Orally Active, Hydrolytically Stable, Semisynthetic, Antimalarial Trioxanes in the Artemisinin Family

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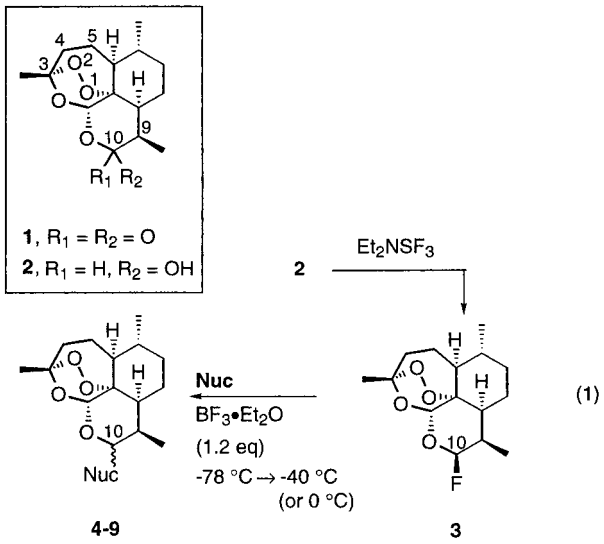
In only three chemical operations, natural trioxane lactone artemisinin (**1**) was converted into a series of C-10 carbon-substituted 10-deoxoartemisinin compounds **4**−**9**. The three steps involved lactone reduction, replacement of the anomeric lactol OH by F using diethylaminosulfur trifluoride, and finally boron trifluoride-promoted substitution of F by aryl, heteroaryl, and acetylide nucleophiles. All of these C-10 nonacetal, chemically robust, enantiomerically pure compounds **4**−**9** have high antimalarial potencies in vitro against *Plasmodium falciparum* malaria parasites, and furans **5a** and **5b** and pyrrole **7a** are antimalarially potent also in vivo even when administered to rodents orally.

The infectious disease malaria is endemic in many parts of the world.[1] In these tropical and subtropical areas, where 300−500 million people now have malaria, chemotherapeutic cure is becoming progressively more difficult because of the rapidly increasing multidrug resistance of the *Plasmodium falciparum* malaria parasites to antifolates and to standard quinoline antimalarial drugs (e.g., chloroquine).[2] In these areas, effective use of a new class of nonalkaloidal trioxane drugs is becoming widespread; the natural lactone artemisinin (qinghaosu, **1**) and the semisynthetic ether and ester derivatives of lactol dihydroartemisinin (**2**) are increasingly available to the local population.[3−14] Because of the presence of a hydrolytically unstable acetal group at C-10 in all ether and ester derivatives of dihydroartemisin (**2**),[15] these derivatives may be acting in vivo as prodrugs for release of their parent dihydroartemisinin. Because dihydroartemisinin (**2**) has been shown to have some toxicity,[16,17] however, an international search has been mounted to design new chemical entities in the endoperoxide[18−20] and trioxane[5] families of compounds that would combine low toxicity with high hydrolytic stability and high antimalarial efficacy. Toward this goal, others[21−27] and we[28] have prepared some C-10 nonacetal analogues of dihydroartemisinin (**2**). Following our recent preliminary report on an effective and efficient semisynthetic method for direct conversion of the dihydroartemisinin C-10 pyranose anomeric OH → F → R_{nuc} (eq 1),[28] we record here full details for preparation and characterization of a wide variety of such C-10 carbon-substituted analogues and, for the first time, their in vitro as well as their in vivo antimalarial activities.

Replacing the anomeric C-10 hydroxyl group in pyranose dihydroartemisinin (**2**) by a fluorine atom occurs smoothly even on multigram scale using diethylaminosulfur trifluoride (DAST);[28−30] the initial mixture of anomeric α- and β-fluorides can be purified easily by immediate column chromatography using Florisil. Although exposure of the crude fluoride product mixture to water causes rapid hydrolysis of these pyranosyl fluorides back into the reactant lactol **2**, purified 10β-fluoride **3** is a crystalline solid that is stable to storage at −20 °C for several weeks.[28]



Electrophilic pyranosyl fluoride **3** undergoes chemoselective, boron trifluoride-promoted, Friedel−Crafts alkylation with various nucleophilic aromatics and heteroaromatics,[31−33] as well as chemoselective coupling with aluminum acetylides.[34] In all of these C−C bond-forming reactions, the trioxane O−O bond survives. Our results are summarized in Table 1, including tabulation of in vitro antimalarial potencies relative to that of artemisinin (**1**).

As seen from Table 1, the major Friedel−Crafts coupling product in all cases studied thus far is the C-10α diastereomer. In some instances (e.g., see eqs 2 and 3), a minor alkylation product is formed. In the case of furan as nucleophile, the vastly major coupling product **5a** was characterized by the typical ^{1}H NMR coupling constant for the C-9,C-10 methine hydrogen

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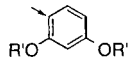
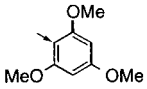
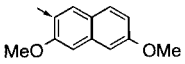
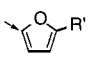
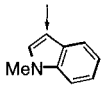
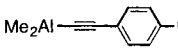
Table 1. Semisynthetic C-10 Substituted Trioxanes

Aryl Nucleophile and Site of Attachment (↓)	10-Nuc Stereo-chemistry	Product Trioxane	Yield of Purified Product	IC_{50} (nM)[a]
	α	**4a**, R' = Me	71%	4.2
	α	**4b**, R' = allyl	58%	6.6
	α	**4c**	95%	7.8
	α	**4d**	80%	9.0
	α	**5a**, R' = H	72%	1.4
	α	**5b**, R' = Me	71%	5.2
	α	**5c**, R' = Et	22%	8.6
	α	**5d**, R' = *t*-butyl	95%	10
	α	**6**	35%	5.1
	α	**7a**, R' = Me	90%	4.6
	α	**7b**, R' = $PhCH_2$	88%	16
	α	**7c**, R' = 	74%	9.4
	α	**7d**, R' = $EtOOCCH_2$	56%	9.1
	α	**8**	72%	4.0
	β	**9a**, R' = Cl	69%	11
	β	**9b**, R' = F	74%	8.3
	β	**9c**, R' = SMe	19%	8.4
Artemisinin		**1**		9.9 ± 1.3

[a] Antimalarial activity was determined against the chloroquine-sensitive NF54 strain of *P. falciparum* as reported previously.[35] The standard deviation for each set of quadruplicates was an average of 10% (≤52%) of the mean. R^2 values for the fitted curves were ≥0.984. Artemisinin activity is mean ± standard deviation of concurrent control (n = 17).

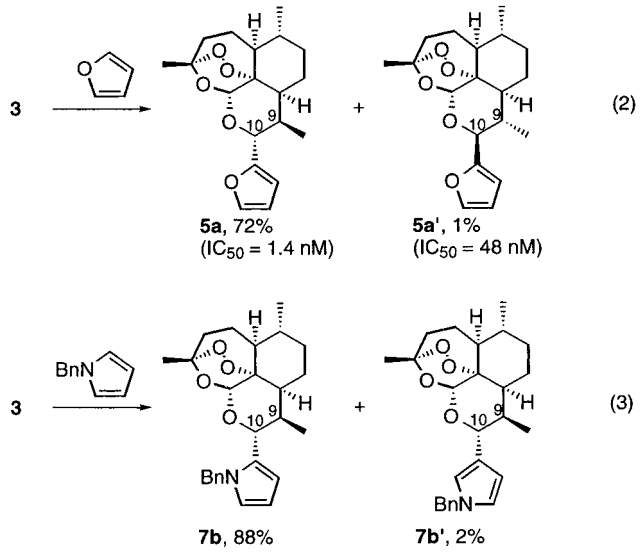
atoms ($J_{9,10}$ = 10−11 Hz for trans product **5a** in contrast to an expected $J_{9,10}$ = 5.6−6.7 Hz for a potential cis product).[22,25] The minor C-9,C-10 trans coupling product **5a′** was characterized by its C-9α methyl doublet appearing at δ 1.0. Noteworthy is the 35-fold higher in vitro antimalarial activity of natural C-9β-methyl diastereomer **5a** vs the corresponding C-9α-methyl diastereomer **5a′**. In the case of *N*-benzylpyrrole as nucleophile, the major coupling product involved attachment to C-2 of the pyrrole ring (i.e., **7b**), whereas the minor coupling product involved attachment to C-3 (i.e., **7b′**, eq 3). In both eqs 2 and 3, the major and minor products were separated from each other by column chromatography. In stereochemical contrast, aluminum acetylide coupling with pyranosyl fluoride **3** produces only C-10β diastereomers **9**.

The antimalarial activities of these C-10 carbon-substituted dihydroartemisinin analogues were determined initially in vitro against *P. falciparum* parasites;[35] their IC_{50} values are included in Table 1. Strikingly, 12 of the 13 C-10 aryl and heteroaryl analogues are at least as potent as artemisinin! The most potent of these analogues is C-10α furan **5a**, with an IC_{50} of 1.4 nM relative to artemisinin's IC_{50} of 10 nM.

Table 2. In Vivo Antimalarial Activities against *Plasmodium berghei* N

C-10 substituted trioxane	10-α-nuc	ED_{50} (mg/kg)[a] subcutaneous	ED_{50} (mg/kg)[a] oral	ED_{90} (mg/kg) subcutaneous	ED_{90} (mg/kg) oral
5a		1.2	9.5	2.0	24.0
5b		0.9	15.5	2.0	43.0
7a		0.7	4.5	1.2	8.5
artemisinin (**1**)		3.0		8.5	
arteether		0.3		0.5	6.0
chloroquine		1.8		3.1	

[a] Four different doses (1, 3, 10, and 30 mg/kg) were administered each day for 4 days to 5 mice per dose regimen to establish the ED values, a protocol previously reported.[37]



As we have done before using in vitro antimalarial potencies as a reliable guide,[36] three of these C-10 analogues were selected for in vivo evaluation; their in vivo antimalarial activities are summarized in Table 2, including subcutaneous and oral administration routes. Hydrolytically stable[26] C-10 dihydroartemisinin furan **5a**, methylfuran **5b**, and *N*-methylpyrrole **7a** are more potent in vivo than artemisinin and chloroquine when administered subcutaneously. *N*-methylpyrrole **7a** is comparable to arteether in terms of oral potency. Similar to the finding with 10-propyldeoxoartemisinin,[22] recent preliminary in vivo acute toxicity testing results indicate that furans **5a** and **5b**, when administered to male CD-1 mice intraperitoneally as a single dose in sesame oil, are comparable to artemether in terms of safety.

How do such trioxanes kill malaria parasites? Current understanding of the trioxanes' fundamental chemical[5] and biological[6] mechanism(s) of action supports the following sequence of events: (1) heme iron activation (i.e., reductive cleavage) of the peroxidic O−O bond to form initially an oxy radical;[38] (2) reorganization of this

oxy radical into one or more carbon-centered radicals;[39] and finally (3) formation of an alkylating epoxide and of an oxidizing high-valent iron-oxo species.[40] *Any one or a combination of these reactive and cytotoxic intermediates may kill the malaria parasites.* Recent evidence has confirmed the intermediacy of an epoxide[41] and of carbon-centered radicals;[41−43] isolation of a covalent adduct between the trioxane skeleton and a porphyrin unit was observed when artemisinin (**1**) was treated with a heme model, *meso*-tetraphenylporphyrin.[43] Therefore, following our previous protocol,[40] we have exposed methylfuran **5b** to iron(II) and have found evidence for the intermediacy of a C-4 carbon radical intermediate (i.e., a C-4 hydroxylated product was isolated) as well as a typical ring-contracted tetrahydrofuran-type product; also, rearrangement of hexamethyl Dewar benzene into hexamethylbenzene was observed, suggesting possibly a high-valent iron-oxo intermediate.[40] Thus, the chemical mechanism of action of these C-10 carbon-substituted 10-deoxoartemisinin compounds seems to be the same as that of natural artemisinin (**1**) itself and of its clinically used semisynthetic ether derivatives (e.g., artemether, arteether).

In summary, very short semisynthesis has generated a series of enantiomerically pure, C-10 nonacetal carbon analogues of dihydroartemisinin (**2**) having high in vitro antimalarial activities. Several of these new 10-deoxoartemisinin trioxanes are highly efficacious in vivo, even when administered orally to rodents. These potent trioxanes in the artemisinin family, therefore, are now candidates for further preclinical evaluations as part of the worldwide effort to combat malaria via chemotherapy.[44]

Experimental Section

General. Unless otherwise noted: Reactions were run in flame-dried round-bottomed flasks under an atmosphere of ultrahigh purity (UHP) argon. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride prior to use. All other compounds were purchased from Aldrich Chemical Co. and used without further purification. Analytical thin-layer chromatography (TLC) was conducted with silica gel 60 F_{254} plates (250 mm thickness, Merck). Column chromatography was performed using short path silica gel (particle size <230 mesh), flash silica gel (particle size 400−230 mesh), or Florisil (200 mesh). Yields are not optimized. Purity of products was judged to be >95% based on their chromatographic homogeneity. High-performance liquid chromatography (HPLC) was carried out with a Rainin HPLX system equipped with two 25 mL/min preparative pump heads using Rainin Dynamax 10 mm × 250 mm (semipreparative) columns packed with 60 Å silica gel (8 mm pore size). Melting points were measured using a Mel-Temp metal-block apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-400 spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrometer. Resonances are reported in wavenumbers (cm^{-1}). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained with electronic or chemical ionization (EI or CI) at Johns Hopkins University on a VG Instruments 70-S spectrometer run at 70 eV for EI and run with ammonia (NH_3) as a carrier gas for CI. Combustion analyses were conducted by Atlantic Microlab (Norcross, GA).

10α-(2′,6′-Dimethoxyphenyl)-10-deoxoartemisinin (4a). 10β-Fluoro-10-deoxoartemisinin (**3**, 0.026 g, 0.090 mmol) and 1,3-dimethoxybenzene (0.063 g, 0.454 mmol) were dissolved in dry dichloromethane (1 mL). The solution was cooled to −78 °C and boron trifluoride diethyl etherate (0.013 mL, 0.109 mmol) was added slowly by syringe. After 15 min, the reaction was warmed to −40 °C and stirred for 2 h. Saturated aqueous sodium bicarbonate (1 mL) was added. The solution was extracted with dichloromethane (3 × 2 mL). The combined organic solution was dried with magnesium sulfate, concentrated under vacuum, chromatographed on Florisil (10% ethyl acetate in hexanes), and then crystallized from pentane to provide **4a** (0.026 g, 0.064 mmol, 71%) as a white solid. Mp: 136−138 °C. $[\alpha]_D^{25} = +94.6$ ($c = 0.67$, $CHCl_3$). HPLC: 10:90 ethyl acetate:hexanes, 3 mL/min, 264 nm, $R_t = 21.6$ min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54 (1H, d, $J = 8.4$ Hz), 6.54 (1H, dd, $J = 2.4$, 8.4 Hz), 6.39 (1H, d, $J = 2.4$ Hz), 5.40 (1H, s), 4.94 (1H, d, $J = 10.4$ Hz), 3.79 (3H, s), 3.76 (3H, s), 2.45−2.58 (1H, m), 2.40 (1H, dt, $J = 4.0$, 13.6 Hz), 2.03 (1H, ddd, $J = 3.2$, 5.2, 14.8 Hz), 1.86−1.93 (1H, m), 1.42 (3H, s), 1.0−1.8 (8H, m), 0.98 (3H, d, $J = 6.0$ Hz), 0.57 (3H, d, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.8, 157.5, 128.6, 122.3, 105.0, 104.0, 97.7, 92.1, 80.7, 69.1, 55.4, 55.3, 52.0, 46.2, 37.4, 36.4, 34.7, 34.3, 26.0, 24.8, 21.6, 20.4, 13.2. IR ($CHCl_3$): 2933, 1614, 1509, 1378, 1278, 1156, 1128, 1041, 880, 838 cm^{-1}. Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.21; H, 7.97. Found: C, 68.19; H, 7.93.

10α-(2′-Furyl)-10-deoxoartemisinin (5a). 10β-Fluoro-10-deoxoartemisinin (**3**, 0.386 g, 1.35 mmol) and furan (0.459 g, 6.75 mmol) were dissolved in dry dichloromethane (5 mL). The solution was cooled to −78 °C, and boron trifluoride diethyl etherate (0.020 mL, 0.159 mmol) was added very slowly by syringe. The reaction was warmed to −50 °C and stirred for 4 h. Saturated aqueous sodium bicarbonate (5 mL) was added. The solution was extracted with dichloromethane (2 × 15 mL). The combined organic solution was dried with magnesium sulfate, concentrated under vacuum, and chromatographed on Florisil (1% to 5% ethyl acetate in hexanes) to provide **5a** (0.325 g, 0.972 mmol, 72%) as a white solid. Mp: 97−98 °C. $[\alpha]_D^{25} = +72.9$ ($c = 0.28$, $CHCl_3$). HPLC: 20:80 ethyl acetate: hexanes, 3 mL/min, 264 nm, $R_t = 6.3$ min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (1H, d, $J = 1.2$ Hz), 6.28−6.30 (2H, m), 5.35 (1H, s), 4.43 (1H, d, $J = 10.8$ Hz), 2.79−2.88 (1H, m), 2.36 (1H, dt, 4.0, 14.0 Hz), 2.00 (1H, dt, $J = 3.8$, 14.4 Hz), 1.83−1.90 (1H, m), 1.67−1.76 (2H, m), 1.56−1.64 (1H, m), 1.38 (3H, s), 1.20−1.55 (3H, m), 0.94 (3H, d, $J = 6.4$ Hz), 0.8−1.1 (2H, m), 0.60 (3H, d, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.1, 142.0, 110.0, 108.3, 104.2, 92.2, 80.3, 71.1, 52.0, 45.7, 37.3, 36.3, 34.1, 21.5, 26.1, 24.7, 21.3, 20.3, 13.7. IR ($CHCl_3$): 2926, 2872, 1455, 1377, 1196, 1153, 1127, 1100, 1043, 924, 880, 848, 741 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84; Found: C, 68.38; H, 7.80.

$FeBr_2$-Induced Degradation of 10α-(5′-methyl-2-furyl)-deoxoartemisinin (5b). Analogue **5b** (75.0 mg, 21.5 mmol) was degraded with $FeBr_2$ (46.5 mg, 21.5 mmol) in dry THF (1.0 mL) using our previously reported protocol.[40] As seen previously, two of the major products were a ring-contracted tetrahydrofuran and a C-4 hydroxylated cyclic ether.

Ring Contracted Product. ^{1}H NMR ($CDCl_3$) δ: 6.20 (d, $J = 3.2$ Hz, 1 H), 6.18 (s, 1 H), 5.87 (m, 1 H), 4.50 (d, $J = 11.2$ Hz, 1 H), 4.33 (ddd, $J = 10.0$, 8.0, 2.0 Hz, 1 H), 3.93 (q, $J = 16.4$, 8.0 Hz, 1 H), 2.73 (m, 1 H), 2.25 (d, $J = 0.8$ Hz, 3 H), 2.09 (s, 3 H), 2.00−1.60 (m, 5 H), 0.94 (d, $J = 6.4$ Hz, 3 H), 0.90−0.70 (m, 4 H), 0.66 (d, $J = 7.24$ Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 169.1, 152.2, 150.2, 110.0, 106.0, 92.6, 80.3, 72.8, 68.7, 55.4, 48.0, 35.4, 32.7, 30.4, 27.7, 21.8, 21.7, 20.6, 13.7, 13.5. HRMS (EI) m/z Calcd for $C_{20}H_{28}O_5$: 348.1937. Found: 348.1935.

C-4 Hydroxylated Product. ^{1}H NMR ($CDCl_3$) δ: 6.14 (d, $J = 2.8$ Hz, 1 H), 5.88−5.87 (m, 1 H), 5.33 (s, 1 H), 4.43 (d, $J = 10.8$ Hz, 1 H), 3.60−3.55 (m, 1 H, C_4H−OH), 2.82−2.73 (m, 1 H), 2.27 (d, $J = 0.8$ Hz, 3 H), 2.20−1.60 (m, 7 H), 1.50−1.0 (m, 3 H), 0.90 (d, $J = 6.4$ Hz, 3 H), 0.70 (d, $J = 7.2$ Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ: 152.0, 108.9, 108.0, 106.0, 95.2, 94.3, 83.8, 71.1, 69.7, 42.4, 42.1, 34.8, 34.3, 30.3, 29.8, 22.2, 21.0, 18.8,

14.4, 13.7. Mp: 120−124 °C. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{28}O_5$: 348.1937. Found: 348.1932.

10α-(2′-Thienyl)-10-deoxoartemisinin (6). 10β-Fluoro-10-deoxoartemisinin (**3**, 0.110 g, 0.384 mmol) and thiophene (0.162 g, 1.92 mmol) were dissolved in dry dichloromethane (1 mL). The solution was cooled to −78 °C, and boron trifluoride diethyl etherate (0.071 mL, 0.576 mmol) was added very slowly by syringe. The reaction was warmed to −50 °C and stirred for 4 h. Saturated aqueous sodium bicarbonate (1 mL) was added. The solution was extracted with dichloromethane (3 × 2 mL). The combined organic solution was dried with magnesium sulfate, concentrated under vacuum, and chromatographed on Florisil (3% ethyl acetate in hexanes) to provide **6** (0.047 g, 0.134 mmol, 35%) as a colorless oil. $[\alpha]_D^{25} = +83.4$ ($c = 0.54$, $CHCl_3$). HPLC: 50:50 dichloromethane: hexanes, 3 mL/min, 235 nm, $R_t = 7.7$ min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25 (1H, dd, $J = 1.2, 5.2$ Hz), 7.00 (1H, dd, $J = 1.2, 3.6$ Hz), 6.93 (1H, dd, $J = 3.6, 5.2$ Hz), 5.40 (1H, s), 4.67 (1H, d, $J = 10.8$ Hz), 2.58−2.67 (1H, m), 2.40 (1H, dt, $J = 4.0, 14.0$ Hz), 2.04 (1H, ddd, $J = 2.8, 4.8, 14.4$ Hz), 1.87−1.94 (1H, m), 1.71−1.80 (2H, m), 1.42 (3H, s), 1.2−1.7 (4H, m), 0.98 (3H, d, $J = 6.0$ Hz), 0.8−1.2 (2H, m), 0.64 (3H, d, $J = 7.2$ Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 126.0, 125.2, 125.0, 104.3, 92.0, 80.4, 73.9, 51.9, 46.0, 37.4, 36.3, 35.0, 34.2, 26.0, 24.8, 21.5, 20.3, 14.1. IR ($CHCl_3$): 2924, 2871, 2360, 1455, 1276, 1196, 1126, 1100, 1056, 927, 880, 830, 695 cm^{-1}. HRMS (CI, NH_4^+) *m*/*z* Calcd for $C_{19}H_{30}NO_4S$ ($M + NH_4^+$): 368.1896. Found: 368.1901.

10α-(*N*-Methyl-3′-indolyl)-10-deoxoartemisinin (8). 10β-Fluoro-10-deoxoartemisinin (**3**, 0.038 g, 0.133 mmol) and *N*-methylindole (0.087 g, 0.664 mmol) were dissolved in dry dichloromethane (2 mL). The solution was cooled to −78 °C, and boron trifluoride diethyl etherate (0.020 mL, 0.159 mmol) was added slowly by syringe. The reaction was warmed to −40 °C and stirred for 4 h. Saturated aqueous sodium bicarbonate (2 mL) was added. The solution was extracted with dichloromethane (3 × 3 mL). The combined organic solution was dried with magnesium sulfate, concentrated under vacuum, and chromatographed on Florisil (15% ethyl acetate in hexanes) to provide **8** (0.038 g, 0.096 mmol, 72%) as a white foam. $[\alpha]_D^{25} = +126.7$ ($c = 1.06$, $CHCl_3$). HPLC: 25:75 ethyl acetate: hexanes, 3 mL/min, 257 nm, $R_t = 9.3$ min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.04 (1H, d, $J = 7.6$ Hz), 7.26 (1H, d, $J = 8.0$ Hz), 7.20 (1H, dd, $J = 7.2, 8.0$ Hz), 7.10 (1H, dd, $J = 7.2, 7.6$ Hz), 7.02 (1H, s), 5.46 (1H, s), 5.67 (1H, d, $J = 10.4$ Hz), 3.73 (3H, s), 2.92−3.15 (1H, m), 2.43 (1H, dt, $J = 4.0, 14.0$ Hz), 2.05 (1H, ddd, $J = 3.0, 4.8, 14.4$ Hz), 1.88−1.95 (1H, m), 1.73−1.80 (2H, m), 1.42 (3H, s), 0.99 (3H, d, $J = 6.0$ Hz), 0.8−1.6 (6H, m), 0.60 (3H, d, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.4, 127.0, 126.5, 121.5, 121.0, 119.0, 114.4, 108.9, 104.2, 92.0, 80.7, 72.3, 52.0, 46.1, 37.4, 36.4, 34.3, 32.6, 26.1, 24.8, 21.2, 20.3, 14.5. IR ($CHCl_3$): 2926, 2871, 1476, 1375, 1128, 1100, 1057, 1042, 880, 741 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.36; H, 7.94; N, 3.40.

10β-(4′-Chlorophenyl)ethynyl-10-deoxoartemisinin (9a). 1-Chloro-4-ethynylbenzene (0.111 g, 0.810 mmol) was dissolved in dry diethyl ether (1 mL). The solution was cooled to 0 °C. Methyllithium (1.4 M in diethyl ether, 0.550 mL, 0.770 mmol) was added slowly by syringe, and the clear solution was stirred at 0 °C for 30 min. Dimethylaluminum chloride (1.0 M in hexanes, 0.770 mL, 0.770 mmol) was added by syringe. The cloudy white suspension was stirred at 0 °C for 2 h. The solution was cooled to −78 °C, and a solution of 10β-fluoro-10-deoxoartemisinin (**3**, 0.116 g, 0.405 mmol) in dry dichloromethane (10 mL) was added by cannula. Boron trifluoride diethyl etherate (0.060 mL, 0.486 mmol) was immediately added, and the reaction was stirred for 15 min at −78 °C. The solution was then warmed to −40 °C and stirred for 4 h. Distilled water (5 mL) was added, and the reaction was extracted with dichloromethane (3 × 10 mL). The combined organic solution was dried with magnesium sulfate, concentrated under vacuum, and chromatographed on Florisil (10% ethyl acetate in hexanes) to provide **9a** (0.123 g, 0.316 mmol, 78%) as a colorless oil. $[\alpha]_D^{25} = +64.5°$ ($c = 1.33$, $CHCl_3$). HPLC: 10:90 ethyl acetate:hexanes, 3 mL/min, 264 nm, $R_t = 12.1$ min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23−7.38 (4H, m), 5.61 (1H, s), 4.95 (1H, d, $J = 5.6$ Hz), 2.83 (1H, m), 2.37 (1H, m), 2.45 (3H, s), 1.11−2.22 (10H, m), 1.02 (3H, d, $J = 7.3$ Hz), 0.95 (3H, d, $J = 6.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.4, 132.6, 128.6, 121.1, 104.2, 89.5, 87.9, 87.6, 80.9, 67.8, 52.6, 45.3, 37.4, 36.2, 34.6, 30.3, 26.1, 24.6, 23.0, 20.3, 13.9. IR ($CHCl_3$): 2940, 1488, 1377, 1277, 1188, 1090, 1052, 1014, 990, 960, 924, 874, 825 cm^{-1}. HRMS (CI, NH_4^+) *m*/*z* Calcd for $C_{23}H_{31}ClNO_4$ ($M + NH_4^+$): 420.1942. Found: 420.1950.

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Supporting Information Available: ^{1}H and ^{13}C NMR, IR, and mass spectral data for those compounds for which such spectroscopic data are not described in the Experimental Section (5 pages). Ordering information is given on any current masthead page.

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