−2.70 (m, 1H), 2.48−2.26 (m, 6H), 2.08−1.98 (m, 3H), 1.82−1.78 (m, 3H), 1.71−1.42 (m, 4H), 1.41 (s, 3H, CH_3-15), 1.27−1.21 (m, 2H), 0.95 (d, 3H, *J* = 5.3 Hz, CH_3-13), 0.87 (d, 3H, *J* = 7.2 Hz, CH_3-14), 0.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 177.3, 176.6, 175.1,174.7, 104.3, 89.0, 81.5, 76.9, 52.8, 52.1, 44.9, 37.6 36.8, 34.8, 34.5, 30.4, 27.1, 26.2, 25.1, 24.9, 21.0, 20.6, 13.7. IR (KBr): υ_{max} 3346 (CO_2H), 2942, 2877, 1728 (C═O), 1631 (C═O), 1539, 1453, 1381, 1202, 1051, 912, 880 (O−O), 732 cm^{-1}. LCMS (ESI): *m/z* 492 ([M + Na]$^+$). Anal. ($C_{23}H_{35}NO_9$) C, H, N.

Preparation of Deoxoartemisinin Trimer 17 from *N*-[12-(*β*-Deoxoartemisinin)propionyl]-L-glutamic Diacid (16). A solution of *N*-[12-(*β*-deoxoartemisinin)propionyl]-L-glutamic diacid (**16**) (22 mg, 0.047 mmol) in dry CH_2Cl_2 (2 mL) was treated with HOBt (27 mg, 0.141 mmol) and EDC (31 mg, 0.141 mmol). The reaction mixture was stirred at room temperature for 30 min, and then, 12-(2′-aminoethyl)deoxoartemisinin (**9a**) (29 mg, 0.093 mmol) was added and further stirred at room temperature for 19 h. The mixture was extracted with ethyl acetate (30 mL × 3) and washed with brine (20 mL × 2). The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude product and was purified by a silica gel column (hexane/ethyl acetate = 1/2 as eluent) to obtain trimer **17** (73.3 mg) in 74% yield as a colorless solid; $[\alpha]_D^{24}$ = +102.7° (c 0.41, $CHCl_3$); mp 138 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.13−7.04 (m, 2H, NH), 6.83−6.81 (m, 1H, NH), 5.32 (s, 2H, H-5), 5.29 (s, 1H. H-5), 4.39−4.34 (m, 3H, H-12), 4.29−4.26 (m, 1H), 3.55−3.48 (m, 2H), 3.32−3.27 (m, 2H), 2.65−2.63 (m, 3H), 2.36−2.31 (m, 7H), 2.17−1.93 (m, 11H), 1.91−1.51 (m, 17H), 1.39 (s, 9H, CH_3-15), 1.33−1.21 (m, 7H), 0.95 (d, 9H, *J* = 5.4 Hz, CH_3-13), 0.88−0.83 (m, 9H, CH_3-14), 0.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 174.4, 174.3, 173.2, 173.1, 103.5, 103.4, 89.9, 89.8, 81.5, 81.4, 76.8, 53.2, 53.1, 52.8, 52.6, 52.4, 37.7, 36.8, 34.7, 31.3, 30.8, 30.7, 30.0, 29.1, 26.4, 26.4, 25.1, 20.5, 20.4, 13.2, 13.1. IR (KBr): υ_{max} 3308 (NH), 2933, 2875, 1667 (C═O), 1535, 1465, 1377, 1102, 1061, 1014, 938, 874 (O−O), 751 cm^{-1}. HRMS (FAB): *m/z* 1056.6392 ([M + H]$^+$, obsd), 1055.6294 (calcd for $C_{57}H_{89}N_3O_{15}$). Anal. ($C_{57}H_{89}N_3O_{15}$) C, H, N.

Biology. In Vitro Antitumor Assay. The in vitro cytotoxicity of deoxoartemisinin and its related trioxanes to the murine and human cancer cells was defined by the microculture tetrazolium assay as described by Carmichel et al.[44] Adriamycin, mitomycin, and taxol were used as the reference substances, exhibiting the activity with an IC_{50} (μg/mL) as shown in Table 1 toward mouse and human cell lines.

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